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STRUCTURE OF SECURININE

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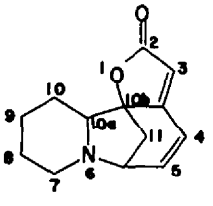
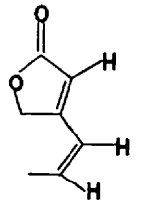
Abstract—The structure (XXVII) proposed for securinine is confirmed by synthetic structural proof of the key degradation products, lactam-carbinol B (XXIII) and quinolizidine B (XX).

SECURININE[1,2] is the major alkaloid of *Securinega suffruticosa Rehd.*, which was first isolated by Murav'eva and Ban'kovskii in 1956. In a preliminary communication,[3] this alkaloid is represented by the skeletal structure I and more recently, a preliminary communication[4] establishes the steric structure XXVII. The synthesis of lactam-carbinol B (XXIII) and quinolizidine B (XX), which play an important role in the derivation of the structures I and XXVII are described in this paper.



I



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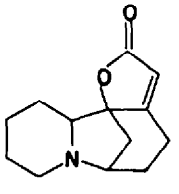

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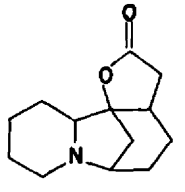


IV

[1] V. I. Murav'eva and A. I. Ban'kovskii, *Dokl. Akad. Nauk SSSR* **110**, 998 (1956).
[2] Z. Horii, T. Tanaka, Y. Tamura, S. Saito, C. Matsumura and N. Sugimoto, *J. Pharm. Soc. Japan* **83**, 602 (1963).
[3] S. Saito, K. Kotera, N. Sugimoto, Z. Horii and Y. Tamura, *Chem. & Ind.* 1652 (1962).
[4] S. Saito, K. Kotera, N. Shigematsu, A. Ide, Z. Horii and Y. Tamura, *Chem. & Ind.* 689 (1963).

Structure of securinine

Murav'eva and Ban'kovskii characterized securinine as a base of the formula $C_{13}H_{15}NO_2$ with a tertiary basic nitrogen (no N-methyl group), a lactone and a conjugated unsaturated system. In the first full account,[2] the analytical and spectral results confirm the molecular formula and the presence of these functional groups and also that securinine has no C-methyl group and, on catalytic hydrogenation, the dihydro-[5] and tetrahydrosecurinine, indicate the presence of two double bonds in securinine.

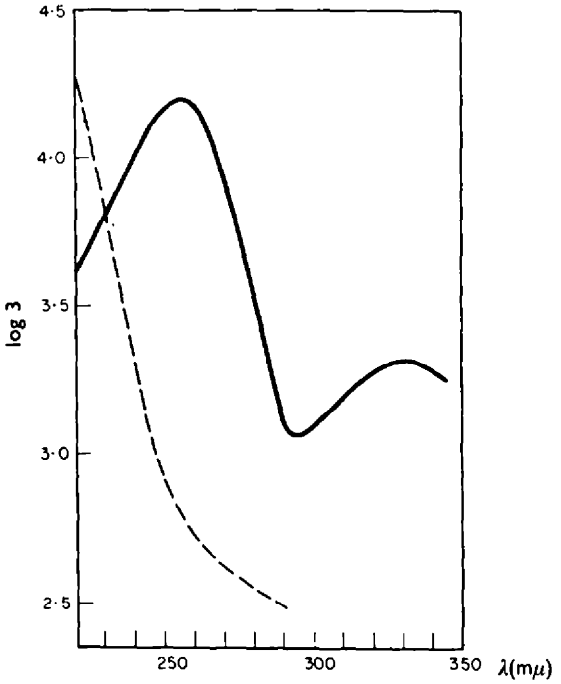


FIG. 1. Ultraviolet spectra of securinine and dihydrosecurinine in EtOH.
——— securinine
- - - - - - - dihydrosecurinine

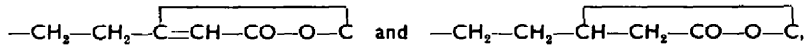
The existence of a lactone–conjugated unsaturated system (II) in securinine is confirmed by spectral studies. Securinine shows a strong absorption at 256 mμ (log ε 4·27) in the UV spectrum, which is absent in dihydro- and tetrahydro-securinine and which is attributable to an α, β and γ, δ-unsaturated lactone[6] (Fig. 1). The IR spectrum shows a split band at 1840 (weak) and 1760 cm^{-1} (strong), which is associated with an α,β-unsaturated γ-lactone with a hydrogen in α position to the lactone carbonyl.[7] Dihydrosecurinine shows no UV absorption above 220 mμ, but the

[5] Dihydrosecurinine was also isolated as a minor alkaloid from *Securinega suffruticosa Rehd.* (Z. Horii, N. Shigematsu and S. Saito, *J. Pharm. Soc. Japan* **83**, 800 (1963).)

[6] K. Meyer, *Helv. Chim. Acta* **29**, 718 (1946); A. Aebi and T. Reichstein, *ibid.* **33**, 1013 (1950); L. Ruzicka, Pl. A. Plattner and J. Pataki, *ibid.* **28**, 1360 (1945); L. Ruzicka, Pl. A. Plattner and H. Heusser, *ibid.* **29**, 473 (1946).

[7] R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.* **81**, 5242 (1959); R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Can. J. Chem.* **37**, 2007 (1959).

characteristic split band at 1815 and 1770 cm^{-1} in the IR spectrum, suggests the presence of a double bond conjugated with the lactone.[7] A single carbonyl stretching band at 1790 cm^{-1} in the IR spectrum of tetrahydrosecurinine is indicative of γ-lactone. The spectral data indicating that securinine, dihydro- and tetrahydrosecurinine possess the partial structures (II),



respectively, is confirmed by N.M.R. spectral studies (Fig. 2). Securinine shows in

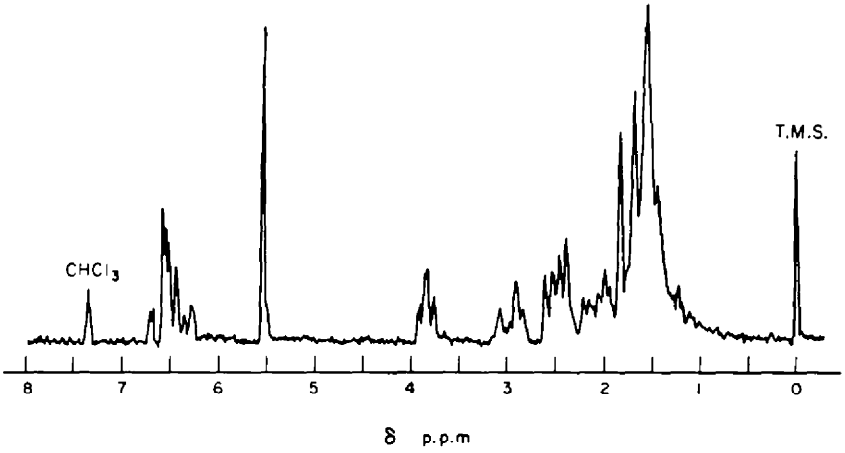
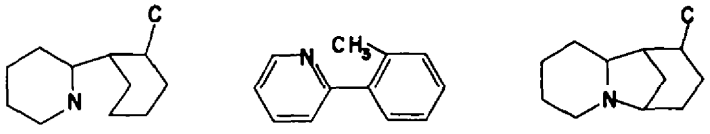


