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# The Reactions of Activated Amides. I[1]. The Reactions of Iminoethers derived from the Secondary Amides with the Nucleophiles[2]

Takeshi Oishi, Masako Nagai, Takeshi Onuma, Hitoshi Moriyama, Koichi Tsutae, Miwako Ochiai, and Yoshio Ban

*Faculty of Pharmaceutical Sciences, Hokkaido University*[3]

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The reactions of the iminoether (VII) derived from α-piperidone with alkyl cyanoacetate, ethyl acetoacetate, and acetylacetone were investigated. The highly conjugated condensation products were then converted to the saturated compounds. Thus, isopelletierine (XVIII) was synthesized by the reduction of XIII, followed by reoxidation of the secondary alcohol (XVII) into the corresponding ketone. Then, condensation of the oxindole iminoethers with ethyl cyanoacetate was carried out and their reactivity was found to be considerably less than that of simple iminoethers.

The activation of the amide carbonyl through conversion into the corresponding imidochloride has been widely studied and comprehensively reviewed by Eilingsfeld, *et al.*[4] The conversion has been achieved by using rather drastic reagents such as phosgene, thionyl chloride and phosphoryl chloride, which inherently prevents this method from being applied to the activation of the amides having other functional groups in the same molecule. Moreover, the use of these reagents should be avoided for the simple activation of secondary amides because the considerable side reactions are generally observed.[5]

Meanwhile, Meerwein, *et al.*[6] found that triethyloxonium tetrafluoroborate (Meerwein reagent) reacts readily with tertiary amides to give O-ethylated species, which are converted to the amide acetals (I) on alkoxide treatment. A variety of nucleophiles react now with the amide acetals to give enamine derivatives. The enhanced reactivity of the amide acetals can be understood by considering that they are in a rapid equiliblium with the corresponding salts (II). Recently, Eschenmoser, *et al.*[7] showed that the α-pyrrolidones (III) are O-ethylated by the Meerwein reagent to give iminoether salts, which were converted to the free bases (IV) by the aqueous base treatment.[8] The iminoether (IV) thus obtained reacted with *t*-butyl cyanoacetate to give the enamino cyanoesters (V). However, the condensation of imino ethers with other active methylene groups seems to have attracted little attension.[9] Bredereck,

1) Part II: T. Oishi, M. Nagai, and Y. Ban, *Tetrahedron Letters*, **1968**, 491.
2) Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, Tokushima, October 1965 and at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *Kita-12, Nishi-6, Sapporo.*
4) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).
5) W. Jentzsch, *Chem. Ber.*, **97**, 1361 (1964); H.H. Bosshard and H. Zollinger, *Helv. Chem. Acta*, **42**, 1659 (1959).
6) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Ann.*, **641**, 1 (1961). See also ref. 10).
7) E. Bertele, H. Boos, J.D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H.P. Grible, H. Gschwend, E.F. Meyer, M. Pesaro, and R. Schefforld, *Angew. Chem. Intern. Ed. Engl.*, **3**, 490 (1964).
8) For hitherto reported methods of preparation of iminoethers, see R. Roger and D.G. Neilson, *Chem. Review*, **57**, 179 (1960). The reactions of iminoethers with nucleophiles other than active methylene compounds are also reviewed in this article.
9) Petersen has reported the condensation of iminoether derived from caprolactam with various active methylene compounds, but the details are not described in there. S. Petersen, *Angew. Chem.*, **64**, 602 (1952).

*et al.*[10] reported that N,N-dimethyl-N'-phenylformamidine (VI) failed to condense with acetone or methyl ethyl ketone, whereas the amide acetals reacted with them to give keto enamine derivatives although the yields were not satisfactory. From the structural similarity between VI and iminoethers, the relatively poor reactivity of the latters could also be anticipated.

