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RECENT DEVELOPMENT IN THE SYNTHESIS AND STEREOCHEMISTRY OF TROPANE ALKALOIDS

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Abstract—Two years ago several comprehensive reviews [1,2,3,4] on the stereochemistry of tropane alkaloids which dealt with earlier and more recent results were presented. Since then, however, an additional number of findings and, in particular, some stereospecific syntheses have been recorded in this field. Accordingly, it is deemed of interest to give an account of recent developments.

The main features of most of the recent research are as follows:

1. Stereospecific syntheses of some new epimeric ecgoninols and ecgonines as well as that of scopolamine, valeroidine, dihydrometeloidine, oscine.
2. Establishing of the configuration of the nitrogen atom in tertiary amines and quaternary salts of the tropane series related to (−)ecgoninol, (±)3α·6β-dihydroxy-tropane and (±)oscine.
3. Enol isomerism and ring opening in the tropines.
4. Investigations and considerations concerning the structure of dioscorine.
5. Recent stereochemical aspects of the problem of biogenesis of scopolamine and hyoscyamine.

1. STEREOSPECIFIC SYNTHESES

(a) *Synthesis of some new ecgoninols and ecgonines*

SYNTHESIS of the hitherto unknown third and fourth racemic cocaines, and of the fourth ecgonine racemate as well as their optically active components has been attempted on different lines.

Chronologically: first the synthesis of two new epimers of 2-hydroxymethyl-tropan-3-ols (2β-hydroxymethyl-3α-tropanol, and of 2α-hydroxymethyl-3α-tropanol) has been realised in order to submit, subsequently, these diols to selective oxidation. Another line of approach dealing with the third racemate of ecgonine ester arising from hydrogenation of methyl tropinone-2-carboxylate has, according to Willstätter, been converted into the corresponding cocaine, while epimerisation of the third racemic ester led to the fourth racemic ecgonine methyl-ester, which in turn has been benzoylated to the fourth (±)cocaine.

(−)2β-Chloromethyl-3β-tropanol underwent rearrangement into the hydrochloride of a base to which several alternative structures, envisaged in previous papers[3,5] could be allotted initially. The choice among them in favour of the structure of 2′,3-anhydro-2β-hydroxymethyl-3β-tropanol was made possible by the following facts (Fig. 1):

(1) 2β-chloromethyl-3β-acetoxy-tropane failed to undergo rearrangement, showing the participation of the C_3-OH group in this reaction.[5]

(2) The hydrochloride of the base has been reconverted by hydrochloric acid into the chloromethyl derivative from which we started.[5]

[1] A. Stoll and E. Jucker *Angew. Chem.* **66**, 376 (1954).
[2] E. Jucker *Chimia* **9**, 25 (1955).
[3] G. Fodor *Acta Chim. Acad. Sci. Hungar.* **5**, 379–442 (1955).
[4] G. Fodor *Exper.* **11**, 129–141 (1955).
[5] Ö. Kovács, G. Fodor, and I. Weisz *Helv. Chim. Acta* **37**, 892 (1954).

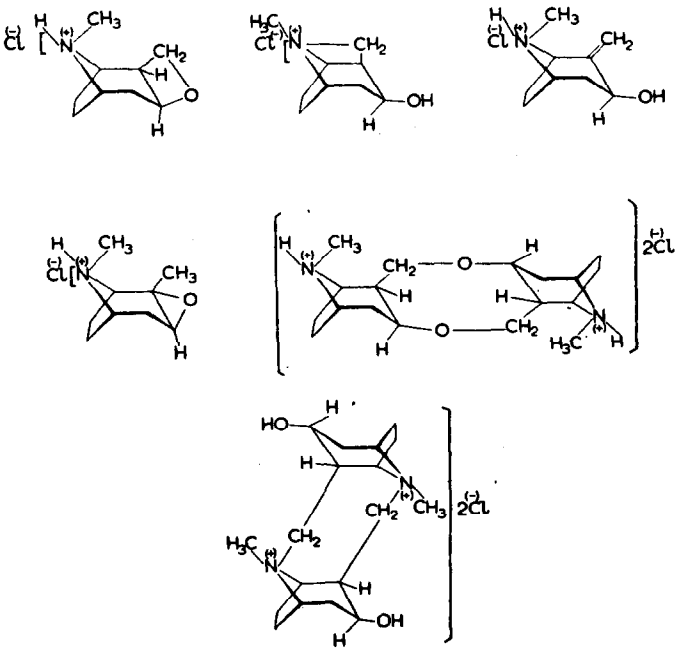


FIG. 1.

(3) The molecular weight of the compound has been found[6] by the ebullioscopic method, 197·5 as an average.

(4) The rate of the rearrangement has been determined both by polarimetric and argentometrical methods,[6] indicating independence of rate from concentration, i.e. pointing to a truly unimolecular mechanism.

(5) Methiodide of 2β-chloromethyl-3β-tropanol[6] underwent similar rearrangement, but in the presence of a molecule of alkali to give the methiodide of the cyclic ether. The methochloride of this latter has been reconverted by acetyl chloride in acetic anhydride into the acetyl derivative of 2β-chloromethyl-3β-tropanol methochloride.

(6) Ring cleavage of the cyclic ether itself has been achieved either by acetic anhydride or alkali. The first reactant gave rise to a mixture of diacetyl ecgoninols: 2β-acetoxymethyl-3β-acetoxy tropane, besides the dominating epimeric modification which can only be its 3α-isomer. Hydrolysis of these diacetates gave rise to 2β-hydroxymethyl-3β-tropanol and to the new ecgoninol, 2β-hydroxymethyl-3α-tropanol. Action of hydroxyl ions on the ether ring led to the same epimers. The 3α-modification may be formed only by means of a nucleophilic attack of hydroxyl ions towards the asymmetric bridgehead of the ether ring. This reaction showed indeed a pure bimolecular course, its point of attack being carbon atom No. 3. Further evidence in favour of the four-membered ring ether structure has been provided by infra-red spectroscopic investigations—in collaboration with Basle University[6]—of the compound in play, comparing their curves with those of trimethylene oxides.[7] These results may serve as the first contributions to the stereochemistry of formation and cleavage of

[6] Ö. Kovács, I. Weisz, P. Zoller, and G. Fodor *Ibid.* 39, 99 (1956).
[7] G. M. Barrow and S. Searles *J. Amer. Chem. Soc.* 75, 1175 (1953).

four-membered ring ethers. Another paper[8] dealing with the stereochemistry of the cleavage of a 1·3-oxido-bridged *cyclo*hexane appeared formerly as the single precursor in this field. The reactions carried out with electrophilic and nucleophilic reactants mainly show a close resemblance with the steric course of the cleavage of epoxides[6] while the four-membered ring ether resists catalytic hydrogenolysis at variance with epoxides.

Authentic 2β-hydroxymethyl-3α-tropanol has thus been obtained, the absolute configuration of which being given by the correlation of (−)cocaine with L(+) glutamic acid according to Hardegger and Ott[9] (Fig. 3a).

As a further step, this could be converted by sodium amyloxide and benzophenone as a catalyst by way of a half cell oxidation reduction[10] procedure into a hitherto unknown tropandiol to which the structure of 2α-hydroxymethyl-3α-tropanol could be allotted, due to inversion at C_2 only, since otherwise epimerisation of the starting material at C_3 would lead to ecgoninol, while affection of both C_2 and C_3 centres should give ψ-ecgoninol. Hence the "exclusion principle" supports this configuration.[6] Oxidation experiments have in turn been commenced with all the four 2-hydroxymethyl-3-tropanols (Fig. 2).

