# Synthesis of 1,2,4,6,7,11b-Hexahydrobenzo[*a*]quinolizin-3-one and of Some Related Compounds

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High yield syntheses of 3-ethylidene-1,2,4,6,7,11b-hexahydrobenzo[*a*]quinolizine and the corresponding 3-ketone, and of 3-ethyl-2,3,4,6,7,11b-hexahydro-1*H*-benzo[*a*]quinolizine, are described, starting from 1-ethoxycarbonylmethyl-3,4-dihydroisoquinoline.

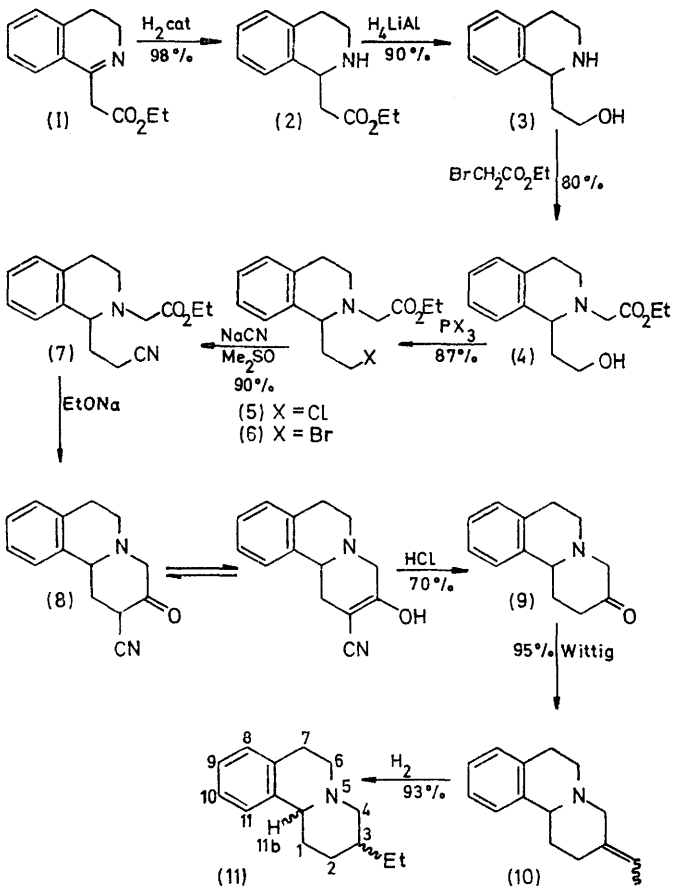
THERE has been considerable interest from the pharmacological point of view in syntheses of benzo[*a*]quinolizine derivatives, generally starting from a hydroisoquinoline structure.[1-5] The present paper describes the synthesis of an important intermediate, 1,2,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-3-one, and some of its derivatives, from 1-ethoxycarbonylmethyl-3,4-dihydroisoquinoline (1), prepared by the method of Sobotka and his co-workers.[4]

Among the various methods available for the preparation of isoquinoline derivatives, the cyclisation of nitrilium salts [6,7] has proved to be useful, notably in the synthesis of 8-azasteroids.[3,4] We therefore attempted to make 1-ethoxycarbonylethyl-3,4-dihydroisoquinoline, which would have been a useful starting material, by condensation of ethyl 3-cyanopropionate with (2-chloroethyl)benzene. Unfortunately, this reaction gave non-basic products; we therefore decided upon chain lengthening of the previously described 1-ethoxycarbonylmethyl-3,4-dihydroisoquinoline (1) [2,4] (Scheme 1).

Hydrogenation of 1-ethoxycarbonylmethyl-3,4-dihydroisoquinoline over Adams catalyst in acetic acid quantitatively yielded the tetrahydroisoquinoline (2). Hydride reduction of this ester gave the crystalline 1,2,3,4-tetrahydro-1-(2-hydroxyethyl)isoquinoline (3) (Russian workers described this compound as a liquid [2]).