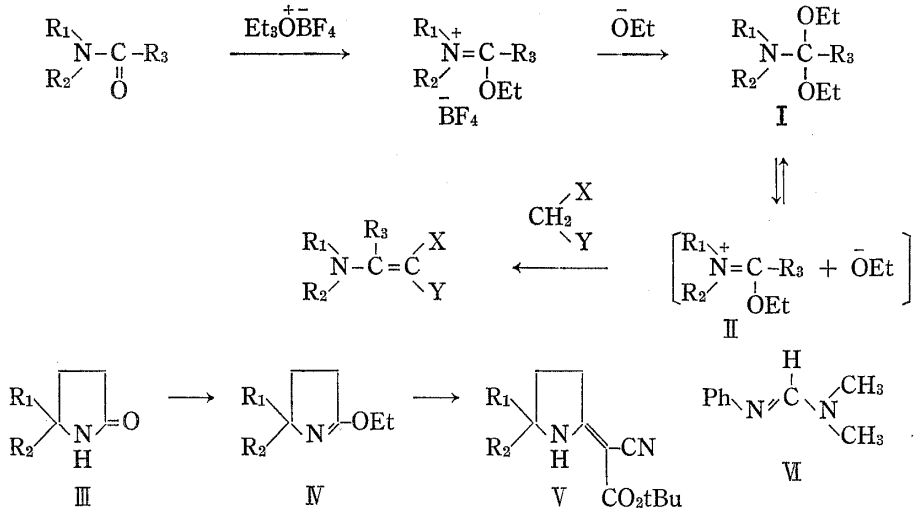

Chart 1

In the course of our synthetic studies of indole alkaloids, we intended the conversion of readily obtainable $\beta,\beta$-disubstituted oxindole derivatives[11] into corresponding indolines having suitable substituents on the $\alpha$-position. The requisite steps for this purpose include the activation of lactam carbonyl and subsequent condensation of activated amide (imino ether) with nucleophiles. By taking account of the supposed poor electrophilicity of the iminoethers, it seemed necessary to investigate further their reactivity toward various nucleophiles. The present work deals with the reactions of the simple iminoether with active methylene compounds, followed by the requisite conversion of the products to the suitable compounds for the further synthetic steps and also includes the model experiments for the construction of alkaloid framework starting from the oxindole derivatives using the above reaction pattern.

A readily available $\alpha$-piperidone was chosen as a secondary amide and it was converted into the iminoether (VII) by the standard method.[7] The iminoether (VII) undergoes smooth condensation with alkyl cyanoacetates in the presence of a catalytic amount of triethylamine at room temperature to give the enamino cyanoesters (VIIIa,b,c), expectedly. On the other hand, with ethyl acetoacetate and acetylacetone, much drastic condition was necessary. The condensation products (X and XIII) were obtained in the yield of 40—50% only after the reaction mixtures were heated for 100 hr at 50—60° in a sealed tube. The well-known heat-induced migratory tendency of the ethyl group in an iminoether[12] from oxygen to nitrogen prohibits the reaction from being carried out at high temperature, whereas such care is not necessary when the amide acetales (I) are the partners. Quite interestingly, only the deacetylated product (XIII) was obtained from the reaction between VII and acetylacetone through XII.

Next, as the substitution patterns of the condensation products are not suited for the subsequent synthetic steps, hydrolysis and concomitant decarboxylation of the products were attempted. Cyano *t*-butyl ester (VIIIb) and benzyl ester (VIIIc) undergo facile decarboxylation by trifluoroacetic acid treatment or catalytic hydrogenation with 10% palladium-charcoal, respectively, to afford the enamino–nitril (IX). On the other hand, although the cyano ethyl

10) H. Bredereck, F. Effenberger, and H. Botsch, *Chem. Ber.*, **97**, 3397 (1964).
11) Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **11**, 442, 446, 451 (1963).
12) S. Peterson and E. Tietze, *Chem. Ber.*, **90**, 909 (1957). See also ref. 8).

