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THE SYNTHESIS OF 9-AZASTEROIDS—I

ATTEMPTED SYNTHESIS OF 4-OXOBENZO [c] QUINOLIZIDINES

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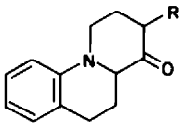
Abstract—4-Oxobenzo [c] quinolizidines have been examined as possible precursors of 9-azasteroids. 4-Oxo- and 3-methyl-4-oxobenzo [c] quinolizinium salts have been prepared and reduced to 4-hydroxybenzo [c] quinolizidines, but attempts at oxidation of these alcohols have failed. 4-Oxobenzo [c]-quinolizidine has been prepared by a previously described route[1] but has been found too unstable for further use.

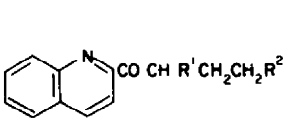
WHILE the number of natural steroids converted into azasteroids is large, only a few successful total syntheses of azasteroids have been reported. Of these the azasteroids having a bridgehead nitrogen atom are the 8-azasteroids,[2] the 8, 9 and 13-azasteroids bearing *gem*-dimethyl groups,[3] and the 14-azasteroids.[4] We report in this and subsequent papers the synthesis of a number of tricyclic ketones, keto-esters, and keto nitriles, which can be used for rings A, B, and C of a 9-azasteroid system and in which the functional groups in ring C are correctly placed for elaboration of ring D.

The first attempts were aimed at production of ketones of type I (R = H or CH_3) which might be used in syntheses modelled on Johnson's classical approach to equilenin.[5] We have previously reported[6] the synthesis of 4-oxo-1, 2, 3, 4-tetrahydrobenzo [c] quinolizinium bromide (V, X = Br) from 2-(γ-ethoxybutyryl) quinoline (II). The yield obtained in the cyclization procedure has been improved by isolation of the crude γ-bromobutyryl quinoline (III), followed by heating without solvent at 85–90°. Similarly, from the γ-ethoxy-α-methylbutyryl quinoline (IV), the methyl derivative (VI) was obtained, though in poorer yield. While the tricyclic compound (V) was undoubtedly in the keto form as shown (ν_{max}, 1720 cm^{-1}), various samples of the methylated compound (VI) showed IR absorption both at 1720 cm^{-1} and at 3350 cm^{-1}. Extraction with chloroform left almost pure ketone (VI), which on recrystallization was converted into pure enol (VII), which appears to be the more stable form. The NMR spectrum of the ketone (VI) in D_2O showed a doublet centred at 1·3 ppm (relative to TMS) due to the ketone (VI) methyl group, with a small singlet at 2·2 ppm. After 1 hr at 35° the D_2O solution showed signals of equal weight at 1·3 and 2·2 ppm,

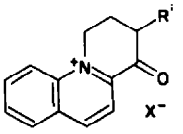
[1] G. R. Clemo, J. G. Cook and R. Raper, *J. Chem. Soc.* 1318 (1938).
[2] R. I. Meltzer, D. M. Lustgarten, R. J. Stanaback and R. E. Brown, *Tetrahedron Letters* 1581 (1963).
[3] A. I. Meyers, J. Schneller and N. K. Ralhan, *J. Org. Chem.* **28**, 2944 (1963); A. I. Meyers and N. K. Ralhan, *Ibid.* **28**, 2950; A. I. Meyers, B. J. Betrus, N. K. Ralhan and K. Babu Rao, *J. Heterocyclic Chem.* **1**, 13 (1964).
[4] R. H. Poirier, R. D. Morin, F. Benington and T. F. Page, *Abstracts of Papers* **44**, *Division of Organic Chemistry* 145*th Meeting of the American Chemical Society*, New York, N.Y. September (1963).
[5] W. S. Johnson, J. W. Petersen and C. D. Gutsche; *J. Amer. Chem. Soc.* **69**, 2942 (1947).
[6] E. E. Glover and G. Jones, *J. Chem. Soc.* 3021 (1958).



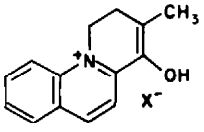
I



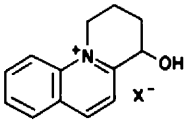
II (R^1 = H, R^2 = OC_2H_5)
III (R = H, R^2 = Br)
IV (R^1 = CH_3, R^2 = OC_2H_5)



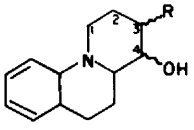
V (R^1 = H)
VI (R^1 = CH_3)



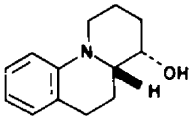
VII



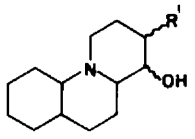
VIII



IX (R^1 = H)
X (R^1 = CH_3)



IX a



XI (R^1 = H)
XII (R^1 = CH_3)

and after 12 hr at 35° the solution showed only the singlet at 2·2 ppm due to the enol methyl group. In trifluoroacetic acid the major methyl peak was the ketonic doublet at 1·3 ppm with only vestigial absorption at 2·2 ppm. The ketone (VI) formed a picrate which was stable to recrystallization and differed in m.p. and IR absorption from the enol (VII) picrate. The enol and the ketone showed identical UV absorption in acidic or in basic solutions but differed at pH 7.

