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THE TOTAL SYNTHESIS OF STRYCHNINE*

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STRYCHNINE.[1] The fearsome poisonous properties of this notorious substance attracted the attention of XVIth century Europe to the *Strychnos* species which grow in the rain forests of the Southeast Asian Archipelagos and the Coromandel Coast of India, and gained for the seeds and bark of those plants a widespread use for the extermination of rodents, and other undesirables, as well as a certain vogue in medical practice—now known to be largely unjustified by any utility. The isolation of the pure alkaloid from the beans of *Strychnos ignatii* in 1818 by Pelletier and Caventou[3] was an event of some historical importance, in that it provided a convincing and elegant demonstration of the correctness of the then only recently proposed and revolutionary suggestion that acid-fixing substances are produced in the vegetable kingdom.† Thus did circumstance early place ready at the hand of any interested chemist an abundant supply of a pure crystalline compound whose constitution and construction could hardly fail to excite curiosity. But organic chemistry, in its first hundred years, was scarcely equipped for the attack on so formidable an objective, and apart from the determination of the correct empirical formula of the alkaloid, and the discovery of a few simple transformations, no substantial progress was made until the commencement of the massive investigations of the present century. Then, over a period of forty years, one of the great classics of structural organic chemistry was constructed. In that effort, described in more than two hundred and fifty separate communications, Robert Robinson played a brilliant and commanding role, and the extensive beautiful experimental contributions of Hermann Leuchs were of definitive importance. In 1947, the task was finished,[4]

* A preliminary communication[1] and a general account[2] describing this investigation have been published earlier.

† Pelletier and Caventou attributed this pioneer idea to Vauquelin, and in spite of that investigator's modest demurrer, wished to signalize his contribution by naming their new substance *vauqueline*. They were thwarted in their generous design by the officers of the Académie des Sciences at Paris, who delivered themselves of the opinion "*qu'un nom chéri ne pouvait être appliqué à un principe malfaisant*."

[1] R. B. Woodward, Michael P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, *J. Amer. Chem. Soc.* **76**, 4749 (1954).

[2] R. B. Woodward, *Experientia Supplementum* II, p. 213. Birkhauser Verlag, Basel and Stuttgart (1955).

[3] P. J. Pelletier and J. B. Caventou, *Ann. Chim. Phys.* **8**, 323 (1818); *Ibid.* **10**, 142 (1819).

[4] R. Robinson, *Experientia* **2**, 28 (1946); H. T. Openshaw and R. Robinson, *Nature, Lond.* **157**, 435 (1946); L. H. Briggs, H. T. Openshaw and R. Robinson, *J. Chem. Soc.* 903 (1946); H. L. Holmes, H. T. Openshaw and R. Robinson, *Ibid.* 908 (1946); R. Robinson, *Nature, Lond.* **159**, 263 (1947); R. N. Chakravarti and R. Robinson, *Ibid.* **160**, 18 (1947); R. Robinson in *Les Prix Nobel en* 1947, p. 123. Imprimerie Royale, P. A. Norstedt and Soner, Stockholm (1949); A. S. Bailey and R. Robinson, *Nature, Lond.* **161**, 433 (1948); R. Robinson and A. M. Stephen, *Ibid.* **162**, 177 (1948). Cf. also V. Prelog and S. Szpilfogel, *Helv. Chim. Acta* **28**, 1669 (1945); V. Prelog and M. Kocór, *Ibid.* **30**, 359 (1947); *Ibid.* **31**, 237 (1948); R. B. Woodward, W. J. Brehm and A. L. Nelson, *J. Amer. Chem. Soc.* **69**, 2250 (1947) and R. B. Woodward and W. J. Brehm, *Ibid.* **70**, 2107 (1948).

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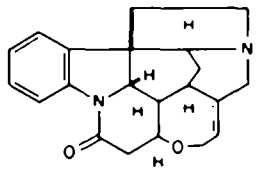
and strychnine stood revealed as I.* Almost coincident with the conclusion of the chemical studies, two separate X-ray crystallographic investigations[8] culminated



I

in confirmatory presentations of the same structure, and provided firm evidence for stereochemical aspects which at least in part must otherwise have been objects for surmise and further experimentation.† It was now possible to contemplate the synthesis of the substance of which it has been said: "*For its molecular size it is the most complex substance known.*"‡§

* A number of general accounts of the investigation are available.[4] The obituary notice of Hermann Leuchs[6] contains a valuable complete list of Leuchs' 125 papers, and Robinson's Bakerian Lecture in 1931[7] presents a fascinating account of the status of the work at a penultimate stage.

† The *absolute configuration* of the natural strychnine molecule was only established, in the sense shown above, at a later date, also by X-ray crystallographic methods.[9]

‡ Admittedly, by one whose special familiarity with the intricacies of its structure and behavior might excuse a certain prejudice,[10] but with six nuclear asymmetric centers and seven rings constituted from only twenty-four skeletal atoms, the case is a good one.

§ It will not be lost upon the reader—nor was it on at least some of the observers of the chemical scene in the late nineteen forties-- that the almost simultaneous outcomes of the decades-long chemical degradative assault, and the incomparably shorter X-ray crystallographic investigations, presaged a future in which so singular an edifice as the chemical structure determination of strychnine was unlikely to find parallels.

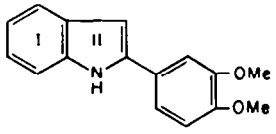
But it is worth while to point out here that the establishment of the structure of strychnine was accompanied by no surcease of interesting chemical developments. The elucidation and further development of the fascinating chemistry of vomicine,[11] the dramatic establishment of the relationships between strychnine and the calabash curare alkaloids,[12] the discovery of intricate new transformations of the strychnine skeleton,[13] the even now rapidly unfolding exciting new chapters in the story of the biogenesis of the *Strychnos* and related alkaloids,[14] and perhaps also the synthesis here recorded, may be selected as only a few high points[15] in the continuing evolution of the chemistry of strychnine during the last fifteen years.

This short history should give pause to those whose talent for despair is lavished upon an organic chemistry ornamented and supplemented—or as they fancy, burdened—by magnificent new tools which permit the establishment in days or weeks of enlightenments which once would have required months or years. While it is undeniable that organic chemistry will be deprived of one special and highly satisfying kind of opportunity for the exercise of intellectual *élan* and experimental skill when the tradition of purely chemical structure elucidation declines, it is true too that the not infrequent dross of such investigation will also be shed; nor is there any reason to suppose that the challenge for the hand and the intellect must be less, or the fruits less tantalizing, when chemistry *begins* at the advanced vantage point of an established structure.

Of course, men make much use of excuses for activities which lead to discovery, and the lure of unknown structures has in the past yielded a huge dividend of unsought fact, which has been of major importance in building organic chemistry as a science. Should a surrogate now be needed, we do not hesitate to advocate the case for synthesis.

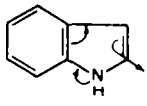
[4] T. A. Henry in *The Plant Alkaloids* p. 553. Blakiston Company, Philadelphia and Toronto (1949); H. L. Holmes in *The Alkaloids* (Edited by R. H. F. Manske and H. L. Holmes) Vol. I, p. 375. Academic Press, New York (1950); R. Huisgen, *Angew. Chem.* **62**, 527 (1950); R. Robinson in

An indole of some kind was an obvious choice as starting material for the synthesis of strychnine, and the one we chose was 2-veratrylindole (II), which was readily

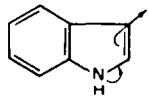


II

preparable from acetoveratrone,[16] either by direct condensation with phenylhydrazine in the presence of polyphosphoric acid,[17] or by bromination and condensation of the resulting ω-bromoketone[18] with aniline.[19] In the selection of II as our point of departure, we had it in mind that indoles are readily susceptible to the attack of electrophilic agents in either the α or the β position, in consequence of the electronic processes



III



IV

outlined in III and IV. We placed the veratryl group at the α position in order to block condensations at that center, and force the reactions we wished to use for the

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Progress in Organic Chemistry (Edited by J. W. Cook) Vol. I, p. 1. Butterworths, London (1952); H. L. Holmes in *The Alkaloids*, (Edited by R. H. F. Manske and H. L. Holmes) Vol. II, p. 513, Academic Press, New York (1952); J. B. Hendrickson in *The Alkaloids* (Edited by R. H. F. Manske) Vol. VI p. 179, Academic Press, New York and London (1960); G. F. Smith in *Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol. IVc, p. 2110, Elsevier, Amsterdam (1960).

[6] F. Kröhnke, *Chem. Ber* **85**, LV (1952).

[7] R. Robinson, *Proc. Roy. Soc.* **A130**, 431 (1931).

[8] C. Bokhoven, J. C. Schoone and J. M. Bijvoet, *Proc. K. Ned. Akad. Wet.* **51**, 990 (1948); *Ibid.* **52**, 120 (1949); *Idem, Acta Cryst.* **4**, 275 (1951); J. H. Robertson and C. A. Beevers, *Nature, Lond.* **165**, 690 (1950); *Idem, Acta Cryst.* **4**, 270 (1951).

[9] A. F. Peerdeman, *Acta Cryst.* **9**, 824 (1956).

[10] R. Robinson in *Progress in Organic Chemistry*, (Edited by J. W. Cook) Vol. I, p. 2. Butterworths, London (1952).

[11] Cf. J. B. Hendrickson in *The Alkaloids* (Edited by R. H. F. Manske) Vol. VI, p. 195, Academic Press, New York and London (1960).

[12] Cf. K. Bernauer, *Fortsch. Chem. Org. Naturstoffe* **17**, 183 (1959); A. R. Battersby and H. F. Hodson, *Quart. Rev.* **14**, 77 (1960).

[13] Ch. Weissmann, H. Schmid and P. Karrer, *Helv. Chim. Acta* **45**, 62 (1962).

[14] E. Leete, S. Ghosal and P. N. Edwards, *J. Amer. Chem. Soc.* **84**, 1068 (1962).

[15] Cf. H. -G. Boit, *Ergebnisse der Alkaloid-Chemie bis* 1960. Akademie-Verlag, Berlin (1961) for many others.

[16] C. Mannich, *Arch. Pharm.* **248**, 137 (1910).

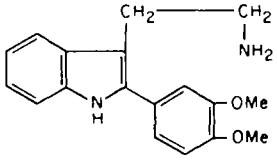
[17] Cf. H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Amer. Chem. Soc.* **74**, 3948 (1952).

[18] C. Mannich and F. L. Hahn, *Ber. Dtsch. Chem. Ges.* **44**, 1549 (1911).

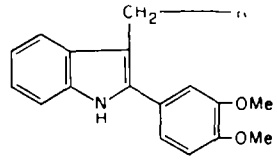
[19] Cf. W. C. Sumpter and F. M. Miller, *The Chemistry of Heterocyclic Compounds*, Vol. 8, p. 12. Interscience, New York (1954).

construction of ring V* to take place at the desired β site. And beyond that, we hoped that while the relatively stable assemblage of atoms comprising the blocking group would withstand our operations in the early stages, it could be modified at a subsequent time in a direction useful for the elaboration of rings III, IV and VI of the alkaloid.

The first steps in the construction of ring V involved the transformation of 2-veratrylindole (II) into 2-veratryltryptamine (V), and were readily accomplished following models which had been well worked out by others in the case of tryptamine

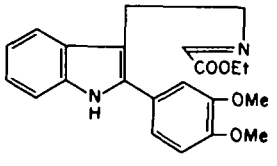


V



VI

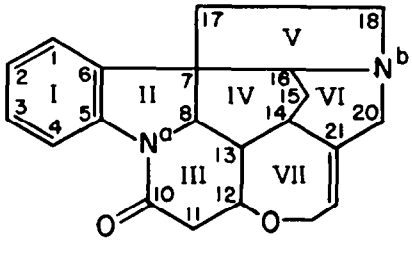
itself.[20] Thus, the indole (II) condensed smoothly with formaldehyde and aqueous dimethylamine in dioxane and acetic acid to give the gramine (VI: R = NMe_2), whose methiodide (VI: R = $\overset{+}{N}Me_3]I^-$) was converted by sodium cyanide in dimethylformamide to the nitrile (VI: R = CN), which in its turn was reduced by lithium aluminum hydride in hot tetrahydrofuran to the desired amine. Condensation of the 2-veratryltryptamine with ethyl glyoxylate[21] in warm benzene to give the corresponding Schiff base (VII) proceeded without incident. Only one bond of the desired ring V



VII

remained to be constructed, and in order to forge it, we now faced for the first time a situation of some novelty. We were cognizant of the possibility that the protonated Schiff base function might attack the β position of the indole ring (VIII, *arrows*). But

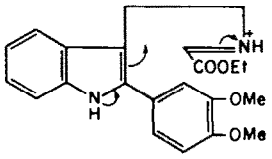
* The accompanying diagram shows the numbering system used for strychnine throughout this paper.



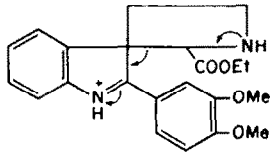
[20] H. Kuehn and O. Stein, *Ber. Dtsch. Chem. Ges.* **70**, 567 (1937); H. R. Snyder, C. W. Smith and J. M. Stuart, *J. Amer. Chem. Soc.* **66**, 200 (1944); C. Schoepf and J. Thesing, *Angew. Chem.* **63**, 377 (1951); J. Thesing and F. Schuelde, *Chem. Ber.* **85**, 324 (1952); T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.* **74**, 3916 (1952).

[21] C. Weygand, *Organic Preparations* p. 455. Interscience, New York (1945); W. Oroshnik and P. E. Spoerri, *J. Amer. Chem. Soc.* **63**, 3338 (1951).

we were aware too that the resulting indoleninium salt (IX) would be formed only with a not inconsiderable loss of aromatic stabilization. In the event, the action of

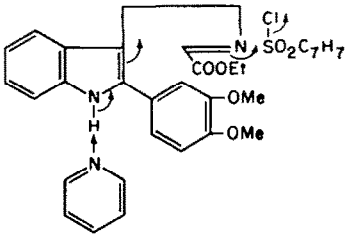


VIII

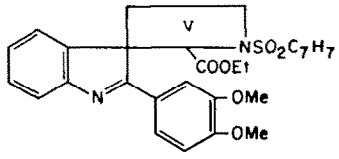


IX

acid catalysts on the Schiff base (VII) under various conditions led to no useful result; it is a matter of some interest that subsequent developments have revealed a number of interesting cases in which the precise reverse (IX, *arrows*) of the bond-forming process at issue here has played a role in the degradation of a number of indole alkaloids.[22] In order to drive forward the desired process, we felt that it would be necessary to stabilize the product in some way, and chose to do so through de-protonation of N^a, coupled with the replacement of the simple amine function at N^b by an amide group. In fact, when the Schiff base (VII) was treated with toluenesulfonyl chloride in pyridine (X, *arrows*), the indolenine (XI) was smoothly produced. It is perhaps worthy of



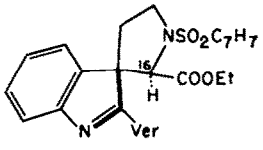
X



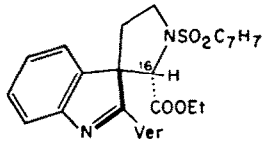
XI

mention that this reaction may well be facilitated in the special case at hand by a favorable interaction, in the product, between the C=N bond and the conjugated, electrically complementary veratryl group.

Now we must advert briefly to a stereochemical point. It is noteworthy that while a new asymmetric center is generated in the change VII → XI, only one product was observed. We cannot say for certain whether that single product possesses the structure XII or XIII. Although the argument based on models is scarcely of the convincing



XII



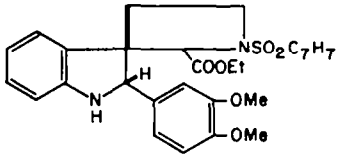
XIII

kind, it seems possible that steric factors in the two relevant transition states are such as to favor the process leading to XIII. Now, since the carbethoxyl carbon atom of

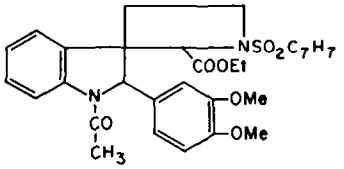
[22] G. F. Smith and J. T. Wrobel, *J. Chem. Soc.* 792 (1960); K. Biemann and G. Spiteller, *Tetrahedron Letters* 299 (1961); Ch. Weissmann, H. Schmid and P. Karrer, *Helv. Chim. Acta.* **45**, 62 (1962); H. -J. Teuber and A. Walter, *Angew. Chem.* **74**, 512 (1962).

the product is fated to become part of ring IV of the strychnine molecule, it is clear that XIII could not be used without inversion at C.16. But, since the attachment of a carbethoxyl group at that position renders just such an inversion possible, we saw no occasion for stereochemical concern at this stage in our work.

In order to set the stage for more considerable operations, two simple changes were now effected. First, the indolenine (XI) was readily reduced by sodium borohydride in ethanol to the corresponding indoline (XIV); the new asymmetric carbon atom generated in the sole product in this reduction very probably possesses the



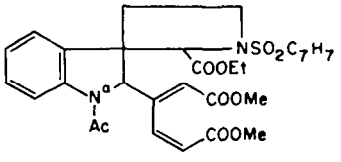
XIV



XV

configuration shown in XIV, since the borohydride ion almost certainly attacks from that face of the trigonal C.8 which is least hindered; in any event the point is not one of importance, since the asymmetry here introduced at C.8 is destined to be lost at a subsequent stage. Next, the indoline (XIV) in its turn was converted into the N-acetyl derivative (XV) by the action of acetic anhydride and pyridine.

Our veratryl group had now served admirably its function of directing the processes involved in the elaboration of ring V, and at this point we undertook to examine whether it could be made to perform its second function. We believed that two of the aromatic rings present in XV, namely, that of the tosyl function and that one which is incorporated in the N-acetyl indoline system would be relatively inert to electrophilic attack, since the sulfonyl function is strongly electron-attracting and the acetylamino group is an indifferent source for electron release. By contrast, it was not unreasonable to expect that the veratryl ring, containing as it does two powerful electron-releasing methoxyl groups, would be readily attacked by electron-demanding oxidants, and further, it might be expected that any such attack would occur most readily at that bond to which were directly attached the groups which should render the array vulnerable. These expectations were now realized. While peracids, which readily cleave simple methoxylated aromatic systems,[23] seemed to be without action on XV,



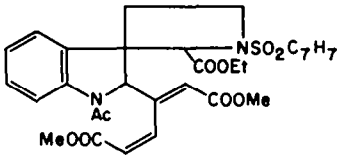
XVI

ozone in aqueous acetic acid attacked it in just the desired sense, with the formation of the muconic ester (XVI).