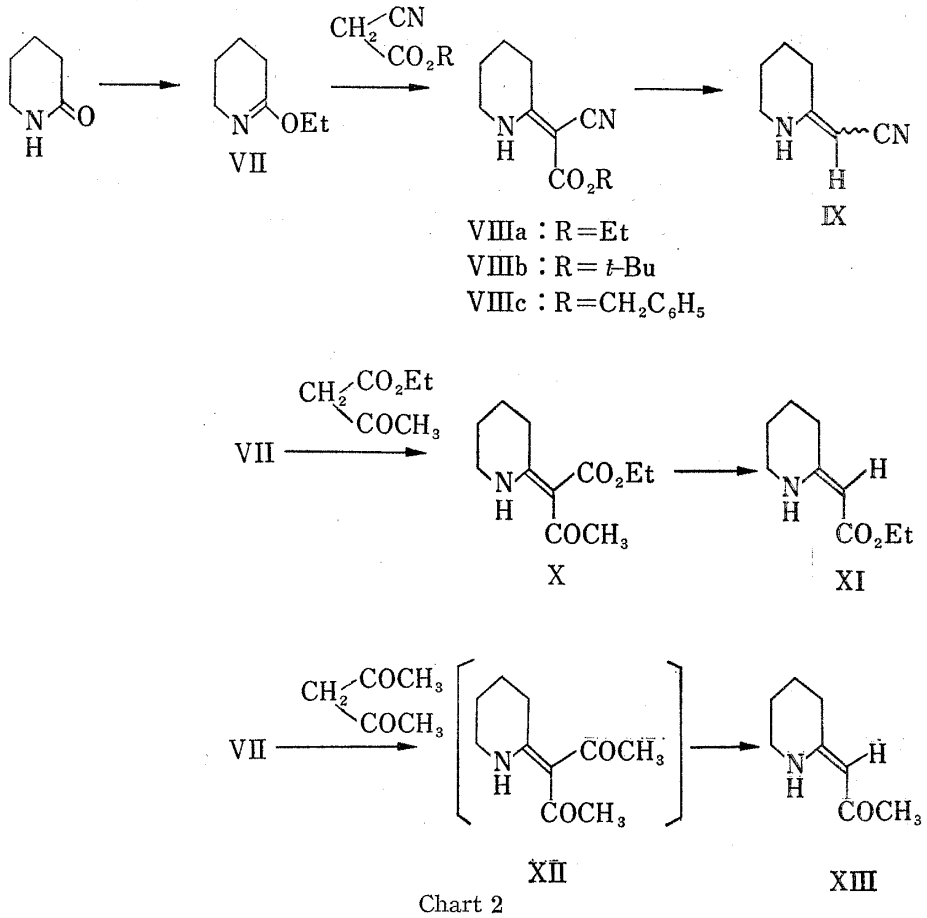


Chart 2

ester (VIIIa) remains unchanged when refluxed in trifluoroacetic acid, the keto ethyl ester (X) affords the deacetylated product (XI). This unexpected facile deacetylation is reminiscent of the earlier observation that the intermediary compound (XII) was deacetylated to give XIII during the reaction.

The first stage of usual deacetylation reaction is considered to be the addition of base to a carbonyl group.[13] In the present systems, the addition of base to the highly enolized enaminoketones (X′ and XII′) would be facilitated by the presence of the additional carbonyl groups. That the compound (XIII) remained unchanged on acid treatment supports this carbonyl group participation. The favorable reaction path could be considered as is shown in Chart 3. However, further experimental evidences are needed for the elucidation of the precise mechanism of these anomalous reactions. The *cis* configuration of both XI and XIII

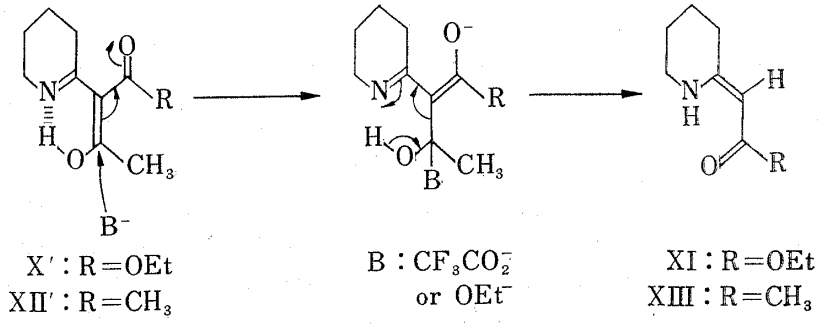


Chart 3

13) D.J. Cram and G.S. Hammond, "Organic Chemistry," McGraw-Hill Book Company, INC., New York, 1959, p. 261.

have been unequivocally established from infrared (IR) and nuclear magnetic resonance (NMR) data, which are comparable with those of related compounds reported by R. Huisgen, *et al.*[14] (*cf.* experimental section).

The reduction of highly conjugated vinylogous amides thus obtained was then carried out according to the modified Schenker's procedure.[15] The principle of the method is to reduce the protonated species with sodium borohydride. The remarkable observation was that the reduction of the O-protonated species (XVI) which still include the conjugated double bond system in its molecule[16] proceeded quite smoothly. Chromic anhydride oxidation of the amino alcohol (XVII) gave *dl*-isopelletierine (XVIII) in high yield.