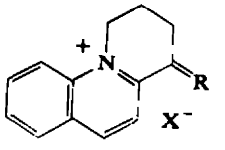
Reduction of the ketone bromide (V, X = Br) with Pd–C at atmospheric pressure gave the hydroxytetrahydrobenzo [c] quinolizinium bromide (VIII, X = Br). Reduction of the ketone (V) with Adams' catalyst in ethanol gave the benzoquinolizidine alcohol (IX) hydrobromide. The free base from the crude hydrogenation mixture showed three peaks (two minor and one major) on gas chromatography, and the IR spectrum showed two peaks in the region of hydroxyl stretching, at 3626 cm^{-1} (weak) and 3550 cm^{-1} (strong). Chromatography of the crude hydrogenation bases on neutral alumina gave a small fraction with an IR absorption spectrum identical with that of benzo [c] quinolizidine (XV); the deoxygenated material is presumably formed by hydrogenolyis of the intermediate alcohol (VIII). The major product was isolated in a pure state from the alumina chromatography and is formulated as the axial, hydrogen-bonded epimer (IXa), showing absorption in dilute solution in carbon tetrachloride at 3555 cm^{-1} (the reported[7] absorption of axial hydrogen-bonded 3-piperidinols is 3539 cm^{-1}). Later fractions from the chromatographic separation showed increasing enhancement of the IR absorption peak at 3626 cm^{-1} and this is presumed to be due to the equatorial epimer. The B:C ring fusion in IXa is assumed

[7] G. Hite, E. E. Smissman and R. West: *J. Amer. Chem. Soc.* **82**, 1207 (1960).

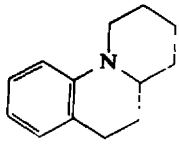
to be *trans* by analogy with other quinolizidines,[8–10] and because of the strong Bohlmann band[11] at 2850 cm^{-1}. The same mixture of products was obtained by reduction of the ketone (I, R = H) formed by hydrolysis of the keto ester (XX).

Reduction of the methyl ketone (VI) or the enol (VII) gave a sharp melting hydrobromide after recrystallization but the free base (X) after distillation had m.p. 63–70° and showed a similar pair of hydroxyl absorptions to those of the crude alcohol (IX), and no attempt was made to isolate individual epimers. Both ketones (V and VI), on prolonged reduction, took up six molecules of hydrogen to give perhydroderivatives. Although physical properties (notably the lack of absorption above 2200 Å) and the analytical figures were in agreement with structures XI and XII, attempts to obtain derivatives gave mixtures melting over a wide range, and no effort was made to isolate individual isomers.

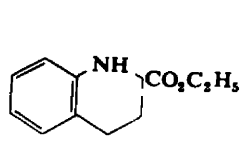
The mixture of alcohols (IX) obtained by partial reduction of the ketone (V) was used for oxidation experiments, which were uniformly unsuccessful. Among the reagents used were manganese dioxide, N-bromosuccinimide and chromium trioxide, but the alcohols (IX) were either unchanged or converted into intractable tars. Warnhoff and Reynolds-Warnhoff successfully oxidized some complex piperidinols by a modified Oppenauer procedure, using fluorenone as hydrogen acceptor;[12] this procedure applied to alcohols (IX and X) gave a poor yield of products showing carbonyl absorption at 1710 cm^{-1}, but no pure ketone was isolated. Attempts to prepare the ketones (I) by this route were abandoned since it appears that the ketones are unstable under oxidizing conditions. Leonard *et al.* have reported[13] that N-phenyl-3-piperidone is very unstable in air and the ketones (I) have obvious structural resemblances to this compound. Attempts were made to avoid the oxidation stage by selective reduction of the quinolizinium system in compound V while protecting the carbonyl function. The oxime (XIII) and the semicarbazone (XIV) were prepared, but attempts at reduction gave no identifiable products. An attempt to reduce the ketone (V) with formic acid and triethylamine gave only benzo [c]-quinolizidine (XV), characterized as its picrate.



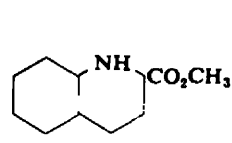
XIII (R = NOH)
XIV (R = $NNHCONH_2$)



XV



XVI

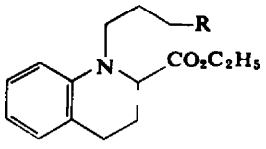


XVII

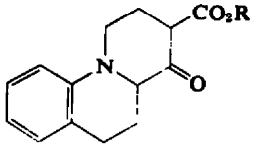
Further attempts to prepare tricyclic intermediates were centred on keto-esters and nitriles; initial experiments were aimed at the keto-ester (XX) which could be synthesized un-ambiguously and had the attraction of providing an alternative route to

[8] H. S. Aaron, G. E. Wicks and C. P. Rader, *J. Org. Chem.* **29**, 2248 (1964).
[9] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).
[10] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *J. Amer. Chem. Soc.* **86**, 3364 (1964).
[11] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).
[12] E. W. Warnhoff and P. Reynolds-Warnoff, *J. Org. Chem.* **28**, 1431 (1963)
[13] N. J. Leonard, G. Fuller and H. L. Dryden, *J. Amer. Chem. Soc.* **75**, 3727 (1953).