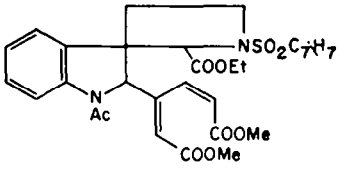
It was our plan to build ring III of the strychnine molecule by inducing lactam

[23] H. Fernholz, *Angew. Chem.* **60**, 62 (1948); *Idem, Chem. Ber.* **84**, 110 (1951); D. Taub, *Dissertation*, Harvard (1949).

formation between N^a and one of the carbomethoxyl groups of the muconic ester (XVI). If the alternative conformations XVII and XVIII, which may be written for

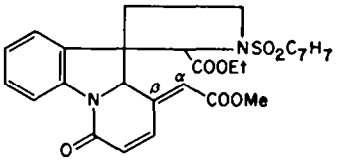


XVII

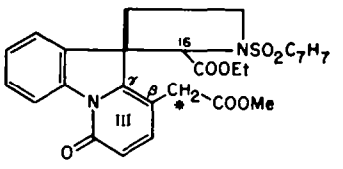


XVIII

XVI, be examined, it will be noted that the stereochemistry of the ester is such as precisely to favor the cooperation of the apposite groups in 6-membered lactam formation, while the alternative formation of a 5-membered lactam, involving the second available carbomethoxyl group, is prohibited by the *trans* disposition of the relevant functions about a double bond. Further, it may be expected that an initially formed lactam (XIX) would be unstable with respect to an aromatic isomer (XX), and



XIX



XX

that a path for the ready transformation of the one into the other will be available, since the change would be simply a special case of the well-known isomerization of an α,β-unsaturated ester into its β,γ-unsaturated isomer. Finally, one might hope that the formation of such a very stable array as XX would carry the sequence of desired processes forward smoothly, and without serious interfering side reactions. Clearly, the initiation of the desired processes required prior removal of the acetyl group at N^a, and we were most pleased to observe that when the ester was treated with boiling methanolic hydrogen chloride in order to bring about that cleavage, all of the changes just outlined took place at once, and the pyridone ester (XX) was formed in excellent yield. As an important practical point, it may be noted that the presence in this, and subsequent intermediates, of the N-phenylpyridone system was readily established through observation of its highly characteristic ultraviolet[24] [Fig. 1] and infrared absorption.

So far our operations had proceeded very directly towards our objective. Now we were to embark on a brief excursion, which is not without intrinsic interest, and necessitated a minor tactical change in our plans. We had it in mind that the pyridone ester (XX) contains an activated methylene group (starred) at which it seemed probable that condensation could be brought about with the carbethoxyl group six carbon atoms distant. As noted above, this condensation could take place directly if the carbethoxyl group were already properly oriented, as in XII, but would require a prior inversion at C.16 if the alternative configuration obtained at that center. These considerations dictated the initial choice of a hydroxylic medium for the proposed

[24] Cf. V. Prelog, M. Kocór and W. I. Taylor, *Helv. Chim. Acta.* **32**, 1052 (1949).

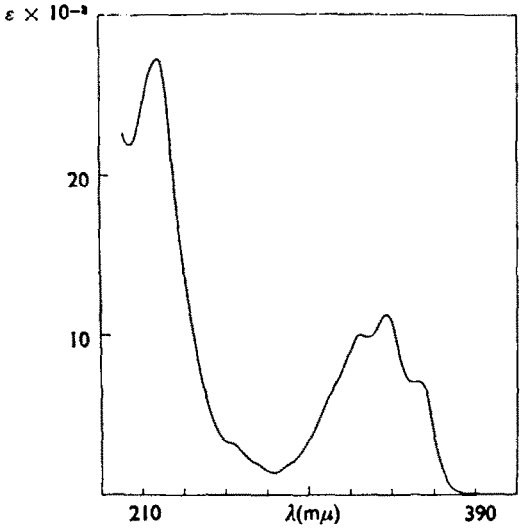


FIG. 1. Ultraviolet spectrum of XX in EtOH

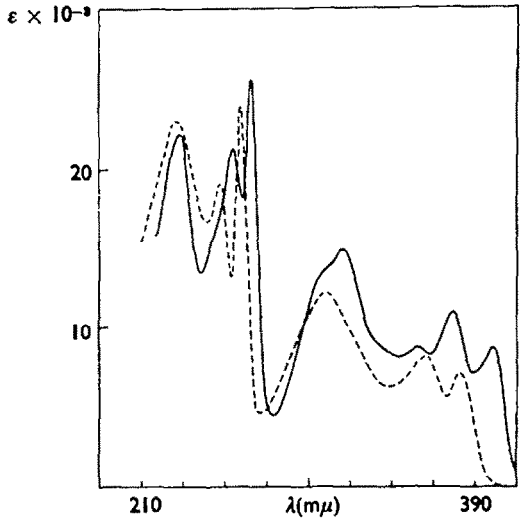
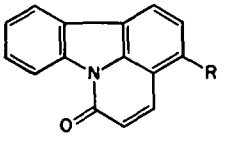


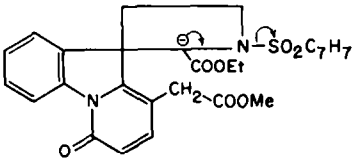
FIG. 2. Ultraviolet spectra in EtOH
———XXI, R = COOMe
- - - -XXI, R = H

Dieckmann condensation. When in the event the diester (XX) was treated with sodium methoxide in hot methanol, a beautifully crystalline product separated from the reaction mixture in a short period of time. The striking ultraviolet absorption spectrum of this substance [Fig. 2] revealed at once that it was not the desired cyclic keto ester, and comparison with the known[25] polycyclic aromatic compound (XXI, R = H) suggested that we had prepared the corresponding ester (XXI, R = COOMe),

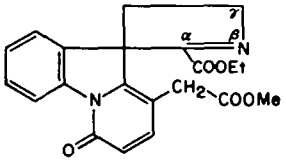


XXI

a view which was confirmed when the new substance was found to have the required composition. How had these changes which had led to the collapse of our carefully constructed ring V come about? It will be noted that that ring is peculiarly constructed, in that the very anion (XXII) which is required for the stereochemical inversion

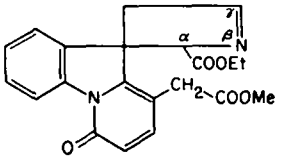


XXII

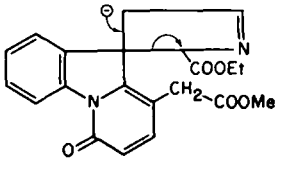


XXIII

discussed above contains an electron pair one carbon atom removed from an aryl-sulfonyl group. Consequently, the possibility exists of β elimination of the stable toluenesulfinate anion (XXII, *arrows*). It would not be surprising were the resulting α,β unsaturated ester (XXIII) to be a participant in an equilibrium with the corresponding β,γ isomer (XXIV). In the latter the opportunity exists for anion formation

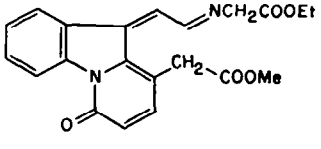


XXIV

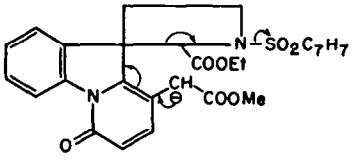


XXV

at a new center, to give XXV which can undergo a further elimination (XXV, *arrows*), leading to XXVI. Alternatively, the toluenesulfonyl group in XX might be extruded by another, but equally disruptive process (XXVII, *arrows*), which could give the



XXVI

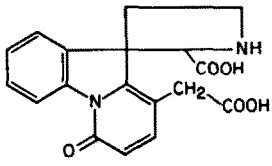


XXVII

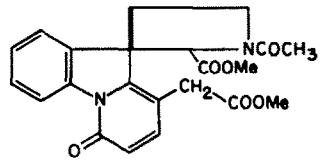
[25] V. Prelog, S. Szpilfogel and J. Battegay, *Helv. Chim. Acta* **30**, 366 (1947).

same intermediate (XXVI) by simple prototropic modification of the initial decomposition product. In either event, the subsequent condensation of the activated methylene group in XXVI with the aldimine function six atoms removed, and the terminal β elimination of glycine ethyl ester to give the observed product (XXI, R = COOMe) scarcely require special comment.

Fortunately, it was a simple matter to overcome the difficulty posed by the circumstances just described. Clearly the offending toluenesulfonyl group had to be removed, and the required change was brought about by treating the ester (XX) with hot hydriodic acid in the presence of red phosphorus. These reagents hydrolyzed as well both the methyl and ethyl ester groups of XX. The resulting imino diacid (XXVIII)

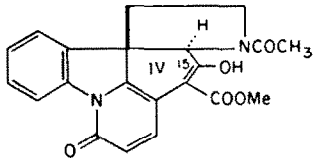


XXVIII

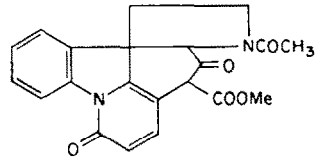


XXIX

was then converted by esterification and acetylation into the N-acetyldimethyl ester (XXIX), which was now free of the seed of potential decay with which its predecessor was afflicted. When the new ester was subjected to the action of sodium methoxide in hot methanol, again a beautifully crystalline substance separated shortly from the reaction mixture, and in this case the substance obtained was the sodium salt of the desired cyclization product (XXX). The free enol ester was readily procured by



XXX



XXXI

acidification of its sodium salt, and that it possessed the enol structure (XXX), rather than the possible tautomeric keto ester structure (XXXI) was clear from its ultraviolet spectrum [Fig. 3], which differed markedly from those of the simple N-phenyl pyridones with which we were familiar. It is further worthy of note that the enol ester was sufficiently acidic to permit its extraction into sodium bicarbonate solution. This observation was our first intimation of the very powerful, and perhaps not entirely expected, electron-withdrawing effect which the pyridone ring exerts, even upon a substituent fixed at its γ position.

The Dieckmann condensation just described had resulted in the completion of the carbon skeleton of ring IV, the fifth of those we must build. It was now necessary to remove the oxygen atom at C.15. In planning our program we had supposed that we might be able to make use, for example, of thioketals derived from the keto ester (XXXI), but when the enol ester (XXX) actually came to hand, its pronounced enolic properties provided a basis for suspicion that the preparation of such derivatives of the keto form might be a matter of some difficulty. This concern was justified in the

event, when it was found that all attempts to prepare thioketals of the desired type were fruitless, nor was any other useful result obtained from such experiments. On the other hand, it was possible to take positive advantage of the special characteristics of

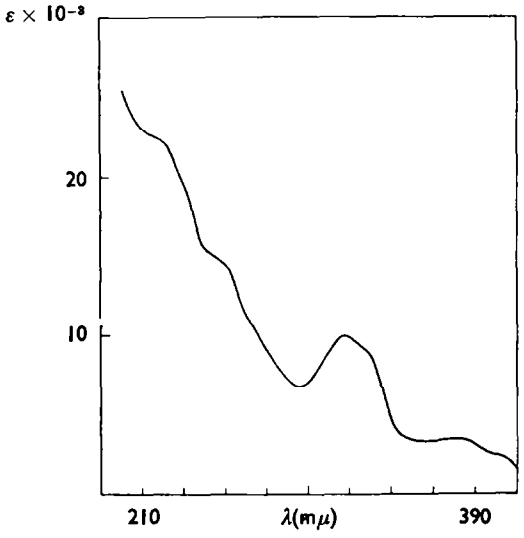
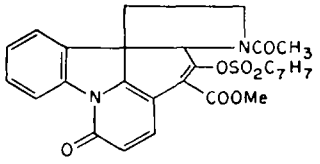


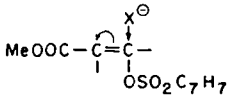
FIG. 3. Ultraviolet spectrum of XXX in EtOH

the highly stabilized enol system in XXX, which was found to be smoothly transformable into the corresponding O-tosyl derivative (XXXII) by treatment with toluenesulfonyl chloride in pyridine. It should be noted that enol esters which enjoy less

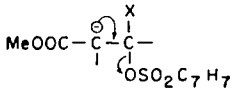


XXXII

advantage in stability with respect to the corresponding keto esters, and lack an electron-withdrawing group comparable with our pyridone function at the central carbon atom, do not readily undergo O-tosylation; in such simpler cases chlorination or sulfone formation is the usual reaction. It was now possible to contemplate displacement of the entire toluenesulfonyloxy group in XXXII by anion addition and β-elimination (XXXIII → XXXIV, *arrows*), and in fact this possibility was smoothly reduced to practice when it was found that the action of sodium benzylmercaptide on

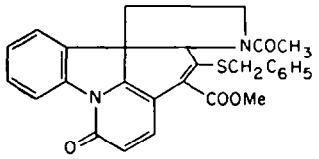


XXXIII

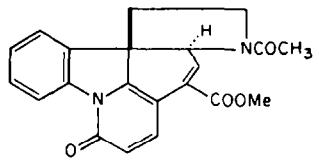


XXXIV

XXXII in methanol at room temperature gave the β-benzylmercaptoester (XXXV). From the latter, the benzylmercapto group was removed without difficulty by treatment with deactivated Raney nickel in hot ethanol. The resulting unsaturated ester

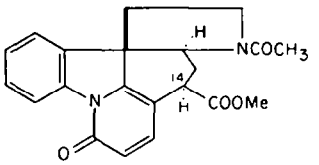


XXXV

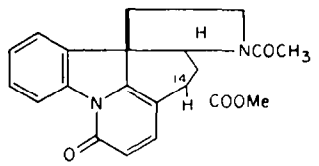


XXXVI

(XXXVI) was then reduced with hydrogen in the presence of palladium on charcoal to give as major product the *cis* saturated ester (XXXVII), along with a small amount

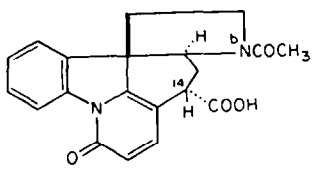


XXXVII



XXXVIII

of the isomeric *trans* compound (XXXVIII). A brief discussion of stereochemical aspects is in order at this point. A model of the unsaturated ester (XXXVI) leaves no doubt that hydrogen should be delivered to the latter from a catalyst surface to give by preference the *cis* ester (XXXVII), and further, that that ester should be unstable with respect to the corresponding *trans* isomer (XXXVIII). These presumptions were confirmed when it was found that alkaline hydrolysis of the major product from the hydrogenation gave an acid (XXXIX) from which on esterification with diazomethane



XXXIX

an ester identical with the minor product from the hydrogenation was produced. It is of course well known that the hydrolysis of relatively hindered invertible esters is frequently preceded by inversion to the more stable and more readily hydrolyzed isomers, and it may further be noted that our prior observations were such as to suggest that inversion in the case at hand, through removal of the proton at C.14, should be an exceptionally ready process.

With the obtention of the *trans* N-acetyl acid (XXXIX), we had reached a point of intersection with a substance of the same structure which we were able to prepare by degradation of strychnine, and we were pleased now to be able to verify that our operations had in fact followed the course envisaged, through the observation that the infrared spectrum of the racemic synthetic acid (XXXIX) and that of its ester were identical with those of the corresponding optically active compounds prepared by

degradation.* Further, the synthetic acid was readily resolved, using quinidine. The quinidine salt obtained from the resolution as well as the free acid generated from it, and the methyl ester prepared in turn by the action of diazomethane, were all identical in melting point and infrared spectra with the corresponding substances in the natural series. The identification was further secured through the observation of identical specific rotatory powers for the synthetic and natural esters of the structure (XXXVIII).†

With these identifications established, we were now possessed of the further advantage that the acid (XXXIX), which was somewhat (though not a great deal) more readily available from natural sources than by the synthetic processes outlined above, could be used as a relay in the further development of our synthetic operations.

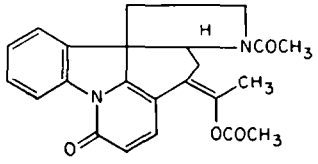
* The degradation proceeded essentially along known lines, though some reactions were significantly modified, and a few simple new terminal stages were added. Thus, following Leuchs,[26] strychnine was oxidized by potassium permanganate to strychninonic acid, which in our hands was found to be smoothly convertible by successive sodium amalgam reduction and base treatment to the well-known strychninolone *a* (LVIII, R = H), without isolation of the intermediary strychninolic acid.[27] The acetate of strychninolone *a* (LVIII, R = Ac) was found to be better preparable using acetic anhydride and pyridine than by the published procedure.[27] Isomerization to strychninolone *b* acetate (LV)[28] proceeded without incident. Prelog had dehydrogenated ring III of both strychninolone derivatives to dehydrostrychninolone acetate,[24] using N-bromosuccinimide. We were able essentially to reproduce his results in small scale experiments, but could not develop the method into a satisfactory one for relatively large scale operations. Consequently, we were fortunate in finding that mercuric acetate in boiling acetic acid effected the desired dehydrogenation with exceptional smoothness (in the *b*, but *not* the *a* series), and that the new method was reproducibly useful on any scale. Hydrolysis of the acetyl group to give dehydrostrychninolone, using aqueous ammonia,[24] presented no difficulty, but it was found advantageous to effect oxidation to dehydrostrychninone (XLV) using pyridine and chromium trioxide rather than chromic acid in acetic acid.[24] Dehydrostrychninone was then oxidized with hydrogen peroxide and barium hydroxide, and the resulting iminoacid was converted by acetic anhydride and pyridine into the laevorotatory form of the *trans* N-acetyl acid (XXXIX). It will be noted that inversion at C.14 occurs in the course of the oxidation of dehydrostrychninone, quite possibly at the stage of an intermediary *a*-ketoacid.

† Some general remarks are perhaps in order about this ready resolution. Our experience in this and other cases suggests that resolution through separation by crystallization of diastereomeric salts is most likely to succeed without difficulty when the acidic and basic salt-forming centers of both components are proximate in space to those factors which render each asymmetric. This presumption is a reasonable one, in that in such cases the differences between the diastereomeric salts are likely to be maximal. This principle suggests that the often-used method of effecting resolutions through the use of acid succinates and the like should be attended by difficulty, as indeed it has been—so much so as to account in large part for the frequent, and largely unjustified, trepidation felt by many investigators faced with a problem of resolution.

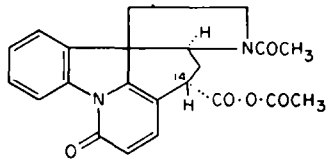
It is also worthwhile to point out the advantages of exploring the salt-forming properties of a naturally available substance prior to attempting a resolution of the corresponding racemic material. In the case at hand it was observed that the natural *trans* N-acetyl acid (XXXIX) readily formed a beautifully crystalline quinidine salt but gave no crystallizable material with quinine. These observations augured well for the forthcoming resolution, since quinine and quinidine, in the vicinity of the salt-forming basic nitrogen atom, are enantiomeric, and it could be expected that the quinidine salt of the unnatural enantiomer of the acid (XXXIX) would resemble the quinine salt of the natural isomer in its relative lack of capacity for crystallization. Such exploratory experiments are of course even less ambiguous in their implications when they can be carried out with an actually fully enantiomeric pair of potential resolving agents.