FIG. 2. NMR spectrum* of securinine.

the N.M.R. spectrum a singlet peak at $\delta = 5{\cdot}54$ (C_3—H), two quartet peaks centered at $\delta = 6{\cdot}67$ and $6{\cdot}42$ (C_4—H, C_5—H) and triplet peaks at $\delta = 3{\cdot}86$ (C_{5a}—H), among which the signals originating in the three protons at $C_4(A)$, $C_5(B)$ and $C_{5a}(X)$ may be interpreted as forming a typical ABX spin coupling[8] ($J_{AB} \approx 9$ cps, $J_{BX} \approx 5$ cps and $J_{AX} \approx 1{\cdot}5$ cps). Of the signals mentioned, peaks at $\delta = 6{\cdot}67$, $6{\cdot}42$ are absent in dihydrosecurinine and all peaks are absent in tetrahydrosecurinine. On the basis of structure I postulated for securinine, dihydro- and tetrahydrosecurinine may be formulated as III and IV, respectively.



V VI VII

The first indication that securinine contains the partial structure V was given by the formation of 2-(2′-tolyl)-pyridine (VI) on the degradation of securinine. Hydrolysis

* The solution (20% W/V) in $CDCl_3$ was measured on high resolution NMR spectrometer (Japan Electron Optics Co., JNMC-60) at 60 M c/s with tetramethylsilane as internal reference.

[8] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* pp. 57, 272. McGraw-Hill, New York (1959).

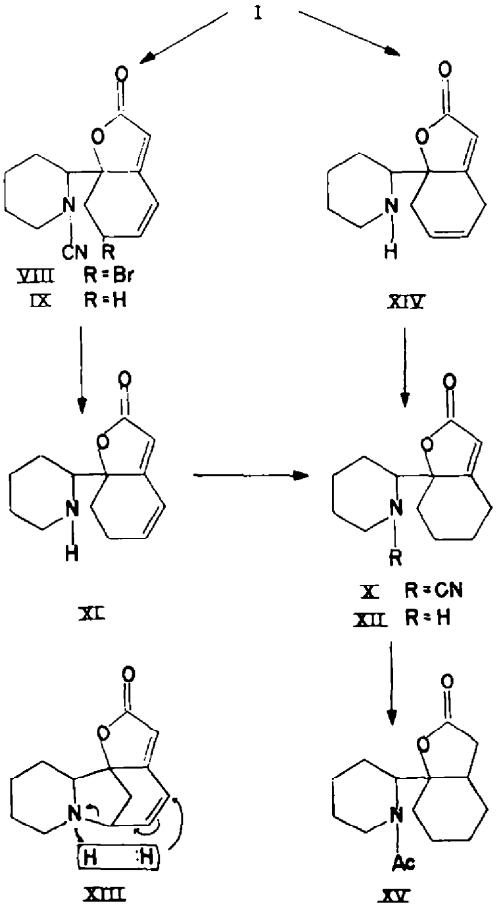
of securinine with potassium hydroxide solution followed by catalytic hydrogenation over Raney nickel gives a lactam-carbinol, m.p. 185°, $C_{13}H_{21}NO_2$, which we designate lactam-carbinol A. Palladium dehydrogenation of lactam-carbinol A yields VI, which was identified by direct comparison with an authentic specimen.[9]

This partial structure V, which defines twelve of the thirteen carbon atoms involved in securinine, is supported by the formation of phthalic acid during oxidation of tetrahydrosecurinine with potassium permanganate in oxalic acid solution.

Zinc-dust distillation of securinine yields phenol, characterized as phenyl carbanilate, *o*-cresol, identified by paper-chromatography, and *p*-toluidine, characterized as the N-acetyl derivative. The formation of *p*-toluidine permits the expansion of the partial structure V to VII, provided that no rearrangement takes place during dehydrogenation.

Consideration of the partial structures II and VII, leads to the complete skeletal structure I for securinine.

Finally, structure I is confirmed by the following stepwise degradation of securinine.



[9] C. K. Bradsher and K. B. Moser, *J. Amer. Chem. Soc.* **81**, 1941 (1959).

Treatment of I with cyanogen bromide gives the cyanide VIII, $C_{14}H_{15}BrN_2O_2$ in 60% yield. Compound VIII has practically the same UV spectrum as I and also shows similar peaks in the double bond regions of the IR spectrum. It is, therefore, conceivable that VIII is formed by selective cleavage at the C_{5a}—N bond of I, since C_{5a} corresponds to an allylic position.[10]

Catalytic hydrogenation of VIII with one mole of hydrogen over palladium on carbon in the presence of sodium acetate gives the cyanide (IX), $C_{14}H_{16}N_2O_2$ together with the dihydro-cyanide (X), $C_{14}H_{18}N_2O_2$, which is also obtained by further catalytic hydrogenation of IX. Hydrolysis of IX with 6% hydrochloric acid results in simultaneous decarboxylation to give the secondary amine XI, $C_{13}H_{17}NO_2$. The structures of IX and XI follow from their UV spectra, which still shows the characteristic chromophore in I and VIII.

A more convenient method of preparation of XI in a 50% yield consists in the hydrogenation of securinine with aluminum amalgam in wet ether to XIV followed by distillation under reduced pressure. The structure XIV follows from a similarity of its UV spectrum with that of III and the easy transformation by distillation into XI. The hydrogenation of I to XIV may be interpreted as proceeding accordingly to an *SN*—2′ mechanism as shown in XIII.

Catalytic hydrogenation of XI and XIV with palladium on carbon and absorption of one mole hydrogen yields dihydroamine (XII), $C_{13}H_{19}NO_2$, which is also obtained as a minor product by catalytic hydrogenation of securinine. The structures X and XII follow from the UV and IR spectra, which are similar to those of III. Acetylation, followed by catalytic hydrogenation, converts XII into the tetrahydroacetate (XV).

Hydrolysis of XII with potassium hydroxide solution followed by catalytic hydrogenation over Raney nickel gives a 53% yield of a lactam-carbinol, which is identical with the lactam-carbinol A derived directly from I. On the other hand, catalytic hydrogenation of XII over platinum oxide in ethanol gives a 60% yield of a lactam-carbinol, m.p. 223—224°, $C_{13}H_{21}NO_2$, which we designate lactam-carbinol B. The IR spectra of both lactam-carbinols A and B show bands at 3370 (hydroxyl) and 1630 cm^{-1} (lactam). Bands near 1150 cm^{-1} are assigned to a tertiary hydroxyl group,[11] since treatment of both lactam-carbinols with deuteriun oxide results in a partial replacement of the hydroxyl hydrogen with deuterium and, therefore, a diminution of the intensity of these bands. Further, both lactam-carbinols A and B give VI[9] on dehydrogenation with palladium. Thus, it may be concluded that lactam-carbinols A and B are C_{7a} epimers represented by the structure XVI.