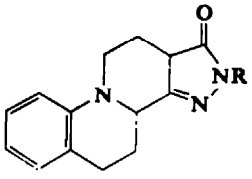
ketone I (R = H). Clemo *et al.* have reported[1] the synthesis of ketone I (R = H) from the ester (XXI) by hydrolysis and decarboxylation, but did not characterize the intermediate keto-ester (XXI). Ethyl quinaldinate was reduced by Adams' catalyst in ethanol to give a high yield of the tetrahydro-ester (XVI) with only a trace of a more volatile impurity on gas chromatographic analysis (reduction of methyl quinaldinate in acetic acid is reported[1] to give appreciable quantities of the decahydro-ester, XVII). A previous alkylation procedure was modified to give a higher yield of the di-ester (XVIII) by employing a higher temperature (160–170°) and isolating and re-cycling γ-butyrolactone (from the γ-bromo-butyric ester used) and un-alkylated tetrahydroquinaldinate. The di-ester (XVIII) was isolated as a high boiling viscous liquid. An alternative route to the di-ester (XVIII) which avoided losses due to lactonization was the alkylation of ethyl tetrahydroquinaldinate (XVI) with γ-bromobutyronitrile; the resulting cyano-ester (XIX) was converted by treatment with ethanolic hydrogen chloride into the diester (XVIII). Dieckmann cyclization of the di-ester (XVIII) was



XVIII (R = $CO_2C_2H_5$)
XIX (R = CN)



XX (R = C_2H_5)
XXI (R = CH_3)



XXII (R = H)
XXIII (R = C_6H_5)

performed in boiling xylene under nitrogen, using either sodium or sodium ethoxide. The sodium salt of the keto-ester (XX) failed to separate from the solution, and was only extracted partially by water or by aqueous alkali. The most efficient isolation procedure was to precipitate a mixture of sodium chloride and the keto-ester (XX) hydrochloride by passage of a stream of dry hydrogen chloride into the reaction mixture. The keto-ester (XX) could be isolated from the precipitate by careful treatment with alkali and extraction with ether. As isolated, the keto-ester (XX) was almost pure and the yield was good (85%) but it was unstable to heat and resinified on standing in air. The hydrochloride was stable at room temperature but was recrystallized with difficulty because of dissociation. The IR spectrum of the keto-ester (XX) showed the expected four peaks at 1740 cm^{-1} and 1720 cm^{-1} (ester and ketone carbonyl stretching in the ketonic form), 1655 cm^{-1} and 1620 cm^{-1} (ester carbonyl stretching and double bond stretching in the enolic form). The recrystallized hydrochloride showed only the peaks due to the enolic form. Distillation of the β-keto-ester (XX) even under very low pressures led to extensive decomposition. No concordant analyses could be obtained on the distillate, but the IR spectrum showed a single carbonyl stretching absorption at 1720 cm^{-1}. The keto-ester (XX) reacted readily with hydrazine and with phenylhydrazine to give the pyrazolones XXII and XXIII respectively.

Several attempts were made to hydrolyse and decarboxylate the keto-ester (XX) and to isolate the ketone (I, R = H), but the products were always dark unstable oils, giving poor analysis results. In one experiment the product from acid hydrolysis of the keto-ester (XX) was immediately hydrogenated, when a mixture of alcohols similar to that obtained by reduction of ketone V was obtained. There seems no doubt that the

ketone (I, R = H) is formed, but is too unstable to be of further synthetic use. Further experiments aimed at the synthesis of 9-azasteroids have been concentrated on the ester (XX) and similar tricyclic compounds, and are described in subsequent papers.

EXPERIMENTAL

M.ps were determined on a Kofler block. IR spectra were determined on a Perkin–Elmer 221 or Unicam S.P. 700 spectrometer, UV spectra on a Unicam S.P. 700 spectrometer, and NMR spectra on a Perkin–Elmer 60 Mc. instrument.

1,2,3,4-Tetrahydro-4-oxobenzo [c] *quinolizinium Bromide* (V, X = Br)

A solution of II (5·1 g)[6] in 50% HBr (50 ml) was boiled under reflux for 1 hr, then concentrated under red. press. until a precipitate formed. The concentrate was poured into ice-water and the oily bromo-amine (III) extracted with $CHCl_3$. $NaHCO_3$ was added to the aqueous solution until the pH was approximately 4, and the aqueous layer again extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and the $CHCl_3$ removed under red. press. The oily residue (5·4 g) was heated at 90–95° (oil bath) with occasional stirring for 30 min. The light brown solid residue was ground in a mortar and triturated with $CHCl_3$, (20 ml) giving almost pure V(X = Br) m.p. 187–189° (5·2 g, 89%); ν_{max} 1720 cm^{-1} (Nujol) λ_{max} 2020, 2530, 3250 Å ($\log_{10}\varepsilon$ 4·47, 4·53, 3·92) in H_2O: λ_{max} 2330, 3010, 4360 Å ($\log_{10}\varepsilon$ 4·45, 3·93, 3·23) in 10% NaOH aq.