Alkylation of the latter by ethyl bromoacetate in dry acetone yielded 2-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-1-(2-hydroxyethyl)isoquinoline (4) which was directly converted into the 1-(2-chloroethyl) derivative (5) by phosphorus trichloride in dry benzene. The bromo-derivative (6) was prepared analogously.

The halogeno-compound was converted into the




SCHEME 1

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[2] G. G. Agbalyan, A. D. Nshanyan, and L. A. Nersesyan, *Izvest. Akad. Nauk Arm. S.S.R., Ser. khim. Nauk.*, 1963, **16**, 77 (*Chem. Abs.*, 1963, **59**, 5132b).
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[5] G. Jones and J. Wood, *Tetrahedron*, 1965, **21**, 2529, 2961.
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nitrile (7) by reaction with sodium cyanide–potassium cyanide in dry dimethyl sulphoxide.[8,9] The best yield was obtained with the chloro-compound; the bromo-derivative proved much too reactive towards dimethyl-sulphoxide.

1-(2-Cyanoethyl)-2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (7) was cyclised by the action of sodium ethoxide in dry toluene[5] to give 2-cyano-1,2,4,6,7,11b-hexahydrobenzo[*a*]quinolizin-3-one (8), which was converted into 1,2,4,6,7,11b-hexahydro-benzo[*a*]quinolizin-3-one (9) by refluxing in azeotropic hydrochlorhydric acid.

The cyano-ketone (8) was obtained in the enolic form, as shown by the i.r. spectrum (presence of OH and conjugated CN bands but not CO band).

The highly unstable 3-ketone was rapidly transformed into the 3-ethylidene derivative (10) by a Wittig reaction in dimethyl sulphoxide.[10] Hydrogenation of this product over platinum in acetic acid gave a mixture of isomeric 3-ethyl-2,3,4,6,7,11b-hexahydro-1*H*-benzo[*a*]-quinolizines (11), the composition of which was studied by n.m.r.

*Stereochemistry of the Hexahydrobenzo*[a]*quinolizine.*—The 100 MHz n.m.r. spectra of the ketone (9), the ethylidene derivative (10), and the reduction product in deuteriochloroform were measured. Our interpretation of the results is based on the assigments for conformational isomers of benzo[*a*]quinolizidine given by Brossi and his co-workers.[11] They found that the difference in chemical shift for the angular proton is a characteristic of the conformation: a low-field signal below δ 3·8 p.p.m. is characteristic of both *cis*-conformations, which may be distinguished by the splitting pattern of this signal.

In the spectrum (Figure 1) of 1,2,4,6,7,11b-hexahydro-benzo[*a*]quinolizin-3-one (9), a quartet centred at δ 4·73 p.p.m. is thus attributable to the angular 11b-proton of the *cis*-quinolizidine form (b) (Scheme 2). The signal shows a small *ax–eq* (3 c./sec.) and a large *ax–ax* (8 c./sec.) coupling and integrates for 0·25H. No discernible signal for the *cis*-quinolizidine form (c) is present; thus an equilibrium mixture of 75% *trans* and 25% *cis* (b) form is present in deuteriochloroform.

