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THE SYNTHESIS OF 9-AZASTEROIDS—II[1]

SYNTHESIS OF β-CYANO- AND β-CARBETHOXY-3- AND 4-OXO-1,2,3,4,5,6-HEXAHYDROBENZO [C] QUINOLIZINES

G. JONES and J. WOOD
Department of Chemistry, University of Keele, Staffs.

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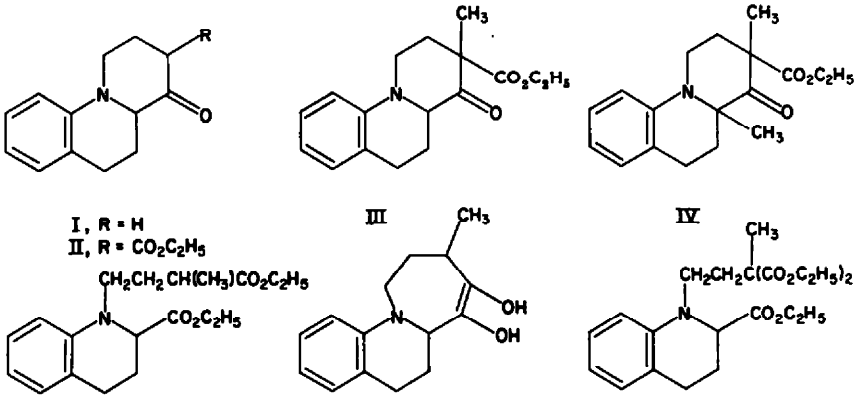
Abstract—The synthesis of 3-cyano-4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XIV), of 2-carbethoxy-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XVII), and of 4-cyano-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XXIX) is reported. Attempts to methylate 3-carbethoxy-4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (II) were unsuccessful, although the keto-ester (II) was nitrated successfully to give the nitro compound (X). Similar nitration of the di-ester (VIII) gave the nitro diester (IX). Methylation of the keto-ester (XVII) with subsequent decarboxylation gave the methyl ketone (XXI). The isomeric ketone (XX) has been synthesized.

IN THE previous paper[1] we have reported unsuccessful attempts to prepare 4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (I) for use in a synthesis of 9-azasteroids. In this paper we report the synthesis of a number of 3- and 4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizines carrying further reactive groups (ester or nitrile) so placed as to allow the addition of a fourth ring (ring D of the final aza-steroid).



The first compound of this type to be examined was the keto-ester (II) prepared as reported in the previous paper.[1] First attempts were directed at C-methylation to obtain the non-enolizable keto-ester (III). Treatment of the sodium salt of ester II with methyl iodide gave as major product an ionic material, insoluble in organic solvents and yielding no organic material on careful neutralization. The toluene mother liquors from the reaction yielded a small amount of organic material, separated by chromatography into two isomers. Both showed IR absorption characteristic of a non-enolizable keto-ester, but gave analysis figures consistent with a formula

[1] G. Jones and J. Wood, *Tetrahedron* **21**, 2529 (1965).

$C_{18}H_{23}NO_3$ rather than the expected $C_{17}H_{21}NO_3$. As the NMR spectrum of the major isomer showed a total of nine protons in the methyl region (one triplet due to the methyl of the ester and two singlets) the two alkylation products are tentatively formulated as stereo-isomers of general formula IV. As the major product was water-soluble it seemed probable that N-methylation was occurring preferentially, and two alternative routes to the keto-ester (III) were investigated.

The first route involved the cyclization of the di-ester (V) which could be prepared in good yield from ethyl 1,2,3,4-tetrahydroquinaldinate and ethyl α-methyl-γ-bromobutyrate. Treatment of the di-ester (V) with potassium t-butoxide in boiling xylene gave, unexpectedly, an insoluble potassium salt, from which an unstable compound was obtained on neutralization. Analyses on the hydrochloride and on the liberated base showed a formula $C_{15}H_{19}NO_2$, and the IR absorption was in agreement with the acyloin shown as formula VI (or the alternative tautomeric form). A variant on this approach to the keto-ester (III) which was considered involved the preparation of the bicyclic tri-ester (VII); all attempts to alkylate ethyl 1,2,3,4-tetrahydroquinaldinate with diethyl 2-bromoethylmethylmalonate gave only small yields (8%) of the tri-ester (VII), most of the bromoethyl malonate being converted into 2-carbethoxy-2-methyl-4-butyrolactone.

Since the major difficulty in alkylating the cyclic keto-ester (II) appeared to be competitive N-alkylation (McElvain and Barnett report a similar experience with N-methyl-4-piperidone-3-carboxylic ester[2]) attempts were made to reduce the basicity of the nitrogen in the ester (II). The most obvious way to reduce the basicity seemed to be the introduction of an electron-withdrawing group into the benzene ring; nitration in the position *para* to the nitrogen would lead to maximum de-activation, and would provide a potential hydroxyl group in the 3-position of the eventual aza-steroid. Schaarschmidt *et al.*, have reported that N,N-dimethyl aniline is nitrated in the *para*-position in 86% yield by dinitrogen tetroxide in carbon tetrachloride.[3]

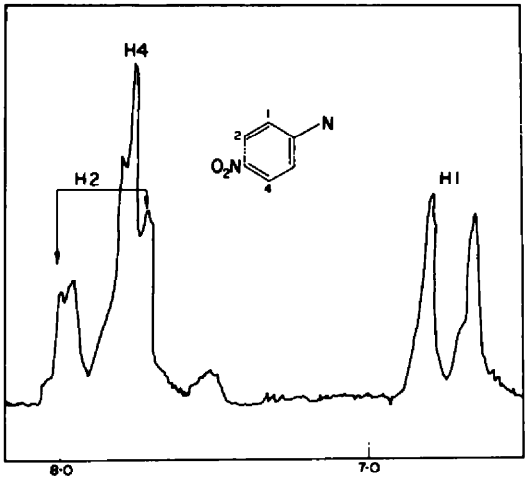
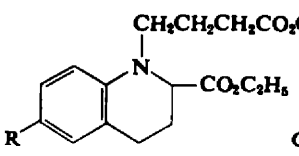
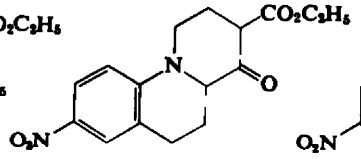


FIG. 1 NMR spectrum of nitro-compound (IX) in CCl_4. Values in ppm from TMS $J_{1,2} = 9$ c/s, $J_{3,4} = 2.5$ c/s.

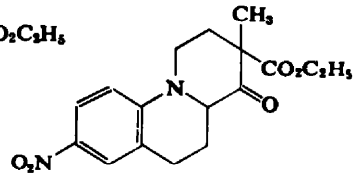
[2] S. M. McElvain and M. D. Barnett, *J. Amer. Chem. Soc.* **78**, 3140, (1956).
[3] A. Schaarschmidt, H. Balzerkiewicz, and J. Gante, *Ber. Dtsch. Chem. Ges.* **58**, 499 (1928).