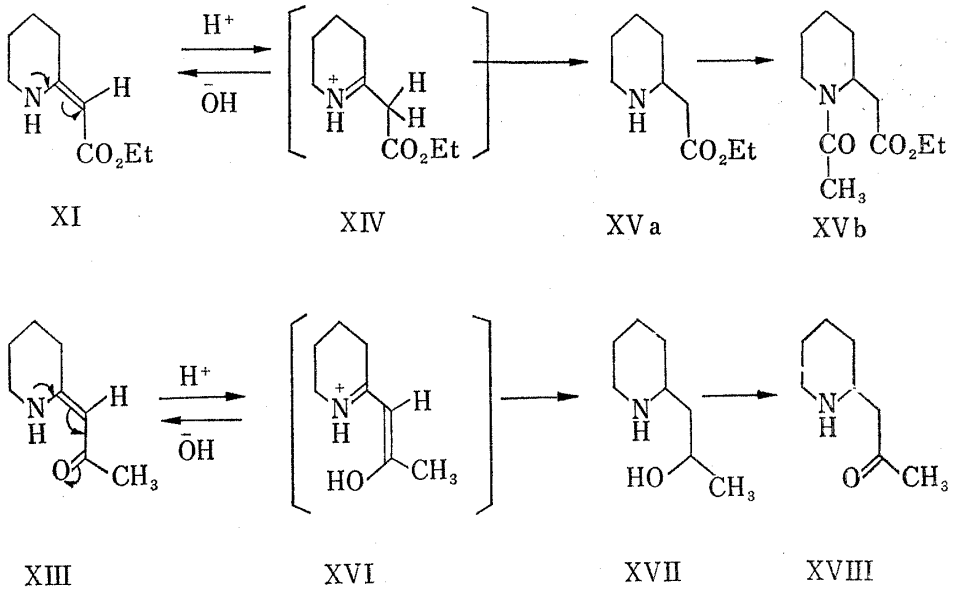


Chart 4

Then, the reaction of alkyl cyanoacetates with the more complicated iminoether (XX) was undertaken. The compound (XX) was obtained from the tetrahydro-$\beta$-carboline derivative (XIX) *via* chloroindolenine (XIX') according to the procedure developed by Finch and Taylor.[17] The direct ethylation of the corresponding oxindole (XX') by Meerwein reagent was not attempted in this case because the tertiary amine also could be ethylated by this reagent.[18] The reaction of XX with ethyl cyanoacetate in the presence of triethylamine faild to proceed at room temperature but on being kept the mixture for 100 hr in a sealed tube at 60—65°, the condensation product (XXIa) was obtained in 30% yield. Similarly, the *t*-butyl ester (XXIb) was obtained in the yield of 13%. Attempts to decarboxylate XXIb by trifluoroacetic acid treatment were unsuccessful. That the ultraviolet spectrum of the reaction medium exhibits an indole chromophore suggests that the acid-induced fragmentation of XXIb or XXII should have taken place during the reaction as is shown in Chart 5. Therefore, the catalytic hydrogenations of the corresponding benzyl ester both in protic and aprotic solvents were undertaken. However, the result was essentially the same. It was

14) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
15) K. Schenker and J. Druey, *Helv. Chem. Acta*, **42**, 1960 (1959).
16) Wenkert, *et al.* have shown that the protonation of enamino ketones give O-protonated species whereas that of enamino nitrils and esters prefer C-protonation from the inspection of spectral data and also suggested that O-protonation of enamino ketones reflects the inertness of these systems toward nucleophiles in the acidic medium. E. Wenkert, K.G. Dave, F. Haglid, R.G. Lewis, T. Oishi, R.V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968). However, the hydride addition was proved to occur readily on the O-protonated species from the present experiments.
17) N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **89**, 3871 (1962).
18) H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.*, (2), **147**, 17 (1937).

assumed that the above facile fragmentation could be minimized by fixing the Nb lone pair. Thus, the preparation of Nb tosyl derivative (XXIV) was attempted. Condensation of oxytryptamine (XXIII) with propionaldehyde followed by tosylation with *p*-toluenesulfonyl chloride in pyridine gave a mixture of $\beta,\beta$-disubstituted oxindoles (XXIVa and XXIVb) in the yield of 80% from XXIII. These isomers epimeric at C1′ position were readily separated by alumina chromatography. The purified XXIVa and XXIVb were treated with Meerwein reagent and the resulted salts were neutralized with 10% $K_2CO_3$ solution to give the imino-ethers (XXVa and XXVb), respectively.[19] In the above reactions, Nb tosyl groups were