[26] H. Leuchs and G. Schwaebel, *Ber. Dtsch. Chem. Ges.* **46**, 3693 (1913).
[27] H. Leuchs and G. Schwaebel, *Ber. Dtsch. Chem. Ges.* **47**, 1552 (1914).
[28] H. Leuchs and W. Bendixsohn, *Ber. Dtsch. Chem. Ges.* **52**, 1443 (1919).

We now took in hand the construction of ring VI, and it seemed that our available intermediate was well designed as a basis for the task at hand, containing as it did both N^b and a carboxyl group, either of which might represent a site for the attachment of the required extra carbon atom, suitably accompanied, if necessary, by any activating groups needed for the facilitation of the particular reactions chosen. This apparently simple task presented in the event considerable difficulty, much of it devolving from the fact that the *trans* disposition of N^b and the carboxyl group in XXXIX rendered the formation of a new ring joining those centers impossible without prior inversion at C.14. We have alluded to and described briefly elsewhere[2] some of the false paths down which we trod, and will describe here only the exceptionally simple method which ultimately proved to be successful. When the *trans* N-acetyl acid (XXXIX) was heated at reflux with acetic anhydride and pyridine, it was transformed into the enol acetate (XL). Undoubtedly this reaction involves the initial formation of a mixed

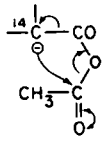


XL

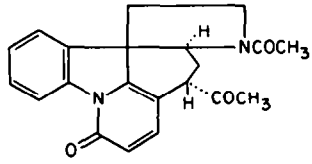


XLI

anhydride (XLI). The evidence already available suggests strongly that the hydrogen at C.14 in (XLI) should be readily ionizable, and the processes leading from the resulting ion (XLII) to the methyl ketone (XLIII) are unexceptional (*arrows* in XLII,



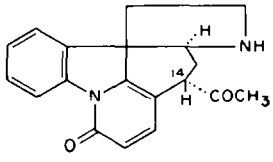
XLII



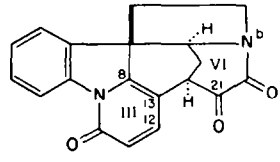
XLIII

or a bimolecular equivalent). Finally, in the light of the experience already available, the conversion of the ketone to the enol acetate need occasion no surprise. It is worthy of note that similar conversions of acids to methyl ketones are known in simpler cases.[29]

Vigorous hydrolysis of the enol acetate (XL) with aqueous hydrochloric and acetic acids now afforded the basic free aminoketone (XLIV), which was used directly for



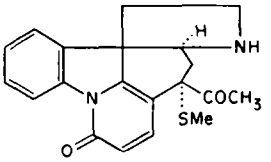
XLIV



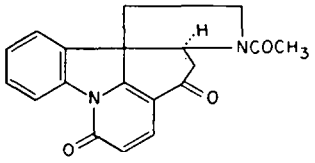
XLV

[29] H. D. Dakin and R. West, *J. Biol. Chem.* **78**, 95 (1928); R. Stoermer and H. Stroh, *Ber. Dtsch. Chem. Ges.* **68**, 2113 (1935); J. A. King and F. H. McMillan, *J. Amer. Chem. Soc.* **73**, 4911 (1951); *Ibid.* **77**, 2814 (1955).

the final step in the elaboration of ring VI. Thus, oxidation of XLIV with selenium dioxide in ethanol led directly to dehydrostrychninone (XLV), which was shown to be identical in all respects with a sample from natural sources.[24] It is well known that selenium dioxide attacks methyl groups in preference to methylene and methine groups,[30] but the success of the reaction in our case may occasion surprise in view of the very ready enolizability of the methyl ketone (XLIV), towards C.14. This facile enolization, which was expected on the basis of our previous experience with the activating effect of the pyridone ring, was confirmed by the reconversion of XLIV to the enol acetate (XL) by the action of hot acetic anhydride and pyridine, through the formation, from the ketone, of the methylmercapto derivative (XLVI) in a ready potassium acetate catalyzed reaction with methyl *p*-toluenethiosulfonate, and by the

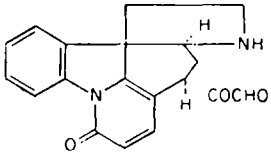


XLVI

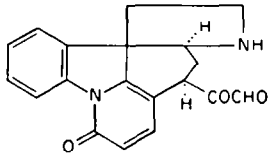


XLVII

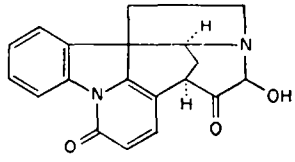
production of the degraded ketone (XLVII) when the enol acetate (XL) was hydrolyzed with methanolic sodium hydroxide in the presence of atmospheric oxygen.[31] The course of our selenium dioxide reaction therefore suggests strongly that readiness of enolization is not to be correlated with ease of attack by that oxidant. It is of much interest that, subsequent to our work, Corey has shown[32] that strong electron-attracting groups such as the *p*-nitrophenyl group, which promote enolization, and may be compared with our pyridone ring, facilitate the initial step in selenium dioxide oxidations, but strongly inhibit the subsequent processes which must occur for actual introduction of oxygen adjacent to the original carbonyl group. Thus, we presume that selenium dioxide attacks the methyl group of the ketone (XLIV) to give the glyoxal (XLVIII). It would be expected that enolization of the ketonic carbonyl group in XLVIII would be even readier than that in the several cases already discussed,



XLVIII



XLIX



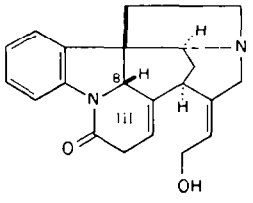
L

and it may therefore be anticipated that the *trans* glyoxal will be easily convertible, albeit in an unfavorable equilibrium, to the *cis* isomer (XLIX). In the latter, there exists the opportunity for a ring–chain tautomeric change, in which the closed form (L) will be vastly predominant, in view of the known very high tendency of contiguous carbonyl groups to achieve the tetrahedral condition. The final oxidation of L to the observed product, dehydrostrychninone (XLV), requires no special comment.

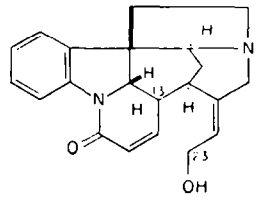
We may pause here to survey our remaining tasks. Clearly, it is necessary to

[30] G. R. Waitkins and C. W. Clark, *Chem. Rev.* **36**, 250 (1945).
[31] Cf. W. von E. Doering and R. M. Haines, *J. Amer. Chem. Soc.* **76**, 482 (1954).
[32] E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.* **82**, 918 (1960).

attach two further carbon atoms at C.21 for incorporation into ring VII, and our most advanced intermediate, dehydrostrychninone (XLV), possesses a ketonic carbonyl group, which would be expected to be highly reactive, in a position apposite to that purpose. Further, changes are necessary in the oxidation states of rings III and VI. No special difficulty was anticipated with the latter, but the changes required in ring III could have posed a formidable problem. Thus, no less than three new asymmetric centers must be created, with correct orientations, at C.8, C.12 and C.13. But in part, this problem could be considered solved, in that the known substance isostrychnine I[33] (LI) had already been reconverted, by the action of ethanolic potassium hydroxide,



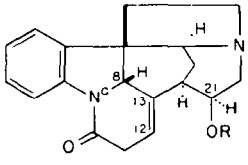
LI



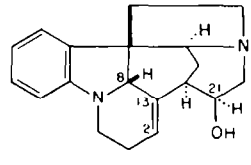
LII

to strychnine itself.[34] This reaction clearly involves the equilibration of isostrychnine I with its conjugated isomer (LII), followed by β-addition of an alkoxide ion attached at C.23, and leads to the stereospecific creation of the asymmetric centers at C.12 and C.13, in the desired sense.

Clearly then, our objective was isostrychnine I, and in respect to ring III, our task was to effect reduction of the aromatic α-pyridone ring present in dehydrostrychninone (XLV) to the $\Delta^{12,13}$-dihydro-α-pyridone oxidation level, by addition of hydrogen at C.8, *on the concave, more hindered side of the molecule.* Consequently, when, in model experiments to assure ourselves that there would be no special difficulty attached to the removal of the ring VI amide carbonyl group at C.20, we subjected dehydrostrychninone (XLV) to reduction with lithium aluminum hydride in boiling ether, we were surprised and delighted to discover that the problem in ring III was solved as well. The product from the reduction was the base (LIII, R = H), in which the pyridone ring had been reduced precisely to the desired dihydro level. The structure of this



LIII

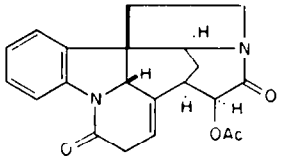


LIV

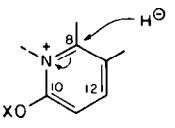
substance was demonstrated, and in particular the presence of the $\Delta^{12,13}$ double bond and the configurations at C.8 and C.21 were verified, through the observation that the corresponding acetate (LIII, R = Ac) was further reduced, again by lithium aluminum hydride, to a new base (LIV), which was also produced directly by similar reduction of strychninolone *b* acetate (LV).[28] It may be suggested that the mechanism of the pyridone reduction involves prior co-ordination of the N^a amide carbonyl oxygen

[33] H. Leuchs and H. Schulte, *Ber. Dtsch. Chem. Ges.* **75**, 1522 (1942).
[34] V. Prelog, J. Battegay and W. I. Taylor, *Helv. Chim. Acta* **31**, 2244 (1948).

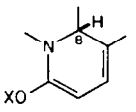
atom with an electron-deficient species, perhaps some form of AlR_3, or even the lithium cation. The subsequent discharge of the now cationoid ring by hydride ion addition (LVI, *arrows* → LVII) is a process for which there is abundant precedent,[35]



LV

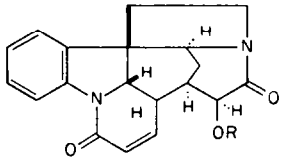


LVI

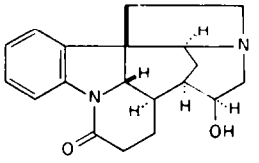


LVII

and the scheme accounts further for the survival of the N^a amide group, as a consequence of its protection as an enolate species. These views receive confirmation from the interesting observation that strychninolone *a* acetate[27] (LVIII, R = Ac) is reduced under similar conditions to LIX, as expected if a co-ordinated intermediate

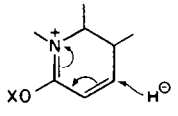


LVIII

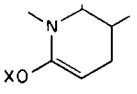


LIX

analogous to that presupposed above be accepted (cf. LX, *arrows* → LXI). However, reasonable though these postulates be, they are not of themselves sufficient for the



LX



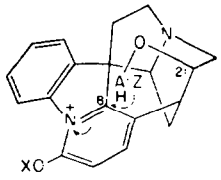
LXI

rationalization of two striking aspects of the observed phenomena. First, simple N-substituted α-pyridones do *not* undergo analogous smooth reductions to $\Delta^{4,5}$ dihydro derivatives. By contrast, attack occurs in general at the carbonyl carbon atom, as with simple disubstituted amides, and may be followed by various complicated further changes.[36] But above all, the specific attack of hydride ion at C.8 (cf. LVI), rather than at the more accessible C.10 or C.12, and *from the most highly hindered side of the molecule*, requires explication. Clearly, a very special factor is needed to account for the venue of the reaction at that point shown by models to be the most inaccessible site in the entire array. We suggest that that factor is *intramolecular delivery of hydride ion within an intermediate such as* LXII. The expected very ready reduction of the C.21 carbonyl group of dehydrostrychninone (XLV) has been shown above to

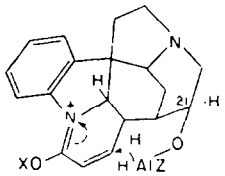
[35] Cf. H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949) and K. Schenker and J. Druey, *Ibid.* **42**, 1960 (1959).

[36] J. A. Berson and J. S. Walia, *J. Org. Chem.* **24**, 756 (1959); A. G. Anderson, Jr. and G. Berkelhammer, *J. Amer. Chem. Soc.* **80**, 992 (1958); K. Winterfeld and E. Schneider, *Ann. Chem.* **581**, 66 (1953); P. de Mayo and W. Rigby, *Nature, Lond.* **166**, 1075 (1950); O.E. Edwards and L. Marion, *J. Amer. Chem. Soc.* **71**, 1694 (1949); P. L. Julian and A. Magnani, *Ibid.* **71**, 3207 (1949).

take place as it should from the relatively unhindered convex face of the molecule, and gives a β-oriented oxygen at C.21 which must necessarily be involved in complex formation of the suggested type (in which Z represents two further hydrogen atoms, or alkoxyl groups). Beyond that, the geometrical circumstances within LXII are



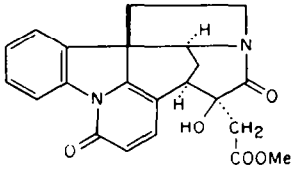
LXII



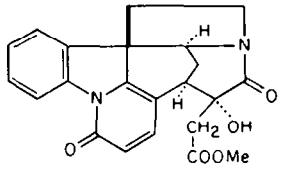
LXIII

precisely such as to facilitate the delivery of hydride ion specifically at C.8, in the observed sense. It remains only to allude to the fact that entirely similar considerations apply in the case of the strychninolone *a* acetate reduction (cf. LXIII), though the geometrical particulars are substantially different, in the required sense.

We could now turn with confidence to the last phase of our studies. Dehydrostrychninone (XLV) exhibited the carbonyl reactivity to be expected of a substance with strongly opposed contiguous dipoles. It crystallized from methanol as a hemiketal, and it combined readily with methyl bromoacetate in the presence of zinc, to give isomeric β-hydroxyesters, of which one was largely predominant, and is undoubtedly LXIV,* while the minor product is LXV. But most suited to our purpose

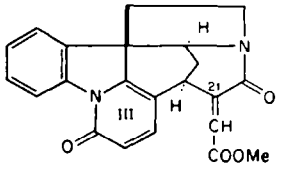


LXIV

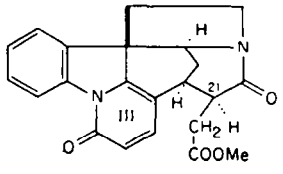


LXV

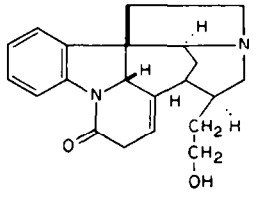
* This hydroxyester was converted into the corresponding β-acetoxyester, by treatment with boiling acetic anhydride, and thence, by pyrolysis, into the α,β-unsaturated compound (i). Reduction of the latter in ethanol with hydrogen over palladium charcoal gave the saturated ester (ii). When



i



ii

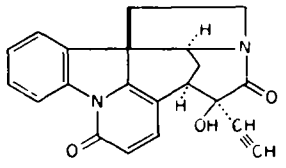


iii

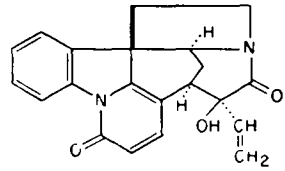
either (i) or (ii) was treated with lithium aluminum hydride, the ensuing reactions were very complex, and no pure products were isolated. In particular, the formation of dihydroisostrychnine I[87] (iii) from (ii) could not be definitively established. These results provide confirmatory evidence for the view that the presence of a 21β hydroxyl group is required for the smooth stereospecific reduction of the pyridone ring III, as discussed above.

[87] H. Leuchs and A. Dornow, *Ber. Dtsch. Chem. Ges.* **68**, 2234 (1935).

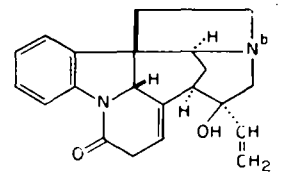
was the reaction with sodium acetylide in tetrahydrofuran, which gave the ethinyl carbinol (LXVI). This substance was reduced by hydrogen in the presence of Lindlar



LXVI



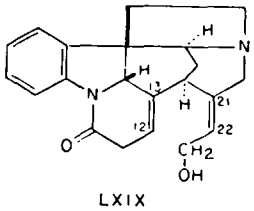
LXVII



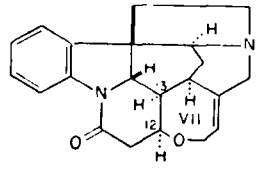
LXVIII

palladium[38] to the corresponding vinyl compound (LXVII), and the latter in its turn was transformed by lithium aluminum hydride in boiling ether into the base (LXVIII). This compound is an allylic isomer of the known isostrychnine I[33] (LI). Although it resisted conditions of mild acidity which suffice for the isomerization of simple tertiary allylic carbinols, no doubt because the necessary presence of a positive pole at N^b in acidic media suppresses reactions which proceed through cationoid intermediates, it was rearranged by hydrogen bromide in acetic acid at 120° to a mixture of halo compounds, from which hydrolysis with boiling aqueous sulfuric acid produced isostrychnine I (LI ≡ LXIX), identical in all respects with a sample prepared from strychnine. Our examination of the available transition states for the allylic rearrangement of the tertiary alcohol (LXVIII) reveals little preference for one or the other of those which lead respectively to isostrychnine I (LXIX), or to a geometrical isomer with the alternative configuration at the $\Delta^{21,22}$ double bond, except that somewhat greater isolation of the separate positive charges at N^b and within the allylic system may favor the former. Nor can we say that none of the isomer is formed along with the observed isostrychnine.

It had already been established[34] that the action of base on isostrychnine I (LXIX) leads to the closure of the seven-membered oxide ring, VII (*vide supra*). It should be reiterated here that the reaction is accompanied by the stereospecific generation of the last two asymmetric centers of the alkaloid, at C.12 and C.13; all of the isomeric seven-membered oxides differing in configuration from strychnine itself at those centers are impossibly strained. Now, when our synthetic isostrychnine I was treated with ethanolic potassium hydroxide, it was converted into strychnine (I ≡ LXX), whose melting point, and infrared spectrum were identical with the corresponding properties of the natural alkaloid, and whose melting point was undepressed on admixture with the latter. The total synthesis of strychnine was complete.



LXIX



LXX

[38] H. Lindlar, *Helv. Chim. Acta* **35**, 446 (1952).