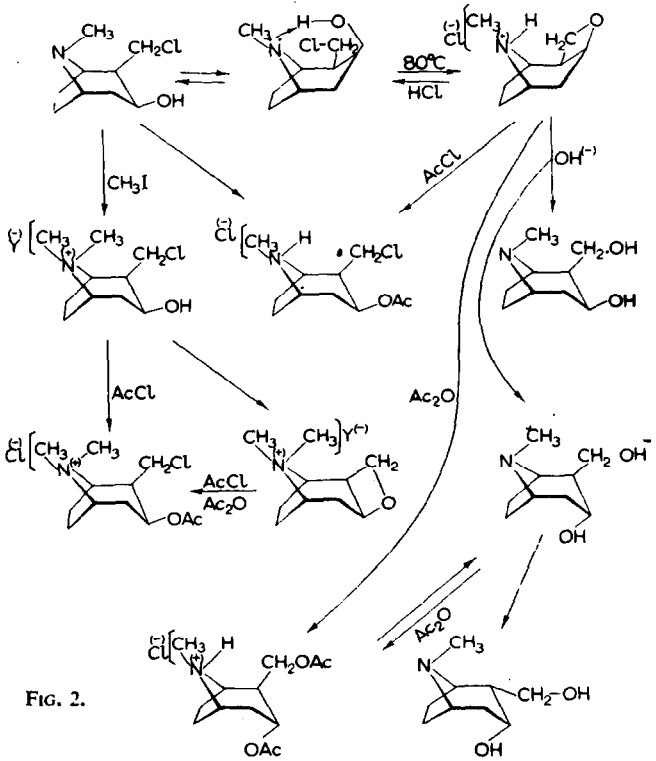


FIG. 2.

2β-Hydroxymethyl-3β-tropanol (ecgoninol) and 2α-hydroxymethyl-3β-tropanol (ψ-ecgoninol) furnished, on oxidation with silver oxide, good yields—the latter rather than the former—of the corresponding carboxylic acids, i.e. ecgonine and ψ-ecgonine.[11]

[8] R. B. Clayton and H. B. Henbest *Chem. and Ind.* 1315 (1953).
[9] E. Hardegger and H. Ott *Helv. Chim. Acta* **38**, 312 (1955).
[10] W. v. E. Doering and T. C. Ashner *J. Amer. Chem. Soc.* **75**, 397 (1953).
[11] M. Halmos, Ö. Kovács, and G. Fodor *J. Org. Chem.* (In the press).

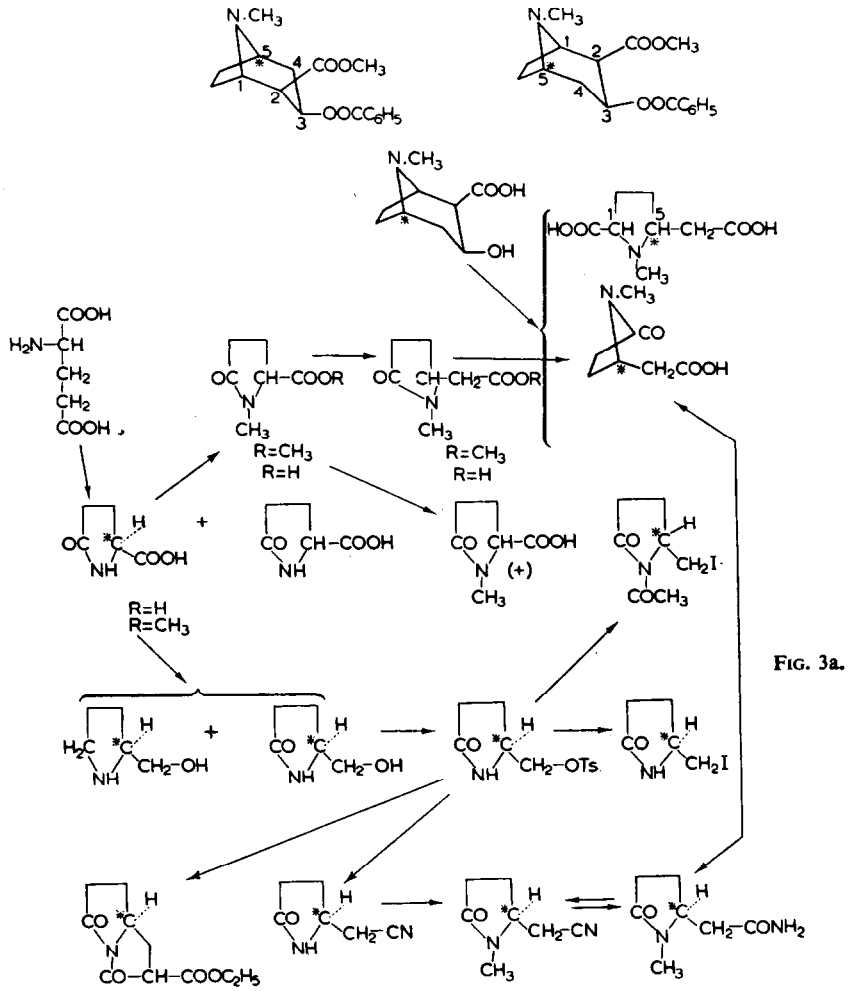


FIG. 3a.

(Fig. 3b). Unfortunately, however, the 3α-hydroxylated derivatives did not undergo this selective oxidation at all, for the 2α·3α-modification has been recovered completely unchanged, while the 2β·3α-derivative has been oxidised partly to a tar in addition to a considerable amount of unchanged diol.

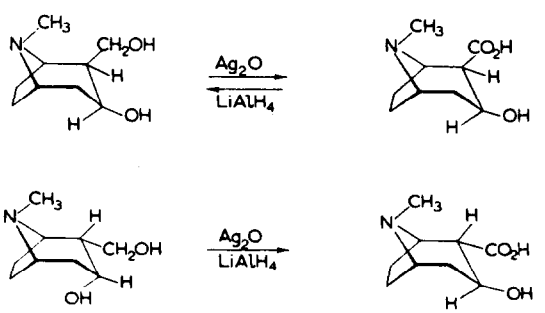


FIG. 3b.

The second method outlined above was rather classical, and in the hands of German and American colleagues gave a positive response to the questions of synthesis.

The "third" racemate prepared according to Willstätter[12] has been benzoylated to the new cocaine.[13] Somewhat later hydrogenation of methyl tropinone-2-carboxylate over Adams platinum catalyst has been described to afford 80% yield of the "third" racemic ecgonine methyl ester.[14] Alkaline hydrolysis furnished a mixture of ecgonines, presumably of the "third" and "fourth" racemates, both of which have been benzoylated into the cocaines. Unfortunately, the physical constants recorded by the two teams show a marked and unaccountable discrepancy. To the "third" racemate the configuration of 2β-methoxycarbonyl-3α-tropanol has been allotted by analogy to ecgonine (epimerisation by alkali during both hydrolysis and quaternisation with methyl iodide)[14] the fourth representing consequently the 2α·3α-modification (Fig. 4).