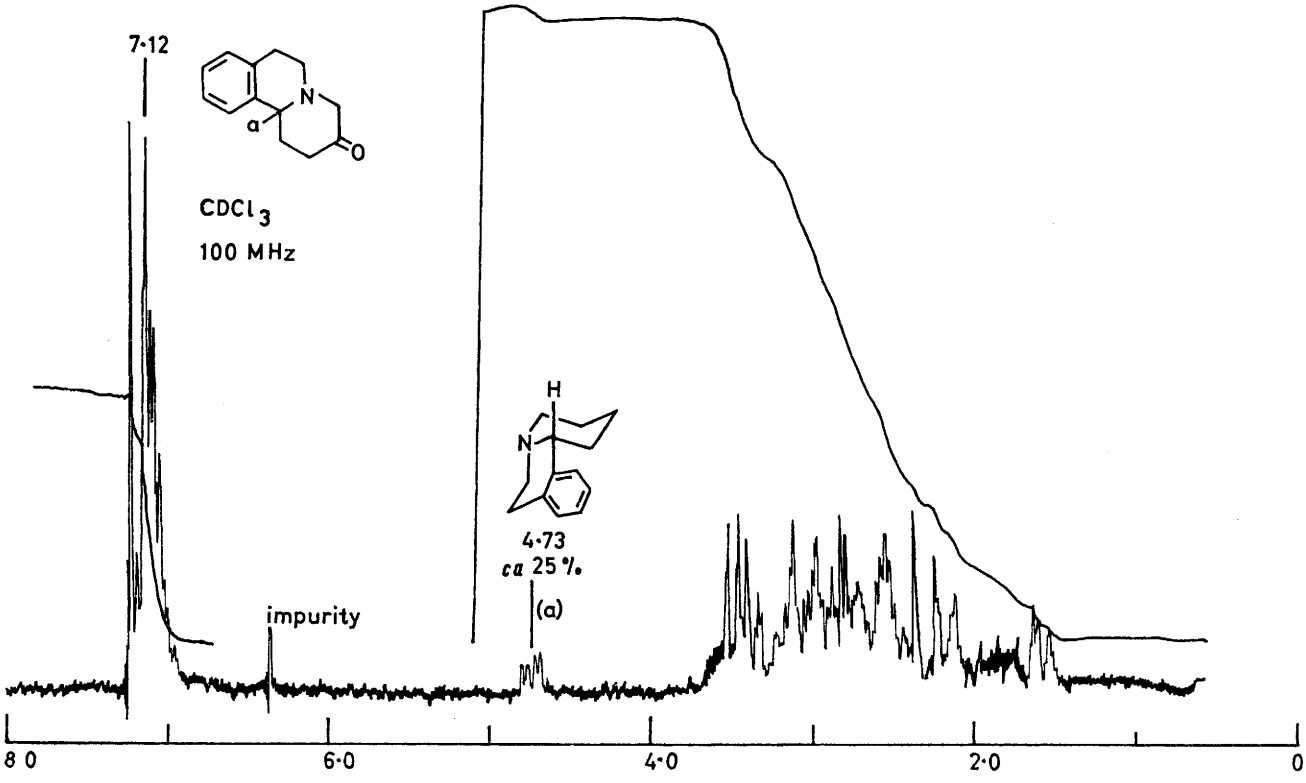


FIGURE 1

Similarly, in the spectrum of 3-ethylidene-1,2,4,6,7,11b-hexahydro[*a*]benzoquinolizine (10) (Figure 2), the signal of the angular 11b-proton of the *cis* (b) form appears as a quartet ($J_{ax,ax}$ 8, $J_{ax,eq}$ 3 c./sec.) centred at δ 4·73 p.p.m. (0·25H). Thus the equilibrium mixture contains 75% *trans* and 25% *cis* (b) form.

The spectrum of 3-ethyl-2,3,4,6,7,11b-hexahydro-1*H*-benzo[*a*]quinolizine (11) (Figure 3) shows a quartet (0·25H) centred at δ 4·74 p.p.m. with the same couplings