After synthesis of *rac*-lactam-carbinol B, it was shown that the IR spectra of this compound in solution are identical with those of lactam-carbinol B. This unequivocally establishes that lactam-carbinol B has the structure XVI and, consequently confirms structure I. The synthesis of *rac*-lactam-carbinol B is described later in this paper.

Configuration of securinine

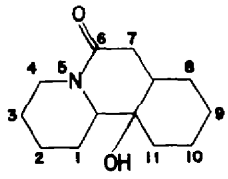
Lithium aluminum hydride reduction converts lactam-carbinol A into 11a-hydroxyperhydrobenzo[*a*]quinolizidine (XVII), m.p. 163–165°, $C_{13}H_{23}NO$, which we

[10] H. A. Hageman, *Organic Reactions VII*, p. 198. John Wiley, New York (1953).

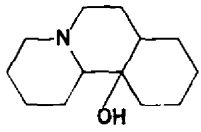
[11] J. R. Quinan and S. Wiberley, *Anal. Chem.* **26**, 1762 (1954); L. T. Bellamy, *The infrared spectra of complex molecules* pp. 108–111. Methuen, London (1958).

designate quinolizidine A. Similarly, lactam-carbinol B gives quinolizidine B, m.p. 60–61°, $C_{13}H_{23}NO$.

A study of molecular models of eight theoretically possible isomers represented by the structure XVII indicates that *trans*- quinolizidine bands[12,13] and bands due



XVI



XVII

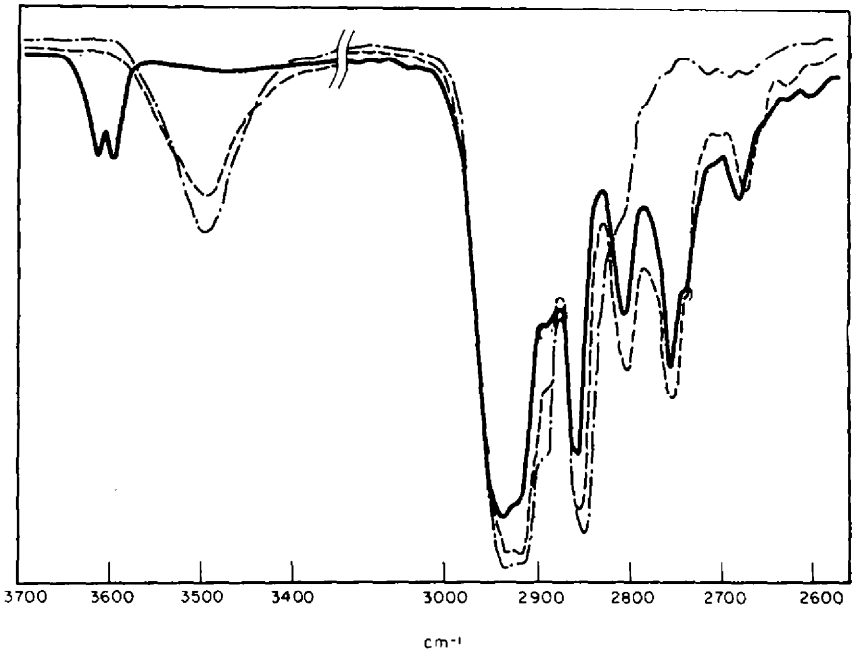


FIG. 3. Infrared spectra* of quinolizidines in CCl_4

quinolizidine A (XVIII)† ——— (20% soln., 0·5 mm thickness)
quinolizidine B (XX) — · — (7% soln., 1·0 mm thickness)
quinolizidine (XXV) - - - - - (8% soln., 1·0 mm thickness)

* Measured on grating infrared spectrometer (Japan Spectroscopic Manufacturing Co., DS402G).

† Split of a band at 3620 cm^{-1} would be interpreted as caused by Fermi resonance (E. B. Wilson, Jr., J. C. Deciuc, *Molecular Vibration*, p. 198, McGraw-Hill, N.Y. (1955)).

[12] F. Bohlmann, *Chem. Ber.* **91**, 2157, 2167 (1958).
[13] W. A. Ayer and G. G. Iverach, *Tetrahedron Letters* No. 3, 87 (1962).

to intramolecular hydrogen bonding between the electron pair of the bridgehead nitrogen and the hydroxyl group[13,14] in the IR spectra identify the configuration of XVII as shown in the Table.

In Fig. 3 the IR spectra (carbon tetrachloride) of quinolizidine A show the presence

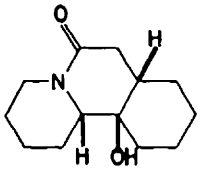
TABLE 1.—CONFIGURATION (C_{7a}-C_{11a}-C_{11b}-N)

	Stable Form	TH*	Unstable Form	TH*
XVIII	cis-syn-trans XIX	+ −	cis-syn-cis	− +
XX	trans-syn-cis XXI	− +	trans-syn-trans	+ −
XXIV	cis-anti-trans	+ +	cis-anti-cis	− −
XXV	trans-anti-trans XXII	+ +	trans-anti-cis	− −

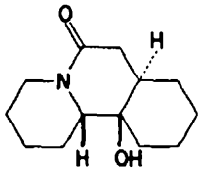
* T: *Trans*-quinolizidine Bonds
H: Intramolecular Hydrogen Bonding

[14] E. L. May and H. Kugita, *J. Org. Chem.* **26**, 188, 1954 (1961); S. Saito and E. L. May, *ibid.* **26**, 4536 (1961).

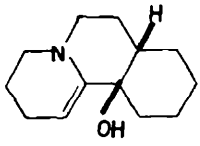
of the *trans*-quinolizidine bands (2760 and 2682 cm^{-1}) and the absence of a band due to the intramolecular hydrogen bonding, whereas the spectra of quinolizidine B show the absence of the former bands and the presence of the latter band (3505 cm^{-1}). Therefore, it is reasonable to conclude that quinolizidine A has a structure XVIII, probably existing in a more stable conformation XIX, and quinolizidine B a structure XX, probably in a conformation XXI, since both compounds are C_{7a} isomers and must have the same configurational relationship regarding C_{11a} and C_{11b}. Accordingly, lactam-carbinols A and B are assigned structures XXII and XXIII, respectively.