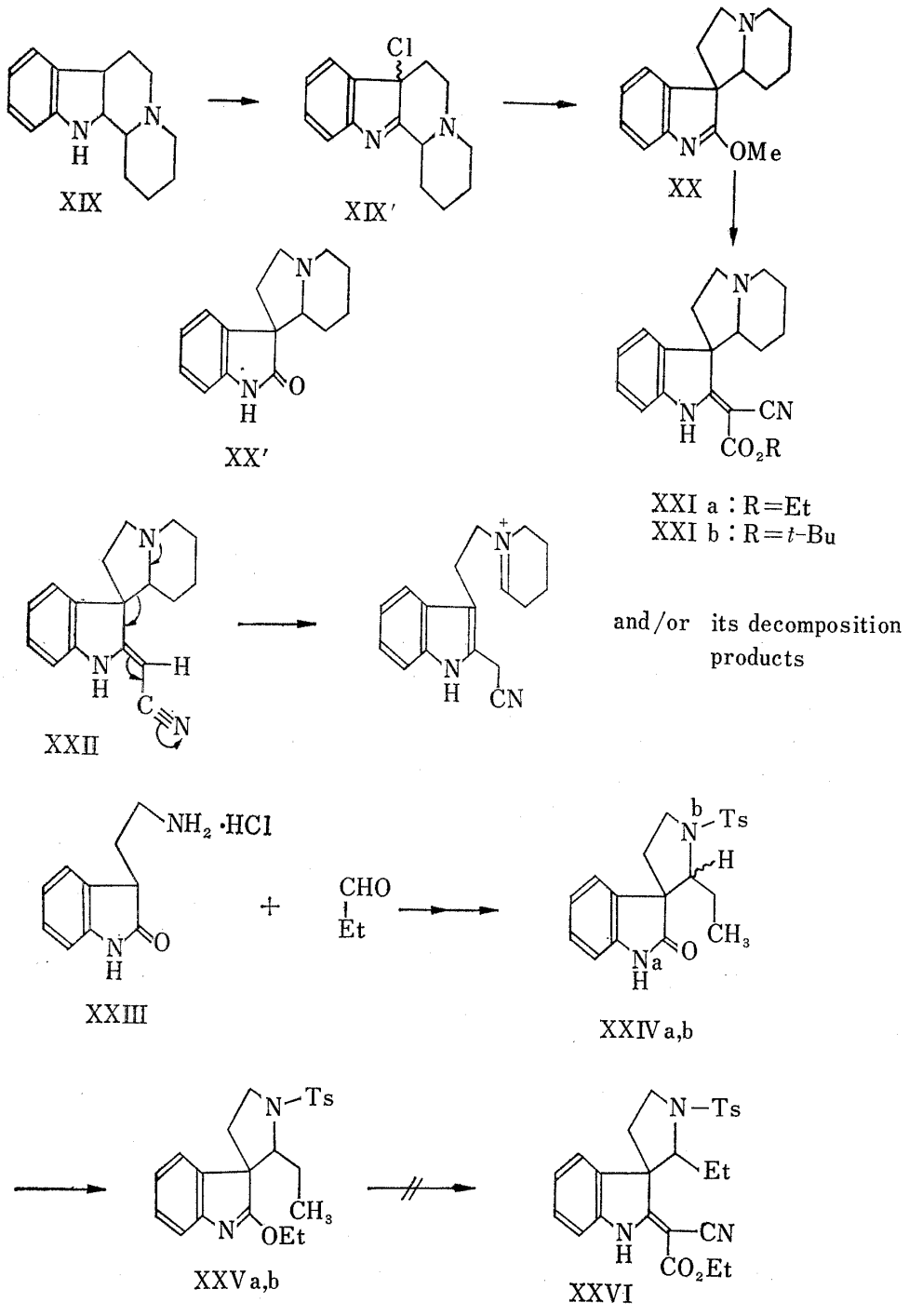


Chart 5

19) *cf.* J. Harley-Mason and T.J. Leeney, *Proc. Chem. Soc.*, **1964**, 368.

found to be unaffected by the Meerwein reagent. The condensation of both isomers (XXVa and XXVb) with ethyl cyanoacetate were, however, unsuccessful even if the drastic conditions were employed. From the above results, the reactivity of iminoethers derived from oxindole derivatives prooved to be considerably less than that of simple iminoethers.

By taking account of the above model experiments, we attempted the intramolecular condensation of oxindole iminoether with active methylene groups and succeeded in the synthesis of $\beta,\beta$-disubstituted indoline moiety of natural bases, which was reported already in part II of this series.[1)]

## Experimental[20)]

**2,3,4,5-Tetrahydro-6-ethoxypyridine (VII)**——To a solution of 5.14 g of $\alpha$-piperidone in 40 ml of $CH_2Cl_2$ was added 20 g of dried triethyloxonium tetrafluoroborate. The clear solution was refluxed for 4 hr and then made basic by the addition of 5N $K_2CO_3$ solution under ice cooling. The $CH_2Cl_2$ layer was separated and the aqueous layer was extracted twice with $CH_2Cl_2$. The combined extracts were dried over anhydrous $K_2CO_3$ and evaporated. The residual oil was distilled under reduced pressure to give 5.3 g of a colorless oil of VII, bp 86—88° (70 mmHg). Yield, 80%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1680 (–N=C–).

**Ethyl 2-Piperidylidenecyanoacetate (VIIIa)**——A mixture of 2.33 g of VII, 4.1 g of ethyl cyanoacetate and 180 mg of triethylamine was kept for 2 days at room temperature. The separated solid was filtered and washed with *n*-hexane–EtOH. Recrystallization from *n*-hexane–benzene gave 1.78 g of colorless needles of VIIIa, mp 99—100°. Yield, 51%. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2203 (–C≡N), 1665, 1600. *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.81; H, 7.40; N, 14.08.

***t*-Butyl and Benzyl 2-Piperidylidenecyanoacetate (VIIIb and VIIIc)**——The condensation of VII with *t*-butyl and benzyl cyanoacetate under the above reaction conditions and work-up afforded VIIIb (mp 183—185°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2203, 1660, 1620. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.77; H, 8.11; N, 12.75) and VIIIc (mp 105—106°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2203, 1665, 1610. *Anal.* Calcd. for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.15; H, 6.33; N, 10.61). The yields after recrystallization were 56% and 68%, respectively.