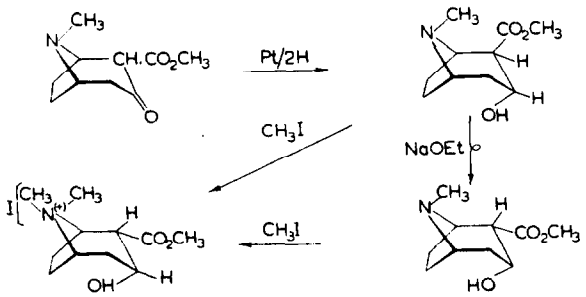


FIG. 4.

(b) *The total synthesis of scopolamine and hyoscine*

Until 1923 the suggested chemical constitution of this alkaloid was accepted,[15] although none of the fourth steric structures could be ascribed to it. During recent years the configuration of (±)3α-tropyloxy-6·7β-epoxy tropane has been verified for scopolamine, based upon modern interpretation of its conversion into oscine,[16,17,18] and into scopinium bromide,[17,18] respectively, to which lent support also its hydrogenolysis[19] into (±)3α·6β-dihydroxy tropane. This latter has been obtained by total synthesis from malic dialdehyde,[20] followed by the resolution[19] of the latter into the alkamine[21] of valeroidine.[22]

Synthesis had been attempted earlier than this recent stereochemical work, but no success was recorded; e.g. epoxy-succinic dialdehyde prepared both by periodic acid oxidation of conduritoxide,[23] and from 2·5-dimethoxy-2·5-(2H)-furan[24] was submitted to Robinson condensation with methyl amine and acetone dicarboxylic

[12] R. Willstätter, O. Wolfes, and O. Mäder *Lieb. Annalen* **434**, 111 (1923).
[13] K. Zeile and W. Schultz *Ber.* **89**, 678 (1956).
[14] St. P. Findlay *J. Org. Chem.* **21**, 711 (1956).
[15] R. Willstätter and E. Berner *Ber.* **56**, 1079 (1923).
[16] G. Fodor *Nature* **170**, 278 (1952).
[17] J. Meinwald *J. Chem. Soc.* 712 (1952).
[18] R. C. Cookson *Chem. and Ind.* 337 (1953).
[19] (a) G. Fodor, Ö. Kovács, and L. Mészáros *Research* **5**, 534 (1952).
(b) G. Fodor and Ö. Kovács *J. Chem. Soc.* 2341 (1953).
[20] A. Stoll, B. Becker, and E. Jucker *Helv. Chim. Acta* **35**, 1263 (1952).
[21] O. Wolfes and O. Hromatka *Merck's Jahresber* **47**, 45 (1934).
[22] G. Barger, F. Martin, and W. F. Mitchell *J. Chem. Soc.* 1820 (1937).
[23] Cl. Schöpf and L. Schmetterling *Angew. Chem.* **64**, 691 (1952).
[24] J. C. Sheehan and B. M. Bloom *J. Amer. Chem. Soc.* **74**, 3825 (1952).

acid, which gave a tricyclic hydroxy derivative instead of the expected ketone, i.e. scopinone. Thus the use of a building stone containing the preformed epoxide bridge proved unsuitable for this synthesis.

A different line of approach has been suggested by Preobrashenski, who intended to oxidise $\Delta_{6,7}$-tropenol to scopine and teloidine (Fig. 5.) The key intermediate, 6-

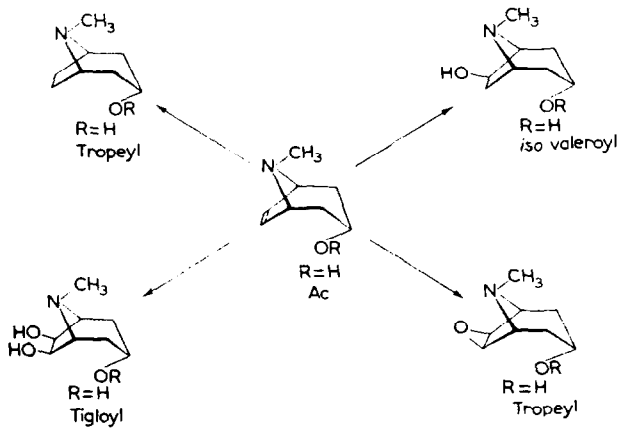


FIG. 5.

tropen-3-one, was described as early as 1945 by the Russian authors; unfortunately, however, its preparation from maleic dialdehyde has never been successful in the hands of other authors.[26] The product seems to have consisted of impure tropan-3-one.[27]

Even if this unsaturated ketone were available there is ample reason to anticipate its easy aromatisation into tropone,[27] the more so since tropanone methiodide gives in an analogous manner dihydrotropone[28] (Fig. 6.)*

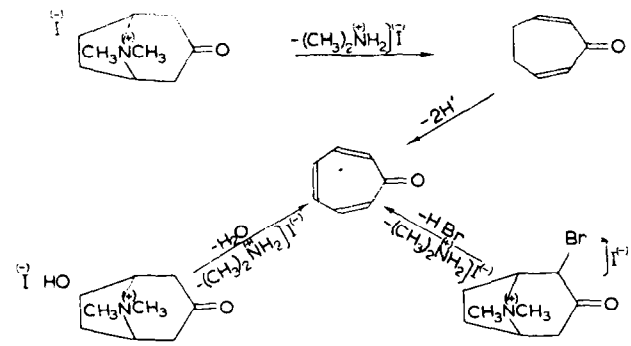


FIG. 6.

To overcome this undesirable intermediate, but adopting tropenol as a key, our team[29] chose a devious way, by selective dehydration, of 3α·6β-tropandiol, i.e. of a

[25] N. A. Preobrashenski, I. A. Rubtzov, T. F. Dankova, and V. P. Pavlov *J. Gen. Chem.*, Moscow **15**, 952 (1945).

[26] J. Kebrle and P. Karrer *Helv. Chim. Acta.* **37**, 484 (1954).

[27] This concept has been suggested by Prof. Cl. Schöpf.

[28] G. Büchi, N. C. Yang, S. L. Emermann, and J. Meinwald *Chem. and Ind.* 1063 (1953); *J. Amer. Soc.* 77, 4401 (1955); * *Added in proof.* Meanwhile E. E. van Jamelen succeeded in converting 6-hydroxy-tropan-3-one methiodide directly into tropone.

[29] G. Fodor, J. Tóth, I. Koczor, I. Vincze, and P. Dobó The Institute of Organic Chemistry, The University of Szeged, Hungary.

stable tropane derivative with subsequent oxidation of the double bond to the epoxide bridge.

There were four theoretical questions to be considered before commencing experimental work.

(1) Dehydration of tropan-3α·6β-diol to be carried out in a selective manner;

(2) If so, would the unsaturated tropane which forms be not too stained to survive isolation and oxidation?

(3) What could be expected concerning the steric course in oxidising the double bond?

(4) How to avoid competitive oxidation of the nucleophilic nitrogen of tropenol.

To the second question a positive answer has been given as a result of having examined Leybold atomic scale models of 6-tropen-3-ol prepared according to Stuart and Briegleb, since this seemed, unexpectedly, to bear lower strain than the dihydro derivative, tropine.

As to the third problem, the oxidation on the ethylenic bond of trop-6-en-3α-yl acetate was expected to take an *exo*-course, for in analogous bridged bicyclic systems this rule[32] proved of general use.