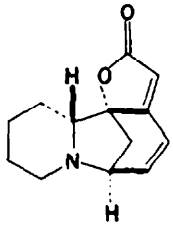
XXII



XXIII



XXVI



XXVII

In order to prove that the assignment is rational, an attempt was made to obtain the isomers, XXIV and XXV. Mercuric acetate dehydrogenation converts XVIII into the dehydroquinolizidine XXVI, the structure of which follows from the IR spectrum. Catalytic hydrogenation of XXVI or sodium borohydride reduction of its hydrochloride give only XVIII in a quantitative yield. Birch reduction of XXVI results in recovery of the starting material. However, the successful syntheses of *rac*-XX and *rac*-XXV, proves unequivocally the structures assigned to quinolizidine A and B and are described later in this paper.

Securinine (I) contains three asymmetric carbon atoms. Of these, relative configuration of C_{5a} and C_{10b} is defined, since the C_{10a}—C_{10b} and C_{5a}-N bonds form the central five-membered ring and, thus, must be *cis* to each other. Therefore, the stereochemical problems remaining to be determined are a configurational relationship of 10_{10a} to C_{10b} or C_{5a} in I, which is compared with a configurational relationship between C_{11a} and C_{11b} in XVII. It is now concluded, from a study of models, that only the steric structure XXVII of securinine can explain the formation of XVIII and XX.

Syntheses of lactam-carbinol B (XXIII) *and quinolizidine* B (XX)

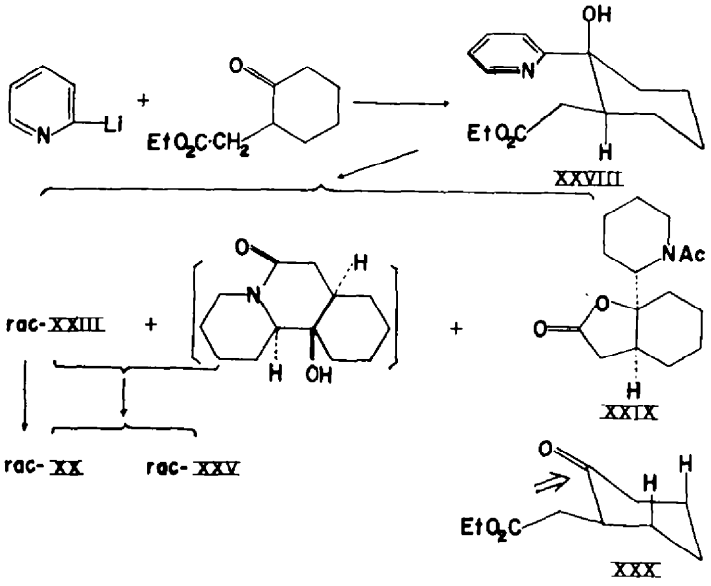
Condensation of 2-pyridyllithium[15] with ethyl 2-oxocyclohexylacetate[16] in dry ether at −50° gives ethyl 2-hydroxy-2-(2′-pyridyl)cyclohexylacetate (XXVIII) in 53% yield.

[15] H. Gilman and S. M. Spatz, *J. Org. Chem.* **16**, 1485 (1951).

[16] A. Mondon, *Chem. Ber.* **92**, 1461 (1959); H. Booth and F. E. King, *J. Chem. Soc.*, 2688 (1958); C-K. Chuang and C-M. Ma, *Ber.* **68**, 871 (1935).

Catalytic hydrogenation of XXVIII over platinum oxide in glacial acetic acid gives an oily lactone, characterized as the N-acetate (XXIX), and a crystalline mixture of the lactam-carbinols, from which only *rac*-XXIII, m.p. 211·5–212·5°, was isolated in a pure state. Reduction of *rac*-XXIII with lithium aluminum hydride yields the pure *rac*-XX, m.p. 86–87·5°. The IR spectra of *rac*-XXIII and *rac*-XX in solution are identical with those of lactam-carbinol B and quinolizidine B, respectively. On the other hand reduction of the mixture of the lactam-carbinols obtained above with lithium aluminum hydride gives a mixture of the *rac*-XX, m.p. 86–87·5°, and *rac*-XXV, m.p. 92–94°, after chromatographic separation.

The other quinolizidine, *rac*-XXV, shows absorption at 3509 (intramolecular hydrogen bonding), 2757 and 2681 cm^{-1} (*trans*-quinolizidine bands) in the IR spectrum (carbon tetrachloride), which was not identified with those of quinolizidine A and B (Fig. 3). The structural assignment of *rac*-XXV is based on the mechanism of the condensation reaction leading to XXVIII.



If 2-pyridyllithium attacks ethyl 2-oxo-cyclohexylacetate from its less-hindered side as shown by an arrow in XXX, the hydroxyl group and hydrogen in XXVIII must be *trans* with respect to the cyclohexane ring, and in this case, the formation of *rac*-XX and *rac*-XXV by successive reduction is to be expected. Thus, the assignment of the structure *rac*-XXV, probably existing in a more stable conformation XXXI, is very probable.

EXPERIMENTAL

M.p.s and b.p.s are uncorrected.

Hydrogenation of securinine (I)

Securinine (10 g) was hydrogenated in 300 ml ethanol over 10% palladium on carbon for 1 hr (1·5 moles hydrogen were rapidly absorbed and the yellow colour of the solution disappeared). Filtration followed by evaporation of ethanol from the filtrate gave 10 g of a syrupy residue, which was heated in 30 ml acetic anhydride on a steam bath for 2 hr. Excess of acetic anhydride was

evaporated and the residue shaken with a mixture of ethyl acetate and 5% hydrochloric acid. The aqueous acid layer was made alkaline with conc aqueous ammonia and extracted with ether. The dried extract was evaporated and the residue distilled at 158–164°/0·1 mm to give 6·4 g of crude oily dihydrosecurinine (III). The hydrochloride of III (5·2 g, 44%) was prepared in hot acetone and recrystallized from methanol–ether in colourless needles, m.p. 256–258°, $[\alpha]_D^{23}$ −71·5° (*c*, 1 in ethanol). (Found: C, 61·13; H, 6·77; N, 5·52. $C_{13}H_{18}ClNO_2$ requires: C, 61·05; H, 7·09; N, 5·48%). The hydrochloride was treated with aqueous ammonia, extracted with ether and after evaporation of the dried extract, distillation of the residue at 160–164°/0·1 mm gave an oil which solidified and recrystallized from pet ether (b.p. 30–60°) in colourless flakes of dihydrosecurinine (III), m.p. 58–60°, $[\alpha]_D^{20}$ nearly 0° (*c*, 1 in ethanol). $\nu_{max}^{CCl_4}$ cm^{-1}: 1815, 1770 (conjugated γ-lactone); 1652 (double bond). (Found: C, 71·51; H, 7·46; N, 6·22. $C_{13}H_{17}NO_2$ requires: C, 71·20; H, 7·82; N, 6·39%).