EXPERIMENTAL

M.p.'s, unless otherwise stated, were determined on a micro hot-stage, and are not corrected. UV spectra were measured in ethanol solution. IR measurements were used for control purposes throughout this investigation, and spectra, taken in chloroform solution, of all pure substances prepared were determined. Spectra are ordinarily recorded here only for substances in the main line of the synthesis. In each case, the abscissa is plotted in wave lengths (2–12 μ), and the ordinate in percentage transmission (0–100%). For other substances, pertinent features of the spectra are described textually where desirable.

Synthesis of 2-*Veratryltryptamine*

2-*Veratrylindole* (II)

(a) *From acetoveratrone and phenylhydrazine by treatment with polyphosphoric acid.* Acetoveratrone[16] (25 g) and phenylhydrazine (16 ml) were added to polyphosphoric acid (110 g) in a 500 ml Erlenmeyer flask and warmed with swirling on the steam-bath. The incipient orange two-phase reaction mixture turned soon into a brown homogeneous melt, and a vigorous exothermic reaction set in, which was kept under control by cooling with cold water. The reaction was then completed by heating on the steam-bath for 10 min. The hot melt was poured into ice-water, and the resulting flocculent precipitate dissolved in hot chloroform (250 ml). The organic layer was separated, extracted with water (100 ml) and dried over anhydrous sodium sulfate. The solvent was then removed until crystals began to form. By gradual displacement of the boiling chloroform with methanol, three consecutive crops of 2-veratrylindole, m.p. 185-189°, were collected. The total yield was 19·0 g (54·4%). For analysis a sample was recrystallized twice from methylene chloride–methanol, m.p. 190–192°.

(Found: C, 75·36; H, 6·03; N, 5·95; calc. for $C_{16}H_{15}O_2N$: C, 75·87; H, 5·97; N, 5·53%).

(b) *From ω-bromoacetoveratrone and aniline.* ω-Bromoacetoveratrone (15 g), prepared according to the procedure of Mannich and Hahn,[18] was heated in an oil-bath with aniline (50 ml). After the initial vigorous reaction had subsided, the mixture was refluxed for 1 hr (oil-bath temp 175°), then cooled to 50°, and poured into ice-cold water (500 ml) to which dilute hydrochloric acid (50 ml) had been added. The yellow precipitate was filtered, washed with an excess of water, and dissolved in chloroform. The chloroform solution was dried over anhydrous sodium sulfate, and then filtered through alumina (50 g). After evaporation of the solvent the residue was crystallized from ethanol–methanol: colorless prisms (5·8 g; 39·5%) of 2-veratryl-indole, m.p. 185–188°, identical with the product prepared by method a (above).

2-*Veratrylgramine* (VI, R = NMe_2)

To a cold solution of 25% aqueous dimethylamine (6·3 g) and 37% aqueous formaldehyde (1·71 g) in acetic acid (15 ml), 2-veratrylindole (5·6 g), dissolved in a mixture of dioxane (30 ml) and acetic acid (5 ml), was added. The reaction mixture was allowed to stand at room temp for 2 hr. Dilution with water (300 ml) brought about precipitation of a small amount of material [probably methylene-*bis*-2-veratrylindole], which was removed by filtration. The clear filtrate was made alkaline with ice-cold aqueous potassium hydroxide. A colorless crystalline precipitate was produced immediately, and was collected, washed thoroughly with water, and dried *in vacuo* for 12 hr at 60°. Yield: 6·3 g (92%) of crude 2-veratrylgramine, m.p. 122–124°. This material was used directly for the preparation of the corresponding methiodide.

For analytical purposes the picrate was prepared: yellow prisms from acetone–ethanol, m.p. 182–183°.

(Found: C, 55·27; H, 4·39; N, 12·83. Calc. for $C_{18}H_{22}O_2N_2 \cdot C_6H_3O_7N_3$: C, 55·65; H, 4·67; N, 12·98%).

2-*Veratrylgramine methiodide* (VI, R = $NMe_3]^+I^-$)

The above crude 2-veratrylgramine (6·3 g) was dissolved in boiling benzene (25 ml) and filtered hot to remove a small amount of insoluble material. After addition of methyl iodide (20 g) in benzene (50 ml), the reaction mixture was allowed to stand in the ice-box for 2 hr. The methiodide was then collected, and washed with ether to give a virtually quantitative yield (9·2 g) of light pink crystals which were used directly for the next reaction.

2-*Veratryl-3-cyanomethylindole* (VI, R = CN)

2-Veratrylgramine methiodide (9·0 g) was mixed with sodium cyanide (1·22 g) in dimethyl formamide (70 ml) and then refluxed gently with stirring in an atmosphere of nitrogen. After 1 hr no further trimethylamine was evolved. The clear yellow solution was cooled, poured into ice-cold water (350 ml), and the crystalline precipitate was collected. The filter cake was washed well with water and dried at 60° *in vacuo*: 5·63 g (97%) of colorless 2-veratryl-3-cyanomethylindole, m.p. 231–234°. The analytical sample was recrystallized from ethanol, m.p. 237–238°.

(Found: C, 74·11; H, 5·68; N, 9·34. Calc. for $C_{18}H_{16}O_2N_2$: C, 73·95; H, 5·52; N, 9·58%).

2-*Veratryltryptamine* (V)

Lithium aluminum hydride (50 g) was suspended in absolute tetrahydrofuran (1100 ml). With vigorous stirring, twelve 10 g portions of 2-veratryl-3-cyanomethylindole were added at 5 min intervals. The reaction mixture turned red, and towards the end of the reduction a viscous mass separated which solidified upon scratching and had to be broken up mechanically into small fragments. Two hr of stirring and refluxing led to a suspension of fine grey powder. The reaction flask was cooled with ice while a saturated aqueous solution of sodium sulfate (100 ml) was added cautiously, followed by chloroform (1000 ml) and anhydrous sodium sulfate. Filtration through Celite and evaporation of the filtrate *in vacuo* left a viscous syrup which on trituration with ether (500 ml) gave light-yellow crystals of 2-veratryltryptamine (104 g; 85%), melting at 142–145°. Two recrystallizations of the base from benzene yielded colorless material, m.p. 146–148°.

(Found: C, 73·64; H, 6·90; N, 9·20; Calc. for $C_{18}H_{20}O_2N_2$: C, 72·95; H, 6·80; N, 9·45%). The *hydrochloride*, obtained by treatment of the base with methanolic hydrogen chloride, was recrystallized three times from methanol: slightly green needles, m.p. 270–280° (dec).

(Found: C, 64·68; H, 6·60; N, 8·25. Calc. for $C_{18}H_{20}O_2N_2 \cdot HCl$: C, 64·95; H, 6·36; N, 8·42%).

Construction of Rings V, III, *and* IV

Preparation of Schiff base (VII) *from 2-veratryltryptamine and ethyl glyoxylate*

Ethyl glyoxylate (33·6 g), freshly prepared from the corresponding ethylhemiacetal[21a] by the method of Oroshnik and Spoerri[21b] was dissolved in benzene (250 ml) and added in several portions to a solution of 2-veratryltryptamine (97 g) in warm benzene (500 ml). The reaction mixture came to a boil spontaneously, and a yellow solid separated. Five hr of boiling at reflux with a water separator yielded 5 ml (theoretical, 5·9 ml) of water. The reaction mixture was then allowed to stand overnight in the cold-room; ether (500 ml) was added with swirling, and the Schiff base collected by filtration (96 g; m.p. 165–178°). The filtrate was concentrated on the steam-bath, and on dilution with ether gave a second crop (8·5 g). Addition of petroleum ether (b.p. 30–60°) finally produced a third crop (9·4 g) of Schiff base. Total yield: 113·9 g (92%). This material was suitable for use in the next reaction. For analysis, the material was recrystallized 3 times from benzene to give a yellow crystalline powder, m.p. 170–180°.

(Found: C, 69·44; H, 6·59; N, 7·26. Calc. for $C_{22}H_{24}O_4N_2$: C, 69·45; H, 6·36; N, 7·36%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 224 mμ (31,600), ~245 (16,400), 308 (20,800).

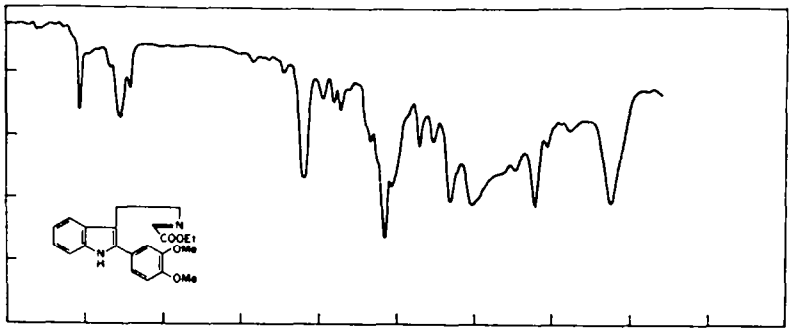


Plate 1

Treatment of Schiff base (VII) *with* p-*toluenesulfonyl chloride–pyridine*

Indolenine XI. A mixture of the Schiff base (45 g) and *p*-toluenesulfonyl chloride (45 g) in pyridine (225 ml) was allowed to stand at room temp for 18 hr. Water (300 ml) was then added to destroy excess tosyl chloride and to precipitate the indolenine. The reaction mixture was cooled in ice-water for 30 min, and the product was then collected and washed, first with water and then with cold methanol. When the material was dried at 60° *in vacuo*, 40·9 g (64·4%) of colorless crystals, m.p. 143–145°, was obtained. Recrystallization from methanol raised the m.p. to 145–146°.

(Found: C, 64·25; H, 5·82; N, 5.24; S, 6·00. Calc. for $C_{29}H_{30}O_6N_2S$: C, 65·16; H, 5·66; N, 5·24; S, 5·99%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 234 mμ (23,600), 339 (15,600).

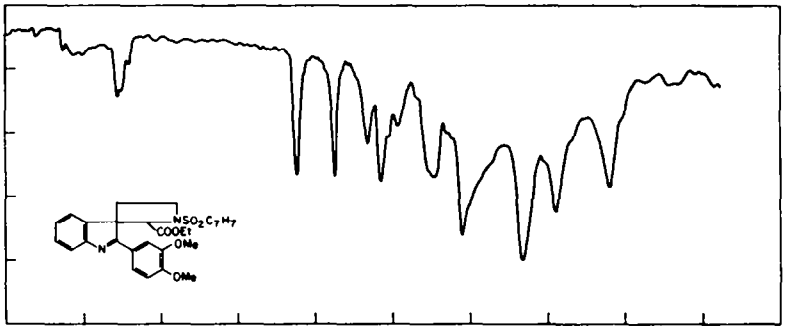


Plate 2

Reduction of the indolenine (XI) *with sodium borohydride*

Indoline (XIV). Sodium borohydride (2·5 g) was dissolved in water (2·5 ml) and ethanol (20 ml), and slowly added to a hot solution of the indolenine (6 g) in ethanol (70 ml). A crystalline precipitate began to form almost immediately. The reaction mixture was heated gently for 1 hr. The now clear solution was diluted with water until crystallization set in. The reaction mixture was cooled to 5° and the product was collected, washed well with water and dried *in vacuo* at 60°: 5·11 g (85%) of pale yellow crystals, m.p. 172–178°. For analysis a sample of the indoline was recrystallized twice from chloroform–methanol to give colorless crystals, m.p. 180–181°.

(Found: C, 64·59; H, 6·06; N, 5·47; S, 5·57. Calc. for $C_{29}H_{32}O_6N_2S$: C, 64·91; H, 6·01; N, 5·22; S, 5·98%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 233 mμ (24,200), 287 (4500), ~300 (3200).

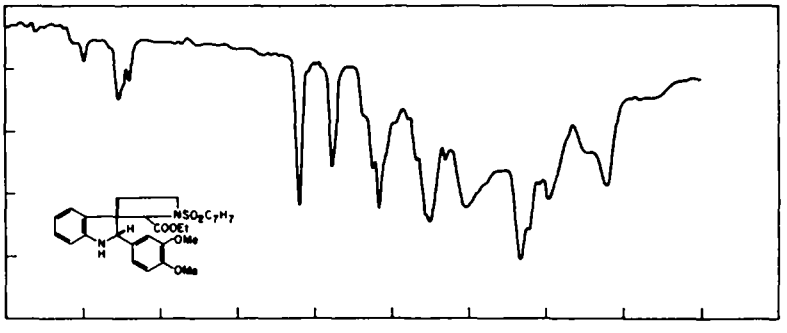


Plate 3

N-*Acetylindoline* (XV). The indoline (XIV; 11·6 g) was heated on the steam-bath with acetic anhydride (20 ml) and pyridine (10 ml) for 1 hr. Water was then added to the somewhat cooled solution until crystals began to appear. The reaction mixture was allowed to stand in the cold for 2 hr.

Methanol (10 ml) and more water (20 ml) were needed to complete crystallization. Filtration gave 12·29 g (98·5%) of crude N-acetylindoline, m.p. 202–203°. For analysis the substance was recrystallized from methanol–chloroform, m.p. 206°.

(Found: C, 64·46; H, 5·75; N, 5·05; S, 5·42. Calc. for $C_{31}H_{34}O_7N_2S$: C, 64·35; H, 5·92; N, 4·84; S, 5·54%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 235 mμ (26,800), ~256(18,000), ~280 (8000).

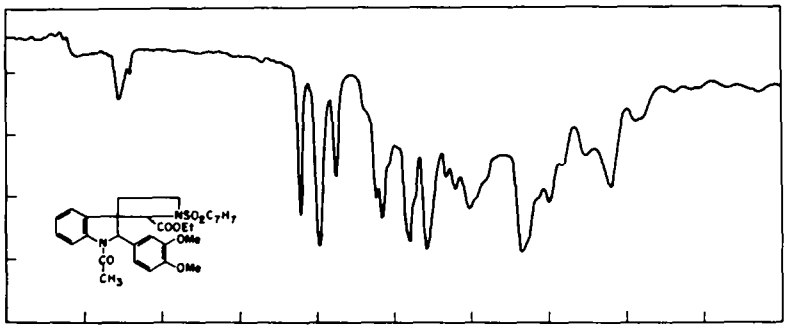


Plate 4

Ozonolysis of the N-*acetylindoline* (XV)

Tri-ester (XVI). Through a solution of the N-acetylindoline (1·16 g) in acetic acid (25 ml) and water (10 drops), ozonized oxygen was passed for 22 min. The ozone content of the oxygen used was such that a similar stream passed into a blank solution at the same rate for 2 min contained active oxygen equivalent to 11·8 ml of 0·1 N sodium thiosulfate (0·295 millimoles of ozone per min). The reaction mixture was poured into water, and the solid which separated was dissolved in chloroform. The chloroform solution was extracted with aqueous potassium carbonate to remove acidic material and evaporated. The neutral residue was crystallized from methanol to give the desired tri-ester (351 mg; 29%). The compound was obtained in two polymorphic forms, m.p. 165° and 184°.

(Found: C, 60·67; H, 5·56; N, 4·83; S, 5·45. Calc. for $C_{31}H_{34}O_9N_2S$: C, 60·97; H, 5·61; N, 4·59; S, 5·24%).

Ultraviolet spectrum: increasing absorption below 310 mμ with weak ill-defined shoulder at 285 and shallow maximum at 230 (ϵ 24, 100).

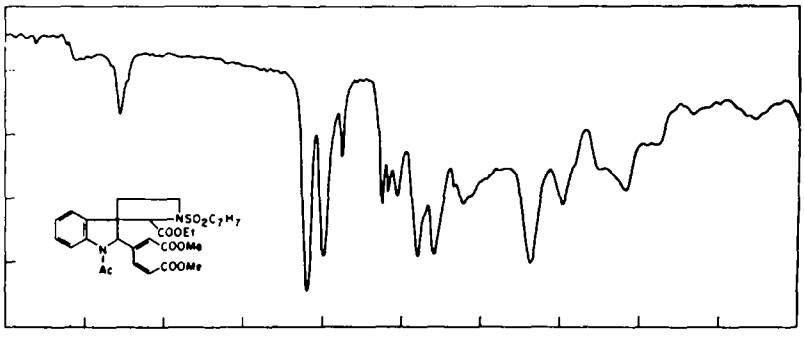


Plate 5

Treatment of tri-ester (XVI) *with methanolic hydrogen chloride*

Pyridone (XX). The tri-ester (800 mg) was heated under reflux with 5% methanolic hydrogen chloride (30 ml) for 10 hr. The crystalline residue obtained upon evaporation of the solvent was dissolved in methanol (20 ml) and chloroform (2 ml), and the solution was concentrated to ca. 10 ml. When the concentrate was allowed to stand in the cold-room for several hours, the desired pyridone separated

as colorless plates (510 mg; 75%), m.p. 181–182°. For analysis a sample was recrystallized from methanol, m.p. 187–188°.

(Found: C, 62·46; H, 5·29; N, 5·50; S, 5·92. Calc. for $C_{28}H_{28}O_7N_2S$: C, 62·68; H, 5·26; N, 5·22; S, 5·97%).

Ultraviolet spectrum: see Fig. 1.

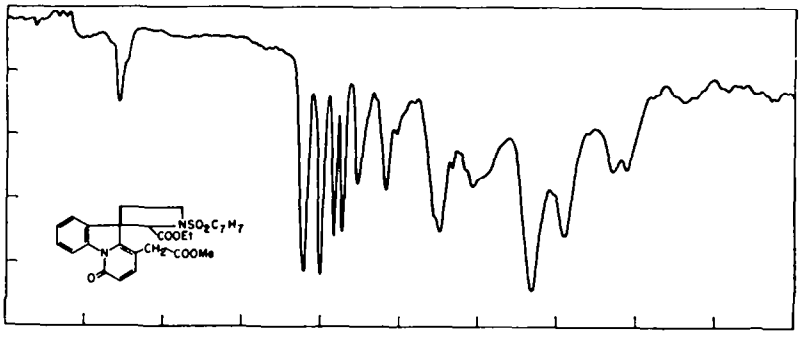


Plate 6

It was not necessary to isolate the tri-ester from the ozonization. When the total crude neutral product (15·95 g) from the ozonolysis of the N-acetylindoline (18·55 g) was subjected to the action of methanolic hydrogen chloride, the pyridone (XX) was obtained in an over-all yield of 30% (5·1 g).

An Excursion. Action of sodium methoxide on the pyridone (XX)

3-*Carbomethoxy*-6H-*pyrido*[3,2,1-jk]*carbazole*-6-*one* (XXI, R = COOMe). The pyridone (250 mg) was refluxed under nitrogen with a solution of sodium (25 mg) in absolute methanol (4 ml). From the cooled reaction mixture, pale yellow needles (53 mg; 41%), m.p. 180–181°, separated. Recrystallization from ethanol did not raise the melting point.

(Found: C, 73·48; H, 4·02; N, 4·85. Calc. for $C_{17}H_{11}O_3N$: C, 73·64; H, 4·00; N, 5·05%).