Selective dehydration of the tropandiol prepared from 2·5-dimethoxy-2·5-dihydro furan according to Clauson-Kaas and his pupil[30] could be performed in two different ways. (1) Action of phosphorus oxychloride led by an S_N2i mechanism to (±)-3α·6α-oxydo tropane, the levorotatory form of which was already described[21] as early as 1934. Ring cleavage of the racemate with acetyl bromide gave rise to a bromotropanyl acetate which, in turn, could be dehydrobrominated by collidine into tropen-yl acetate. The location of the double bond at $C_{6,7}$ and that of the esterified hydroxyl group at C_3 arose from its hydrogenation leading to tropan-3α-yl acetate. Thus ring cleavage has been introduced by an S_N2 attack of bromine upon the C_6-bridgehead of the oxydo group and the acetylated oxygen function remained linked to C_3 (Fig. 6).

The same unsaturated alcohol has been produced by converting 6β-hydroxy-tropan-3-one into its phenyl urethane followed by (1) hydrogenation, acetylation of 3α·6β-dihydroxy tropane 6-phenylurethane, and (3) cleavage of 3α-acetoxy-6β-phenylcarbamyloxy-tropane into 6β-hydroxy tropane-3α-yl acetate. Tosylation and subsequent heating with collidine of the toluene-sulphonic ester yielded trop-6-en-3α-yl acetate again[31] (Fig. 7).

The greatest difficulty was caused by competition of nucleophilic nitrogen in tropenol concerning oxidation with electrophilic reactants, e.g. with organic peracids. Slight excess of monoperphtalic acid gave rise to the *N*-oxide, while with 20 moles subsequent epoxidation has been realised also into acetyl-scopine *N*-oxide which has been identified by its hydrogenolysis into (±)3α-acetoxy-6α-hydroxy tropane.[33] The yields, however, have not been satisfactory; in addition, this second step of oxidation took a month.

The low conversion achieved by monoperphthalic acid has been explained by R. B.

[30] P. Nedenskov and N. Clauson-Kaas *Acta Chem. Scand.* **8**, 2295 (1954).
[31] (a) Fodor and co-workers, lecture, XIVth International Congress of the I.U.P.A.C., Zürich, 21 July 1955; (b) G. Fodor, J. Tóth, I. Koczor, and I. Vincze *Chem. and Ind.* 1260 (1955).
[32] K. Alder and H. A. Dortmann *Ber.* **86**, 1544 (1953).
[33] G. Fodor, J. Tóth, I. Koczor, P. Dobó, and I. Vincze *Chem. and Ind.* 764 (1956).

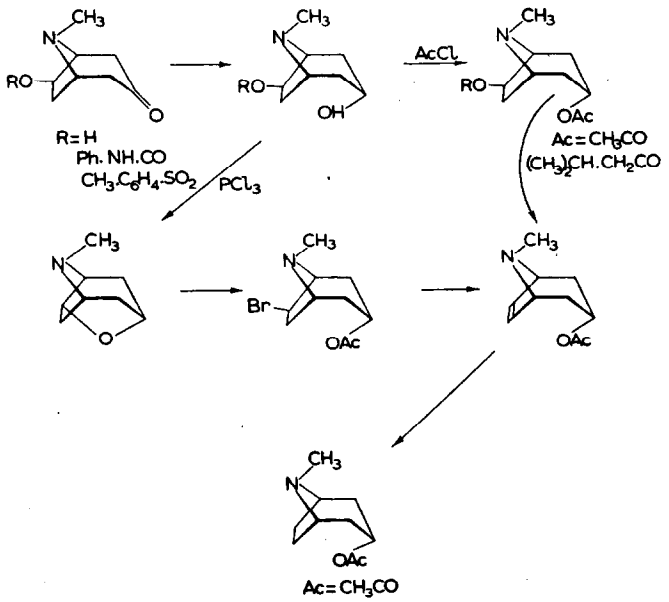


FIG. 7.

Woodward,[34] who postulates a catalytic role of aminoxydes in decomposing peracids according to the following equation:

$$R_3N \rightarrow O + R{\cdot}CO_3H = R_3N: + O_2 + R{\cdot}COOH$$

Consequently, blocking of nitrogen before oxidation seemed preferable. Both the hydrochloride and perchlorate of tropenyl acetate, however, withstood any attempt of oxidation[33] indicating a marked decrease in nucleophilic activity of the double bond induced by the *—I* effect of quaternary ammonium nitrogen.

To overcome this difficulty the stronger electrophilic trifluoroperacetic acid[35] has been adopted in place of monoperphtalic acid, allowing it to react upon the trifluoroacetic-acid salt of tropenyl-acetate, which led to acetyl scopine.[33] Identification has been carried out by means of an authentic sample obtained on acetylation of scopine, this latter being prepared by mild hydrolysis from scopolamine, according to Willstätter and Berner.[15]

After having fulfilled the four above-mentioned prerequisites for synthesis, we had as our last task to reconvert scopine into acetyl scopolamine and hyoscine, respectively.

Selective hydrolysis of the acetyl group has been performed under very mild conditions according to the method outlined by Kunz and Hudson,[36] i.e. using N NaOH in acetone.

In tropylation reaction, however, several difficulties arose.

After a series of unsuccessful attempts, acylation of scopine hydrochloride could be realised by using excess acetyltropyl chloride in nitrobenzene at 65°C. Separation of acetyl scopolamine has been achieved by partition chromatography on cellulose powder column,[33,37] followed by selective hydrolysis which led to scopolamine hydrochloride, identical in every respect with the natural alkaloid (Fig. 8). Since the

[34] Personal communication to the author, Zürich, 23 July 1956.
[35] W. D. Emmons and A. S. Pagano *J. Amer. Chem. Soc.* **77**, 89 (1955).
[36] A. Kunz and C. S. Hudson *Ibid.* **48**, 1982 (1926).
[37] G. Fodor, Lecture, Joint Colloquy of the Chemical Institute of the University and of the Organic Chemical Institute of Swiss Federal High School, Zürich, 3 May 1956.

latter was already resolved in 1919 by King[38] into the dextrorotatory form, and later by Preobrashenski[39] into both antipodes, this synthesis may be considered as an equivalent of that of hyoscine.

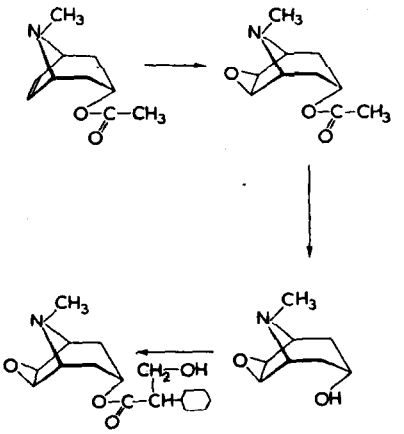


FIG. 8.