The ethyl acetate layer was evaporated and the residue distilled at 250° (bath temp)/0·1 mm to give 2·7 g (22%) of the N-acetate of 2-hydroxy-2-(2′-piperidyl)cyclohexylideneacetic acid lactone (XII), which recrystallized from ethyl acetate in colourless cubics, m.p. 166–167°, $[\alpha]_D^{26}$ +134·3° (*c*, 1 in ethanol). ν_{max}^{Nujol} cm^{-1}: 1765 (conjugated γ-lactone), 1640 (amide). (Found: C, 68·56; H, 8·05; N, 5·24. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04; N, 5·32%). The N-formate, colourless needles from ethyl acetate-n-hexane, m.p. 135–137°. (Found: C, 67·35; H, 7·67; N, 5·51. $C_{14}H_{19}NO_3$ requires: C, 67·44; H, 7·68; N, 5·62%).

Tetrahydrosecurinine (IV)

Dihydrosecurinine (III; 3·6 g) was hydrogenated in 20 ml ethanol over 0·2 g platinum oxide for 12 hr (1 mole hydrogen was absorbed). After filtration and removal of ethanol from the filtrate, the residue was distilled at 177–178°/4 mm to give an oil which solidified. Recrystallization from pet ether (b.p. 30–50°) gave 2·8 g (78%) of tetrahydrosecurinine (IV) in colourless needles, m.p. 67–68°, $[\alpha]_D^{20}$ +21·5°(*c*, 1 in ethanol). $\nu_{max}^{CCl_4}$ cm^{-1}: 1790 (γ-lactone). (Found: C, 70·50; H, 8·68; N, 6·16. $C_{13}H_{19}NO_2$ requires: C, 70·55; H, 8·65; N, 6·33%). The hydrochloride recrystallized from methanol–ether in colourless needles, m.p. 263–265°, (Found: C, 60·33; H, 7·69; N, 5·61. $C_{13}H_{20}ClNO_2$ requires: C, 60·57; H, 7·87; N, 5·43%).

Zinc-dust distillation of securinine (I)

An intimate mixture of 1·5 g and 25 g zinc-dust was thickly coated with another 25 g zinc-dust. The mixture was distilled under a stream of nitrogen at bath temp of 400–500° for 20 min.

The yellow oily distillate was shaken with a mixture of ether and 10% hydrochloric acid. The ether layer was extracted with 10% sodium hydroxide solution. The alkaline extract was acidified with 10% hydrochloric acid and then extracted with ether. The dried ethereal extract was evaporated and the residue distilled at 140° (bath temp)/55 mm. The distillate showed a positive ferric chloride colour-test (blue-violet) and, on treatment with phenylisocyanate, gave phenyl carbanilate, m.p. 123–125° (from benzene), which was identified with an authentic sample. Paper chromatography of this distillate, carried out according to the direction of Hossfeld,[17] indicated the presence of both *o*-cresol and phenol.

The aqueous acid layer was made alkaline with potassium carbonate and extracted with ether. Evaporation of the dried extract followed by distillation at 120–130° (bath temp)/15 mm gave an oily aromatic base which showed a positive diazo-coupling test (red). Treatment of this oily base with acetic anhydride followed by recrystallization from water gave the N-acetate, m.p. 140–142°, which was identical with an authentic specimen of N-acetyl-*p*-toluidine in m.p., mixed m.p. and IR spectrum.

The uncondensed gas was introduced into a solution of picric acid in anhydrous ether to give a picrate, m.p. 275–278° (dec), identical with an authentic sample of ammonium pierate.

Potassium permanganate oxidation of tetrahydrosecurinine (IV)

To a solution of 1·1 g IV and 0·45 g oxalic acid in 50 ml water a 1% potassium permanganate solution containing 0·53 g potassium permanganate was added dropwise with stirring at −2 ~ 0°. After the addition was complete, an inorganic substance was removed by filtration and washed

[17] R. L. Hossfeld, *J. Amer. Chem. Soc.* **73**, 852 (1951).

with dil. hydrochloric acid. The filtrate and washings were combined and shaken with chloroform. The chloroform layer was dried and evaporated to give 170 mg of a yellowish viscous oil, which was not characterized.

The aqueous acid layer was made alkaline with potassium carbonate and shaken with chloroform. Evaporation of the chloroform layer gave 500 mg of yellowish solid, m.p. 65–67°, after purification by vacuum distillation, and identical with tetrahydrosecurinine.

The aqueous alkaline layer was acidified with dil hydrochloric acid and evaporated to dryness under red. press. at 45–50°. The residue was extracted with ether and then boiling ethanol. From the ethereal extract, colourless crystals identical with oxalic acid by direct comparison with an authentic specimen were obtained. The ethanol extract after chromatography on silica gel yielded 120 mg of colourless oil, which showed an absorption at 1718 cm^{-1} in the IR spectrum. This oil was refluxed with a solution of 200 mg potassium hydroxide in 15 ml 90% ethanol. After cooling, the reaction mixture was acidified with dil hydrochloric acid, extracted with a large amount of ether and dried. Evaporation of the solvent gave a crystalline product of m.p. 193–196° (dec), identical with an authentic specimen of phthalic acid by comparison of their IR spectra and by conversion into phthalic anhydride in the following manner. The crystalline product was refluxed with thionyl chloride in ether for 2 hr. The solvent and excess of thionyl chloride were removed under red. press. and the residue sublimed to give colourless needles m.p. 128–129·5°, identical with an authentic specimen of phthalic anhydride.

Cyanogen bromide reaction of securinine (I)

To a stirred solution of 0·27 g cyanogen bromide in 10 ml chloroform, a solution of 0·5 g securinine (I) in 10 ml chloroform was added at 40° and the mixture refluxed 1 hr. The cooled mixture was washed with 5% hydrochloric acid, water, 5% sodium bicarbonate and then water, dried and evaporated. The residual solid was recrystallized from ethyl acetate–n–hexane to give 0·45 g (60·4%) 4-bromo-2-(N-cyano-2′-piperidyl)-2-hydroxy-cyclohex-5-enylideneacetic acid lactone (VIII) in colourless prisms, m.p. 154–155°. λ_{max}^{EtOH} 259·5 mμ (log ε 4·22), ν_{max}^{Nujol} cm^{-1}: 2200 (CN); 1770, 1750 (conjugated γ-lactone); 1640 (double bond). (Found: C, 52·19; H, 4·73; N, 8·68; Br, 24·62. $C_{14}H_{15}BrN_2O_2$ requires: C, 52·02; H, 4·68; N, 8·67; Br, 24·73%).

2-(N-*cyano*-2′-*piperidyl*)-2-*hydroxycyclohex*-5-*enylideneacetic acid lactone* (IX)

A mixture of 2·6 g VIII, 1·3 g sodium acetate and 30 ml ethanol was hydrogenated over 0·5 g 10% palladium on carbon until 1 mole of hydrogen was taken up. The filtered solution was evaporated to dryness and the residue chromatographed on alumina in chloroform. A colourless solid was eluted and recrystallized from isopropyl ether to give 0·3 g of IX in colourless needles, m.p. 103–104°. ν_{max}^{Nujol} cm^{-1}: 2200 (CN); 1765 (conjugated lactone); 1650 (double bond). λ_{max}^{EtOH} 258 mμ (log ε 4·12). Found: C, 68·92; H, 6·63; N, 11·73. $C_{14}H_{16}N_2O_2$ requires: C, 68·83; H, 6·60; N, 11·47%).