Ultraviolet spectrum: see Fig. 2.

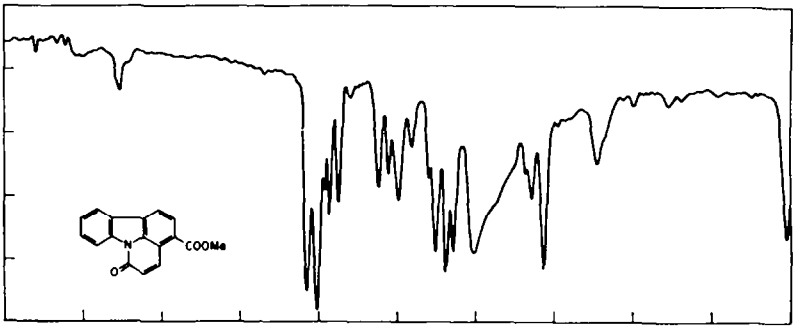


Plate 7

Conversion of pyridone (XX) *into* N-*acetylpyridone dimethyl ester* (XXIX)

(a) *Vigorous hydrolysis with hydriodic acid.* The pyridone (750 mg) was boiled under reflux for 3½ hr with a mixture of aqueous hydriodic acid (47% w/v, 5 ml), acetic acid (5 ml) and red phosphorus (250 mg). The solution was then filtered, evaporated to dryness *in vacuo*, and the residue boiled down several times with acetic acid until crystallization set in. Trituration with acetone (5 ml) gave the *hydriodide of the iminodiacid* (480 mg; 72%) as an almost colorless crystalline powder which was acetylated directly. (b) *Acetylation.* The above hydriodide (400 mg) was dissolved in pyridine (3·2 ml) and acetic anhydride (4 ml), and allowed to stand at room temp for 1 hr. Water (2 ml) was then added,

and after 30 min the solution was taken to dryness *in vacuo*. The remaining semi-crystalline material was rinsed with ether and then dissolved in hot water (8 ml). Concentrated hydrochloric acid (8 drops) was added, and the solution was cooled. The desired N-acetylpyridone diacid crystallized in pale-yellow rhombs (308 mg; 94·4%), m.p. 275° (dec). (c) *Esterification.* The crude crystalline product from the above acetylation (300 mg) was dissolved in methanol (20 ml). A cold ethereal solution of freshly prepared diazomethane was added until no further evolution of nitrogen was observed. The yellow reaction mixture was then set aside in the cold for 1 hr. Excess diazomethane was destroyed with a few drops of acetic acid, and the solvents were distilled off. The residue was taken up in a small volume of ethyl acetate and diluted, first with ether, and then with cyclohexane. The N-acetyl-pyridone dimethyl ester (XXIX) was obtained in colorless crystals (270 mg; 84%), m.p. 181–182·5°, unchanged when recrystallized from ethyl acetate–ether.

(Found: C, 63·88; H, 5·32; N, 6·19. Calc. for $C_{22}H_{22}O_6N_2$: C, 64·38; H, 5·40; N, 6·83%).

Ultraviolet spectrum: Typical N-phenylpyridone chromophore, cf. Fig. 1.

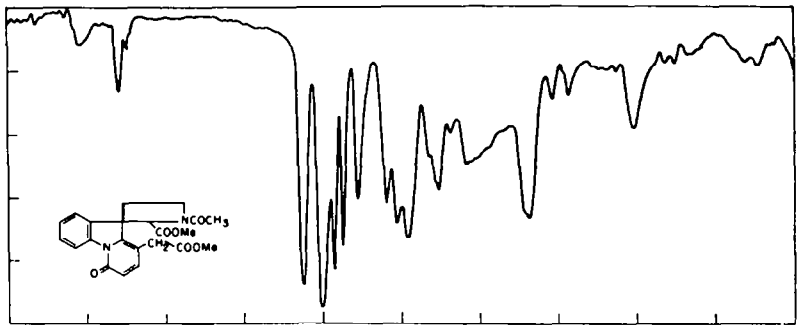


Plate 8

Dieckmann condensation with the N-*acetylpyridone dimethyl ester* (XXIX)

Enol-ester (XXX). The dimethyl ester (900 mg) was refluxed gently under nitrogen with a solution of sodium (1 g) in absolute methanol (20 ml) for 20 min, and then allowed to stand in the cold overnight. The sodium salt of the enol-ester (768 mg; 87·5%) was obtained as a fine yellow crystalline powder which was used directly for the reaction with *p*-toluenesulfonyl chloride to prepare the enol-ester tosylate (XXXII). The sodium salt, on standing in air, picked up one mole of water.

(Found: C, 60·05; H, 4·65; N, 6·53. Calc. for $C_{21}H_{17}O_6N_2Na \cdot H_2O$: C, 60·35; H, 4·58; N, 6·69%).

The *free enol-ester* was isolated by dissolving the sodium salt (100 mg) in water, acidifying with hydrochloric acid and extracting with chloroform. The chloroform solution was dried over anhydrous sodium sulfate, evaporated, and the residue crystallized from methanol. The enol-ester (80 mg; 85%) formed pale-yellow needles, m.p. 200–205°. Recrystallization from methanol did not raise the melting point further.

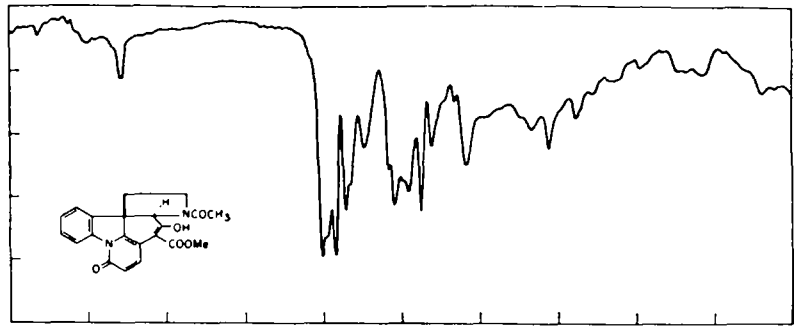


Plate 9

(Found: C, 66·43; H, 4·86; N, 7·56. Calc. for $C_{21}H_{18}O_5N_2$: C, 66·66; H, 4·80; N, 7·40%).

The compound showed a positive ferric chloride reaction (blue); it dissolved readily in saturated aqueous sodium bicarbonate to give a bright yellow solution.

Ultraviolet spectrum: see Fig. 3.

Enol-tosylate (XXXII). To a solution of *p*-toluenesulfonyl chloride (3·7 g) in pyridine (23 ml) the sodium salt of the enol-ester (XXX; 768 mg) was added. The reaction mixture was allowed to stand at room temp for 10 hr. Water (10 ml) was then added, followed after a short period by 5 N hydrochloric acid (80 ml). The product was extracted with chloroform. The chloroform solution was washed with aqueous potassium carbonate and water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue crystallized completely upon addition of a small volume of acetone to give the enol-tosylate (976 mg; 95%), m.p. 215–217°. For analysis a sample was recrystallized from acetone: yellow rhombs, m.p. 217°.

(Found: C, 63·15; H, 4·66; N, 4·70; S, 6·17. Calc. for $C_{28}H_{24}O_7N_2S$: C, 63·15; H, 4·54; N, 5·26; S, 6·01%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 234 mμ (23,900), 312 (13,800), 317 (13,700), 350–380 (3800).

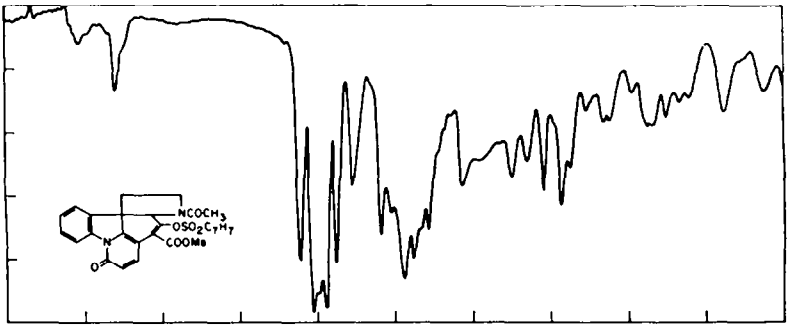


Plate 10

Benzylmercaptoester (XXXV). A solution (12 ml) of sodium benzylmercaptide [prepared from sodium (122 mg), absolute methanol (100 ml) and benzylmercaptan (670 mg)] was added to the enol-tosylate (XXXII; 230 mg). The reaction mixture was heated until a clear solution was obtained, and then allowed to stand at room temperature under nitrogen. Crystalline material soon began to separate. After 3 hr the precipitate was collected by filtration and washed thoroughly with cold methanol. Yield: 160 mg (77%) of yellow needles, m.p. 252–253°. For analysis the benzylmercaptoester was recrystallized from chloroform–methanol, m.p. 256–257°.

(Found: C, 68·81; H, 4·93; N, 5·57; S, 6·48. Calc. for $C_{28}H_{24}O_4N_2S$: C, 69·41; H, 4·99; N, 5·78; S, 6·63%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 207 mμ (31,000), 253 (13,000), 312 (14,000).

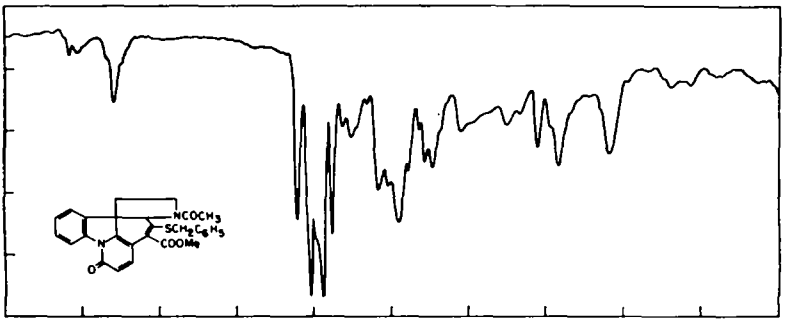


Plate 11

Desulfurization of the benzylmercaptoester (XXXV) *with Raney nickel*

Unsaturated ester (XXXVI). The benzylmercaptoester (500 mg) in ethanol (100 ml) was boiled under reflux with deactivated Raney nickel (3 ml of ethanolic slurry) for 3 hr. [Deactivation of the catalyst was achieved by refluxing 3 hr with acetone, and a further 3 hr with ethyl acetate; the latter solvent was then replaced by ethanol.] The Raney nickel was filtered off and washed extensively with hot ethanol (100; 50; 50; 50 ml). The combined filtrates were concentrated *in vacuo*, leaving a yellow residue (398 mg) which was dissolved in a small volume of acetone. Dilution with ether gave the crude unsaturated ester (313 mg; 84%), m.p. 180–215°, presumably contaminated with the saturated methyl ester (XXXVII). This crude material was subjected directly to catalytic hydrogenation. For analysis a sample of the unsaturated ester was recrystallized twice from acetone–ether to give almost colorless rods, m.p. 234°.

(Found: C, 69·71; H, 5·12; N, 7·45. Calc. for $C_{21}H_{18}O_4N_2$: C, 69·60; H, 5·00; N, 7·73%).
Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 232 mμ (25,600), 310 (12,100), 365 (4150).

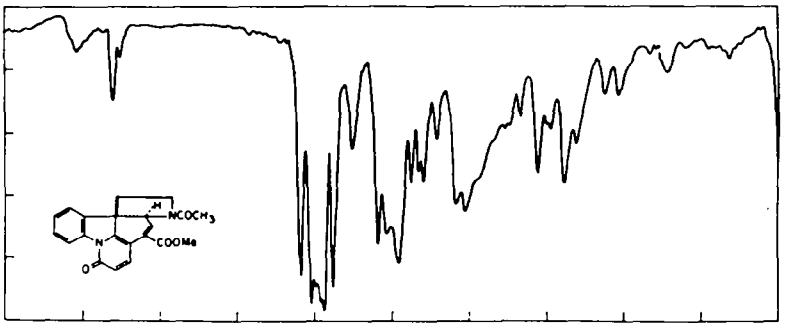


Plate 12

Catalytic hydrogenation of the unsaturated ester (XXXVI)

Racemic cis *ester* (XXXVII). The crude unsaturated ester, m.p. 185–215°, (252 mg) was hydrogenated in ethanol (75 ml) at room temp in the presence of 10% palladized charcoal (50 mg). During the first 2 min one mole equivalent (16 ml) of hydrogen was absorbed. The hydrogenation did not proceed further. The catalyst was removed by filtration, the solvent distilled off, and the residue (235 mg) was crystallized from acetone–ether to give the racemic *cis* methyl ester (184 mg; 72·5%) in clusters of colorless needles, m.p. 185–186°. The analytical sample was recrystallized from acetone–ether. When heated slowly, it showed m.p. 186° (with softening at 160°). It melted at 160°, without resolidification, when heated rapidly.

(Found: C, 69·12; H, 5·55; N, 7·10. Calc. for $C_{21}H_{20}O_4N_2$: C, 69·21; H, 5·53; N, 7·69%).
Ultraviolet spectrum: typical N-phenylpyridone chromophore, cf. Fig. 1.

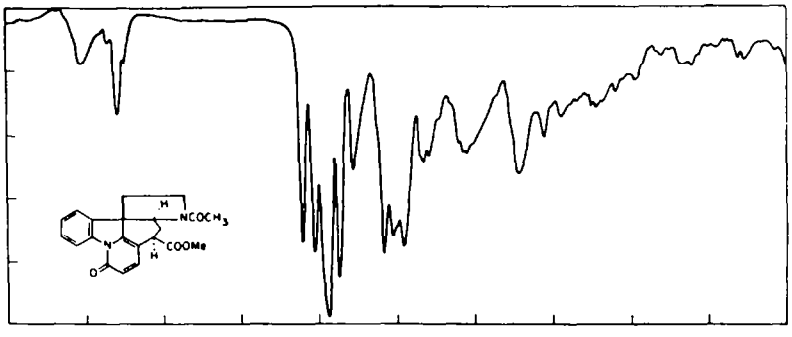


Plate 13

From the mother liquors on prolonged standing a small amount (20 mg) of highly crystalline racemic *trans* ester (XXXVIII), m.p. 210–211°, was obtained, which upon recrystallization from

acetone–ether had m.p. 212°. The compound was identical in all respects with the racemic *trans* ester prepared by treatment of the racemic *cis* ester (XXXVII) with alkali followed by esterification.

Conversion of racemic cis *ester* (XXXVII) *into racemic* trans *acid* (XXXIX)

The *cis* ester (440 mg) was heated under reflux for 1 hr with a solution of potassium hydroxide (220 mg) in water (5 ml) and methanol (10 ml). Most of the methanol was then removed *in vacuo*, the remaining solution was diluted with water (10 ml) and the non-acidic material (16 mg) was extracted with chloroform. Acidification of the alkaline layer with dilute sulfuric acid followed by exhaustive extraction with chloroform yielded the acidic material (388 mg), which on recrystallization from methanol gave the desired racemic *trans* acid (XXXIX) (249 mg; 59%) as colorless rhombs, m.p. 271° (on rapid heating). For analysis the acid was recrystallized 3 times from chloroform–methanol, m.p. 284° (dec) (slow heating).

(Found: C, 68·36; H, 5·50; N, 7·53. Calc. for $C_{20}H_{18}O_4N_2$: C, 68·56; H, 5·18; N, 8·00%).

Infrared spectrum: identical with those of the corresponding synthetic resolved acid and the acid from degradation of strychnine (see below).

When the methanolic mother liquors were treated with diazomethane, crude ester (122 mg; 28%) was recovered, from which on hydrolysis as above a further 48 mg of racemic *trans* acid, m.p. 270–271°, was obtained.

Racemic trans *methyl ester* (XXXVIII). To a methanolic solution of *trans* acid (XXXIX; 30 mg), excess ethereal diazomethane was added. The yellow solution was evaporated *in vacuo*, and the residue was recrystallized twice from acetone to give the *trans* methyl ester (24 mg; 77%), m.p. 208–211·5°. One further recrystallization from acetone–ether gave colorless plates (20 mg), m.p. 212°.

(Found: C, 69·32; H, 5·46; N, 8·25. Calc. for $C_{21}H_{20}O_4N_2$: C, 69·21; H, 5·53; N, 7·69%).

Infrared spectrum: identical with those of the corresponding synthetic resolved ester and the ester from degradation of strychnine (see below).

This *trans* ester was shown to be identical in every respect with the methyl ester, m.p. 212°, isolated as by-product from the hydrogenation of the unsaturated ester (XXXVI) (see above).

Resolution of the synthetic trans N-*acetyl acid* (XXXIX) *with quinidine*

Laevorotatory trans N-*acetyl acid* (XXXIX). Synthetic *trans* acid (249 mg) was heated gently with quinidine (231 mg, recrystallized from chloroform–methanol, colorless prisms, m.p. 163–164°) in a mixture of chloroform (2 ml) and methanol (2 ml) until a clear solution was obtained. After the solvents had been evaporated the semi-solid residue was crystallized from chloroform–acetone to give the dihydrate of the quinidine salt (114 mg; 24%), m.p. 160–172°, unchanged on admixture with *trans* N-acetyl acid quinidine salt (m.p. 160–172°) prepared by degradation from natural strychnine [see *Ancillary degradative studies* (below)].

The free laevorotatory trans N-*acetyl acid* (XXXIX) was obtained in the following manner: The synthetic quinidine salt dihydrate (114 mg) was dissolved in water (5 ml) and 10% aqueous potassium carbonate (5 ml). The solution was extracted with chloroform to remove quinidine, acidified, and again extracted with chloroform to give the *trans* acid: 51 mg (87%) of colorless crystals, m.p. 295–300° after two recrystallizations from chloroform–methanol. The melting point behavior of the resolved synthetic acid was identical with that of the acid of the same structure (XXXIX), m.p. 295–300°, derived from strychnine by degradation [see *Ancillary degradative studies* (below)].

