614. *Quinolizines. Part II.* A Synthesis of Alkyl- and of Aryl-quinolizinium Salts.*

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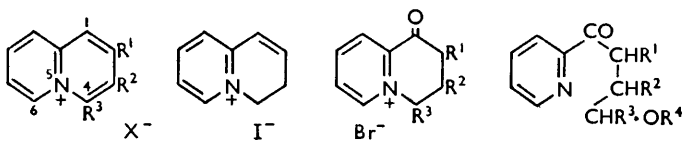
The synthesis of a number of substituted 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromides is reported. When boiled in acetic anhydride these ketones were converted in high yield into the corresponding substituted quinolizinium salts. From the tricyclic ketones (XXVIII), (XXIX), and (XXX), by similar treatment, the three benzoquinolizinium compounds were obtained.

THE simple quinolizinium salts (I; X = I, ClO_4, and picrate) were first obtained by Boekelheide and Gall,[1] by dehydrogenation of the dihydroquinolizinium iodide (II). This method has also been successfully applied to the synthesis of 4-methylquinolizinium salts [2] (XXIV) but has failed to give 4 : 6-dimethylquinolizinium salts.[3] A second synthesis was reported by Richards and Stevens,[4] who have extended it subsequently to the preparation of a number of alkyl- and aryl-quinolizinium compounds.[5] More recently, Nesmeyanov and Rybynskaia have described a synthesis which is specific for the preparation of 2-substituted quinolizinium salts.[6]



R^1	R^2	R^3	R^4				
H	H	H	Et	(I)	(II)	(III)	(IV)
Me	H	H	Et	(XI)	—	(IX)	(VII)
Ph	H	H	Et	(XII)	—	(X)	(VIII)
H	Me	H	Me	(XIX)	—	(XVIII)	(XVII)
H	H	Me	Et	(XXIV)	—	(XXIII)	(XXII)

In a preliminary communication [7] we recorded the conversion of 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide [8] (III) into a quinolizinium salt, isolated as quinolizinium picrate (I; X = picrate), by treatment with boiling acetic anhydride containing a drop of sulphuric acid. We now record improvements in this synthesis, together with

* Part I, *J.*, 1958, 1750.

[1] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.
[2] Boekelheide and Ross, *ibid.*, 1955, **77**, 5691.
[3] Personal communication from Professor Boekelheide.
[4] Richards and Stevens, *Chem. and Ind.*, 1954, 905.
[5] Richards, Ph.D. Thesis.
[6] Nesmeyanov and Rybynskaia, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 93.
[7] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[8] *Idem*, *J.*, 1958, 1750.

its extension to the preparation of 2-, 3-, and 4-substituted quinolizinium salts, and of the three types of benzoquinolizinium salts.

Earlier [7] we reported that the cyclic ketone (III), when boiled with acetic anhydride containing a trace of sulphuric acid, gave a mixture from which quinolizinium picrate (I; X = picrate) could be isolated in 63% yield. We have since found that boiling with acetic anhydride alone converts the ketone (III) into quinolizinium bromide (I; X = Br) which can be isolated in 96% yield. By this modification an overall yield of 48% has been achieved from the starting material (2-cyanopyridine). The bromide (III) was obtained by cyclization of the 2-pyridyl ketone (IV), which was prepared by Craig's method [9] from 2-cyanopyridine and 3-ethoxypropylmagnesium bromide. By suitable modification of the pyridine, or of the aliphatic precursor, a general synthesis of quinolizinium salts can be achieved. For the preparation of simple quinolizinium salts of the type (XI), (XII), (XIX), and (XXIV) we have found it most convenient to alter the aliphatic precursor.

For the preparation of 2-substituted quinolizinium salts alcohols of the type (V) or (VI) were required. These were readily obtained, in good yield, by interaction of 3-ethoxypropionaldehyde (from 3-ethoxypropionaldehyde diethyl acetal [10]) with Grignard reagents [methylmagnesium iodide gave the alcohol (V), phenylmagnesium bromide gave the analogue (VI)]. By the action of phosphorus tribromide on the alcohols (V) and (VI) the corresponding bromides were obtained, and the Grignard reagents from these bromides reacted with 2-cyanopyridine to give the pyridyl ketones (VII) and (VIII) respectively. Boiling hydrobromic acid converted these pyridyl ketones into the bromo-ketone hydrobromides; these were not isolated in a pure form but converted into the free bases by aqueous sodium carbonate. These intermediate bromo-ketones cyclized rapidly in boiling chloroform to give the oxoquinolizinium bromides (IX) and (X). The bromide (IX) was an oil which could not be obtained in a crystalline state, but both the compounds (IX) and (X) were converted in good yield into the corresponding quinolizinium salts by treatment with boiling acetic anhydride. The bromide (IX) gave 2-methylquinolizinium picrate (XI; X = picrate), and the bromide (X) gave 2-phenylquinolizinium picrate (XII; X = picrate). These picrates were converted into the perchlorates (XI; X = ClO_4) and (XII; X = ClO_4) by anionic exchange.