2-(4'-Ethoxy-2'-methylbutyryl) quinoline (IV)

The Grignard reagent from 3-bromo-1-ethoxybutane[6] (23·5 g) in ether (250 ml) was added to a well-stirred solution of 2-cyanoquinoline (16 g)[14] at such a rate as to maintain gentle boiling. After addition was complete (1 hr) the mixture was boiled and stirred for 18 hr. The cooled mixture was treated with ice-cold 5 N HCl (150 ml), and the acid then neutralized with NH_4OH (sg. 0·880). The ether layer was separated and the aqueous layer again extracted with ether. The ethereal extracts were dried (Na_2SO_4) and distilled at 0·03 mm giving a fore-run fraction of 2-cyanoquinoline (5·1 g) and a crude fraction b.p. 120–140°/0·03 mm. This fraction was re-distilled giving the *butyrylquinoline* (IV) as a yellow oil, b.p. 136–138°/0·03 mm (8·9 g, 37%). (Found C, 74·7; H, 7·3; N, 5·7. $C_{16}H_{19}NO_2$ requires: C, 74·7; H, 7·4; N, 5·4%). ν_{max} 1690 cm^{-1} (liquid film), λ_{max} 2120, 2430, 2890 Å ($\log_{10}\varepsilon$ 4·34, 4·53, 3·86) in EtOH.

1,2,3,4-Tetrahydro-3-methyl-4-oxobenzo [c] *quinolizinium salts* (VI) *and 1,2-dihydro-4-hydroxy-3-methyl benzo* [c] *quinolizinium salts* (VII)

A solution of IV (5·4 g) in 50% HBr aq (50 ml) was boiled under reflux for 0·5 hr. The dark solution was evaporated to about 8 ml, poured into ice-water, and the bromo-amine extracted with $CHCl_3$. Successive additions of $NaHCO_3$ and extraction with $CHCl_3$ were performed until a pH of 5 was reached. The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated under red. press. The residual dark oil was heated at 95° for 0·5 hr with occasional stirring giving a semi-solid material which solidified on trituration with acetone to a greenish-yellow solid (3·07 g; 50%). At this stage the material usually showed IR absorption at 3356 cm^{-1} (OH) and 1720 cm^{-1} (C=O) but a few samples showed only vestigial hydroxyl absorption. From such a sample the *ketone picrate* (VI, X = picrate) was obtained, and recrystallized from acetone m.p. 174°. (Found: C, 54·9; H, 3·4. $C_{20}H_{16}N_4O_8$ requires: C, 54·55; H, 3·7%.) ν_{max} 1720 cm^{-1} (Nujol mull). The purest form of VI (X = Br) was obtained by trituration of the crude cyclization product with $CHCl_3$ in which VII (X = Br) was quite soluble. Such a specimen of VI (X = Br) showed ν_{max} 1720 cm^{-1} (Nujol mull) and λ_{max} 2020, 2530, 3260 Å ($\log_{10}\varepsilon$ 4·49, 4·56, 3·93) in H_2O, and melted first at 143–148°, but attempts at recrystallization from abs. EtOH–acetone mixtures led to the formation of pure *enol bromide* (VII, X = Br) m.p. 165–170°, re-solidifying and melting finally at 268–270°, dec. (Found: C, 54·1; H, 5·4; N, 4·8. $C_{14}H_{14}BrNO \cdot H_2O$, requires: C, 54·2; H, 5·2; N, 4·5%.) ν_{max} 3350 cm^{-1} (Nujol mull); λ_{max} 2010, 2460, 3730 Å ($\log_{10}\varepsilon$ 4·57, 4·29, 3·99) in H_2O. The *enol picrate*, crystallized from acetone, had m.p. 165–166° dec. (Found: C, 54·55; H, 3·7; N, 12·7%.) Both forms showed λ_{max} 2030, 2530, 3270 Å in 50% H_2SO_4, and λ_{max} 2340, 3030, 4230 Å in 0·1 N NaOH.

[14] W. E. Feeley and E. M. Beavers, *J. Amer. Chem. Soc.* **81**, 4004 (1959).

4-Hydroxy-1,2,3,4-tetrahydrobenzo [c] *quinolizinium salts* (VIII)

The ketone (V; 1·0 g) was dissolved in EtOH (100 ml) and reduced at atm. temp and press over 10% Pd–C (0·5 g); absorption ceased after 1 molar equiv H_2. Filtration and evaporation gave the *hydroxybenzo* [c] *quinolizinium bromide* (VIII, X = Br) as a brown solid (0·92 g, 90%), recrystallized from abs. EtOH–ethyl acetate as brown prisms m.p. 182°. (Found: C, 55·5; H, 5·1; N, 5·2; Br, 28·8. $C_{13}H_{14}BrNO$ requires: C, 55·7; H, 5·0; N, 5·0; Br, 28·5%.) λ_{max} 2040, 2390, 3200 Å ($\log_{10}\varepsilon$ 4·55, 4·51, 4·09) in EtOH. The *picrate* (VIII, X = picrate) was recrystallized from abs. EtOH containing a trace of picric acid as brown needles, m.p. 108–109°. (Found: C, 53·0; H, 4·0. $C_{19}H_{16}N_4O_8$ requires: C, 53·3; H, 3·8%.) λ_{max} 2050, 2390, 3200, 3570 Å ($\log_{10}\varepsilon$ 4·60, 4·56, 4·20, 4·19) in EtOH.