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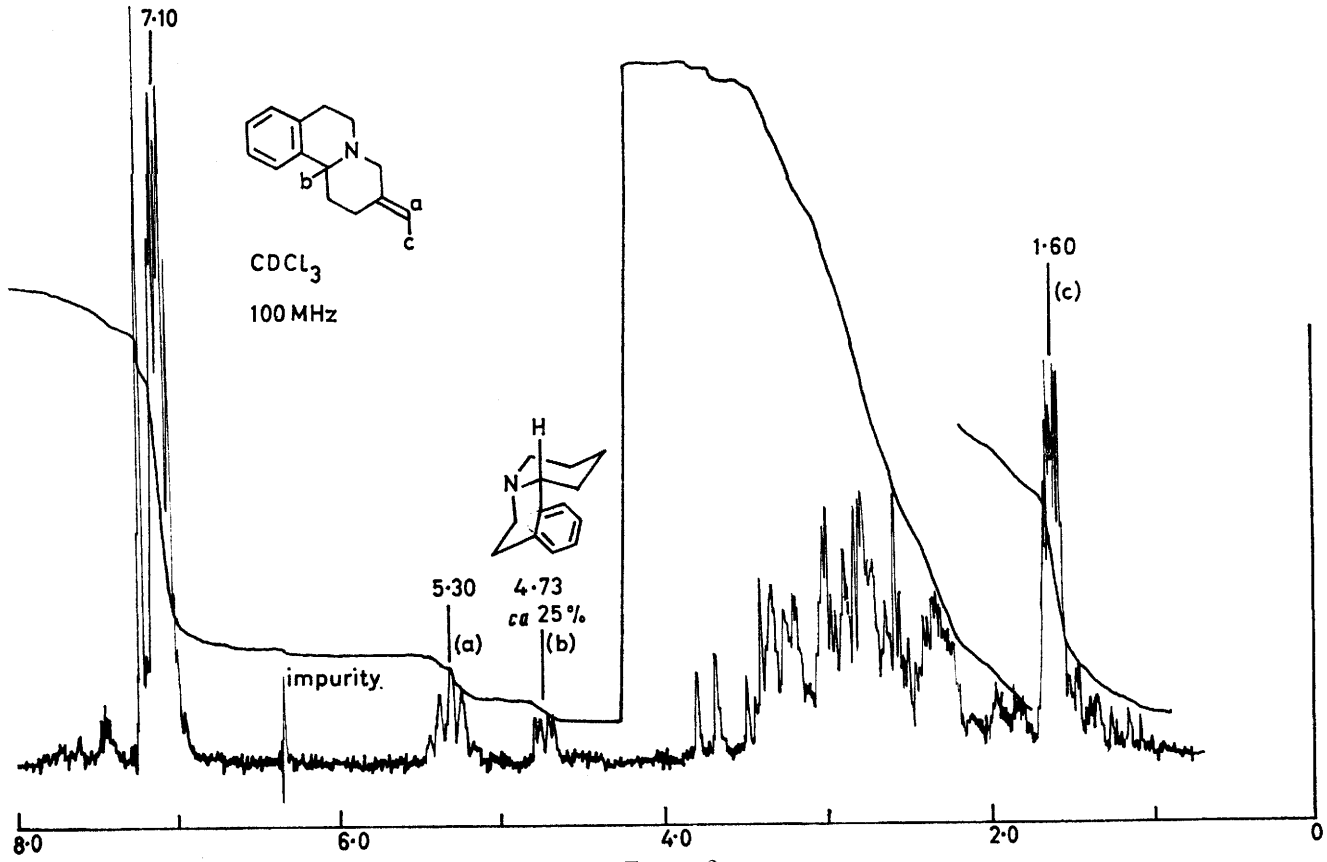