(c) *The total synthesis of valeroidine*

The relative configuration of valeroidine as that of (—)6β-hydroxy-3α-*iso*valeroxy tropane has been established,[19,40,41] while its absolute configuration is still subject to further investigations. The conclusions reached hitherto are supported by the following facts: (1) Hydrogenolysis of scopolamine into the racemic form[19] of the alkamine of valeroidine (so-called valerine) with subsequent resolution into the alkamine, indicated the presence of a 3α-placed hydroxyl, since the rearrangement of scopine into oscine could not take place if this group would have β-location; (2) oxidation of valeroidine gave besides *nor*-valeroidine a compound the analytical data of which pointed to the structure of the cyclic urethane derived of *nor*-valeroidine.[41] This may be considered as evidence for the β position of the unbound hydroxyl group in valeroidine; (3) ($\pm$)valerine furnished on the action of ethyl iodoacetate the $\langle N{\cdot}C_6\rangle$ lactone of N_b-carboxymethyl-3$\alpha{\cdot}$6β-dihydroxy tropanium iodide,* which provides decisive proof for the β-position of the C_6-hydroxyl group.[40]

Concerning synthesis of the alkaloid, ($\pm$)6β-hydroxy tropan-3-one has been resolved[20] and hydrogenated into (+) and (—)3$\alpha{\cdot}$6β-tropandiol.[42] Both have been esterified with *iso*valeryl chloride to yield the di-*iso*valeric ester[42] which, unfortunately, could not be hydrolysed selectively into the 3α-acylated derivative. Similarly, direct monoacylation of the diol also failed.[42]

As a branching off of the route to scopolamine[31,33] (Fig. 8) selective acylation of 3$\alpha{\cdot}$6β-dihydroxy tropane seemed feasible. First, ($\pm$)6β-phenylcarbamyloxy-3β-hydroxy tropane has been converted into the *iso*valeric ester, and this, in turn, cleaved

* For nomenclature of tropanes see G. Fodor and K. Nádor *J. Chem. Soc.* 1952, 721; for that of the configurations of nitrogen in tropanes see G. Fodor, J. Tóth and I. Vincze *Ibid.* (3504) 1955.

[38] A. King *J. Chem. Soc.* **115**, 476 (1919).

[39] M. N. Shchukina, S. S. Okun, D. N. Yurigin, and N. A. Preobrashenski *J. Gen. Chem.* (*URSS*), **10**, 803 (1940).

[40a] J. Tóth, Lecture, Meeting, Union of Hungarian Chemists, Debrecen, 27 September 1953; *Szerves Kémiai Konferencia Debrecen*, cf, **4**, 293 (1953), *Current Chemical Papers* 620 (1954).

[40b] G. Fodor, J. Tóth, and I. Vincze *Helv. Chim. Acta* **37**, 907 (1954).

[41] Wm. Mitchell and E. M. Trautner *J. Chem. Soc.* 1330 (1947).

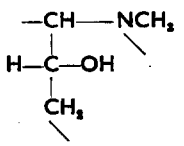
[42] A. Stoll, E. Lindenmann, and E. Jucker *Helv. Chim. Acta* **36**, 1506 (1953).

by thermolysis into (±)valeroidine.[31] The reversible formation of phenylurethanes was earlier studied by Japanese authors,[43] not from the preparative view, but the thermodynamic. This series of reactions could now be adopted to the antipodes arising from the preceding resolution of (±)6-phenyl-carbamyloxy-3α-hydroxy tropane. Consequently, acylation of the levorotatory form and subsequent thermolysis furnished levorotatory 3α·6β-dihydroxy tropane 3-mono-*iso*valeroate, which proved identical[45] in every respect with the natural alkaloid;[44] the dextrorotatory form has also been obtained.

(d) *The absolute configuration of valeroidine*

It has already been intended to correlate (—)3α·6β-dihydroxy tropane and its 3α-*iso*valeric ester, i.e. valeroidine with either D or L-oxo proline[49] by destroying the six-membered ring; this may be by a secondary Beckmann rearrangement of 2·4-dioximoino 6-acetoxy tropan-3-one or of its products of reduction: 6-acetoxy-2·4-dihydroxy-3-amino tropane with periodic acid. These investigations have been commenced by the author's staff as a joint operation with Prof. B. Witkop of the National Institutes of Health, Washington.

However, (—)3α·6β-dihydroxy tropane gave with ethyl iodoacetate the *levorotatory* ester salt, N_b-ethoxy-carbonylmethyl-3α-6β-dihydroxy tropanium iodide, which on heating underwent cyclisation to the *dextrorotatory* ⟨N·C_6⟩ lactone of N_b-carboxymethyl-3α·6β-dihydroxy tropanium iodide. Adopting Hudson's rule valid for γ-lactones[50] it is presumed that the hydroxyl-bearing asymmetric carbon atom concerned in cyclisation belongs to the D series of carbohydrates. Provided this rule can be extended to δ-lactones,[50b] further in considering the group



be depicted by the projection which follows (Fig. 12).

In terms of the recent convention for describing absolute configurations unequivocally, as outlined by Prelog, Cahn, and Ingold,[51] the structure of 3α(R),6β(R)-dihydroxy tropane should be allotted to the alkamine of valeroidine, which, of course, should still be checked by correlation experiments.

(e) *Synthesis of oscine (scopoline)*

The author has been informed by Prof. J. C. Sheehan[46] that the Robinson condensation of (±)tartaric dialdehyde followed by reduction led to 3α·6α·7β-trihydroxy

[43] Muhayama Tanaki, Motoki Shimichi, and Hamada Yasuchi *Bull. Chem. Soc. Japan* **26**, 49 (1953).
[44] I. Vincze, J. Tóth, and G. Fodor *J. Chem. Soc.* 1349 (1957).
[45] Author thanks Dr. Wm. F. Mitchell for having submitted an authentic sample of (—)valeroidine hydrobromide.
[46] Verbal communication the 26 July 1955.
[49] G. Fodor, Lecture, Annual Meeting of the Chemical Society in East Germany, 23 October 1954; *Tagungsberichte* 1954, 137–157 Akademie-Verlag, Berlin (1955).
[50] (a) C. S. Hudson *J. Amer. Chem. Soc.* **32**, 338 (1910); (b) P. A. Levene and H. S. Simms *J. Biol. Chem.* **68**, 737 (1926).
[51] R. S. Cahn, C. K. Ingold, and V. Prelog *Exper.* **12**, 81 (1956).

tropane, a derivative which could be cyclised into oscine, i.e. (±)3α·6α-oxydo-7β-hydroxy tropane (Fig. 9). At present the author is unaware of any further publication on this subject.

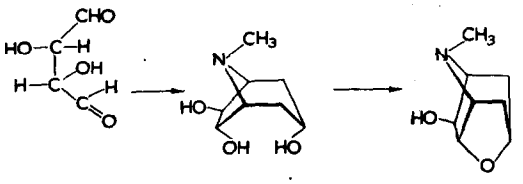
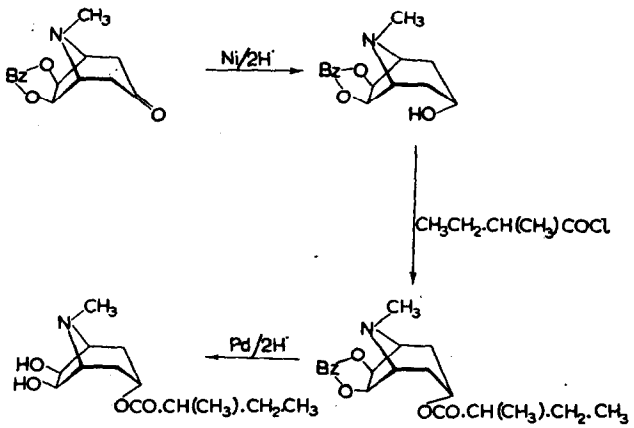


FIG. 9.