Reduction of ketone (V) *with Adams' catalyst*

(a) Compound V (5·7 g) dissolved in EtOH (150 ml) was hydrogenated at room temp and press. over Adams' PtO_2 catalyst (0·2 g) until 3 molar equiv H_2 had been absorbed (up to 20 hr) at which time absorption had become very slow. After filtration, the EtOH was evaporated, to give a solid hydrobromide. This hydrobromide could be crystallized from abs. EtOH with considerable loss to give a sharp melting hydrobromide, m.p. 192°. (Found: C, 55·52; H, 6·69; N, 5·00. $C_{13}H_{18}BrNO$ requires: C, 54·93; H, 6·38; N, 4·93%.) λ_{max} 2080, 2560, 2910 Å ($\log_{10}\varepsilon$ 4·36, 4·00, 3·37) in EtOH; λ_{max} (Nujol mull) 3350 (OH) 2500 cm^{-1} (NH^+). In other experiments the crude hydrobromide was basified with Na_2CO_3 aq, extracted with $CHCl_3$, and the $CHCl_3$ extracts dried and distilled, to give a yellow oil (69%) b.p. 130–135°/0·13 mm. The IR spectrum of the oil showed peaks at 3626 cm^{-1} (weak) and 3550 cm^{-1} (strong) in dil. CCl_4 solution. An analytical gas chromatographic separation on 1% SE-30 absorbed on Gaschrom P showed two peaks with relative intensities equivalent to those of the IR peaks. Chromatography of the mixture in petrol (60–80° b.p.)–benzene (1:1) on Woelm alumina (neutral, activity IV) gave a small first fraction having IR absorption identical with that of benzo [c] quinolizidine in the region 1700–800 cm^{-1}. The major fraction contained a pure *epimer* (IXa), b.p. 140–50°/0·02 mm, m.p. 79–80°. (Found: C, 76·4; H, 8·5; N, 7·1. $C_{13}H_{17}NO$ requires: C, 76·75; H, 8·4; N, 6·9%); ν_{max} 3555 cm^{-1} (dil. solution in CCl_4). The third component was not obtained pure, but later fractions from the chromatographic separation showed peaks of equal intensity at 3555 cm^{-1} and 3626 cm^{-1}.

(b) Hydrogenation over Adams' catalyst as described above was allowed to continue to completion (20 hr) when 6 molar equiv had been absorbed. Filtration and evaporation gave a gum which was treated with Na_2CO_3 aq and $CHCl_3$. The $CHCl_3$ extracts were dried and distilled giving the *perhydroquinolizidine* (XI), b.p. 115–120°/0·03 mm, as a pale yellow oil which partly crystallized on standing. (Found: C, 74·9; H, 11·3; N, 6·6. $C_{13}H_{25}NO$ requires: C, 74·6; H, 11·1; N, 6·7%); ν_{max} 3631 cm^{-1}, 3520 cm^{-1} (in CCl_4). No absorption above 2200 Å was observed.

Attempted oxidation of 4-hydroxybenzo [c] *quinolizidines*

(a) The alcohol mixture (IX; 1·15 g) was oxidized at 55–60° for 0·5 hr by CrO_3 (1 g) in glacial acetic acid (20 ml). Neutralization by NaOH aq and ether extraction gave only unchanged IX (0·1 g). The residual organic material was an ether-insoluble tar.

(b) A mixture of N-bromosuccinimide (0·63 g) and IX (0·72 g) in CCl_4 (12 ml) containing pyridine (0·5 ml) was boiled for 3 hr. After filtration the residue from the CCl_4 solution was chromatographed on neutral alumina giving unreacted alcohol (0·58 g). No ketonic material was obtained.

(c) Oxidation by MnO_2 in EtOH gave no ketonic material.

(d) Potassium t-butoxide was freshly prepared from K (0·26 g) and a solution of IX (0·54 g) in dry benzene (10 ml) was added, followed by fluorenone (2·38 g) in dry benzene (15 ml). The mixture was boiled for 6 hr, cooled, and extracted several times with 10% HCl aq. The HCl solution was basified and the organic bases extracted with ether, dried, and distilled. An orange oil, b.p. 110–120°/0·001 mm (bulb tube; 0·1 g) was obtained, showing an IR maximum at 1710 cm^{-1} but also showing an hydroxyl peak at 3548 cm^{-1} (un-reacted alcohol). Further oxidation increased the carbonyl peak but with considerable loss of material.