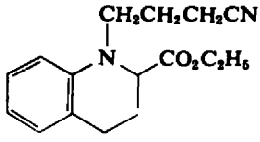
VIII, R = H
IX, R = NO_2
XII, R = NH_2



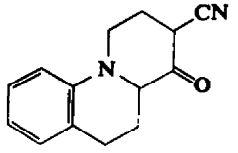
X



XI



XIII



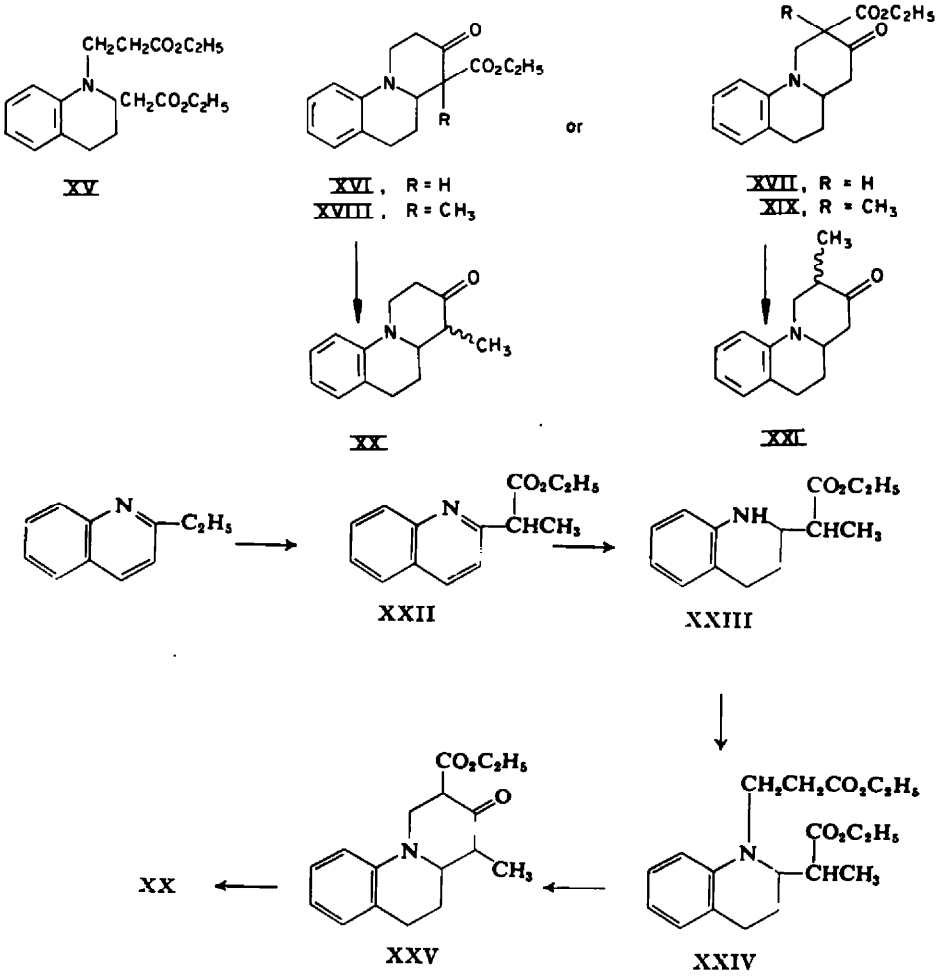
XIV

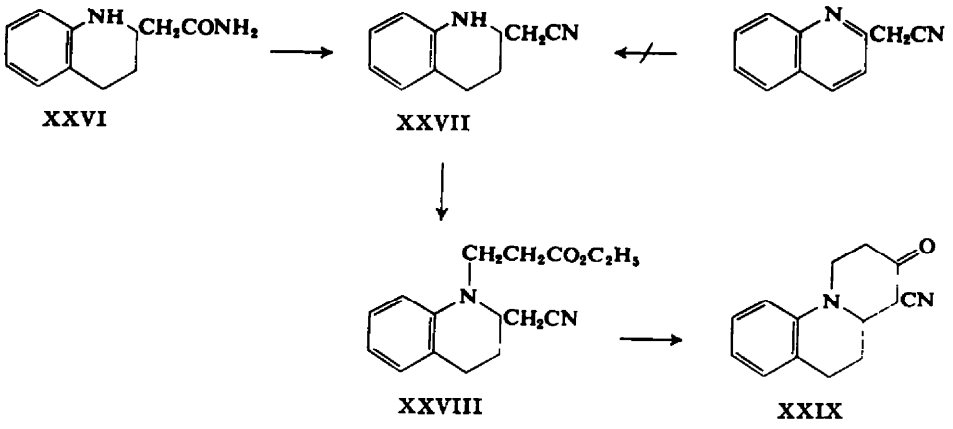
Both the bicyclic di-ester (VIII) and the keto-ester (II) reacted readily with dinitrogen tetroxide in carbon tetrachloride, giving mono nitro derivatives; both were almost non-basic though the yield of the mono nitro di-ester (a high boiling liquid) was much higher than that of the mono nitro keto-ester (an orange solid). The two mono nitro derivatives are formulated as IX and X on the basis of their NMR spectra in the aromatic region, which were almost identical (Fig. 1). The splitting pattern and, in particular, the chemical shifts are only explicable on the basis of nitration *para* to the nitrogen atom. Reduction of the nitro diester (IX) gave an aromatic primary amine (XII). Attempts to methylate the nitro keto-ester (X) using potassium t-butoxide and methyl iodide gave an unstable red oil, whose IR absorption suggested structure XI, but rapid resinification prevented further investigation. The cyano-ester (XIII) synthesized as described in the previous paper[1] was cyclized in high yield to give the cyanoketone (XIV). Nitration of the cyanoketone (XIV) gave an extremely insoluble brown solid, which has not been characterized.

The major difficulty in synthesis involving derivatives of 4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine appears to be the instability of systems which are formally analogous to 3-oxo-N-phenylpiperidine,[4] and later experiments have been directed to the synthesis of derivatives of 3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine, which should be more stable. A number of schemes for elaboration of ring D using the tricyclic keto-ester (XVI) are available, and attempts to synthesize this ester are described next. The simplest approach would be by cyclization of the di-ester (XV) and this has been prepared from ethyl 1,2,3,4-tetrahydro-2-quinolyl acetate and ethyl β-bromopropionate. The experimental temperature of alkylations using the β-bromopropionate was found to be highly important; the optimum temperature appears to be around 140°, higher temperatures leading to rapid conversion of the ethyl bromopropionate into ethyl acrylate. Cyclization of the di-ester (XV) proceeded smoothly, giving a single β-keto-ester, but the spectral properties of the cyclized material did not enable a decision to be made between the alternative structures (XVI and XVII). In contrast to the isomeric keto-ester (II), the new keto-ester was rapidly

[4] N. J. Leonard, G. Fuller and H. C. Dryden, *J. Amer. Chem. Soc.* **75**, 3727 (1953).