FIGURE 2

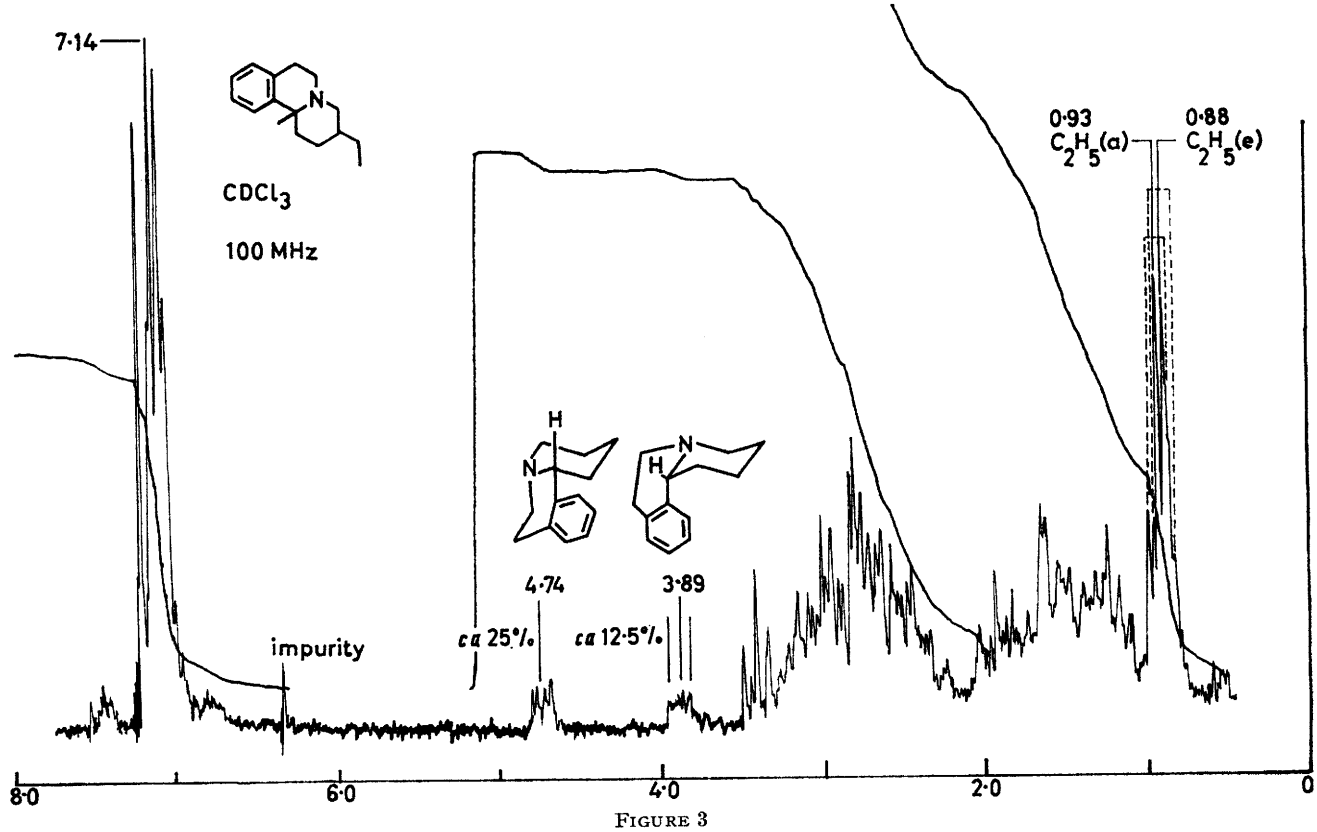
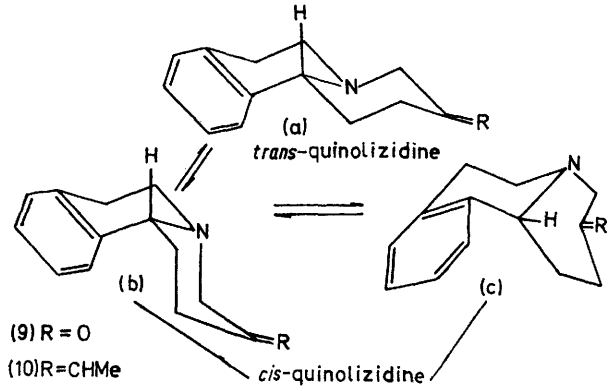