Reduction of 3-methyl-4-oxo-1,2,3,4-tetrahydroquinolizinium bromide

(a) The cyclization mixture consisting of VI and VII (4·06 g) was hydrogenated over Adams' catalyst (0·2 g) in EtOH (150 ml) at room temp and press. After 3 molar equivs had been absorbed (3–5 hr), the hydrogenation was stopped, the solution filtered and evaporated to give crude XII,

(4·05 g; 97%). A sample of hydrobromide was crystallized from abs. EtOH–acetone as colourless needles of 3-*methyl*-4-*hydroxybenzo* [c] *quinolizidine* (X) *hydrobromide*, m.p. 218–219°. (Found: C, 56·6; H, 6·6; N, 4·7; Br, 27·1. $C_{14}H_{20}BrNO$ requires: C, 56·4; H, 6·75; N, 4·7; Br, 26·8%); ν_{max} 3350 (OH) 2550 (NH^+), 765 cm^{-1} (Nujol mull). The bulk of the crude product was basified with Na_2CO_3, extracted with $CHCl_3$, and the $CHCl_3$ extracts dried and distilled. The *quinolizidine* (X), had b.p. 110–115°/0·005 mm (bulb tube), solidifying on standing, m.p. 63–70°. (Found: C, 77·4; H, 9·4; N, 6·1. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8; N, 6·45%.)

(b) A mixture of VI and VII (1·09 g) was hydrogenated as described above, but hydrogenation was allowed to proceed to completion (10–20 hr). Filtration and evaporation gave XII *hydrobromide*, recrystallized from abs. EtOH–acetone as colourless needles, m.p. 221–223°. (Found: C, 56·15; H, 8·6; N, 4·0. $C_{14}H_{26}BrNO$ requires: C, 55·2; H, 8·6; N, 4·6%); ν_{max} 3350 (OH) 2700 (NH^+) cm^{-1} (Nujol mull). The free *base* (XII) had b.p. 85–95°/0·005 mm. (Found: C, 75·4; H, 11·2; N, 6·1. $C_{14}H_{25}NO$ requires: C, 75·3; H, 11·3; N, 6·3%.)

Attempted oxidation of hydroxy quinolizidine (X)

Attempts to oxidize X by the method of Warhoff and Reynolds-Warnhoff as described above gave a product which showed medium intensity absorption at 1710 cm^{-1}, but no crystalline derivatives were obtained.

Benzo [c] *quinolizidine* (XV)

Formic acid (100%; 9·2 g) was added to a suspension of V (5·3 g) in triethylamine (4·0 g) and the mixture boiled under reflux for 6 hr. The dark mixture was cooled, basified, and extracted with ether. Evaporation of the ether and chromatography of the residual oil in benzene on alumina gave XV b.p. 95–100°/0·01 mm; *picrate* m.p. 160–162° (dec) from EtOH. (Found: C, 55·24; H, 5·17; N, 13·03. $C_{19}H_{20}N_4O_7$ requires: C, 54·80; H, 4·84; N, 13·45%.)

4-*Oximino*-1,2,3,4-*tetrahydrobenzo* [c] *quinolizinium salts* (XIII)

A mixture of crystalline sodium acetate (2·1 g) and hydroxylamine hydrochloride (1·0 g) in abs. EtOH (110 ml) was filtered from NaCl and V (X = Br; 1·5 g) added. The solution was boiled for 2 hr, cooled, and poured through a bromide loaded column of Amberlite IRA-400. Concentration of the eluate gave a dark solid (0·56 g; 35%) recrystallized from abs. EtOH as yellow prisms m.p. 308° (dec) of the *oxime bromide* (XIII, X = Br). (Found: C, 53·4; H, 4·0. $C_{13}H_{13}BrN_2O$ requires: C, 53·3; H, 4·5%); λ_{max} 2200, 2430, 2800, 3720 Å ($\log_{10} \varepsilon$ 4·37, 4·48, 4·05) in 95% EtOH. ν_{max} 3350, 3150, 1640 cm^{-1} (Nujol mull). The *oxime picrate* (XIII, X = picrate) crystallized from EtOH as needles, m.p. 265° (dec). (Found: C, 50·7; H, 3·6; N, 15·65. $C_{19}H_{16}N_5O_8$ requires: C, 51·7; H, 3·4; N, 15·9%.)

4-*Semicarbazano*-1,2,3,4-*tetrahydrobenzo* [c] *quinolizinium bromide* (XIV, X = Br)

The semicarbazone (XIV, X = Br) was prepared from V (X = Br; 1·75 g) and a mixture of semicarbazide hydrochloride (2·0 g) and sodium acetate (3·3 g) in water (15 ml). After standing for 12 hr the mixture was filtered, and the crude precipitated semicarbazone dissolved in water and passed through a column of Amberlite IRA-40 (Br). Evaporation of the eluate gave the *semicarbazone bromide* (1·98 g) recrystallized from aqueous EtOH as yellow needles, m.p. 245–246°. (Found: C, 49·2; H, 5·05; N, 16·8; Br, 24·1. $C_{14}H_{15}BrN_4O$ requires: C, 50·2; H, 4·5; N, 16·7; Br, 23·9%.) λ_{max} 2020, 2520, 2880, 3680 Å ($\log_{10} \varepsilon$ 4·48, 4·15, 4·09, 4·47) in 95% EtOH.