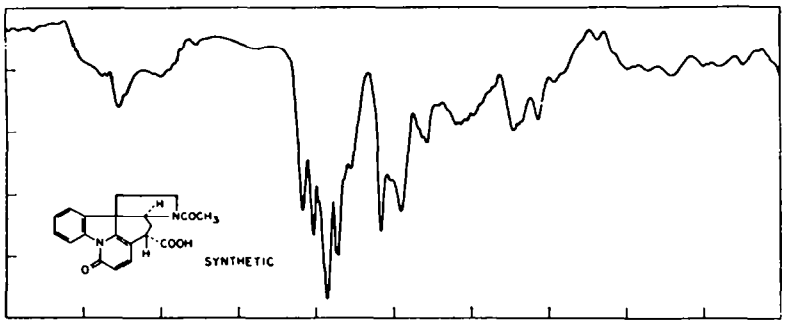


Plate 14a

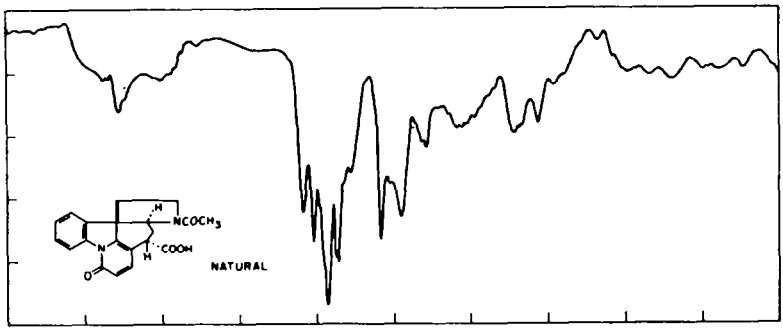


Plate 14b

The infrared spectra of the synthetic and the natural acid were indistinguishable, and identical with that of the racemic *trans* N-acetyl acid (see above).

For additional confirmation of the identity of the synthetic acid, it was converted into the corresponding methyl ester.

Synthetic laevorotatory methyl ester (XXXVIII). A methanolic solution of the synthetic laevorotatory *trans* N-acetyl acid (XXXIX; 20 mg) was treated with excess ethereal diazomethane. The ester crystallized from acetone–ether in colorless blocks (18 mg), m.p. 196°, $[\alpha]_D^{23}$ $-285 \pm 8°$ [*c*, 1·25 ($CHCl_3$)].

The corresponding ester obtained by degradation of strychnine [see *Ancillary degradative studies* (below)] had m.p. 196°, $[\alpha]_D^{21}$ $-292 \pm 5°$ [*c*, 1·14 ($CHCl_3$)]. The melting point of a mixture of the esters from the two sources was undepressed from that of either. The infrared spectra of the specimens were identical, and indistinguishable from that of the racemic *trans* N-acetyl methyl ester (above).

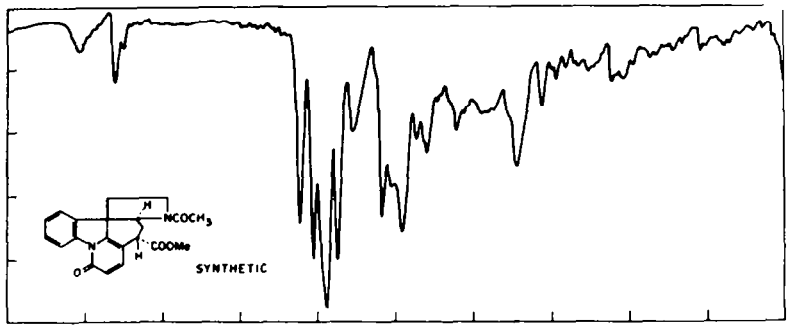


Plate 15a

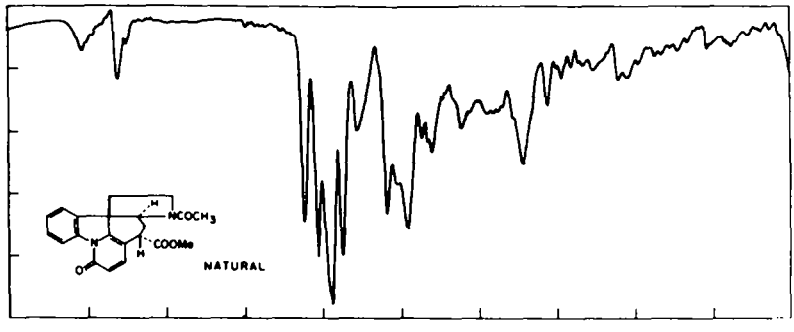


Plate 15b

Construction of Ring VI

Treatment of the trans N-*acetyl acid* (XXXIX) *with acetic anhydride–pyridine.*

Enol-acetate (XL). *Trans* N-acetyl acid (200 mg) was heated for 1 hr under reflux with a mixture of acetic anhydride (10 ml) and pyridine (10 ml). The clear solution was then evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (20 ml) and shaken for 5 min with a cold 10% aqueous solution of potassium carbonate (10 ml). The chloroform layer was separated, washed with water (10 ml) and dried over anhydrous sodium sulfate. The residue obtained by evaporation of the solvent was dissolved in a small volume of benzene (2·5 ml) and chromatographed on neutral alumina (8 g). Elution with benzene gave a yellow oil (235 mg) which upon addition of methylene chloride–ether yielded the crude enol-acetate (93 mg; 42%). Recrystallization from the same solvent mixture left 61 mg (27·5%) of colorless needles, m.p. 250–255°. For analysis the enol-acetate was recrystallized once more from methanol-ether: brilliant cubes, m.p. 260–263°

(Found: C, 71·00; H, 5·83; N, 6·88. Calc. for $C_{23}H_{22}O_4N_2$: C, 70·75; H, 5·68; N, 7·18%).

Ultraviolet spectrum: $\lambda\lambda_{max}(\epsilon)$: 240 m$\mu$ (21,300), 258 (13,200), ~335 (7100), 347 (8400), 362 (5800).

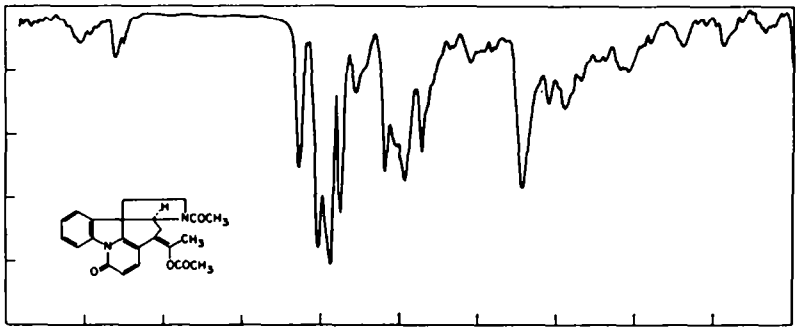


Plate 16

The enol-acetate could also be prepared by replacing pyridine with other bases, e.g., triethylamine, quinoline or anhydrous potassium acetate. In each case, however, the yield was lower than in the procedure described above.

Acid hydrolysis of the enol-acetate (XL)

Methyl ketone (XLIV). The enol-acetate (130 mg) was refluxed vigorously for 6 hr with concentrated hydrochloric acid (2 ml), acetic acid (2 ml) and water (2 ml). The clear solution was evaporated *in vacuo* on the steam-bath. The residue was dissolved in dilute sulfuric acid and washed twice with chloroform, only a trace of non-basic material being isolated. The aqueous layer was made alkaline with concentrated aqueous ammonia, and when extracted with chloroform gave the crude methyl ketone (100 mg) as a nearly colorless oil which did not crystallize, and was used directly in the next step.

Ultraviolet spectrum: typical N-phenylpyridone chromophore, *cf.* Fig. 1.

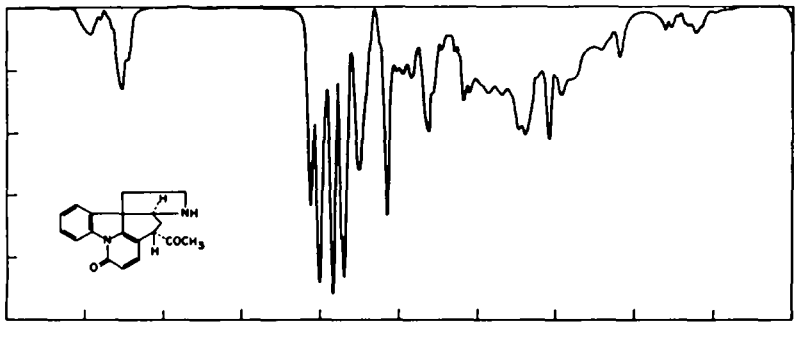


Plate 17

Oxidation of the methl ketone (XLIV) *with selenium dioxide*

Dehydrostrychninone (XLV). The methyl ketone (100 mg) was allowed to stand at room temp for 15 hr with a solution of selenium dioxide (72·5 mg) in absolute ethanol (6 ml). A tobacco-brown precipitate was formed during this time. After the reaction mixture had been refluxed for 1 hr on the steam-bath, charcoal was added, and the separated solids were removed by filtration. The filtrate was evaporated to dryness, the residual material was dissolved in a 1:1 mixture of benzene and chloroform (10 ml) and the solution was filtered again through charcoal. More chloroform (10 ml) was added, and the solution was extracted with two 5 ml portions of dilute sulfuric acid [18 mg of basic material was isolated, the infrared spectrum of which indicated that it was not starting material] and washed successively with water (10 ml), aqueous potassium bicarbonate (10 ml) and water (5 ml) again. Evaporation of the solvents afforded a neutral green oil (50 mg) which still contained traces of selenium. The product was therefore dissolved in methanol (5 ml), shaken in the cold with a small amount of deactivated Raney nickel, filtered and then diluted with water to a volume of 25 ml. The turbid solution was heated on the steam-bath for 5 min), treated with little charcoal and filtered while still hot. The insoluble material on the filter was extracted twice with 5 ml portions of boiling water. The combined filtrates were thoroughly shaken with chloroform and the eluate was evaporated to give a green oily residue (21 mg) which crystallized readily when a few drops of methanol were added. One recrystallization from methanol afforded the characteristic colorless cubes of dehydrostrychninone methanolate (14 mg; 12·4%), melting at 172–174°, resolidifying and remelting at 254–258°, $[\alpha]_D^{24}$ −521 ± 4° [*c*, 1·05 ($CHCl_3$)]. No depression was observed on admixture with authentic dehydrostrychninone methanolate of the same melting points [$[\alpha]_D^{31}$ 512 ± 4° [*c*, 1·17 ($CHCl_3$)][24]], prepared by degradation of strychnine [see *Ancillary degradative studies* (below)].

The infrared spectra of synthetic and natural dehydrostrychninone were superimposable.

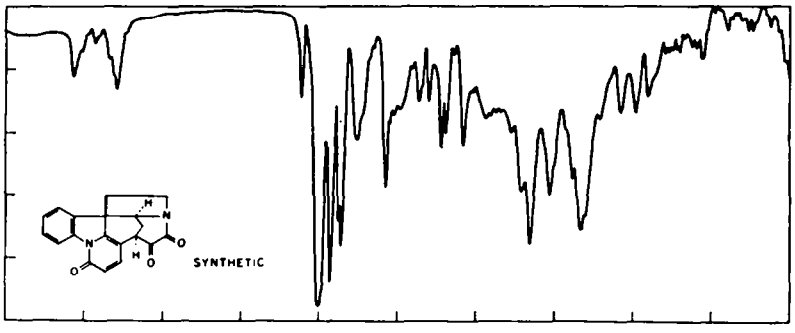


Plate 18a

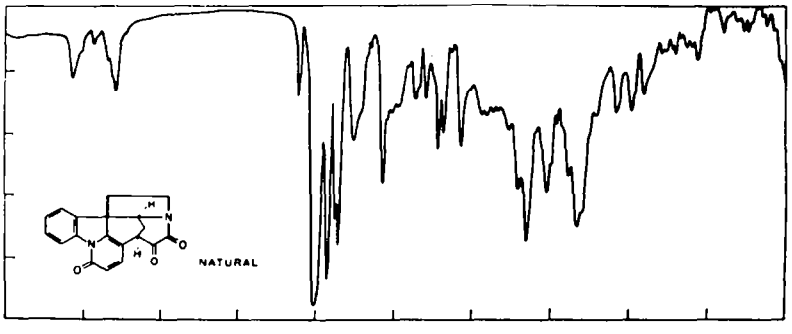


Plate 18b

Miscellaneous Reactions at C.14

Reconversion of methyl ketone (XLIV) *into enol-acetate* (XL)

The methyl ketone (100 mg) was refluxed for 4 hr under nitrogen with acetic anhydride (5 ml) and pyridine (5 ml). The reaction mixture was evaporated *in vacuo* to give a brown residue which was dissolved in chloroform and shaken with 10% aqueous potassium carbonate for 10 min. The chloroform layer was washed with water, dried over anhydrous sodium sulfate and taken down to dryness. The residual oil (143 mg) was chromatographed on neutral alumina (5 g). Elution with a mixture of benzene (30 ml) and chloroform (10 ml) gave a yellow foam (99 mg) which when crystallized from methylene chloride–ether yielded the enol-acetate (XL; 18 mg; 16·6%) in colorless needles, m.p. 260–263°. The compound was identical in all respects with the enol-acetate (XL) obtained by treatment of the *trans* N-acetyl acid (XXXIX) with acetic anhydride and pyridine.

Treatment of the enol-acetate (XL) *with methanolic sodium hydroxide in the presence of oxygen*

Ketone (XLVII). The enol-acetate (100 mg) was heated in an open flask for 30 min on the steam-bath with a solution of 2 N aqueous sodium hydroxide (1 ml) in methanol (5 ml). After addition of water (20 ml) the methanol was removed *in vacuo* at 40°. The remaining aqueous solution was extracted three times with chloroform (20; 10; 10 ml). The aqueous layer on acidification gave 27 mg of acidic material which was not further investigated. The combined chloroform extracts were washed with water (20 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo*. The semi-solid residue (57 mg) was crystallized from methanol to give the ketone (XLVII) (28 mg; 34 %) as almost colorless needles, m.p. 234–236°. For analysis the ketone was recrystallized twice from methanol–ether, m.p. 237°.

(Found: C, 71·07; H, 5·14. Calc. for $C_{19}H_{16}O_3N_2$: C, 71·24; H, 5·03%).

Ultraviolet spectrum: $\lambda\lambda_{max}$ (ϵ): 237 mμ (17,800), 294 (13,200), 319 (9200), 332 (10,300), 347 (7200).

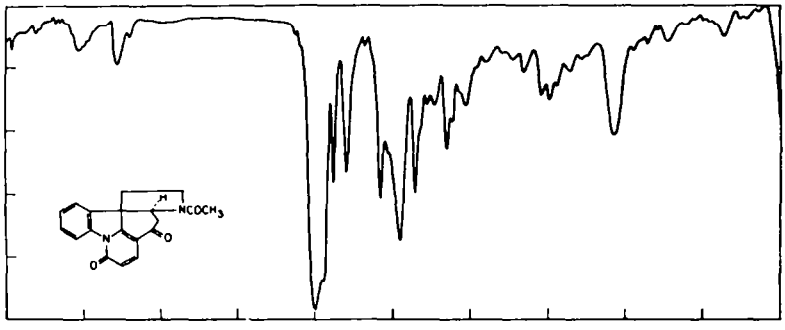


Plate 19

Methylmercapto methyl ketone (XLVI). The methyl ketone (XLIV; 2·18 g), methyl *p*-toluenethiosulfonate (1·66 g) and anhydrous potassium acetate (3·6 g) were refluxed under nitrogen for 4 hr. The solvent was removed at 60° *in vacuo*, and the dark green residue was dissolved in chloroform. The chloroform solution was washed twice with aqueous 2 N sodium carbonate and then extracted with five 10 ml portions of 2 N sulfuric acid. The combined acid extracts were made alkaline with sodium hydroxide and extracted thoroughly with chloroform, the chloroform layers being washed with water, dried and finally evaporated to dryness. The resulting crude methylmercapto methyl ketone (1·94 g) was isolated as hydrochloride monohydrate. After two recrystallizations from methanol, colorless needles (1·236 g; 42·5%), m.p. 183–187°, were obtained. For analysis the hydrochloride was recrystallized once more from methanol, m.p. 187–188°.

(Found: C, 58·96; H, 5·76; N, 6·92; Cl, 8·90. Calc. for $C_{20}H_{20}O_3N_2S{\cdot}HCl{\cdot}H_2O$: C, 58·98; H, 5·69; N, 6·89; Cl, 8·72%).

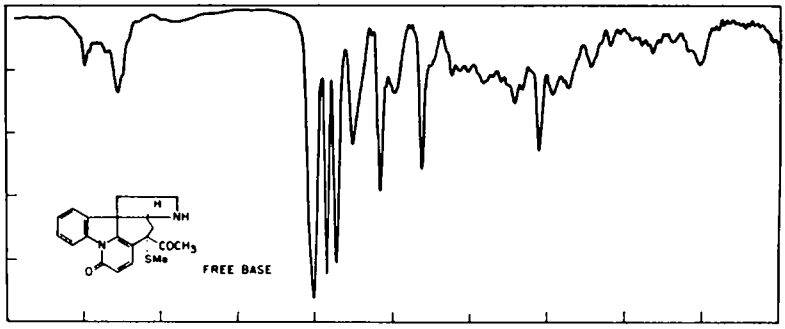


Plate 20

N-*acetyl derivative of the methylmercapto methyl ketone* (XLVI). The hydrochloride of methylmercapto methyl ketone (XLVI; 543 mg) was shaken at room temp with acetic anhydride (5 ml) and pyridine (10 ml) until complete dissolution had occurred (1 hr). The reaction mixture was then allowed to stand at room temp for a further 10 hr. The solvents were removed *in vacuo;* the residual oil was taken up in chloroform (25 ml) and extracted successively with dilute sulfuric acid (10 ml), dilute sodium hydroxide (10 ml) and finally with water (10 ml). The chloroform layer was dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. A colorless foam (476 mg) was obtained which on crystallization from benzene–cyclohexane yielded the desired N-acetyl derivative (393 mg; 82%): slightly colored needles, m.p. 221–223°. For analysis the substance was recrystallized from methanol: colorless crystals, m.p. 223°.

(Found: C, 65·01; H, 6·09; N, 6·72; S, 7·96. Calc. for $C_{22}H_{22}O_3N_2S \cdot CH_3OH$: C, 64·77; H, 6·14; N, 6·57; S, 7·51%).

Ultraviolet spectrum: typical N-phenylpyridone chromophore, cf. Fig. 1.

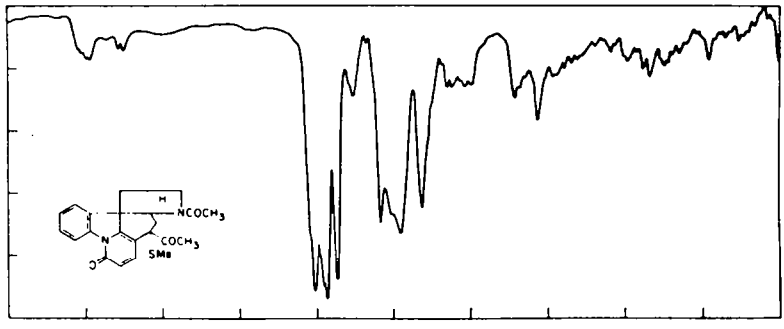


Plate 21

Conversion of Dehydrostrychninone to Strychnine

Reaction of dehydrostrychninone (XLV) *with sodium acetylide*

Ethinyl carbinol (LXVI). Into a two-necked flask equipped with a magnetic stirrer, an inlet and a drying tube [filled with soda lime] and containing approximately 30 ml of liquid ammonia, a gentle stream of acetylene was introduced. The acetylene was purified by passing it successively through an acetone-Dry-ice trap, concentrated sulfuric acid and a drying tower filled with calcium chloride. Small lumps of metallic sodium (150 mg) were added in several portions with good stirring. When the color of the reaction mixture turned from deep-blue to grey the ammonia was allowed to evaporate, and its last traces were removed by heating for 30 min to 70°. The resulting dry sodium acetylide was suspended in freshly prepared absolute tetrahydrofuran (20 ml) with vigorous stirring.