2-(N-*cyano*-2′-*piperidyl*)-2-*hydroxycyclohexylideneacetic acid lactone* (X)

A solution of 0·5 g IX in 20 ml ethanol was hydrogenated over 0·1 g palladium on carbon until 1 mole of hydrogen was taken up. The filtered solution was evaporated to dryness. The residue was recrystallized from ethyl acetate to yield 0·2 g (40%) of (X), m.p. 123–124°. ν_{max}^{Nujol} cm^{-1}: 2200 (CN); 1760 (conjugated lactone); 1660 (double bond). (Found: C, 68·30; H, 7·22; N, 11·41. $C_{14}H_{18}N_2O_2$ requires: C, 68·27; H, 7·37; N, 11·37%).

2-*Hydroxy*-2-(2′-*piperidyl*)*cyclohex*-4-*enylideneacetic acid lactone* (XIV)

A mixture of 5 g I, 300 ml ether, 8 g aluminum amalgam, and 5 ml water was stirred at room temp for 3–5 hr, until the yellow colour of the solution disappeared. Filtration followed by evaporation of the solvents from the filtrate gave 4·7 g of an oil which was converted to the hydrochloride by the usual method. Recrystallization from methanol–ether gave 3·4 g of XIV as the hydrochloride monohydrate in colourless prisms, m.p. 218–220°, $[\alpha]_D^{25}$ +94·8° (*c*, 1 in ethanol). ν_{max}^{Nujol} cm^{-1}: 3380 (H_2O); 1765 (conjugated lactone); 1664, 1655 (double bond). (Found: C, 57·72; H, 6·77; N, 5·18. $C_{13}H_{18}ClNO_2 \cdot H_2O$ requires: C, 57·13; H, 7·36; N, 5·12%). The picrate, yellow plates from methanol–acetone, m.p. 205–208° (dec) (Found: C, 50·70; H, 4·37; N, 12·14. $C_{19}H_{20}N_4O_9$ requires: C, 50·89; H, 4·50; N, 12·50%). The N-acetate was obtained in colourless plates by warming the

crude oil (XIV) with acetic anhydride followed by recrystallization from ethyl acetate, m.p. 134–135°, $[\alpha]_D^{28}$ + 201·9° (*c*, 1 in ethanol). $\nu_{max}^{CS_2}$ cm^{-1}: 1785, 1770 (conjugated lactone); 1655 (amide). (Found: C, 68·58; H, 7·12; N, 5·34. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). The N-formate was prepared by warming the crude oil XIV with a mixture of 98% formic acid and acetic anhydride, followed by recrystallization from ethyl acetate, colourless plates, m.p. 146–148° (Found: C, 67·82; H, 6·98; N, 5·66. $C_{14}H_{17}NO_3$ requires: C, 67·99; H, 6·93; N, 5·66%).

2-Hydroxy-2-(2'-piperidyl)cyclohex-5-enylideneacetic acid lactone (XI)

(a) From XIV *by isomerization of the double bond.* Distillation of 4·7 g XIV at 150–160° (bath temp)/0·6 mm gave 4·5 g of a distillate which was converted to the hydrochloride. It was recrystallized from methanol–acetone to give 4·1 g (81%) of XI as the hydrochloride monohydrate in colourless needles, m.p. 226–227°. $[\alpha]_D^{26}$ −178·1° (*c*, 1 in ethanol). λ_{max}^{EtOH} 258 mμ (log ε 4·15). ν_{max}^{Nujol} cm^{-1}: 3500(H_2O), 1760 (conjugated lactone), 1645 (double bond). (Found: C, 57·56; H, 7·57; N, 5·24. $C_{13}H_{18}ClNO_3 \cdot H_2O$ requires: C, 57·13; H, 7·36; N, 5·12%). The picrate crystallized as yellow cubes from methanol, m.p. 191–193°. (Found: C, 50·67; H, 4·64; N, 12·73. $C_{19}H_{20}N_4O_9$ requires: C, 50·89; H, 4·50; N, 12·50%). The N-acetate crystallized as colourless cubes from ethyl acetate, m.p. 158–160°, $[\alpha]_D^{24}$ nearly 0° (*c*, 0·56 in ethanol). λ_{max}^{EtOH} 261 mμ (log ε 4·16). ν_{max}^{Nujol} cm^{-1}: 1755 (conjugated lactone), 1640 (amide). (Found: C, 68·89; H, 7·20; N, 5·33. $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%). The N-formate crystallized as colourless prisms from ethyl acetate–n-hexane, m.p. 161–163°. (Found: C, 68·12; H, 7·03; N, 5·71. $C_{14}H_{17}NO_3$ requires: C, 67·99; H, 6·93; N, 5·66%).

(b) *From* IX *by hydrolysis followed by decarboxylation.* A mixture of 0·1 g of IX, 3 ml of 6% hydrochloric acid and one drop of glacial acetic acid was refluxed for 24 hr. The cooled mixture was washed with chloroform. The acid layer was concentrated, made alkaline with potassium carbonate and extracted with chloroform. Evaporation of the dried extract followed by distillation of the residue at 210–230° (bath temp)/0·3 mm gave 64 mg (71%) of XI which was converted to both picrate and N-acetate. They were identical respectively in m.p., mixed m.p. and IR spectra with those of XI prepared as described in (a).

2-Hydroxy-2-(2'-piperidyl)cyclohexylideneacetic acid lactone (XII)

(a) *From* XI. Compound XI (5 g) was hydrogenated in 10 ml ethanol over 1 g 10% palladium on carbon for 1–2 hr until 1 mole of hydrogen was taken up. Filtration followed by evaporation of ethanol from the filtrate gave an oil, which was distilled at 150–160°/0·6 mm. The distillate was converted to the hydrochloride, which was recrystallized from methanol–ether, giving 4·1 g (74%) of XII as the hydrochloride monohydrate in colourless cubes, m.p. 221–222°, $[\alpha]_D^{28}$ +74·3° (*c*, 1 in ethanol). ν_{max}^{Nujol} cm^{-1}: 3400 (H_2O), 1740 (conjugated lactone), 1655 (double bond). (Found: C, 56·19; H, 8·00; N, 5·22. $C_{13}H_{20}ClNO_3 \cdot H_2O$ requires: C, 56·62; H, 8·04; N, 5·08%). The picrate crystallized as yellow plates from ethanol, m.p. 213–214° (dec). (Found: C, 51·11; H, 4·94; N, 12·61. $C_{19}H_{22}N_4O_9$ requires: C, 50·66; H, 4·92; N, 12·44%). The N-acetate crystallized as colourless cubes from ethyl acetate, m.p. 166–167°, identical in m.p., mixed m.p. and IR spectrum with the N-acetate obtained in the hydrogenation of securinine as described above for dihydrosecurinine.