Ethyl quinaldinate

(a) This was obtained from quinaldinic acid in 83% yield by using a large excess of H_2SO_4 (as in the preparation of methyl quinaldinate).[15] The ester had b.p. 127–129°/0·03 mm, and solidified on standing m.p. 43–45° (unchanged by recrystallization from petrol b.p. 40–60°) (lit. m.p. 36°,[16] 30–33°[17]).

[15] W. H. Mills and F. M. Hamer, *J. Chem. Soc.* 2011 (1922).
[16] D. Ll. Hammick and W. P. Dickinson, *J. Chem. Soc.* 214 (1929).
[17] R. L. Cobb and W. E. McEwen, *J. Amer. Chem. Soc.* 77, 5042 (1955).

(b) 2-Cyanoquinoline (30 g) and water (3·5 g) were added to abs. EtOH (200 ml) saturated with HCl, and the solution boiled under reflux for 4 hr. The EtOH was removed and the residue treated with cold Na_2CO_3 aq and $CHCl_3$. The $CHCl_3$ extracts were washed with sat. Na_2CO_3 aq, then with water, dried (Na_2SO_4) and distilled to give ethyl quinaldinate (32 g; 82%).

Ethyl 1,2,3,4-*tetrahydroquinaldinate* (XVI)

Ethyl quinaldinate (127 g) in EtOH (1 l.) was hydrogenated over Adams' catalyst (3 g) at room temp and press. Reduction was stopped when 2 molar equivs H_2 had been taken up (ca. 30 hr), the catalyst was filtered off and the ethanolic solution distilled to give the tetrahydroester (126 g; 96%) b.p. 120°/0·05 mm. (Found: C, 70·0; H, 7·2; N, 6·9. Calc. for $C_{12}H_{15}NO_2$: C, 70·25; H, 7·4; N, 6·8%.)

Ethyl N-*benzoyl*-1,2,3,4-*tetrahydroquinaldinate*

This was prepared in pyridine and recrystallized from petrol (b.p. 60–80°) as colourless rhombs m.p. 85–85·5°. (Found: C, 73·6; H, 6·35; N, 4·5. $C_{19}H_{19}NO_3$ requires: C, 73·8; H, 6·2; N, 4·5%.)

Ethyl γ-*Bromobutyrate*

This was prepared from γ-butyrolactone and ethanolic HBr (5 hr boiling). The ester was distilled at 47–48°/0·5 mm (58% yield) as distillation at higher press caused relactonization (ν_{max} 1770 cm^{-1} developed).

Ethyl γ-*chlorobutyrate*

This was similarly prepared from γ-butyrolactone and ethanolic HCl and had b.p. 76–77°/12 mm.

Ethyl N-(3′-*cyanopropyl*)-1,2,3,4-*tetrahydroquinaldinate* (XIX)

A mixture of XVI (10 g), γ-bromobutyronitrile (11 g) and anhydrous K_2CO_3 (8 g) was stirred at 160–170° for 10 hr. The cooled mixture was shaken with cold water and $CHCl_3$, the $CHCl_3$ extracts separated, dried, and the $CHCl_3$ evaporated at 10 mm. Distillation of the residual oil gave a fore-run b.p. 70–130°/0.001 mm, and a viscous yellow oil (10·5 g) b.p. 130–165°/0·001 mm. Redistilled, the *cyano-ester* (XIX) had b.p. 162–164°/0·001 mm (9·3 g, 70%). (Found: C, 70·0; H, 7·5: $C_{16}H_{20}N_2O_2$ requires: C, 70·5; H, 7·4%); ν_{max} 2220 cm^{-1} (C≡N), 1740 cm^{-1} C=O), 745 cm^{-1} (out of phase deform, 4 adjacent H) (liquid film). λ_{max} 2090, 2500, 3010 Å ($\log_{10}$ ε 4·35, 3·92, 3·37) in 95% EtOH.

Ethyl N-(3′-*ethoxycarbonyl propyl*)-1,2,3,4-*tetrahydroquinaldinate* (XVIII)

(a) A mixture of XVI (30 g), ethyl γ-bromobutyrate (42·8 g), anhydrous K_2CO_3 (30 g), and KI (1·2 g) was vigorously stirred at 160°–170° (bath temp) under N_2 for 6 hr. A short air-condenser allowed the water formed during the alkylation to evaporate gradually. After cooling, the mixture was treated with cold water, and thoroughly extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, washed with water, dried and distilled. Distillation of the residue at first under 10 mm press gave a mixture of γ-butyrolactone and ethyl γ-bromobutyrate. Reduction of the press gave a fraction (3 g) b.p. 110–140°/0·001 mm (mainly the un-alkylated ester, XVI), and a main fraction (34·3 g; 74%) b.p. 140–162°/0·001 mm almost all of which boiled between 157–160°. A second distillation gave pure *di-ester* (XVIII), b.p. 158–160°/0·001 mm as a pale yellow viscous oil. (Found: C, 67·2; H, 8·0; N, 4·4. $C_{18}H_{35}NO_4$ requires: C, 67·7; H, 7·9; N, 4·4%); ν_{max} 1740 cm^{-1} (C=O) (liquid film); λ_{max} 2090, 2500, 3010 Å ($\log_{10}$ ε 4·35, 3·93, 3·44) in 95% EtOH. No crystalline picrate, methiodide or hydrochloride could be obtained.