(f) *Synthesis of* (2H) *meteloidine*

Teloidinone, i.e. 6β·7β-dihydroxy-tropan-3-one[42] gave a benzylidene derivative[47] which afforded on hydrogenation over Raney-Ni benzylidene teloidine, i.e. 3α·6β·7β-trihydroxy tropane benzylidene ketal. Acylation of the latter with α-methylbutyric anhydride followed by catalytic hydrogenolysis of the benzylidene group over 30% Pd-charcoal furnished dihydro-meteloidine (Fig. 10), identical in every respect with



Bz=>CH.C_6H_5

FIG. 10.

the product which forms by saturation of the double bond in the natural alkaloid.[47] Synthesis of the genuine alkaloid is now in progress.[46]

In addition, a contribution to the stereochemistry of teloidine and ψ-teloidine by Heusner[48] stands on its own merits. Teloidinone acetonide has been hydrogenated selectively into teloidine acetonide and ψ-teloidine acetonide. The latter gave, after v. Braun-degradation, ψ-*nor*-teloidine acetonide, which, in turn, was condensed with *p*-nitro-benzaldehyde into a *meta*-oxazine derivative (Fig. 11), while *nor*-teloidine 3-acetate with the same aldehyde giving an 1·3-oxazolidine, afforded additional evidence in favour of the structure of 3α·6β·7β-trihydroxy tropane for teloidine[41] and of that of 3β·6β·7β-trihydroxy tropane for ψ-teloidine.

[47] J. C. Sheehan and E. R. Bissell *J. Org. Chem.* **19**, 270 (1954).
[48] A. Heusner *Z. Naturforsch.* **9b**, 683 (1954).

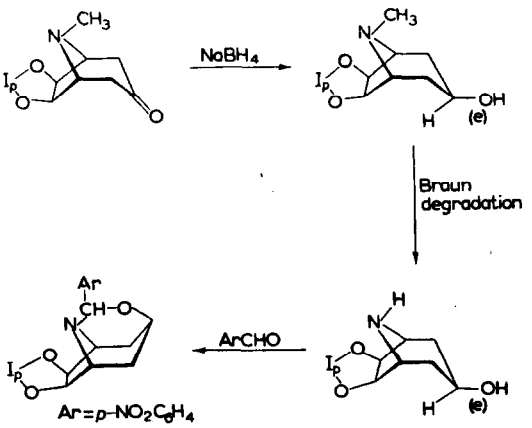


FIG. 11.

2. DETERMINATION OF THE CONFIGURATION OF THE NITROGEN ATOM IN SOME TERTIARY AMINES AND QUATERNARY AMMONIUM SALTS OF THE TROPANE SERIES

A number of preceding papers[52,40,31a,53,54,55] and a review[3,34] dealt with our observations concerning stereospecific routes leading to tropanium salts of definite configurations and with the interpretation[4,53] of this phenomenon. This work, initially done with "direct" and "reverse" quaternisation of tropine and ψ-tropine[52,53] involving direct quaternisation of 3α-6β-dihydroxy tropane, scopolamine, and oscine[41] by means of ethyl iodoacetate into the lactones of the corresponding N-acetic acids, has been extended recently to reverse quaternisation of the latter[53] and to optically active derivatives of the ecgonine[54] and dihydroxy tropane series.[56] These results achieved with some tropane derivatives were treated in detail in a review which appeared last year in *Bulletin de la Société Chimique de France*[57] in terms of the possibility to determine for the first time configurations of asymmetric and of pseudo-asymmetric nitrogen atoms. I intend, therefore, to give but a brief summary of the findings and considerations outlined in this latter contribution which more recent results should help to complete.

(a) (±)3α·6β-dihydroxy tropane gave, on v. Braun degradation, (±)*nor*-3α·6β-dihydroxy tropane, which has been alkylated by means of ethyl iodoacetate to *N*-ethoxycarbonylmethyl-*nor*-3α·6β-dihydroxy tropane.[53] The latter gave, when hydrolysed by hydrochloric acid, the hydrochloride of (±)*nor*-3α·6β-dihydroxy tropane N-acetic acid, but no trace of its lactone salt. Accordingly, the steric conditions of this compound are inadequate to allow ring closure, hence one can deduce the configuration of N_a-carboxymethyl·3α·6β-dihydroxy-*nor*-tropanium chloride for this compound. Quaternisation of the tertiary amine base with methyl iodide gave rise to the tropanium ester salt which could not be cyclised to a lactone after being converted into the betaine and subsequent treatment of the latter with hydrochloric acid. The N-acetic

[52] G. Fodor, Lecture, Meeting of the Union of Hungarian Chemists, Szeged, 20 September 1952.
[53a] G. Fodor, K. Koczka, and J. Lestyán *Magy. Kém. Foly.* **59**, 242 (1953); [b] G. Fodor, J. Tóth, and I. Vincze *J. Chem. Soc.* 3504 (1955).
[54] Ö. Kovács, G. Fodor, and M. Halmos *Ibid.* 873 (1956).
[55] G. Fodor, K. Koczka, and J. Lestyán *Ibid.* 1411 (1956).
[56] G. Fodor, I. Vincze, and J. Tóth To be published in *J. Chem. Soc.*
[57] G. Fodor Lecture Soc. Chim. France, Paris, 27 April 1956; *Bull. Soc. Chim.* 1032 (1956).

acid which formed is represented thence by the structure of (±)N_a-carboxymethyl-3α·6β-dihydroxy tropanium chloride,[53] while the lactone of its epimer, i.e. of (±)-N_b-carboxymethyl-3α·6β-dihydroxy-tropanium iodide arose earlier[40] from a direct action of ethyl iodoacetate upon (±)3α·6β-dihydroxy tropane. The same series of reactions have been carried out with derivatives of oscine and *nor*-oscine,[53] although the results showed marked discrepancy. (Compare Figs. 12 and 13.)

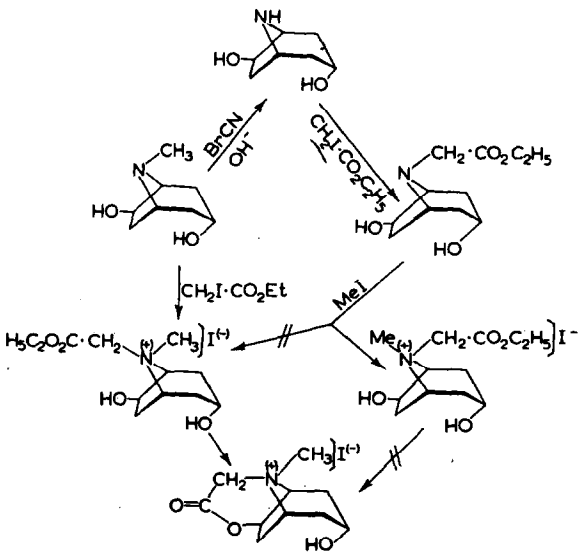


FIG. 12.

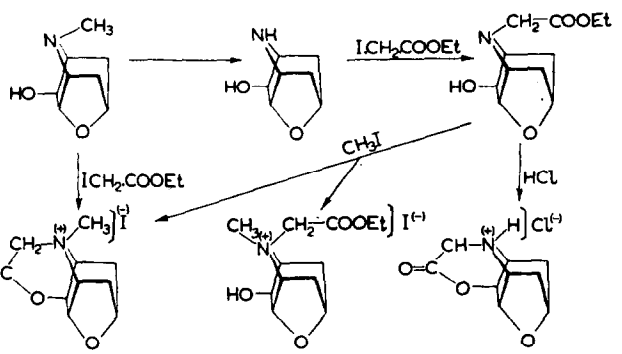


FIG. 13.