C-methylated to give as principal products two isomeric non-enolizable keto-esters, presumably stereo-isomers, of structure XVIII or XIX. Hydrolysis and de-carboxylation of the crude C-methylated keto-esters gave a mixture of epimeric methyl ketones (two methyl doublets were observed in the NMR) epimerized by sodium ethoxide to a single epimer, (XX or XXI; with one methyl doublet only in the NMR). To identify the ketone, and hence to deduce the direction of Dieckmann cyclization in the di-ester (XV), attempts were made to synthesize unambiguously both possible ketones (XX and XXI). Attempts to alkylate ethyl 1,2,3,4-tetrahydro-2-quinolylacetate with ethyl β-bromoisobutyrate were unsuccessful, presumably because of steric hindrance, so it has not been possible to achieve an alternative synthesis of ketone XXI. Treatment of the lithium derivative from 2-ethylquinoline with diethyl carbonate gave ethyl α-(2-quinolyl)propionate (XXII), which was reduced to the tetrahydro-ester (XXIII). Alkylation of the ester (XXIII) with ethyl β-bromopropionate gave the diester (XXIV), and this was cyclized to the methyl keto-ester (XXV). Hydrolysis and de-carboxylation of this keto-ester gave the methyl ketone (XX), which, after equilibration with





sodium ethoxide differed from that obtained by C-methylation and decarboxylation of the keto-ester described above. Hence the C-methylation decarboxylation product must have been XXI, the methylated keto-ester from which it was derived (XIX), and the Dieckmann cyclization of di-ester (XV) gives the keto-ester (XVII), which is unsuitable for further use in a 9-azasteroid synthesis.

In view of the high yield obtained in the cyclization of the cyano-ester (XIII), it was finally decided to prepare and cyclize the isomeric cyano-ester (XXVIII), using the superior electron-withdrawing power of the cyano group to ensure cyclization in the required direction. 2-Quinolylacetonitrile was prepared from 2-chloromethylquinoline using aqueous ethanolic potassium cyanide, but could not be cleanly reduced to the tetrahydro derivative (XXVII). Treatment of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate with methanolic ammonia gave the tetrahydroquinolylacetamide (XXVI), which was dehydrated to the required acetonitrile (XXVII). Alkylation of this nitrile (XXVII) with ethyl β-bromopropionate gave the cyano-ester (XXVIII), which was cyclized by sodium ethoxide to the cyano-ketone (XXIX; IR absorption at 2245 cm^{-1} (C≡N) and 1732 (ketone CO) indicated that the cyclization had proceeded correctly). Since the yields are good throughout this synthesis, the intermediate required for elaboration of ring D is available in quantity.

EXPERIMENTAL

M.ps were determined on a Kofler block. IR absorptions were determined on a Perkin–Elmer 221 or Infracord, or Unicam SP 700 spectrometer; UV absorptions on a Unicam SP 700, and NMR spectra on a Perkin–Elmer 60 mc instrument. Most reactions were performed under an atm. of dry N_2. Gas chromatographic separations were performed on a 10′ column made up of 1% SE-30 on Gaschrome P.

Alkylation of keto-ester (II). Compound II (12·4 g) was dissolved in dry toluene (100 ml) and NaH (1·3 g, 50% paraffin mull) was added in portions. After addition was complete the mixture was boiled and stirred for 1 hr, then cooled to room temp. MeI (9·63 g) in toluene (25 ml) was added, and the stirred solution slowly raised to b.p. (1 hr). The boiling continued for 2 hr during which a copious precipitate formed. The cooled mixture (O°) was diluted with dry ether (100 ml) and filtered. Although the precipitate (13·2 g) showed the presence of organic material in its IR spectrum, no organic material separated on careful neutralization and no derivatives could be obtained. Evaporation of the filtrate gave a brown oil (5·5 g), consisting mainly of two components (gas chromatography using 1% SE-30 on Gaschrom P). Chromatographic separation of the oil on alumina (Peter Spence, Grade O) gave pure samples of the two major components. The *first isomer* (IV) had b.p. 125–130°/2 × 10^{-4} mm (bath). (Found: C, 72·25; H, 8·1; N, 4·5. $C_{16}H_{23}NO_3$ requires: C, 71·7; H,

7·7; N, 4·65%.) ν_{max} 1737 (ester CO), 1718 (ketone CO) cm^{-1} (liquid film). The *second isomer* (IV) had b.p. 140–145°/2 × 10^{-4} (bath). (Found: C, 72·1; H, 7·9; N, 4·7%.) ν_{max} 1732 (ester CO), 1710 (ketone CO) cm^{-1} (liquid film) λ_{max} 2080, 2520, 2930 Å ($\log_{10} \varepsilon$ 4·39, 4·10, 3·47) in EtOH. The NMR spectrum ($CDCl_3$) showed the presence of a triplet, centred at 1·28 ppm (J = 7 c/s) due to the ester CH_3, and two singlets, each of weight 3 protons at 1·33 and 1·44 ppm, assigned to the methyl groups at positions 3 and 4a.

(b) A similar mixture of products was obtained when the xylene solution obtained in the Dieckmann cyclization used to produce II (see preceding paper) was treated with MeI and worked up as described above.

Diethyl methyl malonate prepared as described by Cox and McElvain[5] contained 5–10% of unreacted diethyl malonate, (VPC) and several washings with cold concentrated NaOH aq did not reduce the proportion of impurity below 5%.

2-Ethoxyethyl bromide prepared as described in Organic Syntheses[6] showed a strongly acid reaction and fumed in air, due to the presence of much HBr. A 50% yield of neutral ethoxyethyl bromide was obtained from PBr_3(350 g) and 2-ethoxyethanol (300 g) mixed slowly (below 80°), stirred for 1 hr, and poured into ice-water (500 ml). Separation of the bromide, washing with sat. $NaHCO_3$ aq, and drying ($CaCl_2$) was followed by distillation at 50 mm, b.p. 55° (285 g). Distillation at atm. press. gave a product with a strongly acid reaction.

Diethyl 2-ethoxyethyl methyl malonate. Prepared from K (40·4 g) in dry t-butanol (800 ml), diethyl methylmalonate (150 g), stirred at 50° for 0·5 hr, then 2-ethoxyethyl bromide (178 g) added and the mixture boiled and stirred for 2 hr. Most of the t-butanol was removed, the residue cooled to 0° and treated with ice-water (400 ml) and ether. Distillation of the ethereal solution gave the ethoxy ethyl methyl malonate (161 g, 76%) b.p. 130–132°/10 mm, (lit.[7] b.p. 118–120/7 mm).

Diethyl 2-bromoethylmethyl malonate. Diethyl 2-ethoxyethyl malonate (26 g) was dissolved in abs. EtOH (200 ml) and the solution was saturated with HBr. The solution was stood overnight at room temp, then boiled for 2 hr. The mixture was concentrated under red. press. and the residue poured into ice-water (50 ml). The aqueous layer was basified with $NaHCO_3$, and ether extracted. The ethereal solution was dried and rapidly distilled to give substantially pure bromoethylmethylmalonate (22 g; 74%) b.p. 138–140°/11 mm (lit.[8], b.p. 145–150°/20 mm); a certain amount of lactone was always present, as shown by the presence of an absorption band at 1770 cm^{-1}.

2-Methyl-4-butyrolactone. A solution of diethyl 2-ethoxyethylmethylmalonate (102 g) in conc. HBr (600 ml, 33%) was boiled for 6 hr, the EtBr which formed being periodically distilled off. Removal of the HBr under red. press. left a semi-solid mixture containing some carboxylic acid; neutralization of the distilled HBr and saturation with salt gave a further quantity of lactone, which was extracted with ether. The lactone and the carboxylactone were bulked and heated at 200° for 1 hr, then distilled, giving 2-methyl-4-butyrolactone (30·3 g, 73%), b.p. 81°/11 mm (lit. b.p. 97–99°/19 mm,[9] 103–105°/40 mm[10]).