FIGURE 3

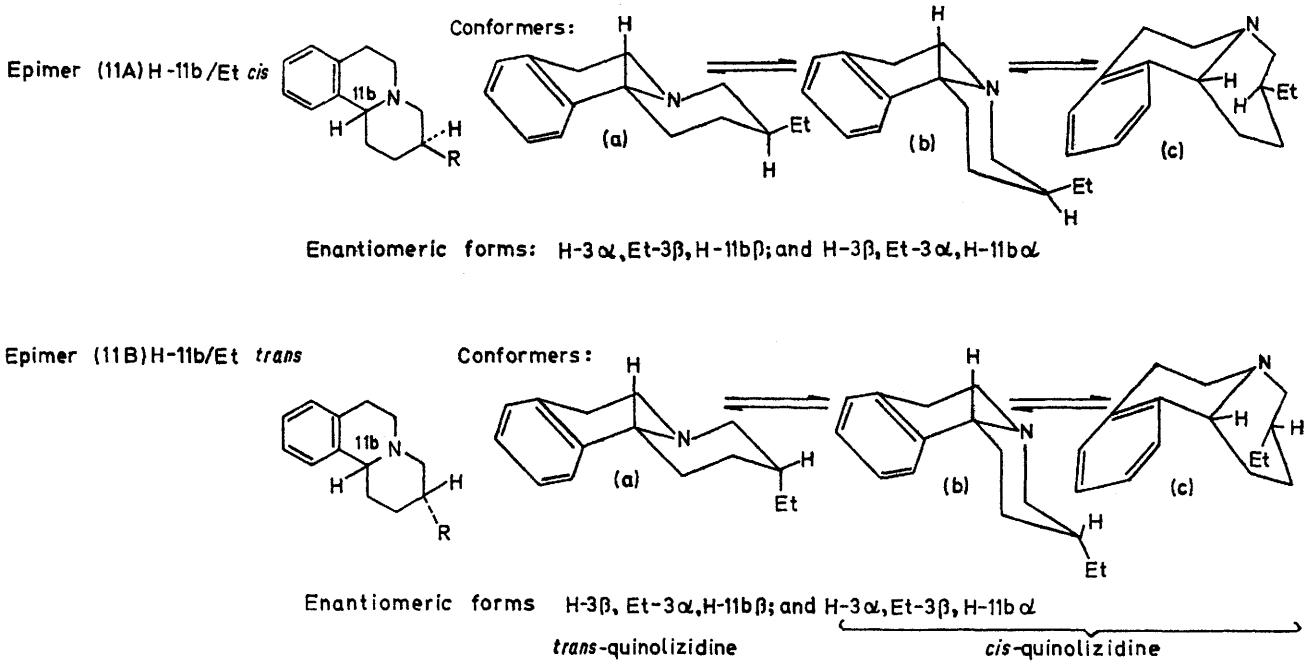
as before, attributable to the *cis*-epimers (11A) (b) and (11B) (b) (Scheme 3), and a multiplet centred at δ 3·89 p.p.m. (0·125H) attributable to the *cis*-epimers




SCHEME 2

(11A) (c) and (11B) (c). The equilibrium values are thus: *trans* 62·5%, *cis* (b) 25%, *cis* (c) 12·5%.

The spectrum also shows the presence of two kinds of ethyl groups: the methyl triplet of Et(*eq*) is centred at




SCHEME 3

δ 0·88 p.p.m. [isomers (11A (a), (11A) (c), and (11B) (b)] and that of Et(*ax*) is centred at 0·93 p.p.m. [isomers (11A (b), (11B) (a), and (11B) (c)]. The relative area of these signals could not be measured and we were unable to separate the epimers.

## EXPERIMENTAL

I.r. spectra were obtained with a Perkin-Elmer 237 instrument, mass spectra with a Hitachi–Perkin-Elmer RMU 6D instrument, and n.m.r. spectra (100 MHz) with a Varian HA100 instrument.

*1,2,3,4-Tetrahydro-1-(2-hydroxyethyl)isoquinoline* (3).—A solution of 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (2) in dry ether (50 ml.) was added to a solution of lithium aluminium hydride (1·25 g.) in dry ether (100 ml.), and the mixture was refluxed for 10 hr. Ethanol (10 ml.) and aqueous 15% sodium hydroxide (10 ml.) were carefully added to the cooled mixture, which was then filtered through sintered glass. The residue was extracted many times with hot ether. The combined extracts were dried and evaporated under vacuum. Reduced pressure distillation of the residue gave the alcohol (3) as a white solid (94%), m.p. 65—66° (from cyclohexane); *picrate*, m.p. 139—140° (from ethanol) (Found: C, 74·7; H, 8·4; N, 8·2. $C_{11}H_{15}NO$ requires C, 74·6; H, 8·5; N, 7·9%).