(b) (±)Oscine with ethyl iodoacetate gave rise to the lactone of N_b-carboxymethyl-3α·6-oxydo-7β-hydroxy tropane,[40] while *nor*-oscine furnished *N*-ethoxycarbonylmethyl-*nor*-oscine. This latter has been submitted to acid hydrolysis, furnishing a lactone to which the configuration of that of (±)N_b-carboxymethyl-3α·6α-oxydo-7β-hydroxy-*nor*-tropanium chloride has been allotted.[53b] The ester of the foregoing tertiary base afforded with methyl iodide a mixture from which the lactone of N_b-carboxymethyl-3α·6α-oxydo-7β-hydroxy-tropanium iodide and an ester salt could be isolated. The last did not undergo cyclisation even after being converted into

the betaine and heated with hydrochloric acid; thus the structure of N_a-carboxymethyl-3α·6α-oxydo-7β-hydroxy-tropanium chloride has been ascribed to it.[53b] All the compounds in play have therefore definite and known relative configurations, including their nitrogen atoms (Fig. 13).

As to the reason of this striking influence of the 3·6-placed oxygen bridge upon stability of configurations at the tertiary amine stage, which is depicted by the tendency of the oscine derivatives to give both *N*-epimeric ammonium salts possible—the marked decrease of Pitzer-strain[58] in the five-membered ring of oscine as compared with that prevailing in 3α·6β-tropandiol is considered responsible. More explicitly, the smaller deviation from coplanarity the smaller the Pitzer effect which may expel the methyl group on nitrogen to assume with greater probability the axial, i.e. N_a position, hence entrance of the quaternising group in either N_a or N_b position seems equally feasible.[53b,57]

(c) A further series of experiences has been collected with derivatives of ecgoninol, i.e. (—)2β-hydroxymethyl-3β-tropanol.[54] "Direct" quaternisation of its diacetate with ethyl iodoacetate gave rise to an ester salt, while *N*-ethoxycarbonylmethyl-*nor*-ecgoninol could be converted on action of methyl iodide into the lactone of (—)-N_a-carboxymethyl-2β-hydroxymethyl 3β-hydroxy-tropanium iodide, conceivably the $\langle 2^1 \cdot N \rangle$ lactone, for this may be formed even in the chair form of the six-membered ring. The epimeric ester salts, carboxylic acids, and betaines involving their (α_D) values have been described in detail.[54]

This is the first time that the absolute configuration of a quaternary ammonium salt having an asymmetric nitrogen could be established, though this model contains a number of asymmetric carbon atoms also.

Provided we are authorised to extend the principles of Ingold, Cahn, and Prelog[51] to designate absolute configurations of tetrahedral nitrogen, the following notations should be allowed: since (—)cocaine has been proved as 2β(R)-methoxycarbonyl-3β-(S)-benzoxy tropane and (—)ecgoninol as 2β(S)-hydroxymethyl-3β(S)-benzoxy-tropane, the compound of direct quaternisation is thus represented by N_b(S)-carboxymethyl-2β(S)-hydroxymethyl-3β(S)-hydroxy tropanium chloride, while its *N*-epimer is N_a(R)-carboxymethyl-2β(S)-hydroxymethyl-3β(S)-hydroxy tropanium chloride (Fig. 14).

(d) The next series of investigations, carried on with optically active 3α·6β-dihydroxy tropane and oscine, may provide information regarding the contribution of the

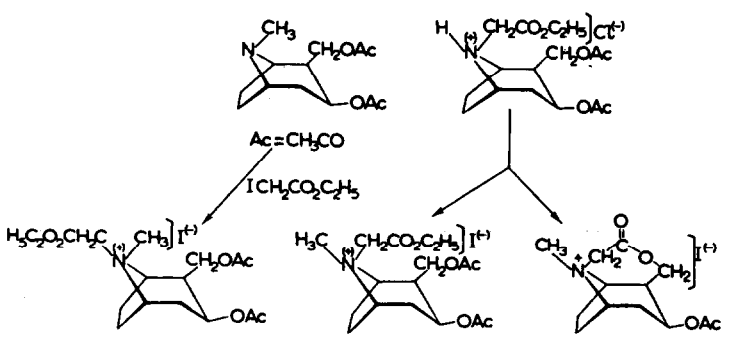


FIG. 14.

[58] Ch. W. Beckett, K. S. Pitzer, and R. Spitzer *J. Amer. Chem. Soc.* 69, 2488 (1947).

steric position of substituents on asymmetric nitrogen to the whole asymmetry of the molecule.[56]

(e) Furthermore, X-ray determinations of the absolute configurations of tropine ethochloride and *N*-ethyl-*nor*-tropine methochloride are still in progress at the University of Amsterdam.[59]

3. ENOL ISOMERISM AND RING OPENING IN THE TROPINES

(a) A tropine derivative, i.e. α-hydroxy-methylene-phenylacetyl tropeine, served as an adequate substrate to study geometrical isomerism around the enolic double bond.[60] The *cis*-modification (concerning carbonyl and hydroxyl) proved by infra-red spectra to be stabilised by hydrogen bonding, while the *trans* form seems to be an enol betaine. Indeed the oxo form seems to be negligible, for no easy stereomutation has been recorded (Fig. 15).

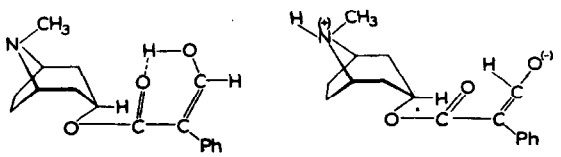


FIG. 15.

(b) Evidence has been presented for the bromination of tropinone to give rise to 2β-bromo tropinone (hydrobromide, m.p. 192°).[61] Sodium borohydride reduction of this latter furnished a bromohydrine (m.p. 125·5°), hydrogenolysis of which over Pd—C leads to 3β-tropanol, while alkaline treatment yielded tropinone. This confirmatory evidence points to the β-placed hydroxyl as being *cis* to bromine. An interesting reversible ring opening has been presented with 3β-tropanol methohydroxide into 6-dimethyl-amino-*cyclo*hept-2-en-1-ol, the dibromide of which has been reconverted by sodium hydrogen carbonate into the methobromide of the same bromo-alcohol.[61] Hence, the eliminated bromine must have been *trans* to the $N(Me)_2$ group, so the preserved one is obviously *cis*-placed to the *N*-methyl bridge in the 2-bromo-tropanol concerned[61] (Fig. 16).

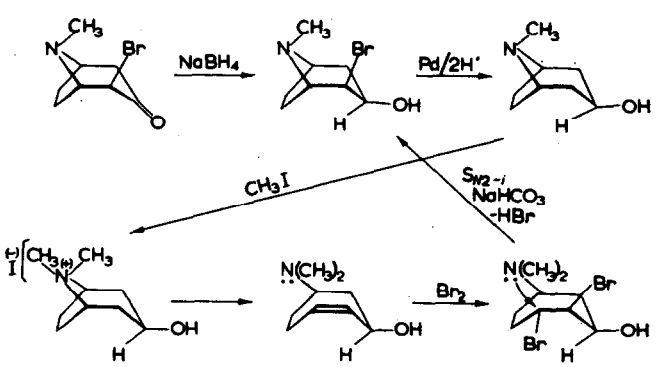


FIG. 16.