Ethyl 4-bromo-2-methylbutyrate. A solution of 2-methyl-4-butyrolactone (32 g) in abs. EtOH (80 ml) was saturated with HBr at 0° and stood at room temp for 24 hr. After re-saturation with HBr the solution was stood for a further 12 hr at room temp and was then poured on to ice (120 g). The ester layer was separated, the aqueous layer extracted with ether, and the combined organic layers washed with sat. $NaHCO_3$ aq and then with water. The dried solution was distilled b.p. 45–50°/1 mm, but contained about 10% lactone. Further washing with water and distillation gave pure *ethyl 4-bromo-2-methylbutyrate* b.p. 47°/1 mm. (Found: C, 40·05; H, 6·26; Br, 38·2. $C_7H_{13}BrO_2$ requires: C, 40·2; H, 6·26; Br, 38·65%.)

Ethyl N-(3-ethoxycarbonylbutyl)-1,2,3,4-tetrahydroquinaldinate (V). A mixture of ethyl 1,2,3,4-tetrahydroquinaldinate[1] (24 g), ethyl 4-bromo-2-methylbutyrate (49 g) anhydrous K_2CO_3 (32·3 g) and KI (1 g) was heated and vigorously stirred at 160–170° for 6 hr. The cooled mixture was treated with cold water and $CHCl_3$, the $CHCl_3$-layer dried and distilled at 10 mm to give 2-methyl-4-butyrolactone (12·1 g) b.p. 78–82°. The press. was reduced and a fraction collected at 104–140°/0·18 mm

[5] R. F. B. Cox and S. M. McElvain, *Organic Syntheses.* Coll. Vol. II; p. 279. J. Wiley, N.Y.
[6] G. C. Harrison and H. Diehl, *Organic Syntheses.* Coll. Vol. III, p. 370.
[7] J. B. Data and B. M. Sutton, U. S. pat. 2,764, 615 Sept. 25th (1956); *Chem. Abstr.* **51**, 4415 (1957).
[8] T. Kobayashi, *Liebigs Ann.* **536**, 156 (1938).
[9] W. Reppe, H. Kröper, H. J. Pistor and H. Schlenck, *Liebigs Ann.* **582**, 38 (1953).
[10] R. Lukes and V. Dodek, *Chem. Listy.* **51**, 2139 (1957).

(8·9 g). Further reduction of the press. gave V b.p. 140–160°/6 × 10^{-4} mm (23·7 g, 61%). Redistillation gave pure V, b.p. 154–156°/6 × 10^{-4} mm. (Found: C, 68·25; H, 8·3; N, 3·9. $C_{19}H_{27}NO_4$ requires: C, 68·4; H, 8·2; N, 4·2%.) λ_{max} 2090, 2500, 3000 Å ($\log_{10}\varepsilon$ 4·38, 3·97, 3·41) in EtOH. ν_{max} 1740 (ester CO).

Ethyl N-(3,3-*di-ethoxycarbonylbutyl*)-1,2,3,4-*tetrahydroquinaldinate* (VII). A mixture of ethyl 1,2,3,4-tetrahydroquinaldinate (11·5 g), diethyl 2-bromoethylmethylmalonate (21·5 g) and anhydrous K_2CO_3 (10·6 g) was heated and stirred at 160° for 7 hr. Working up as described for V above gave mainly unalkylated tetrahydroquinaldinate and 2-ethoxycarbonyl-2-methyl-4-butyrolactone (identified by its IR spectrum). The required *tri-ester* (VII) was obtained b.p. 150°/6 × 10^{-4} mm (1·9 g, 8%). (Found: C, 65·35; H, 7·9; N, 3·15. $C_{23}H_{31}NO_6$ requires: C, 65·15; H, 7·7; N, 3·45%.)

Attempted cyclization of di-ester (V). Compound V (8·65 g) in dry xylene (60 ml) was added over 0·5 hr. to a suspension of potassium t-butoxide in boiling xylene (50 ml) (prepared from 1·09 g K). Slow distillation during and after (0·5 hr) the addition removed butanol as formed. The cooled mixture was treated with dry ether (300 ml) and filtered, giving a hygroscopic potassium salt (6·0 g). The free base from this salt was unstable, but a hydrochloride was obtained, m.p. 96–97°, formulated as the *acyloin* (VI) *hydrochloride*. (Found: C, 63·9; H, 7·7; N, 4·5. $C_{15}H_{19}NO_2$·HCl requires: C, 63·9; H, 7·2; N, 5·0%); ν_{max} 3350, 2500 ($\overset{+}{N}H$), 1725 (C=O) cm^{-1}.

The filtrate from the potassium salt was evaporated but the residual oil (1·8 g) could not be purified and gave no concordant analyses.

Ethyl 6-*nitro*-N-(3′-*ethoxycarbonylpropyl*)-1,2,3,4-*tetrahydroquinaldinate* (IX). Compound VIII (5·0 g) in dry CCl_4 (50 ml) at −5° was stirred vigorously with powdered $CaCO_3$ (1·6 g) while a cooled solution of dinitrogen tetroxide (1·45 g) in CCl_4 (20 ml) was added. The mixture was stirred at −5° for 3 hr during which a dark oil separated and was absorbed by the $CaCO_3$. The mixture was then allowed to warm slowly to room temp, filtered, and the CCl_4 washed with cold 3N HCl (100 ml), sat. $NaHCO_3$ aq, and water. The dried solution was evaporated to give a viscous brown oil (4·76 g, 83%). A sample was distilled in a bulb tube to give the *nitro compound* (IX), b.p. 200–210°/10^{-3} mm. (Found: C, 59·75; H, 6·7; N, 8·05. $C_{18}H_{24}N_2O_6$ requires: C, 59·35; H, 6·6; N, 7·7%); ν_{max} 1737 (ester CO), 1326 (NO_2), 1188 (C—O) in CCl_4. λ_{max} 2090, 2290, 3930 Å ($\log_{10}\varepsilon$ 3·96, 3·73, 3·97) in EtOH. The NMR spectrum in the aromatic region is shown in the Fig., in addition a triplet centred at 1·27 ppm (6 protons) and two overlapping quartets at 4·0–4·4 ppm (4 protons) represented the two ester ethyl groups.

8-*Nitro*-4-*oxo*-3-*ethoxycarbonyl* 1,2,3,4,5,6-*hexahydrobenzo*[c]*quinolizine* (X). Compound II (4·77 g) in CCl_4 (100 ml) at −5° was vigorously stirred while an ice-cold solution of dinitrogen tetroxide (1·69 g) in CCl_4 (40 ml) was added (0·5 hr), and for a further 3 hr. The solution was allowed to warm to room temp, decanted from a reddish-brown tar which had separated; the tar was washed with CCl_4 and the combined solution evaporated to small volume *in vacuo*, giving a reddish-brown solid (1·32 g, 24%). A sample recrystallized from EtOH gave the *nitro keto-ester* (X) as orange hexagons, m.p. 126–129°. (Found: C, 60·25; H, 5·65; N, 8·90. $C_{16}H_{18}N_2O_5$ requires: C, 60·35; H, 5·70; N, 8·80%.) ν_{max} (KBr disc) 1750 and 1715 cm^{-1} (keto-ester C=O stretching) 1656 and 1623 cm^{-1} (enolic ester C=O stretching) 1505, 1325 cm^{-1} (NO_2). λ_{max} 2080, 2460, 3950 Å ($\log_{10}\varepsilon$ 3·99, 4·00, 4·15) in EtOH. The NMR spectrum was as shown in Fig. 1 for the aromatic region; in addition a 3-proton triplet centred at 1·33 ppm, and a two proton quartet centred at 4·2 ppm were due to the ester ethyl group.