(b) Compound XIX (7·4 g) was dissolved in abs. EtOH (100 ml) which had been saturated with HCl, water (1 ml) was added, and the solution boiled for 6 hr. The NH_4Cl was filtered off, and the filtrate concentrated under red. press. The residue was basified with cold sat $NaHCO_3$ aq, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water, dried and distilled giving XVIII (6·5 g, 75%).

4-*Oxo*-3-*ethoxycarbonylbenzo* [c] *quinolizidine* (XX)

A suspension of EtOH in xylene was prepared by adding freshly cut Na (0·7 g) to a solution of abs. EtOH (4 ml) in dry xylene (50 ml), boiling the mixture until all the Na had dissolved, and then

distilling until the vapour temp reached 135°. A solution of XVIII (9·58 g) in dry xylene (75 ml) was added to the boiling solution over 30 min, slow distillation being maintained during this period and for 1 hr after. The brown solution was cooled, diluted with dry ether (200 ml) and dry HCl was passed through the cooled mixture (0°) until precipitation was complete. After decantation of the solvents, the precipitate was washed twice with dry ether and then filtered. The light yellow solid was added with stirring to excess of ice-cold Na_2CO_3 aq, the pH adjusted to 6–7 and the solution extracted with ether. Evaporation of the ethereal extracts gave substantially pure XX (6·95 g, 85%), as an oil which crystallized on standing, m.p. 45–50°. The XX was stable under N_2 at 0°, but was best stored as the hydrochloride. After two further precipitations as hydrochloride a sample of the *keto-ester* XX was dried at 0·1 mm at room temp. (Found: C, 70·0; H, 7·4; N, 5·2. $C_{16}H_{19}NO_3$ requires: C, 70·3; H, 7·0; N, 5·1%); ν_{max} 1740, (C=O), ester), 1720 (C=O, ketone) 1655 (C=O, α,β-unsaturated ester), 1620 (C=C, α,β-unsaturated ester) cm^{-1}. The *hydrochloride* was recrystallized from acetone as yellow prisms, m.p. 117–119°. (Found: C, 61·7; H, 6·7; N, 4·7. $C_{16}H_{20}ClNO_3$ requires: C, 62·05; H, 6·5; N, 4·5%); ν_{max} 2150 (NH^+), 1660 (C=O), 1620 (C=C) cm^{-1} (Nujol mull.) The *methiodide* was prepared in excess methyl iodide at room temp, and crystallized from acetone–ether as colourless prisms, m.p. 136–137°. (Found: C, 49·15; H, 5·5; N, 3·55. $C_{17}H_{22}INO_3$ requires: C, 49·15; H, 5·35; N, 3·4%.) ν_{max} 1660, 1630 cm^{-1} (Nujol mull).

Acid hydrolysis of keto-ester (XX)

The procedure reported[1] was followed. The basic products were distilled b.p. 110–120°/0·001 mm as a brown oil, extremely unstable even under N_2, and giving very poor analyses for I (R = H). In one experiment the freshly distilled oil was immediately hydrogenated, and gave a mixture of alcohols almost identical in IR spectrum and retention times on gas chromatography to the mixture obtained by reduction of V.

Reaction between keto-ester (XX) *and hydrazine or phenylhydrazine*

(a) A solution of XX (0·5 g) and 100% hydrazine hydrate (0·117 g) in abs. EtOH (10 ml) was boiled for 0·5 hr. The solution was cooled and the precipitate (0·366 g; 81%) removed. Recrystallization from abs. EtOH gave irregular crystals of the *pyrazolone* (XXII), m.p. 214–216°. (Found: C, 69·9; H, 6·2; N, 17·05. $C_{14}H_{18}N_2O$ requires: C, 69·7; H, 6·3; N, 17·4%); ν_{max} 2650, 1592, 750 cm^{-1} (Nujol mull); λ_{max} 2080, 2550 Å ($\log_{10}\varepsilon$ 4·46, 4·08) in EtOH; λ_{max} 2500 Å ($\log_{10}\varepsilon$ 4·19) in 2N NaOH.

(b) A mixture of XX (0·54 g) and phenylhydrazine (0·223 g) was heated at 100–110° for 0·5 hr under an atm. of N_2. The brown residue was triturated with ethyl acetate to give a brown solid (0·58 g; 93%), recrystallized from acetone to give the *phenylpyrazolone* (XXIII) as pale brown irregular crystals; m.p. 183–185. (Found: C, 75·7; H, 6·0; N, 13·2. $C_{20}H_{18}N_{20}$ requires: C, 75·7; H, 6·0; N, 13·3%); ν_{max} 2450, 1800, 1592 cm^{-1} (Nujol mull); λ_{max} 2070, 2500 Å ($\log_{10}\varepsilon$ 4·64, 4·43) in EtOH; λ_{max} 2480 Å ($\log_{10}\varepsilon$ 4·31) in 2 N NaOH.

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