*2-(Ethoxycarbonylmethyl)-1,2,3,4-tetrahydro-1-(2-hydroxyethyl)isoquinoline* (4).—Ethyl bromoacetate (10 g.) in dry acetone (30 ml.) was added slowly to the alcohol (3) (5 g.) dissolved in dry boiling acetone (20 ml.). The mixture was then refluxed for 6 hr., cooled, and evaporated, and the residue was dissolved in dilute hydrochloric acid. The solution was washed with ether, cooled in ice, and made alkaline with solid sodium carbonate followed by sodium hydroxide; the oil which appeared was extracted with ether. Evaporation of the extract gave a deep red oil (95%) which was used directly in the following step; *picrate*, m.p. 149—149·5° (from ethanol) (Found: C, 51·0; H, 5·2; N, 11·4. $C_{21}H_{24}N_4O_{10}$ requires C, 51·2; H, 4·9; N, 11·4%).

*1-(2-Chloroethyl)-2-(ethoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline* (5).—Phosphorus trichloride (2 ml.) in dry benzene (50 ml.) was slowly added to compound (4) (7 g.) in dry boiling benzene (50 ml.). After the addition was complete, refluxing was continued for 0·5 hr. To the mixture cooled in ice, iced water was added to destroy unchanged phosphorus trichloride. The product was then made alkaline with 20% aqueous sodium hydroxide and extracted with benzene; the organic layer was extracted with dilute hydrochloric acid. The acid layer was washed

with ether, cooled in ice, and made strongly alkaline with solid sodium carbonate followed by sodium hydroxide. The oil which appeared was extracted with ether and worked up in the usual manner. Distillation under vacuum gave a pale yellow oil (90%), b.p. 182—185°/0·1 torr; *picrate*, m.p. 125° (from ethanol) (Found: C, 49·6; H, 4·4; N, 11·8. $C_{21}H_{23}ClN_4O_9$ requires C, 49·4; H, 4·5; N, 11·0%).

1-(2-*Cyanoethyl*)-2-*ethoxycarbonylmethyl*-1,2,3,4-*tetrahydroisoquinoline* (7).—The chloro-compound (5) (7 g.) was added during 10 min. to a vigorously stirred suspension of potassium cyanide–sodium cyanide (2 g.) in dry dimethyl sulphoxide (50 ml.) heated at 90—95°. The temperature was then raised to 100—110° for 0·5 hr. The mixture was then cooled, diluted with water (250 ml.) made strongly alkaline with aqueous sodium hydroxide, and extracted with ether. The extract was washed well with water and extracted with dilute hydrochloric acid. The aqueous layer was washed with ether and made alkaline, and the oil was extracted with ether. Evaporation of the extract and distillation of the residue under reduced pressure gave a pale yellow oil (93%), m.p. 210°/1 torr; *picrate*, m.p. 137—137·5° (from ethanol) (Found: C, 52·7; H, 4·7; N, 14·0. $C_{22}H_{23}N_5O_9$ requires C, 52·7; H, 4·6; N, 14·0%).