Attempted methylation of nitro-keto-ester (X). A solution of X (1·35 g) in toluene (30 ml) was added slowly to a suspension of potassium t-butoxide (from 0·18 g K) in dry toluene (50 ml). Slow distillation was maintained during and after (0·5 hr) the addition. MeI (1·2 g) in toluene (20 ml) was added to the cooled mixture, the temp slowly raised to b.p. and boiling continued for 3 hr. The cooled filtered solution was evaporated giving an unstable dark gum which could not be purified further. The IR showed peaks at 1740, 1715 (C=O), 1500 and 1300 (NO_2) cm^{-1} as expected for XI.

Ethyl 6-*amino*-N-(3-*ethoxycarbonylpropyl*)-1,2,3,4-*tetrahydroquinaldinate* (XII). Compound IX (0·66 g) in EtOH (100 ml) was hydrogenated over Adams' catalyst (0·1 g) at normal temp and press. When 3 molar equivs H_2 had been absorbed hydrogenation was stopped, the solution filtered and evaporated, giving a brown oil (0·61 g). Distillation gave the *amino di-ester* (XII) b.p. 185–195° (bath)/0·0003 mm. (Found: C, 64·64; H, 8·0; N, 8·35. $C_{18}H_{26}N_2O_4$ requires: C, 64·65; H, 7·85; N, 8·4%); ν_{max} 3425, 3335 cm^{-1} (NH_2) 1737 cm^{-1} (C=O) (CCl_4). λ_{max} 2090, 2600 Å ($\log_{10}\varepsilon$ 4·01, 3·72) in EtOH.

3-Cyano-4-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XIV). A solution of XIII[1] (8·16 g) in dry xylene (75 ml) was added slowly (1 hr) to a boiling, vigorously stirred suspension of EtONa (2·25 g) in xylene (75 ml). Slow distillation was maintained throughout the addition. After the addition the mixture was boiled and stirred for 1 hr then distilled until the vapour temp reached 138°. The ice cooled suspension was treated with ether (100 ml) and water (100 ml). The aqueous layer was separated and the organic layer extracted twice with 1 N NaOH (50 ml). The combined aqueous layers were treated with 5N HCl at 0° to pH 6, then extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution gave a viscous brown gum (6·41 g, 94%) which could be further purified by conversion into its hydrochloride and subsequent regeneration. A sample was distilled giving the *cyano-ketone* (XIV) b.p. 180° (bath)/0·003 mm. (Found: C, 74·4; H, 6·4; N, 12·15. $C_{14}H_{14}N_2O$ requires: C, 74·3; H, 6·25; N, 12·4%); λ_{max} 2090, 2460, 2930 Å ($\log_{10}\varepsilon$ 4·19, 4·02, 3·22) in EtOH; ν_{max} 3400, 1645 cm^{-1} (OH, C═C, enol) and 2240, 1725 cm^{-1} (CN, C═O, ketone). The *hydrochloride*, prepared from dry HCl and XIV in benzene, was crystallized from abs. EtOH containing a trace of HCl as pale green needles, m.p. 163° (dec.). (Found: C, 63·49; H, 5·82; N, 11·01. $C_{14}H_{15}ClN_2O$ requires: C, 63·95; H, 5·75; N, 10·7%.)

Ethyl 2-quinolylacetate was prepared by the reaction of quinaldinyl lithium with di-ethyl carbonate[11] or ethyl chloroformate.[12] Neither method gave consistent or good yields. A much superior method was conversion of 2-chloromethylquinoline hydrochloride to 2-quinolylacetonitrile;[13–15] a solution of the acetonitrile (29·4 g) in abs. EtOH (300 ml) containing water (4 ml) was saturated with HCl at 60°, then boiled for 3 hr. The cooled (0°) mixture was filtered and the filtrate evaporated *in vacuo*. The residue was treated with ice-cold sat. $NaHCO_3$ aq, extracted with ether, and the ethereal extracts dried and distilled. The yield of ethyl 2-quinolylacetate, b.p. 136–137°/0·6 mm, was 28·6 g (76%) (lit. b.p. 128–135°/0·8 mm,[11] 170–180°/1·5 mm.[12])

Ethyl 1,2,3,4-tetrahydro-2-quinolylacetate. Ethyl 2-quinolylacetate (36·65 g) in purified glacial acetic acid (250 ml) was hydrogenated over Adams' catalyst (1·00 g) at room temp and press. until 2 moles H_2 had been absorbed. The suspension was evaporated under red. press. and the residue treated with $NaHCO_3$ aq and ether. The filtered mixture was separated, the ethereal layer dried and distilled. The *tetrahydroquinolylacetate* had b.p. 130–138°/0·6 mm (34·25 g, 92%) (lit.[14] b.p. 144–145°/1 mm) substantially pure on gas chromatography. Reduction in EtOH was slow and incomplete even at 50°, and the product differed in retention time from the pure 1,2,3,4-tetrahydro-2-quinolyl acetate. Reduction as described by Nagata gave a mixture of the 1,2,3,4-tetrahydro-2-quinolylacetate and the product obtained by reduction in EtOH (approx. 1:2).

Ethyl [1-benzoyl]-1,2,3,4-tetrahydro-2-quinolyl acetate prepared in pyridine and crystallized from petrol (60–80° b.p.) as colourless prisms, m.p. 96·5–97°. (Found: C, 74·01; H, 6·60; N, 3·90. $C_{20}H_{21}NO_3$ requires: C, 74·3; H, 6·55; N, 4·33%.)

Ethyl 3-bromopropionate prepared as described by Mozingo and Patterson[16] was strongly acid, and was washed with sat. $NaHCO_3$ aq, then water, dried, and distilled, b.p. 44°/2·5 mm to give a neutral specimen.

Ethyl 1-(2'-ethoxycarbonylethyl)-1,2,3,4-tetrahydro-2-quinolylacetate (XV). A vigorously stirred mixture of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (10 g), ethyl 3-bromopropionate (16·42 g) anhydrous, finely ground K_2CO_3 (9·5 g) and KI (0·38 g) was heated at 140° for 4 hr, a short air condenser allowing water to evaporate. The cooled mixture was treated with water and ether, the ether layer separated and the aqueous layer further extracted with ether. The combined ethereal extracts were washed with water, dried, and evaporated. The residual oil was distilled, first at 12 mm, giving recovered ethyl 3-bromopropionate (4 g) and then at 0·003 mm, giving recovered tetrahydroquinolylacetate (1·7 g) and then the *diester* (XV), b.p. 145–160° (9·0 g, 63%). Redistilled for analysis the diester had b.p. 161°/0·003 mm. (Found: C, 67·2; H, 7·95; N, 4·35. $C_{18}H_{25}NO_4$ requires: C, 67·7; H, 7·9; N, 4·4%), ν_{max} 1739, 1186 cm^{-1} (CCl_4), ν_{max} 2095, 2570, 3060 Å ($\log_{10}\varepsilon$ 4·35, 4·14, 3·40) in EtOH.