Dehydrostrychninone methanolate (220 mg) was heated to 180–190° in high vacuum for 30 min.

The loss of methanol is accompanied by a change of color from white to bright-yellow. The substance was dissolved in tetrahydrofuran (10 ml) and the solution added dropwise to the well-stirred suspension of sodium acetylide at 0°. The ice-cooling was then removed for 1 hr while stirring was contined. Chloroform (25 ml) and 1 N hydrochloric acid (10 ml) were added; the contents of the flask were transferred to a separatory funnel and thoroughly shaken. The organic layer was washed with aqueous potassium bicarbonate and water and finally dried by filtration through anhydrous sodium sulfate. Evaporation of the solvents gave a yellow foam (172 mg), from which the desired ethinyl carbinol (127 mg; 53%), m.p. 290–300°, was obtained on addition of methanol. After 3 recrystallizations from chloroform–methanol the colorless cubes had m.p. 302–305°.

(Found: C, 73·06; H, 4·58; N, 8·47. Calc. for $C_{21}H_{16}O_3N_2$: C, 73·24; H, 4·68; N, 8·14%).

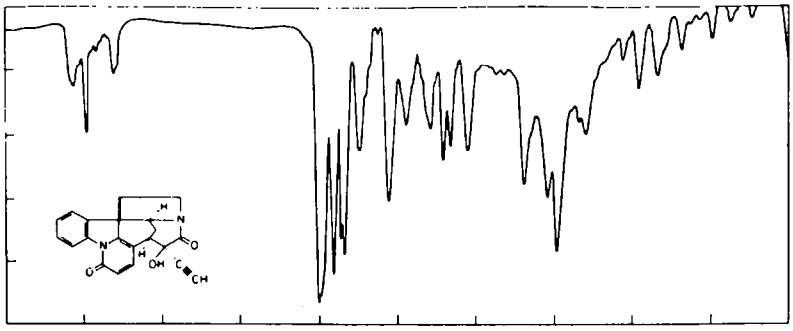


Plate 22

Catalytic hydrogenation of the ethinyl carbinol (LXVI) *to the vinyl carbinol* (LXVII). The ethinyl carbinol (500 mg) was hydrogenated in methanol (50 ml) in the presence of deactivated Lindlar catalyst.[38] After an uptake of 35·3 ml of hydrogen [calc. for 1 mole equivalent: 36·0 ml] within 3 min, the hydrogenation stopped completely. The catalyst was removed by filtration, and the solvent evaporated *in vacuo*. The vinyl carbinol crystallized from methanol in colorless prisms (432 mg; 86%), m.p. 244–245°.

(Found: C, 72·58; H, 5·75; N, 8·24. Calc. for $C_{21}H_{18}O_3N_2$: C, 72·82; H, 5·24; N, 8·09%).

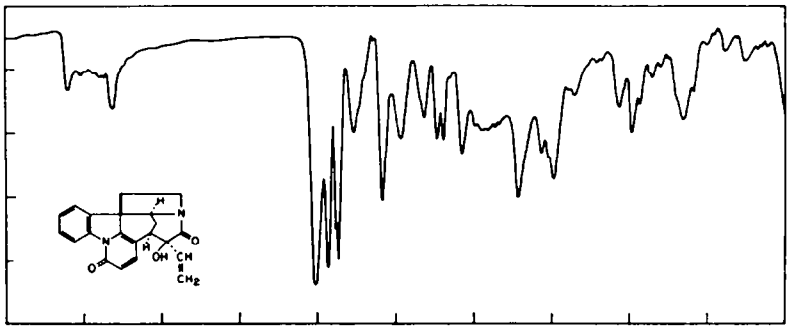


Plate 23

Reduction of the vinyl carbinol (LXVII) *with lithium aluminum hydride*

Carbinol (LXVIII). A suspension of lithium aluminum hydride (200 mg) in absolute ether (40 ml) was heated under reflux in a flask equipped with a magnetic stirrer and a Soxhlet extractor. Each time the thimble was half full, one milliliter of a solution prepared from the vinyl carbinol (LXVII; 260 mg), ether (5 ml) and tetrahydrofuran (5 ml) was injected into it. When the addition was completed, the reaction mixture was heated for an additional hour. It was then cooled to 0°, mixed with chloroform (40 ml) and decomposed with methanol (2 ml) and water (6 ml). On gentle swirling the incipient suspension separated into two phases. The organic layer was pipetted off, and the remaining slurry

of hydroxides was washed three times with chloroform (20 ml). The combined chloroform extracts were shaken with water (30 ml), filtered through anhydrous sodium sulfate and evaporated. The green oily residue (257 mg) was dissolved in chloroform (10 ml) and extracted 3 times with 10 ml portions of 1 N sulfuric acid. The chloroform solution [non-basic material] was discarded. The aqueous layer was made alkaline with concentrated aqueous ammonia and extracted exhaustively with chloroform, which when evaporated gave 243 mg of basic material. The latter was purified by chromatography on neutral alumina (7·5 g). With benzene–chloroform (1:1; 40 ml) a practically colorless oil (156 mg) of the carbinol (LXVIII) was eluted which could not be crystallized. Transformation into the hydrochloride with methanolic hydrogen chloride, however, afforded colorless crystals (98 mg; 30%), m.p. 192–200°. Recrystallization proceeded smoothly from methanol after addition of water (one drop) to give the hydrochloride dihydrate, colorless needles, m.p. 195–205° (dec).

(Found: C, 61·87; H, 6·97; N, 6·97. Calc. for $C_{21}H_{22}O_2N_2 \cdot HCl \cdot 2H_2O$: C, 61·97; H, 6·69; N, 6·89%).

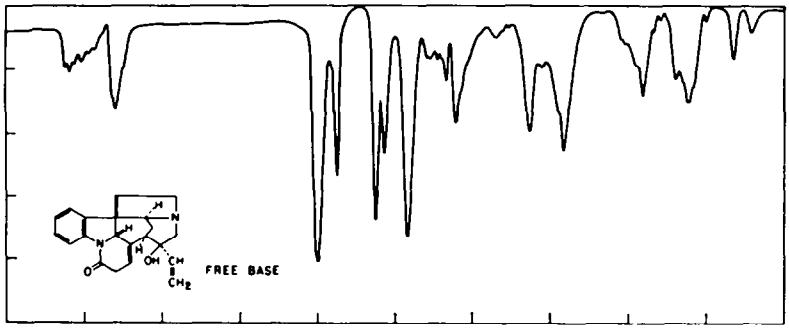


Plate 24

Allylic rearrangement of the carbinol (LXVIII) *to isostrychnine I* (LXIX)

The hydrochloride of the carbinol (LXVIII; 195 mg) was heated in a sealed glass tube of approximately 10 cm length in an oil bath [bath temp: 120°] for 2½ hr with a 30% solution of hydrogen bromide in acetic acid (4 ml) and red phosphorus (20 mg). The tube was immersed in the oil to one-third of its length only, so that refluxing was possible to a certain extent. The phosphorus was then removed by filtration, the filtrate evaporated to dryness *in vacuo*, and the residue boiled at reflux for 30 min with 1 N sulfuric acid (10 ml). After addition of water (10 ml) boiling was continued for another hr. The clear yellow solution was treated with charcoal (200 mg), filtered while still hot and extracted twice with chloroform. The aqueous layer was made alkaline with concentrated aqueous ammonia (3 ml) and extracted 4 times with chloroform. Evaporation of the solvent gave 150 mg of pale-yellow basic material. By careful chromatography on activated neutral alumina (4 g), the following 20 ml fractions were obtained:

Fractions	Solvents	Weight (mg)	Properties
1–3	benzene–chlf. (4:1)	9	yellow oil
4–6	benzene–chlf. (1:1)	2	colorless oil
7	chloroform	30	colorless oil
8	chloroform	40	partially crystalline
9	chloroform	15	partially crystalline
10	chloroform	8	crystalline, m.p. 202–207°
11–13	chloroform	9·5	m.p. 206–209°
14	chloroform	trace	
15–16	chlf–methanol (20:1)	15	yellow oil

Fractions 8–13 were combined, and gave on recrystallization from methanol, isostrychnine I (18·5 mg; 12·5%), m.p. 206–211°. Three further recrystallizations from the same solvent gave colorless crystals, m.p. 208–212°. For the purpose of comparison the melting points of the synthetic isostrychnine I and of authentic isostrychnine I, prepared according to Leuchs and Schulte,[38] were taken in evacuated capillary tubes:

Synthetic isostrychnine I had

m.p. 229–230° and $[\alpha]_D^{25}$ +23 ± 4° [*c*, 2·54 (EtOH)]

Natural isostrychnine I had

m.p. 228–230° and $[\alpha]_D^{25}$ +25 ± 4° [*c*, 2·29 (EtOH)]

A *mixture* of the synthetic and natural samples had

m.p. 228–230°

The infrared spectra of the synthetic and natural samples were identical.

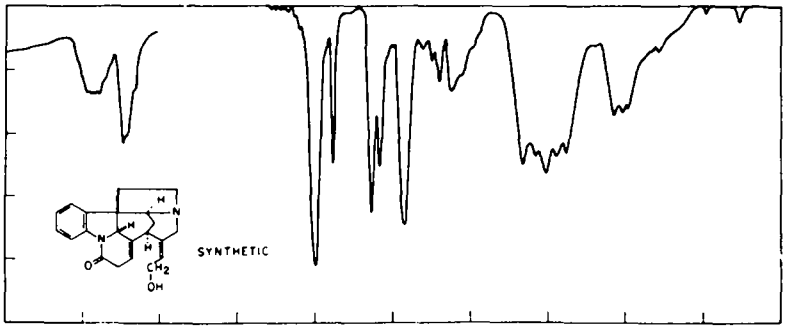


Plate 25a

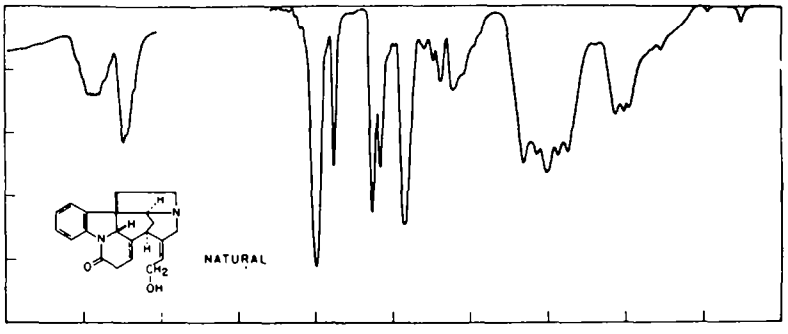


Plate 25b

All of the non-crystalline material from the chloroform fractions 8–13 (above), plus the mother liquors from recrystallizations of isostrychnine I were combined, evaporated *in vacuo* (84 mg), and acetylated at room temp with acetic anhydride (5 ml) and pyridine (0.5 ml). The product was worked up in the usual way to give 98 mg of an oil which was chromatographed on activated neutral alumina (3 g). Elution with benzene–chloroform (5:3) afforded a colorless oil (65 mg), the infrared spectrum of which possessed a strong well-defined ester band at 5·86 μ.

Strychnine (LXX)

Synthetic isostrychnine I (7 mg) and the isostrychnine acetates (65 mg) described above were allowed to stand at room temp for 15 min in a long sealed glass tube with a 1·5% ethanolic solution of

potassium hydroxide (4 ml).[34] The mixture was then heated on the steam-bath for 5 hr. The clear solution soon turned yellow, and after ca. 1 hr a white precipitate began to appear. The fluorescent reaction mixture was diluted with chloroform (20 ml) and washed twice with water. The residue obtained after evaporation of the solvent (70 mg) was chromatographed on activated neutral alumina (4 g). The benzene–chloroform (4:1) fractions yielded an almost colorless oil (9·5 mg) which crystallized spontaneously. The material was dissolved in dilute sulfuric acid (1 ml) and the non-basic products (1·5 mg) removed by extraction with chloroform. The aqueous layer was then made alkaline with aqueous ammonia and extracted thoroughly with chloroform. Eight mg of colorless crystalline strychnine was isolated, which after three recrystallizations from chloroform–ether was obtained in brilliant colorless cubes, m.p. 275–285°, undepressed with admixture of natural strychnine, m.p 275–285°. The infrared spectrum of the synthetic alkaloid was identical in all respects with that of natural strychnine.

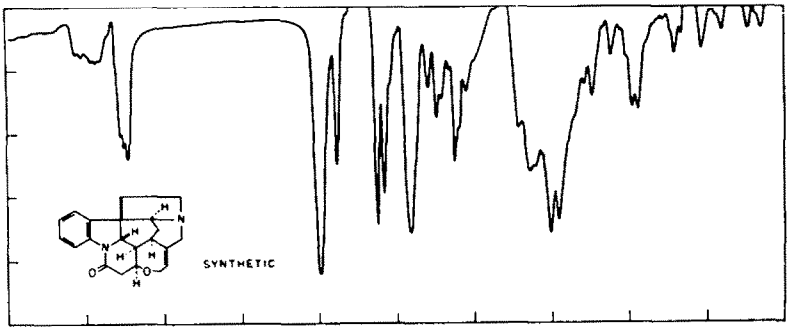


Plate 26a

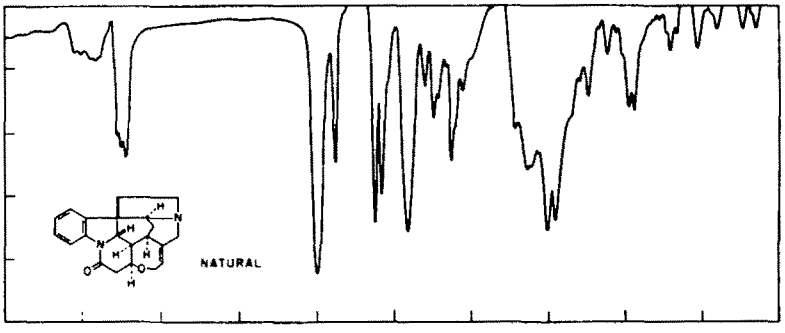


Plate 26b

Miscellaneous Reactions Starting from Dehydrostrychninone

Reformatzky condensation with dehydrostrychninone

Hydroxyester A (LXIV) *and hydroxyester* B (LXV). Dehydrostrychninone (1·016 g) was heated for 2 hr to 200° *in vacuo* (to convert the methanolate into the solvent-free compound) and was then dissolved in dry benzene (100 ml). Activated zinc (3 g),[39] freshly distilled methyl bromoacetate (0·5 ml) and traces of iodine and mercuric chloride were added, and the mixture was heated under reflux with vigorous stirring. Dry purified nitrogen was passed over the reaction mixture during the whole reaction. Within 3 hr five more 2 g portions of zinc and two 0·5 ml portions of methyl bromoacetate were added. Two hrs after the first addition of methyl bromoacetate, the reaction started; the iodine color disappeared, and a voluminous white precipitate was formed. The contents of the reaction flask were cooled to room temp after a total reaction time of 5 hr and enough methanol (ca. 20 ml) was added to give a clear solution. The latter was cooled to 0°, decanted from the zinc slurry into cold

[39] L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.* **62**, 575 (1940).

2 N acetic acid (100 ml), and the zinc was washed twice with 50 ml portions of chloroform. The organic layer was extracted with dilute aqueous ammonia (100 ml) and water (50 ml); the aqueous layer was washed with chloroform (30 ml). The combined chloroform solutions were dried and evaporated to dryness leaving a red-yellow oil (1·365 g). This oil was dissolved in acetone (10 ml) and cooled to 0°. Slightly colored crystals (410 mg) were obtained which on recrystallization from acetone gave the hydroxyester A (LXIV; 270 mg; 24%), colorless crystals, m.p. 260–264°. For analysis a specimen of the ester was recrystallized twice, m.p. 262–265°.

(Found: C, 67·00; H, 5·14; N, 7·26. Calc. for $C_{22}H_{30}O_5N_2$: C, 67·34; H, 5·13; N, 7·14%).

Infrared spectrum: band at 5·78 μ (ester).

The residues from the mother liquors (1·1 g) were chromatographed on neutral alumina (50 g). Elution with benzene–chloroform (1:1) gave a nearly colorless oil (540 mg) which on addition of acetone (5 ml) yielded fine colorless crystals (209 mg) of the hydroxyester A, thus bringing the yield to 479 mg (42·5%).

Concentration of the acetone solution gave a small amount of the stereoisomeric hydroxyester B (LXV; 70 mg; 6·6%) which after 4 recrystallizations from benzene–ether had m.p. 242–244°. Admixture with hydroxyester A resulted in a marked depression of the melting point.

(Found: C, 67·28; H, 5·28; N, 7·32. Calc. for $C_{22}H_{30}O_5N_2$: C, 67·34; H, 5·13; N, 7·14%).

Infrared spectrum: band at 5·83 μ (ester).

Acetylation of hydroxyester A (LXIV). Hydroxyester A (115 mg) was boiled under reflux with acetic anhydride (15 ml) for 5 hr. The solution was then evaporated *in vacuo*, the residue taken up in a small volume of benzene and filtered through neutral alumina (5 g), the elution being completed with benzene–chloroform (1:1), to give a pale-yellow oil (122 mg). From benzene–cyclohexane the acetoxy ester (101 mg; 80%) was obtained in slightly yellow crystals, m.p. 198–203°. For analysis the ester was recrystallized twice from methanol, m.p. 200–203°.

(Found: C, 66·39; H, 5·37; N, 6·23. Calc. for $C_{24}H_{32}O_6N_2$: C, 66·36; H, 5·11; N, 6·45%).

Infrared spectrum: Poorly resolved doublet at 5·77 μ and 5·79 μ.

Pyrolysis of acetoxy ester from (LXIV) *to* α,β*-unsaturated ester* (i). The acetoxy ester (59 mg) was pyrolyzed during 12 hr under high vacuum at 200–250°. A colorless crystalline sublimate was obtained which on recrystallization from methanol afforded the unsaturated ester (i) (45 mg; 89%) in colorless crystals, m.p. 244–248°. For analysis the substance was sublimed at 220° in high vacuum.