(b) *From* XIV. The hydrogenation of XIV, carried out in a similar manner to the experiment described in (a), gave XII in 74% yield.

2-Hydroxy-2-(N-acetyl-2'-piperidyl)cyclohexylacetic acid lactone (XV)

The N-acetate of XII (2 g) was hydrogenated in 150 ml ethanol over 0·3 g platinum oxide for 20 hr until 1 mole of hydrogen was absorbed. Filtration and evaporation of the filtrate followed by recrystallization of the solid residue from ethyl acetate gave 1·8 g (90%) of XV in colourless prisms, m.p. 157–158°, $[\alpha]_D^{26}$ +111·2° (*c*, 1 in ethanol). ν_{max}^{Nujol} cm^{-1}: 1765 (lactone), 1635 (amide). (Found: C, 67·60; H, 8·70; N, 5·41. $C_{15}H_{23}NO_3$ requires: C, 67·89; H, 8·74; N, 5·28%).

Lactam-carbinol A (XXII)

(a) *From securinine* (I). A solution of 1 g I and 0·8 g potassium hydroxide in 50 ml water–tetrahydrofuran (1:2) was hydrogenated over one spoon of Raney nickel (W-7). After rapid uptake of about 2 moles of hydrogen in 30 min, the filtered solution was neutralized to pH 6·5 with 3%

hydrochloric acid and refluxed for 2 hr. Concentration, extraction with chloroform and evaporation of the solvent followed by distillation of the residue at 250° (bath temp)/0·4 mm gave 0·15 g crude XXII. Recrystallization from acetone gave 0·13 g (12%) of XXII in colourless needles, m.p. 184–185°, $[\alpha]_D^{27}$ +3° (*c*, 0·5 in ethanol). $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (hydroxyl), 1630 (lactam). (Found: C, 70·00; H, 9·16; N, 6·16. $C_{13}H_{21}NO_2$ requires: C, 69·92; H, 9·48; N, 6·27%).

(b) *From* XII. A solution of 0·5 g XII hydrochloride and 0·4 g potassium hydroxide in 5 ml water and 1 ml tetrahydrofuran was refluxed for 2 hr. Water (15 ml) was added to the cooled solution and the mixture hydrogenated with one spoon Raney nickel (W-7) resulting in the rapid uptake of 1 mole hydrogen. The mixture was filtered and the filtrate neutralized to pH 6·5 with 3% hydrochloric acid. The solution was refluxed for 2 hr, evaporated and extracted with chloroform. Evaporation of the dried extract and chromatography of the residue on alumina in chloroform followed by recrystallization from acetone gave 0·23 g (53·2%) of XXII, m.p. 184–185°, identical in m.p., mixed m.p. and IR spectrum with lactam-carbinol A obtained directly from securinine by the hydrogenation as described in (a).

Lactam-carbinol B (XXIII)

(a) *From* XII *by hydrogenation.* A solution of 0·2 g XII in 10 ml ethanol was hydrogenated over 50 mg platinum oxide. One mole of hydrogen was taken up in 10 hr. The filtered solution was refluxed for 3 hr and evaporated to dryness. Recrystallization from acetone gave 1·3 g (65%) XXIII in colourless prisms, m.p. 223–224°. $[\alpha]_D^{25}$ +32·6° (*c*, 0·4 in chloroform). $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (hydroxyl), 1630 (lactam). (Found: C, 70·11; H, 9·43; N, 6·19. $C_{13}H_{21}NO_2$ requires: C, 69·92; H, 9·48; N, 6·27%).

(b) *From* XV *by hydrolysis.* A solution of 0·5 g XV in 10 ml 10% potassium hydroxide was refluxed for 6 hr. The cooled solution was acidified to pH 6·5 with 3% hydrochloric acid and refluxed for 3 hr. Extraction of the cooled solution with chloroform and evaporation of the dried extract followed by recrystallization from acetone gave 0·1 g colourless prisms, m.p. 223–224°, identical in m.p., mixed m.p. and IR spectrum with lactam-carbinol B obtained in (a).

Dehydrogenation of lactam-carbinol A (XXII). An intimate mixture of 0·1 g XXII and 0·1 g 10% palladium on carbon was immersed in a metal-bath maintained at 280–290° under a stream of nitrogen for 2 hr. The cooled mixture was extracted with ether and the dried extract evaporated. The residue was distilled at 120–130°/0·4 mm to give 20 mg of a colourless oil, λ_{max}^{EtOH} 233 mμ (log ε 3·91), 268 mμ (log ε 3·79). This was converted to a picrate which recrystallized from ethanol in yellow needles, m.p. 143–145° and was identical in m.p., mixed m.p. and IR spectrum with the picrate of 2-(2′-tolyl)pyridine prepared according to the directions of Bradsher.[9]

Dehydrogenation of lactam-carbinol B (XXIII). Lactam-carbinol B (XXIII) was subjected to dehydrogenation in a similar manner to that described for the dehydrogenation of lactam carbinol A(XXII). The picrate of 2-(2′-tolyl)pyridine, m.p. 143–145°, was obtained and identified with the authentic specimen.[9]

Quinolizidine A (11a-*hydroxyperhydrobenzo[a]quinolizidine*) (XVIII)

To a stirred suspension of 0·3 g lithium aluminum hydride in 20 ml anhydrous ether a solution of 0·55 g XXII in 25 ml tetrahydrofuran was added at 5–10°. After the addition was complete, stirring was continued for 5 hr at room temp and then the mixture was refluxed for 5 hr. The cooled mixture was decomposed carefully with water and filtered. The dried filtrate was evaporated and the residue distilled at 210° (bath temp)/0·5 mm to give 0·51 g crude XVIII. The picrate (0·8 g, 77%) recrystallized from ethanol in yellow needles, m.p. 215–217°. (Found: C, 51·87; H, 5·95; N, 12·70. $C_{19}H_{26}N_4O_8$ requires: 52·05; H, 5·98; N, 12·78%).

The picrate was made alkaline with 2% lithium hydroxide and extracted with ether. Evaporation of the dried extract and distillation of the residue at 210° (bath temp)/0·5 mm gave 0·4 g XVIII which recrystallized from n-hexane in colourless flakes, m.p. 163–165°, $[\alpha]_D^{25}$ +44·1° (*c*, 0·5 in ethanol). (Found: C, 74·17; H, 10·54; N, 6·78. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%).

Quinolizidine B (11a-*hydroxyperhydrobenzo[a]quinolizidine* (XX)

To a suspension of 5·0 g lithium aluminum hydride in 50 ml tetrahydrofuran, a solution of 2·5 g XX in 200 ml tetrahydrofuran was added at 5–10° with stirring. The mixture was worked up as

described above for XVIII to give a crude oil, b.p. 180° (bath temp)/0·6 mm, which was converted to the picrate and recrystallized from ethanol as yellow needles (3·3 g, 67·2%) m.p. 200–201°. (Found: C, 52·31; H, 5·87; N, 12·89. $C_{19}H_{26}N_4O_8$ requires: C, 52·05; H, 5·98; N, 12·78%).