[11] D. Ll. Hammick, E. Johnston and E. D. Morgan, *J. Chem. Soc.* 5073 (1957).
[12] J. D. Kendall, H. R. J. Waddington and G. F. Duffin, *Brit.* 867592, May 10, 1961, *Chem. Abstr.*, **55**, 21927 (1961).
[13] V. Carelli, M. Cardellini and F. Liberatore, *Ann. Chim. Rome* **49**, 709 (1959).
[14] M. Nagata, *Yakugaku Zasshi* **80**, 1414 (1960).
[15] H. Lettre, P. Jungmann and J. C. Salfeld, *Chem. Ber.* **85**, 397 (1952).
[16] R. Mozingo and C. Patterson, *Organic Syntheses.* Coll. Vol. III, 576.

2-Ethoxycarbonyl-3-oxo-1,2,3,4,5,6-tetrahydrobenzo[c]quinolizine (XVII). Compound XV (12·0 g) with EtONa (from 0·95 g Na) in dry xylene (200 ml) was cyclized as described for XIII. The cooled (0°) mixture after cyclization contained a yellow sodium salt (A) and was treated with water (100 ml). The pH of the aqueous layer was adjusted to 6·5, ether was added and the organic layer separated. The organic layer and subsequent ether extracts were combined, dried and evaporated *in vacuo* to give a viscous orange oil (9·5 g, 93%). The oil gave a single peak on gas chromatography, showing no XV to be present, but the low retention time (5·0 min at 180°) suggested decomposition to a more volatile compound. The *keto ester* (XVII) could not be purified by distillation because of thermal decomposition, and a sample was prepared for analysis by regeneration from pure hydrochloride. (Found: C, 70·9; H, 6·9; N, 5·1. $C_{16}H_{19}NO_3$ requires: C, 70·3; H, 7·0; N, 5·15%.) λ_{max} 2100, 2520, 2930 Å ($\log_{10}\varepsilon$ 4·24, 4·14, 3·32) in EtOH, ν_{max} 1730, 1708 cm^{-1} (ketone and ester C=O), 1653, 1612 cm^{-1} ($\alpha\beta$-unsaturated ester) (CCl_4). The *hydrochloride* prepared in ether, and recrystallized from acetone: ether (containing a few drops of conc. HCl) as colourless prisms, m.p. 130° (softening at 113°). (Found: C, 62·03; H, 6·55; N, 4·3. $C_{16}H_{20}ClNO_3$ requires: C, 62·05; H, 6·55; N, 4·5%.) ν_{max} 1662, 1630 cm^{-1} ($\alpha\beta$-unsaturated ester) (KBr disc).

2-Ethoxycarbonyl-2-methyl-3-oxo-1,2,3,4,5,6-tetrahydrobenzo[c]quinolizine (XIX). The suspension of sodium salt described above, (A), prepared from XV (6·0 g) was cooled and MeI (3·06 g) in xylene (25 ml) added. The mixture was stirred at room temp (1 hr), the temp raised to 60°, and maintained at 60° for 8 hr. The cooled mixture was filtered, the precipitate washed with ether and the combined filtrates evaporated to give a light brown oil (3·86 g), (B), shown by gas chromatography to consist principally (85%) of one component. The ester could not be purified by distillation, but chromatography on Woelm alumina (neutral, activity II) in petrol–benzene mixtures gave two pure isomers, the purity of the fractions being checked by gas chromatography. The *minor isomer* (XIX), eluted first, was distilled as a pale yellow viscous oil, b.p. 130–140°/4 × 10^{-4} mm, which crystallized on standing. (Found: C, 70·8; H, 7·60; N, 4·85. $C_{17}H_{21}NO_3$ requires: C, 71·05; H, 7·37; N, 4·87%). λ_{max} 2100, 2540, 2940 Å ($\log_{10}\varepsilon$ 4·37, 4·21, 3·47) in EtOH, ν_{max} 1735 (shoulder), 1720 cm^{-1} (ester and ketone CO not quite resolved). The NMR spectrum (CCl_4) showed a singlet at 1·24 ppm (2-methyl) overlapped by a triplet (J = 7 c/s) centred at 1·19 ppm (methyl of ethoxycarbonyl group), and a one-proton doublet (J = 13 c/s) centred at 4·50 ppm. The *major isomer* (XIX) was a viscous yellow oil, b.p. 150–155°/4 × 10^{-4} mm. (Found: C, 70·6; H, 7·17; N, 4·78%), λ_{max} 2100, 2540, 2960 Å ($\log_{10}\varepsilon$ 4·35, 4·13, 3·34) in EtOH, ν_{max} 1735, (ester CO), 1716 (ketone CO) (CCl_4). The NMR spectrum in CCl_4 differed markedly from that of the minor isomer, showing a singlet at 1·44 ppm (2-methyl), slightly overlapped by a triplet (J = 7 c/s) centred at 1·28 ppm (methyl of ethoxycarbonyl group), a sharp 2-proton singlet at 3·75 ppm (C-1 protons), and a doublet (J = 7 c/s) at 2·46 ppm (C-4 protons).

2-Methyl-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XXI). The crude product (B; 2 g) from the experiment described above was boiled in 5 N HCl (40 ml) for 6 hr, then evaporated to dryness. The free base, obtained by addition of $NaHCO_3$ aq, was extracted with ether and distilled, b.p. 130–140°/0·003 mm (1·1 g, 73%). The NMR spectrum showed two doublets of equal intensity centred at 0·99 and 1·14 ppm; after equilibration with ethanolic EtONa (b.p., 3 hr) the re-distilled *ketone* (XXI) showed only the doublet at 0·99 ppm (J = 7 c/s). (Found: C, 78·0; H, 8·02; N, 6·07. $C_{14}H_{17}NO$ requires: C, 78·10; H, 7·96; N, 6·57%.) ν_{max} 1717 cm.$^{-1}$ (CCl_4 soln) λ_{max} 2100, 2540, 2940 Å ($\log_{10}\varepsilon$ 4·25, 3·98, 3·27) in EtOH.

Further confirmation that XXI, as obtained by decarboxylation of the crude XIX, was a mixture of epimers and not structural isomers, was obtained by hydrolysing and decarboxylating a sample of the pure major isomer (XIX; 0·223 g). The NMR spectrum of the resulting ketone (0·148 g, 88%) still showed doublets centred at 0·99 and 1·14 ppm and was practically identical to that of the ketone obtained from the mixture of keto-esters (XIX).

The *2,4-dinitrophenylhydrazone* was prepared in a similar way to that described by Moyneham *et al.* for ketoquinolizidines.[17] The equilibrated ketone was heated at 100° for 15 min with a solution of 2,4-dinitrophenylhydrazine (molar equiv.) in abs. EtOH/HBr at 100°. The 2,4-dinitrophenylhydrazone hydrobromide obtained after cooling and filtering the solution was dissolved in $CHCl_3$ and the $CHCl_3$-solution vigorously shaken with Na_2CO_3 aq, then water, dried and evaporated. The residual dark gum was recrystallized from MeOH giving the dinitrophenylhydrazone as dark red microcrystals, m.p. 195–198°. (Found: C, 60·9; H, 5·53; N, 17·9. $C_{20}H_{21}N_5O_4$ requires: C, 60·75; H, 5·35; N, 17·71%.)