**2-Piperidylideneacetonitril (IX)**——To a solution of 876 mg of VIIIc in 70 ml of ethanol was added 540 mg of 10% Pd–C and the mixture was subjected to catalytic hydrogenation at the initial pressure of 50 lb using Parr apparatus. After shaking 2.5 hr, the catalyst was filtered and the filtrate was evaporated under reduced pressure to give pale yellow oil, which solidified readily. The yield of crude material was almost quantitative. Recrystallization from *n*-hexane afforded colorless needles of IX, mp 61—63°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3350, 2205, 1600. *Anal.* Calcd. for $C_7H_{10}N_2$: C, 68.85; H, 8.19; N, 22.95. Found: C, 68.66; H, 8.29; N, 23.24. The same compound (IX) was also obtained from *t*-butyl ester (VIIIb) by warming it in $CF_3COOH$.

**Attempted Hydrolysis of the Ethyl Ester (VIIIa)**——The ethyl ester (VIIIa) was dissolved in $CF_3COOH$ and warmed on the water bath for 4—5 hr. The compound which was obtained after usual work-up found to be the starting material.

**Ethyl 2-Piperidylideneacetoacetate (X)**——A mixture of 8 g of freshly distilled VII, 9 g of ethyl acetoacetate, and 12.7 g of triethylamine was heated for 50 hr in the sealed tube at 100°. After the unreacted materials were evaporated off under reduced pressure, the residual brown oil was chromatographed on alumina. Elution with benzene:hexane (1:1) gave a small amount of deacetylated compound (XI). Further elution with benzene afforded 6.83 g of a pale yellow oil. The reaction product thus obtained was still contaminated with a small amount of XI and attempted separation by repeated elution chromatography was unsuccessful. However, as its spectral characteristics are consistent with that considered from structure (X), this oily compound was subjected to the further reaction. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1690, 1605. NMR (in $CDCl_3$) $\delta$: 2.30 (3H, singlet, $-COCH_3$), 1.35 (3H, triplet, $-CH_2C\underline{H}_3$), 4.20 (2H, quartet, $-C\underline{H}_2CH_3$), 12.7 (1H, broad, >NH). UV $\lambda_{max}^{EtOH}$ mμ: 305.

**Ethyl 2-Piperidylideneacetate (XI)**——A solution of 20 g of X in 120 ml of $CF_3COOH$ was heated for 20—30 min at 80° (bath temp.). After cooling, the mixture was made basic by the addition of 10% $Na_2CO_3$ solution and extracted with benzene. The extract was dried over sodium sulfate and evaporated under reduced pressure to yield 14.6 g of an oil, which was distilled to give 10.7 g of XI, bp 104—105° (2 mmHg). Yield, 59%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300 (>NH) (the shape and the position of this peak were unchanged when measured in $CHCl_3$ solution, which shows that >NH in XI is intramolecularly hydrogen-bonded with ester carbonyl[14)]), 1645, 1600. UV $\lambda_{max}^{EtOH}$ mμ (log ε): 292 (4.27) (disappered in the acidic medium). NMR ($CDCl_3$) $\delta$: 1.2 (3H, triplet, $-OCH_2C\underline{H}_3$), 4.05 (2H, quartet, $-OC\underline{H}_2CH_3$), 4.3 (1H, singlet, –C=C<u>H</u>–CO–), 8.7 (1H,

20) Melting points are uncorrected. All NMR spectra were measured with a Hitachi H-60 spectrometer. Chemical shifts are reported as $\delta$ values measured from tetramethylsilane as an internal standard.

broad, –NH[14]). The last two peaks (4.3 and 8.7) were disappeared by the addition of $D_2O$. Picrate, yellow prisms, mp 101—102. *Anal.* Calcd. for $C_{15}H_{18}O_9N_4$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.58; H, 4.83; N, 14.07.

**2-Piperidylideneacetone (XIII)**——A mixture of 7.0 g of VII, 5.5 g of acetylacetone and 1.1 g of triethylamine was heated in a sealed tube for 50 hr at 100° (bath temp.). The resultant brown solution was treated as described in the preparation of X. The product was chromatographed on alumina to give 3.87 g of an oil. The structure of this compound was suggested to be XIII from the following spectral data and confirmed by its conversion into the known isopelletierine. IR $\nu_{max}^{neat}$ $cm^{-1}$: 3300 (broad, >NH[14]), 1730, 1605, 1570. NMR (in $CDCl_3$) $\delta$: 1.89 (3H, singlet, $-COCH_3$), 4.75 (1H, singlet, –C=C<u>H</u>–CO–), 11 (1H, broad, >NH[14]). UV $\lambda_{max}^{EtOH}$ m$\mu$: 315, $\lambda_{max}^{EtOH,\ 10\%HCl}$ m$\mu$: 295.

**The Reduction of Enamine Derivatives**——The addition of $NaBH_4$ in EtOH to the ice cold enamine perchlorate constitute the Schenker's procedure.[15] However, a large amount of starting materials were recovered unchanged when this procedure was applied to the present systems. The modified method gave satisfactory results.