The picrate was treated with 2% lithium hydroxide to give XX, which recrystallized from pet ether (b.p. 30–50°) in colourless prisms, m.p. 60–61°, $[\alpha]_D^{25}$ −13·2° (*c*, 0·5 in ethanol). (Found: C, 74·24; H, 10·61; N, 6·78. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08; N, 6·69%).

11a-*Hydroxy*-2,3,6,7,7a,8,9,10,11,11a-*decahydro*-4H-*benzo[a]quinolizine* (XXVI)

A solution of 0·9 g XVIII, 5·1 g mercuric acetate in 120 ml 5% acetic acid was heated on a steam bath. Mercurous acetate began to precipitate within 30 min and after 3 hr mercurous acetate was removed from the cooled solution by filtration. The filtrate was saturated with hydrogen sulfide. After filtration, 3 ml conc hydrochloric acid was added and the solution was evaporated to dryness to give 0·9 g of the very hygroscopic ketiminium chloride in prisms, ν_{max}^{Nujol} cm^{-1}: 3400 (hydroxyl), 3100 (H_2O), 1672 (C=$\overset{+}{N}$). The chloride was made alkaline with conc sodium hydroxide solution and extracted with ether. The dried extract was evaporated below 20° under red. press. to give XXVI, m.p. 85–87°, which decomposed rapidly in boiling n-hexane. ν_{max}^{Nujol} cm^{-1}: 3400 (hydroxyl); 1650 (double bond).

Ethyl 2-*hydroxy*-2-(2′-*pyridyl*)*cyclohexylacetate* (XXVIII)

A solution of 8·8 g 2-bromopyridine[18] in 30 ml anhydrous ether was added to a stirred solution of n-butyllithium[19] (prepared from 10·5 g lithium and 8·5 g n-butylbromide) in 20 ml anhydrous ether in a stream of nitrogen at −20° over a period of 15 min. After the addition was complete, the stirring was continued for an additional 30 min. The 2-pyridyllithium[15] solution obtained was added to a solution of 11·8 g ethyl 2-oxocyclohexylacetate[16] in 50 ml anhydrous ether with stirring at −50° for 1 hr. After the addition was complete, stirring was continued for 1 hr at −50° in a stream of nitrogen. The resulting complex was decomposed with saturated ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether. The combined ether layers were extracted with 8% hydrochloric acid. The acid extract was made alkaline with aqueous ammonia and extracted with ether. The extract was washed with water, dried and evaporated. Distillation of the residue gave 7·1 g (53% based on 2-bromopyridine) XXVIII as a yellow viscous oil, b.p. 120–127°/0·1 mm, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3378 (hydroxyl), 1718 (ester). (Found: C, 68·55; H, 8·00. $C_{15}H_{21}NO_3$ requires: C, 68·41; H, 8·04%).

Catalytic hydrogeneration of (XXVIII)

Compound XXVIII (4·2 g) was hydrogenated in 15 ml glacial acetic acid over 400 mg platinum oxide at atm press and room temp. The absorption of the theoretical amount of hydrogen ceased after 23 hr. The filtrate, free from catalyst, was made alkaline with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried and evaporated. The residue, (3·5 g) which consisted of crystals and oil, was separated by filtration. Recrystallization of the crystals (2·0 g) from acetone gave colourless prisms of m.p. 195–203°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3378 (hydroxyl), 1628 (lactam). This was chromatographed on 60 g of silica-gel. Elution with acetone gave 0·8 g crystals, which after recrystallization from acetone gave 0·4 g *rac*-(XXIII) in colourless prisms, m.p. 211–212·5°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3378 (hydroxyl), 1630 (lactam) (Found: C, 69·62; H, 9·50. $C_{13}H_{21}NO_2$ requires: C, 69·92; H, 9·48%). The IR spectrum of this compound in chloroform was identical with that of lactam-carbinol B (XXIII). Elution with ethyl acetate gave 0·7 g crystals, which was shown by IR spectrum to be a mixture of *rac*-XXIII and its isomeric lactam-carbinol.

The separated oily portion (0·9 g) was warmed with 19 g acetic anhydride on a water bath for 3 hr. After excess of acetic anhydride was removed under red. press., the residue was added to water, made alkaline with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried and evaporated. The reddish brown oil (0·9 g) was chromatographed on 27 g alumina. Elution with chloroform gave 0·2 g lactone-acetate (XXIX), which recrystallized from ethyl acetate

[18] C. F. H. Allen and J. R. Thirtle, *Organic Syntheses* Coll. Vol. III, p. 136. John Wiley, New York (1955).

[19] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *J. Amer. Chem. Soc.* **71**, 1499 (1949).

in colourless plates, m.p. 145–146°, $\nu_{max}^{CHCl_3}$ 3 cm^{-1}: 1789 (lactone), 1629 (amide) (Found: C, 67·79; 8·69. $C_{16}H_{23}NO_3$ requires: C, 67·89; H, 8·74%). The IR spectrum of XXIX in chloroform was identical with that of XV.

Lithium aluminum hydride reduction of the mixture of lactam-carbinols

Lactam-carbinols (1·0 g), m.p. 195–203°, were refluxed with 1·5 g lithium aluminum hydride in 60 ml anhydrous tetrahydrofuran for 20 hr. The reaction mixture was decomposed with 10% sodium hydroxide and extracted with ether. The extract was dried and evaporated. Distillation of the residue gave 0·7 g white solid, b.p. 115° (bath temp)/0·03–0·04 mm (Found: C, 74·70; H, 11·04. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08%). This was chromatographed on 35 g alumina. Elution with benzene and recrystallization from pet ether (b.p. 45–50°) gave 0·1 g of *rac*-XXV in colourless needles, m.p. 92–94°, $\nu_{max}^{CCl_4}$ cm^{-1}: 3509 (hydroxyl), 2757, 2681 (*trans*-quinolizidine) (Found: C, 74·60; H, 11·06. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08%). Elution with ether and recrystallization from pet ether (b.p. 45–50°) gave 0·4 g of *rac*-XX in colourless plates, m.p. 86–87·5°, $\nu_{max}^{CCl_4}$ cm^{-1}: 3505 (hydroxyl) (Found: 74·64; H, 11·15. $C_{13}H_{23}NO$ requires: C, 74·59; H, 11·08%). The IR spectrum of the latter in carbon tetrachloride was identical with that of quinolizidine B (XX).

Reduction of rac-XXIII

Rac-XXIII (400 mg) was reduced with 500 mg lithium aluminum hydride and worked up in a similar manner to that described above. Recrystallization of the distillate (300 mg), b.p. 115° (bath temp)/0·03–0·04 mm, from pet ether (b.p. 45–50°) gave *rac*-XX as colourless plates, m.p. 86–87·5°, identical with the specimen of *rac*-(XX) obtained above.

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