[59] Author thanks Prof. Dr. Caroline McGillavry for having paid attention to this subject.
[60] C. A. Friedmann and J. M. Z. Gladych *J. Chem. Soc.* 873 (1956).
[61] A. Nickon *J. Amer. Chem. Soc.* 77, 4094 (1955).

4. INVESTIGATIONS AND CONSIDERATIONS CONCERNING THE STRUCTURE OF DIOSCORINE

A tentative formula of the γ-lactone of 2-(α)-*iso*propylidene-carboxymethyl-3-hydroxy tropane has so far been suggested to dioscorine based merely upon positive Legal test, indicating the presence of an $\alpha{\cdot}\beta$-olefinic lactone grouping[62] as well as an exhaustive methylation[62] described in detail in Manske-Holmes' monograph, *The Alkaloids*, Vol. I. The isolation of the alkaloid from different sources;[64] furthermore, its degradation has been recently[64] reinvestigated, adopting modern experimental methods, *inter alia* techniques of infra-red spectroscopy.[65] The base $C_{13}H_{21}N$ obtained first by Hofmann degradation broke down when heated with palladised charcoal into trimethylamine, an unidentified base, and *iso*butyl-benzene, or $\beta{\cdot}\beta$-dimethylstyrene, depending on the activity of catalyst. Another item of exhaustive methylation of this base gave a hydrocarbon, $C_{11}H_{14}$, infra-red spectroscopic data of which support the structure of *iso*butenyl *cyclo*heptatriene, containing a $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C{=}CH_2$ linkage. Hydrogenation of this compound yields, however, a hydrocarbon $C_{11}H_{22}$, infra-red data which are very similar to, those but not identical with the curve of *i*-butyl-*c*-heptane, obtained on synthesis[65] from 4-*i*-butyl-*cyclo*hexanone by ring enlargement with diazomethane, followed by Kishner-Wolf reduction of *i*-butyl *cyclo*heptanone.

On the other hand, two of the structural isomers (1 : 3, 1 : 4) possible of *N*·*N*-dimethyl-*i*-butyl-*c*-heptylamine have been synthesised. The infra-red curves were very close to those of the saturated Hofmann base $C_{13}H_{27}N$, none of them proved, however, identical with that of the base from dioscorine. Configurations have not been taken into consideration, so these data are not sufficiently conclusive. Nevertheless, a new tentative formula has been suggested[65] which takes account for the formation of a $C{=}CH_2$ group on decarboxylation of the hydroxy-acid from dioscorine, i.e. that of the ε-lactone of a tropine derivative with a β-methyl-$\alpha{\cdot}\beta$-butenoic acid side-chain in position 2.[65] Although these new investigations may seem satisfactory in explaining the structural problem, in the author's opinion, they need synthetic confirmation. As to stereochemical predictions, the mydriatic effect of dioscorine supports strongly the presence of a 3α-placed hydroxyl group. Furthermore, Stuart-Briegleb models allow the existence of both *cis* and *trans* anellation of the seven-membered unsaturated lactone ring to the piperidine ring of tropane (Figs. 17 and 18).

5. SOME RECENT CONTRIBUTIONS TO THE PROBLEM OF BIOGENESIS OF SCOPOLAMINE AND HYOSCYAMINE

In preceding reviews[3,4] this question has been discussed both in terms of syntheses under so-called physiological conditions[66] and considering some feeding experiments on living Datura plants, controlled by the isotopic tracer techniques.[67] Establishing of the configurations of all the natural tropane bases valeroidine, scopolamine, and meteloidine bearing oxygen function(s) at the ethylene bridge,[40,41] which proved to be *cis*, i.e. β-placed to the nitrogen allowed the assumption of a common precursor for all

[62] K. Gorter *Rec. Trav. Chim.* **30**, 161 (1911).
[63] K. Gorter *Ann. Jardin Biol. Buit.* (11) Suppl. 3, 385 (1910).
[64] A. Pinder *J. Chem. Soc.* 2236 (1952); 1825 (1953).
[65] A. Pinder *J. Chem. Soc.* 1577 (1956).
[66] Cl. Schöpf and his school *Angew Chem.* **64**, 591 (1952).
[67] L. Marion *et al.* *Canad J. Chem.* **29**, 964 (1951).

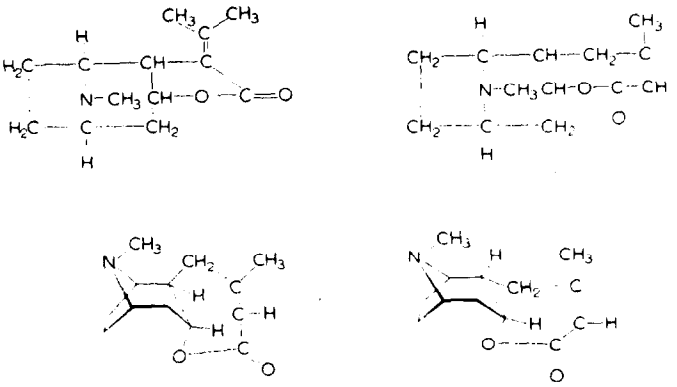


FIG. 17.

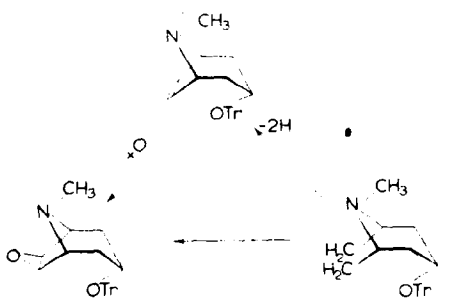


FIG. 18.

these alkaloids. Δ_6-Tropen-3-ol was propounded as early as 1944 as the most probable compound of this type.[68,69] Stereospecific *exo*-additions[32] of different addenda to it may afford the above-mentioned tropeines. Unfortunately, however, until 1955 this key intermediate was not available. Recent synthesis of scopolamine[31b, 33] by way of tropenol makes it possible in the near future to perform feeding experiments with this unsaturated alcohol.

However, we were discouraged by the fact that recent feeding experiments on *Datura strammonium* with α-^{11}C-labelled ornithine led to C_1-radioactive hyoscyamine (atropine) but radio-inactive hyoscine (scopolamine).

Surprisingly, Romeike succeeded in carrying out feeding experiments with young *Datura ferox* plant, itself unable to produce hyoscine, which proved to convert[71] fed hyoscyamine into hyoscine. This latter has been identified by paper chromatography and also by its crystalline picrate.[72]

Hence, the central role of tropenol in biosynthesis of tropanols might not be discarded, but requires still many systematic feeding experiments with tropenol derivatives. These joint efforts are already being carried out in Gatersleben[73] and in the author's laboratory.[29]

[68] B. T. Cromwell *Biochem. J.* **37,** 717–722 (1944).
[69] N. A. Preobrashenskii and E. I. Genkin *Chemistry of Organic Pharmaceutical Products* (in Russian) p. 181, Gozchimizdat, Moscow (1953).
[70] E. Leete, L. Marion, and I. D. Spenser *Nature* **174,** 650 (1954).
[71] A. Romeike *Angew. Chem.* **68,** 124 (1956).
[72] A. Romeike *Flora (Jena)* **143,** 67 (1956).
[73] Two lectures, delivered at the Symposium on Biochemistry and Physiology of Alkaloids by A. Romeike and G. Fodor resp. Quedlinburg, 8–12 October 1956.