**The General Procedure**——To the solution of enamine derivatives (1 mole) was added 70% $HClO_4$ solution in EtOH (1:1) until the solution became just acidic to Congo–Red test paper. This solution was added dropwise to the $NaBH_4$ (5—6 mol) solution in EtOH under vigorous stirring and ice cooling. After stirred for 30 min at room temperature, the solvent was evaporated off under reduced pressure. The resultant white solid was dissolved in minimum amount of water and extracted with $CH_2Cl_2$ repeatedly. The solvent was dried over $Na_2SO_4$ and evaporated to give reduced product.

**Ethyl 2-Piperidylacetate (XVa)**——The reduction of XI under the above reaction conditions and work-up produced 970 mg of reduced product (XVa) as a pale yellow liquid. Yield, 93% (crude). IR $\nu_{max}^{neat}$ $cm^{-1}$: 1740. The starting material was not detected on thin-layer chromatography in this crude oil. Since this compound was found to be fairly unstable, the characterization was done after it was converted into the corresponding acetamide. To the solution of 8 g of crude amino ester (XVa) in acetone was added 8.2 g of anhydrous $K_2CO_3$. To this mixture, 4.4 g of acetyl chloride was added at 0° under stirring. After 1 hr, the acetone layer was separated from the precipitated solid. The solvent was evaporated and the residual oil was distilled under reduced pressure affording 6.83 g of ethyl N-acetyl, 2-piperidyl acetate (XVb). Yield, 71.3%. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1730, 1635. NMR (in $CDCl_3$) $\delta$: 2.15 (3H, singlet, N–$COCH_3$), 1.30 (3H, triplet, $-OCH_2C\underline{H}_3$), 4.10 (2H, q, $-OC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{11}H_{19}O_4N$ (XVb): C, 61.94; H, 8.98; N, 6.57. Found: C, 61.75; H, 8.83; N, 6.48.

**(2-Piperidyl)-2-propanol (XVII)**——The reduction of 287 mg of XIII under the above reaction conditions and work-up yielded the mixture slightly contaminated with the starting material (XIII). Therefore, the reduction was repeated and 228 mg of colorless needles of XVII was obtained. mp 60—61°. Yield, 79%. The melting point of this compound was identical with the reported value.[21]

**Isopelletierine (XVIII)**——To a solution of 291 mg of XVII in 1.6 ml of $CH_3COOH$ was added 120 mg of $CrO_3$ in 0.4 ml of water and the mixture was heated for 4 hr at 150° (bath temp.). The excess $CrO_3$ was destroyed by the addition of MeOH. Excess MeOH was evaporated and the residue was made basic by the addition of $K_2CO_3$ solution. The water solution was extracted to give 268 mg of an oil. IR $\nu_{max}^{neat}$ $cm^{-1}$: 1715. NMR (in $CDCl_3$) $\delta$: 2.15 (3H, singlet, $-COCH_3$), 2.55 (2H, doublet, $CHCH_2CO$–). Picrate, mp 147—148°. The melting point of the picrate was identical with the reported value.[21]

**2-Methoxy-spiro[indolenine-3,3′-indolizidine] (XX)**——To a solution of 226 mg of indoloquinolizidine derivative (XIX) in 10 ml of anhydrous $CH_2Cl_2$ with one drop of triethylamine was added dropwise 108.5 mg of *t*-BuOCl in 10 ml of $CCl_4$ at −10°. After the addition was completed, the mixture was stirred for 30 min keeping the temperature below 0°. Organic solvent was separated and washed with water, dried over $Na_2SO_4$ and evaporated to give 274 mg of a pale yellow oil, which partially solidified on standing. To the crude chloro-indolenine thus obtained in 10 ml of MeOH was added 60 mg of KOH in 2.5 ml of MeOH.

The mixture was refluxed under nitrogen for 2 hr, diluted with water and extracted with $CH_2Cl_2$. The solvent was dried over $Na_2SO_4$ and evaporated to give a brown oil. Chromatography on alumina and elution by benzene yielded 173 mg of a yellow oil of XX. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1582. The imino ether (XX) was subjected to the subsequent condensation reaction without further purification.

**2-(Ethoxycarbonyl, cyanomethylene)-spiro [indoline-3,3′-indolizidine] (XXIa)**——A mixture of 256 mg of XX, 226 mg of ethyl cyanoacetate and 20 mg of triethylamine was heated for 100 hr at 60—65° in a sealed tube. The resultant brown oil was digested with *n*-hexane to give violet solid, which was recrystallized from *n*-hexane affording 120 mg of a pale yellow leaflet, mp 190—191°. Yield, 30%. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2210 (C=C–<u>C</u>N), 1682. UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 335 (4.30). *Anal.* Calcd. for $C_{20}H_{23}O_2N_3$: C, 71.21; H, 6.82; N, 12.46. Found: C, 71.37; H, 6.93; N, 12.83. Similarly, *t*-butyl ester (XXIb) was obtained as colorless prisms, mp 157—158° (recrystallized from EtOH–$H_2O$). *Anal.* Calcd. for $C_{22}H_{27}O_2N_3$: C, 72.32; H, 7.39; N, 11.50. Found: C, 72.47; H, 7.33; H, 11.42.