(Found: C, 70·24; H, 4·80; N, 7·67. Calc. for $C_{22}H_{18}O_4N_2$: C, 70·58; H, 4·85; N, 7·49%).

Infrared spectrum: Band at 5·82 μ (conjugated ester).

Saturated ester (ii). The α,β-unsaturated ester (i) (42 mg) was dissolved in ethanol (10 ml) and hydrogenated in the presence of palladium on charcoal (10 mg). After uptake of nearly 1 mole equivalent (2·6 ml), the hydrogenation came to a stop. The catalyst was removed by filtration, and the filtrate evaporated to dryness. The resulting oil was filtered through activated neutral alumina (2 g) in benzene–chloroform (1:1). Evaporation of the eluate gave a colorless product (43 mg) which was crystallized from methanol, affording 38 mg of colorless plates, m.p. 260–268°. For analysis the ester was recrystallized from chloroform–methanol to give large colorless prisms, m.p. 265–268°.

(Found: C, 69·97; H, 5·36; N, 7·35. Calc. for $C_{22}H_{20}O_4N_2$: C, 70·20; H, 5·36; N, 7·44%).

Infrared spectrum: band at 5·78 μ (ester), and typical triplet N-phenylpyridone absorption (5·98, 6·17 and 6·27 μ).

Reduction of either the unsaturated ester (i) or the saturated ester (ii) with lithium aluminum hydride in ether or tetrahydrofuran (cf. *Model reductions with lithium aluminum hydride*, below) gave very complex mixtures of products, from which, in spite of extensive efforts, no pure materials could be isolated.

Model Reductions with Lithium Aluminum Hydride

Reduction of strychninolone a (LVIII, R = H) *with lithium aluminum hydride.*

Dihydrostrychninol acetate (LIX, OH = OAc). Strychninolone a (300 mg) was dissolved in tetrahydrofuran (15 ml) and then added slowly to a well-stirred suspension of lithium aluminum hydride (300 mg) in tetrahydrofuran (15 ml). The reaction mixture was heated under reflux for 4 hr. It was cooled to 10°, diluted with chloroform (30 ml) and treated with water (5 ml). After gentle swirling of the flask the organic layer could be pipetted off. The residual slurry of metal hydroxides was washed three times with chloroform. The combined chloroform solutions were extracted three times with 10 ml portions of dilute sulfuric acid. The chloroform layer after drying and evaporation gave 10 mg of

non-basic products which were not further investigated. The sulfuric acid extracts were made alkaline with concentrated aqueous ammonia and extracted 3 times with chloroform to give the basic reduction product (275 mg), which could not be induced to crystallize. It was therefore directly acetylated at room temp with acetic anhydride (3 ml) and pyridine (0·3 ml). After 12 hr water (1 ml) was added, and the reaction mixture was worked up in the usual manner. The crude basic acetate (235 mg) was chromatographed on activated neutral alumina (7 g). Elution with benzene afforded 188 mg of yellow material which was crystallized from methanol–ether: slightly colored prisms (102 mg) of dihydrostrychninol acetate (LIX, OH = OAc), m.p. 190–193°. For analysis the substance was recrystallized once from acetone–cyclohexane, m.p. 193–194°.

(Found: C, 72·04; H, 7·00; N, 8·04. Calc. for $C_{21}H_{24}O_3N_2$: C, 71·57; H, 6·86; N, 7·95%).

Ultraviolet spectrum: [*strychnine* type] $\lambda\lambda_{max}$ (ϵ): 254 mμ (15,000), 283 (4500), 292 (3800).

Infrared spectrum: [*strychnine* type] $\lambda\lambda_{max}$: 6·00 μ, 6·23 μ and 5·79 μ (ester).

Reduction of strychninolone b acetate (LV) *with lithium aluminum hydride*

Imino alcohol (LIV). Strychninolone b acetate (300 mg) was reduced under exactly the same conditions described above for the case of strychninolone a. From the crude basic product (237 mg) the imino alcohol (37 mg) crystallized from ethanol in slightly colored needles, m.p. 240–243° (dec).

(Found: C, 77·06; H, 7·48; N, 9·39. Calc. for $C_{19}H_{22}ON_2$: C, 77·52; H, 7·53; N, 9·52%).

Infrared spectrum: *No* band in the 6 μ region. Aromatic bands at 6·20 μ and 6·74 μ. The mother liquors gave on acetylation with acetic anhydride (3 ml) and pyridine (0·3 ml), followed by chromatographic purification on neutral alumina, the *imino acetate* (LIV, OH = OAc; 144 mg), which crystallized from methanol–ether in cream colored beautiful cubes, m.p. 206–209°. For analysis a sample was recrystallized twice from the same solvents, m.p. 208–210°. On admixture with strychninol b acetate (LIII, R = Ac) a melting point-depression of 25° was observed.

Found: C, 74·54; H, 7·05; N, 8·29. Calc. for $C_{21}H_{24}O_2N_2$: C, 74·97; H, 7·19; N, 8·33%). This imino acetate is identical in all respects with the imino acetate isolated from the reduction of strychninol b acetate (LIII, R = Ac) (below) with lithium aluminum hydride.

Infrared spectrum: *No* band in 6 μ region. Aromatic bands at 6·20 μ and 6·75 μ, plus ester band at 5·79 μ.

Reduction of dehydrostrychninone (XLV) *with lithium aluminum hydride*

Strychninol b *acetate* (LIII, R = Ac). Dehydrostrychninone methanolate (190 mg) was placed in the thimble of a Soxhlet extractor and extracted into a boiling suspension of lithium aluminum hydride (200 mg) in absolute ether (30 ml). The reaction was completed after 24 hrs and yielded, when worked up in the usual manner (*vide supra*), 156 mg of basic material. The latter was filtered through activated neutral alumina (4 g). The chloroform eluate (106 mg) was directly acetylated with acetic anhydride–pyridine to give the crude crystalline acetate (97 mg), m.p. 215–218°. For analysis the compound was recrystallized from methanol–ether: colorless needles, m.p. 217–219°. The substance was not identical with either of the two basic acetates (LIX, OH = OAc and LIV, OH = OAc) previously characterized in this series.

(Found: C, 71·67; H, 6·50; N, 7·97. Calc. for $C_{21}H_{22}O_3N_2$: C, 71·98; H, 6·33; N, 8·00%).

Ultraviolet spectrum: [*strychnine* type] $\lambda\lambda_{max}$ (ϵ): 254 mμ (12,100), 284 (4200), 294 (3800).

Infrared spectrum: Closely comparable to that of strychninolone b acetate. Amide band at 6·0 μ, aromatic bands at 6·24 μ and 6·75 μ; ester band at 5·79 μ.

The reduction of both dehydrostrychninolone[24] and dehydrostrychninolone acetate[24] with lithium aluminum hydride by the same procedure also gave strychninol b acetate (LIII, R = Ac).

Reduction of strychninol b acetate (LIII, R = Ac) *with lithium aluminum hydride*

Imino alcohol (LIV). Strychninol b acetate (63 mg) (above) was extracted in a Soxhlet apparatus into a boiling suspension of lithium aluminum hydride (60 mg) in absolute ether (20 ml). The reaction was completed after 4 hr and worked up in the usual manner. The basic material (59 mg) obtained was crystalline [m.p. 215–230°] and after 2 recrystallizations from methanol gave pure imino alcohol (LIV; 44 mg), m.p. 237–240° (dec). The substance was identical in all respects with the imino alcohol, m.p. 240–243°, obtained by reduction of strychninolone b acetate (LV) with lithium aluminum hydride

(see above). The imino alcohol (44 mg) was treated with acetic anhydride–pyridine to give the imino acetate (41 mg); m.p. 206–209°, undepressed on admixture with imino acetate, m.p. 207–209°, produced by reduction of strychninolone b acetate, followed by acetylation (see above). The infrared spectra of the two compounds were superimposable.

Ancillary Degradative Studies

Oxidation of strychnine (I) *with potassium permanganate*

Strychninonic acid. The oxidative degradation of strychnine was carried out according to Leuchs and Schwaebel.[26] The oxidation was usually run with 100 g batches of strychnine, which gave 28–29 g of crude strychninonic acid (23–24%), m.p. 257–259°.

Strychninolone a (LVIII, R = H) was prepared by sodium amalgam reduction of strychninonic acid, followed directly by treatment with alkali.[27] Thus, in a typical example, strychninonic acid (44g) was reduced with 2·5% sodium amalgam (245 g) in water (220 ml), the reaction solution being kept at pH 7–8 by gradual addition of 2 N hydrochloric acid. The clear solution then was made strongly alkaline with 10% aqueous sodium hydroxide (80 ml) affording 32 g (89%) of crude strychninolone a, m.p. 208–213°. Two recrystallizations from ethanol raised the m.p. to 228–231°. (Leuchs and Schneider[40] give m.p. 228–231°.)

Strychninolone a acetate (LVIII, R = Ac). Crude strychninolone a (20 g) was heated on the steam-bath for 2 hr with acetic anhydride (100 ml) and pyridine (10 ml). The solution was evaporated *in vacuo*, the residue was dissolved in chloroform (200 ml) and extracted successively with 1 N hydrochloric acid (20 ml), saturated aqueous potassium bicarbonate (20 ml) and water (50 ml). The chloroform solution was filtered through anhydrous sodium sulfate, and the solvent removed *in vacuo*. The residue was crystallized from methanol–ether yielding strychninolone a acetate (19·82 g; 88%) as pale-yellow leaflets, m.p. 237–242°. Two recrystallizations from ethanol gave almost colorless crystals, m.p. 242–244° (Leuchs and Schwaebel[27] found m.p. 241–243°).

Strychninolone b acetate (LV). Using the method of Leuchs and Bendixsohn[28] strychninolone a acetate (19·8 g) was dissolved in acetic anhydride (300 ml), and at 115° a vigorous stream of dry hydrogen chloride was passed into the solution. The solvent was then removed under reduced pressure. The residual oil was dissolved in chloroform (200 ml) and washed with aqueous potassium bicarbonate (100 ml) and water (100 ml). Evaporation and crystallization of the residue from ethanol gave heavy straw-colored prisms (16·838 g; 85%) of strychninolone b acetate, m.p. 214–218°. The compound melts at 135° with loss of ethanol and solidifies again before the true melting point is observed.

Dehydrogenation of strychninolone b acetate (LV) *with mercuric acetate*

Dehydrostrychninolone acetate. Strychninolone b acetate (9·3 g) and mercuric acetate (17 g) were heated at reflux in acetic acid (900 ml) for 2 hr. The solution was cooled to 60°, decanted from metallic mercury, and then a rapid stream of hydrogen sulfide was passed through for 45 min. The dark-colored precipitate of mercury sulfide(s) was removed by two consecutive filtrations through Celite. The filtrate was evaporated to dryness *in vacuo*; the oily residue was dissolved in chloroform (100 ml) and treated with charcoal (200 mg). Filtration gave a clear solution which was extracted with dilute sulfuric acid (10 ml), aqueous sodium bicarbonate (20 ml) and water (30 ml), dried and evaporated. From the resulting oil, the dehydrostrychninolone acetate crystallized in colorless plates (7·9 g; 86%), m.p. 268–278°, on addition of benzene–ether. Two recrystallizations from methanol raised the m.p. to 282–285° (Prelog, Kocór and Taylor[24] give m.p. 285–287°).

Dehydrogenation of strychninolone a (and its acetate) by the mercuric acetate procedure was unsatisfactory. Only low yields of impure dehydrostrychninolone (acetate) could be secured upon prolonged heating with mercuric acetate in acetic acid.

Dehydrostrychninolone was obtained by saponification of dehydrostrychninolone acetate according to the method used by Prelog *et al.*[24] Thus, treatment of dehydrostrychninolone acetate (7 g) with concentrated aqueous ammonia (800 ml) afforded the desired dehydrostrychninolone (5·7 g; 92%) as colorless crystals, m.p. 228–230°.

[40] H. Leuchs and W. Schneider, *Ber. Dtsch. Chem. Ges.* **42**, 2494 (1909).

Oxidation of dehydrostrychninolone with chromium trioxide in pyridine

Dehydrostrychninone (XLV). Chromium trioxide (5·7 g) was added cautiously to pyridine (50 ml) with external cooling. To the resulting red slurry a solution of dehydrostrychninolone (5·7 g) in pyridine (50 ml) was added. The dark-colored reaction mixture was then kept at room temp overnight. The semi-solid contents of the reaction flask were poured into water (500 ml). Chloroform (500 ml) and Celite (3 g) were then added. The mixture was shaken vigorously and filtered. The two layers of the filtrate were separated; the chloroform layer was washed with water (200 ml); the aqueous layer was extracted three times with chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The solid brown residue was dissolved again in chloroform (100 ml) and washed with 0·5 N sulfuric acid (40 ml), 10% aqueous sodium bicarbonate (20 ml) and water (40 ml). The chloroform solution was dried and evaporated, leaving a brown solid which was purified in the following way: it was dissolved in chloroform (25 ml) and benzene (100 ml), boiled with charcoal and Celite and filtered. The filtrate was boiled down to approximately 25 ml, methanol was added, and heating was continued for a short time. When the solution was allowed to stand in the cold, large colorless prisms of dehydrostrychninone methanolate separated. After collection of the first crop (2·45 g) the mother liquors were concentrated and gave a second crop (1·55 g) of pure material, m.p. 174–180°. The total yield was 4·0 g (68%). Recrystallization from methanol gave colorless prisms melting at 175–180° [loss of methanol], resolidifying to bright yellow crystals with m.p. 254–258°.

When the oxidation of dehydrostrychninolone was carried out with chromium trioxide in acetic acid (according to Prelog *et al.*[24]) at room temp, dehydrostrychninone was isolated in 24% yield only.

Infrared spectrum: see above for comparison with that of synthetic dehydrostrychninone.

Oxidative cleavage of dehydrostrychninone (XLV) *with hydrogen peroxide–barium hydroxide*

The trans N-*acetyl amino acid methyl ester* (XXXVIII). (a) A modification of the procedure used by Leuchs and Diels[41] for the oxidation of strychninonic acid was applied. Pulverized dehydrostrychninone methanolate (250 mg) was shaken with aqueous 0·29 N barium hydroxide (6·7 ml) until a clear yellow solution was obtained (10–20 min). Aqueous 2·10% (w/v) hydrogen peroxide (1·40 ml) was added dropwise within 10 min, and the reaction mixture stirred at room temp for 3 hr. After addition of 1 N sulfuric acid (1·75 ml), stirring was continued for 15 min. Filtration through Celite gave a clear yellow solution (pH ~ 9) which was extracted three times with 10 ml portions of chloroform. The aqueous layer was concentrated *in vacuo* at 50° to a small volume (~2 ml) until crystallization set in. Upon dilution with acetone (~3 ml) and slow cooling, 115 mg (47·5%) of the *trans* amino acid was obtained: grey needles, m.p. 300–305° (dec). The acid could be recrystallized only with considerable loss. From methanol–water–acetone it formed clusters of cream-colored needles, m.p. 305–308° (dec). (b) Trans N-*acetyl amino acid* (XXXIX). Crude *trans* amino acid (200 mg) was allowed to react at room temp overnight with acetic anhydride (5 ml) and pyridine (2 ml). The reaction mixture was then evaporated *in vacuo*. The residue was dissolved in chloroform (20 ml) and extracted with dilute sulfuric acid (4 ml) and water (5 ml). Evaporation of the solvent afforded a semi-solid residue (211 mg) which was recrystallized twice from chloroform–methanol: colorless cubes, m.p. 295–300°, of the *trans* N-acetyl amino acid; the yield was 119 mg (52%).

(Found: C, 67·67; H, 5·30. Calc. for $C_{20}H_{18}O_4N_2$: C, 68·56; H, 5·18%).

Infrared spectrum: see above for comparison with that of the synthetic *trans* N-acetyl amino acid. This acid was identical in all respects with the laevorotatory *trans* N-acetyl amino acid (XXXIX) obtained by resolution of the racemic acid (XXXIX) with quinidine.

The *quinidine salt* of the above *trans* N-acetyl amino acid was prepared as follows: the acid (9 mg) and quinidine (10 mg) were dissolved in chloroform and evaporated to dryness. Two recrystallizations from methanol–acetone gave thin colorless needles (6 mg), m.p. 160–172°, undepressed on admixture with the quinidine salt dihydrate (m.p. 160–172°) isolated from the racemic *trans* N-acetyl acid (XXXIX).

(Found: C, 67·75; H, 6·43; N, 7·97. Calc. for $C_{30}H_{42}O_6N_4 \cdot 2H_2O$: C, 67·59; H, 6·52; N, 7·88%)

(c) The corresponding *methyl ester* (XXXVIII) was prepared from the acid by esterification with diazomethane: colorless crystals, m.p. 196°($[\alpha]_D^{21}$ −292 ± 5° [*c*, 1·14 ($CHCl_3$)]) undepressed on

[41] H. Leuchs and W. Diels, *Ber. Dtsch. Chem. Ges.* **69**, 47 (1936).

admixture with the laevorotatory *trans* N-acetyl methyl ester (XXXVIII) from the synthetic series (see above).

(Found: C, 68·85; H, 5·65; N, 8·34. Calc. for $C_{21}H_{20}O_4N_2$: C, 69·21; H, 5·53; N, 7·69%).

Infrared spectrum: see above for comparison with that of the synthetic ester.

Tosylation and esterification of the amino acid

The N-*tosyl aminomethyl ester* (XXXVIII, $COCH_3 = SO_2C_7H_7$). The crude *trans* amino acid (from (a), preceding section) (34 mg) was boiled under reflux with 5% methanolic hydrogen chloride (2 ml) for 4 hr. The solution was evaporated *in vacuo*, and the solid residue recrystallized from methanol–ether. The hydrochloride of the *trans* amino methyl ester (23 mg; 56%) formed colorless needles, m.p. 245–250° (dec). It was dissolved in pyridine (1 ml) and heated on the steam-bath for 30 min with *p*-toluenesulfonyl chloride (35 mg). The reaction mixture was then treated with water (0·3 ml) and evaporated *in vacuo*. The residue was dissolved in chloroform (10 ml) and ether (20 ml), extracted with dilute sulfuric acid (5 ml), aqueous 10% potassium bicarbonate (5 ml) and water (10 ml). The chloroform–ether solution was dried and evaporated *in vacuo*. The solid residue (26 mg) was recrystallized from methanol–ether. Slightly yellow cubes (20 mg; 68%) of the *trans* tosylamino methyl ester, m.p. 229°, were obtained.

(Found: C, 64·87; H, 5·22. Calc. for $C_{26}H_{24}O_5N_2S$: 65·54; H, 5·08%).

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