[17] T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).

Methyl β-bromoisobutyrate was prepared from methyl methacrylate by the procedure described for ethyl β-bromopropionate. The crude product was washed with $NaHCO_3$ aq and water before distillation; the material b.p. 65–66°/11 mm (lit.[18] b.p. 67°/17 mm) was neutral.

Attempted alkylation of ethyl tetrahydroquinolylacetate by methyl β-bromoisobutyrate. A mixture of ethyl tetrahydro-2-quinolylacetate (9·52 g), methyl β-bromoisobutyrate (15·6 g), anhydrous K_2CO_3 (9·1 g), and KI (0·4 g) was heated at 150° for 5 hr. Working up of the mixture as described for the preparation of XV gave almost entirely material of b.p. lower than 115°/0·002 mm, containing a large proportion of un-alkylated tetrahydroquinolylacetate.

2-Ethylquinoline was obtained in very poor yield as described from tribromoquinaldine.[19,20] A better procedure for large scale preparation was the addition of an ethereal solution of quinaldyl lithium (from 252 g quinaldine) to MeI (268 g) at such a rate that the mixture boiled gently. After addition was complete the mixture was boiled for a further 1 hr, and stood at room temp overnight. 5 N HCl (1300 ml) was added, the acid layer separated and the ether layer re-extracted with acid. The combined acid layers were basified with NH_4OH (sg. 0·880) and the bases extracted (ether), dried, and distilled several times giving quinaldine (47 g) and 2-ethylquinoline (135 g, 57% based on unrecovered quinaldine), b.p. 134–135°/14 mm (lit.[19] b.p. 134–136/16 mm). The material was pure on examination by GPC. Inverse addition (lithium reagent to alkyl halide) is essential, as normal addition gave a third material extremely difficult to separate from the ethylquinoline, and believed to be 2-(2′-propyl)quinoline.

Ethyl 2-(2′-quinolyl)propionate (XXII). A filtered solution of phenyllithium (from 90 g bromobenzene) was added slowly to a stirred solution of 2-ethylquinoline (75 g) in ether (100 ml) and the resulting mixture was boiled (1 hr). The filtered 2-ethylquinolyllithium was then added over 1 hr to a vigorously stirred solution of di-ethylcarbonate (34 g) in ether (100 ml). The resulting solution was boiled (3 hr), then cooled and treated with ice-cold 5 N HCl (500 ml). The acid layer was separated and the ether layer further extracted with 5 N HCl (2 × 100 ml). The combined acid layers were neutralized with ammonia, extracted with ether, and the ethereal solution dried, and distilled. The first fraction was 2-ethylquinoline (29 g) b.p. 60–85°/0·05 mm; the *ester* (XXII; 9·7 g, 15% on unrecovered ethylquinoline) had b.p. 116°/0·05 mm. (Found: C, 73·92; H, 6·70; N, 6·08. $C_{14}H_{15}NO_2$ requires: C, 73·34; H, 6·6; N, 6·1%), λ_{max} 2130, 2290, 2320 Å ($\log_{10}\varepsilon$ 4·35, 4·49, 4·49) in EtOH. ν_{max} 1735, 1180 cm^{-1} (CCl_4 solution). The *picrate* crystallized from EtOH, m.p. 137–140° (rapid heating). (Found: C, 52·3; H, 4·05; N, 12·6. $C_{20}H_{18}N_4O_9$ requires: C, 52·4; H, 3·96; N, 12·2%.)

Ethyl 2-(1,2,3,4-Tetrahydro-2-quinolyl)propionate (XXIII). The ester XXII (15·8 g) was hydrogenated at room temp and atm press. in glacial acetic acid (150 ml) over Adams' catalyst (0·3 g) until 2 molar equivs H_2 had been absorbed. The filtered solution was evaporated *in vacuo*, the residue shaken with sat. $NaHCO_3$ aq and ether. The ethereal extracts were dried and distilled, giving the *tetrahydro ester* (XXIII) as a pale yellow oil b.p. 134–138°/0·7 mm (13·7 g, 85%). (Found: C, 72·3; H, 8·15; N, 6·32. $C_{14}H_{19}NO_2$ requires: C, 72·07; H, 8·2; N, 6·0%.) ν_{max} 3385 (NH), 1730 (C=O), 1187 (C—O) cm^{-1} (CCl_4 solution), λ_{max} 2090, 2500, 3030 Å ($\log_{10}\varepsilon$ 4·30, 3·92, 3·27) in EtOH.

1-(2-Ethoxycarbonylethyl)-2-(1-ethoxycarbonylethyl)-1,2,3,4-tetrahydroquinoline (XXIV). A mixture of XXIII (13·9 g) ethyl β-bromopropionate (21·5 g) anhydrous K_2CO_3 (12·4 g) and KI (0·5 g) was vigorously stirred at 150° for 6 hr. The cooled product was worked up as described for XV. The main fractions were recovered ester XXIII (8·18 g) b.p. 90–120°/0·002 mm and the diester XXIV b.p. 148–154°/0·002 mm (6·03 g, 73% on unrecovered ester XXIII). (Found: C, 68·1; H, 8·44; N, 4·25; $C_{19}H_{27}NO_4$ requires: C, 68·45; H, 8·15; N, 4·2%), ν_{max} 1739, 1185 cm^{-1} (CCl_4 solution) λ_{max} 2100, 2580, 3060 Å ($\log_{10}\varepsilon$ 4·34, 4·18, 3·39) in EtOH.

2-Ethoxycarbonyl-4-methyl-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XXV). Compound XXIV (6·48 g) in xylene (50 ml) was slowly added to a boiling suspension of potassium t-butoxide (from 0·836 g K) in xylene (75 ml). Slow distillation was continued during the addition and for 1 hr after. The mixture was cooled, ice-water (100 ml) added, and acidified to pH 6. The ether extracts were dried and evaporated giving XXV, unstable to distillation, ν_{max} 1733, 1717 (keto-ester) 1667, 1624 (enolic ester) cm^{-1} (CCl_4 solution), λ_{max} 2090, 2520, 2940 Å ($\log_{10}\varepsilon$ 4·37, 4·14, 3·38) in EtOH. The *hydrochloride*, twice precipitated from ether, was unstable to crystallization and melted to a thick glass at 50–55°, becoming mobile at 85–90°. (Found: C, 63·6; H, 6·75; N, 4·23. $C_{17}H_{22}NO_3Cl$ requires: C, 63·1; H, 6·85; N, 14·32%.)

[18] G. R. Clemo and T. A. Melrose, *J. Chem. Soc.* 424 (1942).
[19] K. N. Campbell, C. H. Helbing and J. F. Kerwin, *J. Amer. Chem. Soc.* **68**, 1840 (1946).
[20] B. R. Brown, D. Ll. Hammick and B. H. Thewlis, *J. Chem. Soc.* 1145 (1951).