21) J. Büchi, F. Kracher, and G. Schmidt, *Helv. Chim. Acta*, **45**, 729 (1962).

**2′-Ethyl, 3′-*p*-Toluenesulfonylspiro [indoline-3,1′-pyrrolidine]-2-one (XXIVa,b)**——To an ice cold solution of 1.0 g of oxytryptamine hydrochloride (XXIII) in 3.0 ml of water, mixed with 3.8 ml of ethanol and 2.8 ml of 2N NaOH solution, was added 0.35 g of propionaldehyde in 3.0 ml ethanol and the mixture was allowed to stand for five days at room temperature. After a half of the solvent was evporated off under reduced pressure, the remaining water layer was extracted with $CH_2Cl_2$ twice. The combined $CH_2Cl_2$ solution was shaken with 10% HCl solution several times to extract the basic material. The acidic solution was made basic by the addition of $K_2CO_3$ under ice cooling and extracted again with $CH_2Cl_2$. The solvent was dried with $Na_2SO_4$ and evaporated to give 0.98 g of yellow oil, which gave two closely located spots on thin-layer chromatography and attempted separation of the mixture was unsuccessful. Therefore, characterization was done after converting them into corresponding Nb tosylate. To the solution of 642 mg of the aforementioned mixture in 1 ml of anhydrous pyridine was added 1.14 g of *p*-toluenesulfonyl chloride in 5 ml of anhydrous pyridine at −10°. After standing overnight, 12 ml of 5N $H_2SO_4$ solution was added to the solution. The separated orange solid was collected and washed with water and *n*-hexane successively. The crude mixture (1.0 g) thus obtained was chromatographed on alumina and eluted with $CH_2Cl_2$. The initial fraction contained 215 mg of colorless prisms of XXIVa, mp 178—180°. NMR (in $CDCl_3$) $\delta$: 0.45 (3H, triplet, $-CH_2C\underline{H}_3$), 2.46 (3H, singlet, $-SO_2C_6H_5C\underline{H}_3$-*p*), 8.62 (1H, broad, $-N\underline{H}-$). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2S$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.75; H, 6.14; N, 7.57. A mixture (274 mg) of XXIVa and XXIVb was obtained from the next fraction and further elution with the same solvent afforded 389 mg of colorless prisms of XXIVb, mp 211—212°. NMR (in DMSO-$d_6$) $\delta$: 0.50 (triplet, $-CH_2C\underline{H}_3$), 2.47 (3H, singlet, $-SO_2C_6H_5C\underline{H}_3$-*p*), 10.45 (1H, broad, $-N\underline{H}-$). *Anal.* Calcd. for $C_{20}H_{22}O_3N_2S$: C, 64.85; H, 5.99; N, 7.56. Found: C, 65.12; H, 5.71; N, 7.24.

**2-Ethoxy, 2′-Ethyl, 3′-*p*-Toluenesulfonylspiro [indolenine-3,3′-pyrrolidine] (XXVa and XXVb)**——To a solution of 922 mg of XXIVb in 40 ml of $CH_2Cl_2$ was added 3.0 g of triethyloxonium tetrafluoroborate. After refluxing for 4 hr, the solution was made alkaline by the addition of 20 ml of 10N $K_2CO_3$ solution. The solvent was washed with saturated NaCl solution, dried over $Na_2SO_4$ and evaporated to afford 872 mg (88%) of an oil, which solidified by the addition of small amount of ethanol. Recrystallization of this material from ethanol gave colorless plates of XXVb, mp 148—149°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1575 (–N=C–O–). *Anal.* Calcd. for $C_{22}H_{26}O_3N_2S$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.23; H, 6.57; N, 7.25. Ethylation of XXIVa under the above reaction conditions and work-up yielded XXVa as a colorless prisms of mp 133—134° in the yield of 72%. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1580. *Anal.* Calcd. for $C_{22}H_{26}O_3N_2S$: C, 66.31; H, 6.58; N, 7.03. Found: C, 66.29; H, 6.63; N, 6.89.

**Attempted Condensation of XXVa,b with Ethyl Cyanoacetate**——A mixture of 40 mg of XXVb, 30 mg of triethylamine and 120 mg of ethyl cyanoacetate was heated for 74 hr at 70—80° (bath temp.). Only the starting material was recovered unchanged after usual work-up. Similar condensation using XXVa was also failed.

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