2-*Cyano*-1,2,4,6,7,11b-*hexahydrobenzo*[a]*quinolizin*-3-*one* (8).—A solution of (7) (18 g.) in dry toluene (75 ml.) was added during 1 hr. to a stirred boiling suspension in toluene of sodium ethoxide [from sodium (1 g.)]. The mixture was refluxed for a further 1 hr., then cooled in ice and treated with wet ether (100 ml.) followed by iced water (100 ml.). The aqueous layer was separated and the organic one was extracted with aqueous N-sodium hydroxide (50 ml. portions). The combined extracts were cooled, neutralised to pH 6 with 5N-hydrochloric acid, and extracted with chloroform. Evaporation of the chloroform solution gave an oil which was recrystallised from ethanol. The solid obtained (70%) is very sensitive to air and heat and must be stored under nitrogen in a deep freeze; m.p. 152° (decomp.) (from ethanol). No satisfactory microanalysis was obtained, but the spectroscopic properties agreed with the structure assigned: $\nu_{max.}$ 3400 (enolic OH), 2220 (CN), 1685 (CO), and 750 (aromatic) cm.$^{-1}$, *M* (mass spectrometry), 226 ($C_{14}H_{14}N_2O$), base peak 145.

1,2,4,6,7,11b-*Hexahydrobenzo*[a]*quinolizin*-3-*one* (9).—This was prepared like the cyano-ketone (8), but the isolation procedure was modified as follows: after the cyclisation was complete the mixture was cooled and diluted with iced water (100 ml.) followed by ether (100 ml.). The aqueous layer was then made strongly acid with concentrated hydrochloric acid. Usually a solid was deposited, which was filtered off and dissolved in the minimum amount of pure water. The various aqueous layers were combined and distilled up to 110° (azeotrope hydrogen chloride–water). The distillation was then stopped and, if necessary, the mixture was maintained under reflux until gas evolution ceased. Water was then evaporated off under vacuum, and the ice-cooled residue was made strongly alkaline and extracted with ether. The extract yielded a deep red oil (65%); *picrate*, m.p. 193·5—194° (from ethanol) (Found: C, 53·1; H, 4·2; N, 12·1. $C_{19}H_{18}N_4O_8$ requires C, 53·0; H, 4·2; N, 13·0%); n.m.r. ($CDCl_3$) see Figure 1.

3-*Ethylidene*-1,2,4,6,7,11b-*hexahydrobenzo*[a]*quinolizine* (10).—Ethyltriphenylphosphonium bromide [12] (37·1 g., 0·1 mole) dissolved in dry dimethyl sulphoxide (125 ml.) was treated with methylsulphonylmethanide resulting from attack of sodium hydride (4·9 g., 0·1 mole) on dimethyl sulphoxide (50 ml.). To this solution was added a solution of compound (9) (10 g.) in dry dimethyl sulphoxide (50 ml.) and the whole was warmed at 50° for 12 hr. Iced water (200 ml.) was then added to the cooled mixture, which was afterwards extracted with ether. The extracts were washed well with saturated aqueous sodium chloride followed by pure water, then extracted with dilute hydrochloric acid. The aqueous phase was washed with ether, cooled in ice, and made strongly alkaline with solid sodium carbonate followed by sodium hydroxide. The oil was extracted with ether and worked up as usual (95%), b.p. 174°/1 torr; *picrate*, m.p. 199—200° (from ethanol), $\nu_{max.}$ 2780 and 2720 (CH) and 740 (aromatic) cm.$^{-1}$; n.m.r. ($CDCl_3$) see Figure 2; *m/e* 213 ($M^+$, $C_{15}H_{19}N$) and 130 (base peak).

3-*Ethyl*-2,3,4,6,7,11b-*hexahydro*-1H-*benzo*-[a]*quinolizine* (11).—The ethylidenebenzo[*a*]quinolizine (10) was hydrogenated over Adams catalyst in acetic acid at 4 kg. cm.$^{-2}$ for 2 hr. The solution was made alkaline with solid sodium carbonate followed by sodium hydroxide and extracted with ether. The extract yielded a colourless oil, which was distilled under vacuum (98%), b.p. 157·5°/1 torr. $\nu_{max.}$ 2790 and 2718 (CH) and 740 (aromatic) cm.$^{-1}$; n.m.r. ($CDCl_3$) see Figure 3; *m/e* 215 ($M^+$, $C_{15}H_{21}N$) and 139 (base peak).

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