4-Methyl-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XX). A solution of the crude XXV (2·5 g) in 5 N HCl (50 ml) was boiled for 5 hr. The acid solution was evaporated (water pump) and the residue treated with sat. $NaHCO_3$ aq and ether. The ethereal extracts were dried and distilled giving an oil (1·4 g, 75%) b.p. 135–140°/0·001 mm. The distilled ketone showed two methyl doublets centred at 0·99 and 1·13 ppm respectively. After equilibration (as described for XXI) the *ketone* (XX) showed only one methyl doublet (at 0·99 ppm) and was recrystallized from petrol (60–80°) as colourless rods m.p. 96–97° (Found: C, 77·75; H, 8·3; N, 6·3. $C_{14}H_{17}NO$ requires: C, 78·1; H, 7·95; N, 6·5%), ν_{max} 1717 cm^{-1} (CCl_4 solution). The ketones (XX and XXI) differed markedly in IR absorption between 1450 and 700 cm^{-1} and had retention times of 16·0 and 14·8 min at 150°.

The *2,4-dinitrophenylhydrazone* of XX was prepared as described for XXI and recrystallized from MeOH as very deep red prisms, m.p. 153–155°. (Found: C, 61·1; H, 5·38; N, 17·86. $C_{20}H_{21}N_5O_4$ requires: C, 60·75; H, 5·35; N, 17·71%.)

1,2,3,4-Tetrahydro-2-quinolylacetamide (XXVI). A solution of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (18 g) in dry MeOH (500 ml) was saturated with ammonia at 0° and then heated in an autoclave at 100° for 40 hr. Evaporation of the solution gave a gum crystallizing when triturated with petrol, and recrystallized from petrol (b.p. 60–80°)–benzene mixture to give the colourless *amide* (XXVI) m.p. 98–103° (13·4 g, 85%). A sample recrystallized from benzene had m.p. 103–104°. (Found: C, 69·6; H, 7·6; N, 14·8. $C_{11}H_{14}N_2O$ requires: C, 69·4; H, 7·4; N, 14·75%), λ_{max} 2090, 2490, 3010 Å ($\log_{10}\varepsilon$ 4·28, 3·91, 3·26) in EtOH. ν_{max} 3510, 3475 (free amide NH_2), 3170 (bonded NH_2), 3385 (amine NH), 1692 (CO) cm^{-1} (CCl_4 solution). The *N-benzoyl derivative* prepared in pyridine, crystallized from 95% EtOH as colourless prisms m.p. 198–201° (Found: C, 73·65; H, 6·4; N, 9·25. $C_{18}H_{18}N_2O_2$ requires: C, 73·45; H, 6·15; N, 9·5%), ν_{max} 1675 (primary amide CO), 1623 cm^{-1} (tertiary amide CO) ($CHCl_3$ solution).

1,2,3,4-Tetrahydro-2-quinolylacetonitrile (XXVII). A mixture of XXVI (12·5 g) and dry NaCl (5·93 g) with dry ethylene dichloride (60 ml) was stirred for 15 min at room temp, while $POCl_3$ (8·93 g) in dry ethylene dichloride (10 ml) was added. On warming the mixture a vigorous reaction was observed; the mixture was boiled and stirred for 12 hr. The cooled mixture was treated with a solution of NaOH (8·0 g) in MeOH, shaken twice with a cold brine solution, the organic layer dried, and distilled. The *nitrile* (XXVII) was a pale yellow viscous oil b.p. 124–127°/0·06 mm (8·12 g, 72%) solidifying on standing. (Found: C, 76·55; H, 7·25; N, 16·05. $C_{11}H_{12}N_2$ requires: C, 76·7; H, 7·0; N, 16·25%), λ_{max} 2100, 2500, 3000 Å ($\log_{10}\varepsilon$ 4·37; 4·15, 3·44) in EtOH, ν_{max} 3395 cm^{-1} (NH), 2250 cm^{-1} (CN) (CCl_4 solution). The *N-benzoyl derivative* was prepared in pyridine and crystallized from 95% EtOH as colourless rods, m.p. 130°. (Found: C, 78·15; H, 6·05; N, 10·05. $C_{18}H_{16}N_2O$ requires: C, 78·25; H, 5·85; N, 10·15%), ν_{max} 2255, (CN), 1648 (CO) (CCl_4 solution).

1-Ethoxycarbonylethyl-2-cyanomethyl-1,2,3,4-tetrahydroquinoline (XXVIII). A mixture of XXVII (5·0 g), ethyl β-bromopropionate (10·47 g), anhydrous K_2CO_3 (6·02 g) and KI (0·24 g) was stirred and heated at 140° for 6 hr. Working up as described for XV gave a crude product which still contained a large proportion of unalkylated nitrile (XXVII), and this crude product was again heated at 145° for 8 hr with further ethyl β-bromopropionate (10·5 g) and K_2CO_3 (6 g). Working up as for XV gave a first fraction of recovered XXVII (1·6 g) b.p. 110–135°/6 × 10^{-4} mm, then the *cyano-ester* (XXVIII) b.p. 156–162°/6 × 10^{-4} mm (4·32 g, 80% based on un-recovered nitrile). The XXVIII crystallized on standing, and was recrystallized from petrol (b.p. 60–80°) as colourless hexagons, m.p. 66°. (Found: C, 70·5; H, 7·55; N, 10·75. $C_{16}H_{20}N_2O_2$ requires: C, 70·55; H, 7·4; N, 10·3%), ν_{max} 2245 (CN) 1735 cm^{-1} (C=O) (CCl_4 solution), λ_{max} 2100, 2550, 3020 Å ($\log_{10}\varepsilon$ 4·35, 4·17, 3·41) in EtOH.

4-Cyano-3-oxo-1,2,3,4,5,6-hexahydrobenzo[c]quinolizine (XXIX). A solution of XXVIII (2·96 g) in dry xylene (50 ml) was added over 1 hr to a stirred, boiling mixture of EtONa (from 0·275 g Na) and xylene (60 ml); stirring and distillation were continued for 1 hr after addition was completed. The reaction mixture was worked up as described for XIV, giving the *cyano-ketone* (XXIX) as a light yellow solid, m.p. 132–138° (2·01 g, 82%). Recrystallization from 95% EtOH gave colourless rhombs, m.p. 135–137·5°. (Found: C, 73·9; H, 6·55; N, 12·18. $C_{14}H_{14}N_2O$ requires: C, 74·3; H, 6·25; N, 12·4%), λ_{max} 2100, 2480, 2940 Å ($\log_{10}\varepsilon$ 4·33, 4·11, 3·20) in EtOH, ν_{max} 2245 (CN), 1732 cm^{-1} (CO) (CCl_4 solution). The *hydrochloride* prepared in ether, crystallized from acetone containing a few drops of conc. HCl as colourless prisms, m.p. 133–141° (dec). (Found: N, 10·88. $C_{14}H_{15}ClN_2O$ requires: N, 10·65%.) The *phenylhydrazone* was prepared by boiling a solution of XXIX and an equivalent amount of phenylhydrazine in EtOH for 1 hr and crystallized from 95% EtOH as colourless prisms m.p. 166–167°. (Found: C, 75·65; H, 6·65; N, 17·75. $C_{20}H_{20}N_4$ requires: C, 75·9; H, 6·35; N, 17·7%), ν_{max} 3380, 2245 cm^{-1} (CCl_4 solution).

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