$HO{\cdot}CHR{\cdot}CH_2{\cdot}CH_2{\cdot}OEt$ $MeO_2C{\cdot}CHMe{\cdot}CH_2{\cdot}OMe$ $X{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}OMe$

(V): R = Me (XIII) (XIV): X = OH

(VI): R = Ph (XV): X = Br

(XVI): X = Cl

(XX) $HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OEt$ $EtO_2C{\cdot}CH_2{\cdot}CHMe{\cdot}OEt$ (XXI)

For the preparation of 3-substituted quinolizinium salts, alcohols such as (XIV) were required. The alcohol (XIV) was prepared in high yield by reduction of the ester (XIII), which was prepared by addition of methanol to methyl methacrylate. This addition is reported [11] to give 65% of the methyl ester (XIII) but no experimental details were given. Our yields varied from 0 to 30%, and the addition is very sensitive to changes in experimental conditions. Reduction of the ester (XIII) to the alcohol (XIV) was achieved in excellent yield by lithium aluminium hydride. Conversion of the alcohol (XIV) into the bromide (XV) was attempted but gave poor yields, and the chloride [12] (XVI) was preferred. This chloride gave a Grignard reagent which reacted with 2-cyanopyridine to form the pyridyl ketone (XVII), and this was cyclized, as described before, to the oxoquinolizinium bromide (XVIII). Boiling acetic anhydride converted the oxoquinolizinium compound (XVIII) into 3-methylquinolizinium bromide (XIX; X = Br). Since a number

[9] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.
[10] Alberti and Sollazzo, *Org. Synth.*, Coll. Vol. III, p. 371.
[11] Bieber, *Compt. rend.*, 1952, **234**, 1783.
[12] Elderfield, Pitt, and Wempen, *J. Amer. Chem. Soc.*, 1955, **77**, 5691.

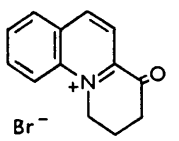
of α-substituted acrylic esters have been prepared from alkynes [13] the route outlined above should provide a general synthesis of 3-substituted quinolizinium compounds.

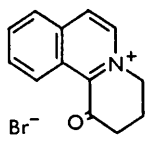
For the 4-methylquinolizinium compounds (XXIV) the aliphatic precursor was 3-ethoxybutanol (XX), obtained by reduction of ethyl β-ethoxybutyrate (XXI) with lithium aluminium hydride. The ester (XXI) was prepared [14] by addition of ethanol to ethyl crotonate in the presence of sodium ethoxide. The butanol (XX), treated with phosphorus tribromide, gave 1-bromo-3-ethoxybutane, and the Grignard reagent from this with 2-cyanopyridine gave the pyridyl ketone (XXII). For the cyclization of the pyridyl ketone (XXII) to the oxoquinolizinium bromide (XXIII) the time of boiling with 35% hydrobromic acid was kept as short as possible; prolonged boiling led to the formation of uncrystallizable oils instead of the expected crystalline bromide (XXIII). Boiling acetic anhydride converted the oxoquinolizinium compound (XXIII) into a 4-methylquinolizinium salt, isolated as the picrate (XXIV; X = picrate) agreeing in melting point and in ultraviolet absorption with that synthesized by Boekelheide and Ross.[2]

By using 2-cyanoquinoline, 1-cyano*iso*quinoline, and 3-cyano*iso*quinoline as starting materials we have synthesized the three benzoquinolizinium compounds (XXXI), (XXXII), and (XXXIII). With 3-ethoxypropylmagnesium bromide the three cyano-compounds gave the ketones (XXV), (XXVI), and (XXVII) respectively.

Cyclization of the quinolyl and *iso*quinolyl ketones gave the cyclic bromides (XXVIII), (XXIX), and (XXX). These were found to be less stable to traces of alkali than the oxoquinolizinium bromides (*e.g.*, III); in absolute ethanol having a very faint alkaline reaction the bromides gave dark green solutions from which no pure product could be isolated. The bromides (XXVIII) and (XXIX) were converted by boiling acetic anhydride into benzo[*c*]quinolizinium salts (XXXI) and benzo[*a*[quinolizinium salts (XXXII) respectively. The bromide (XXX), heated with acetic anhydride containing a trace of sulphuric acid, gave a benzo[*b*]quinolizinium salt, isolated as the picrate (XXXIII; X = picrate) agreeing

R·CO·CH_2·CH_2·CH_2·OEt
(XXV): R = 2-Quinolyl
(XXVI): R = 1-*iso*Quinolyl
(XXVII): R = 3-*iso*Quinolyl


(XXVIII)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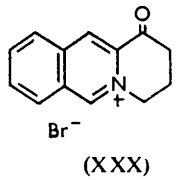
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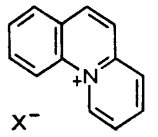
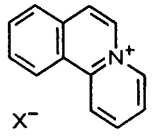

(XXXI)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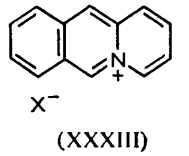
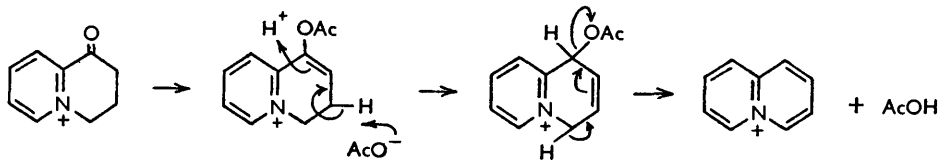

(XXXIII)

in melting point with that reported by Bradsher and Beavers.[15] The same authors have reported [16] a synthesis of 7-methyl- and of 7-phenyl-benzo[*a*]quinolizinium salts, and the ultraviolet absorption of these resembles closely that of the parent benzo[*a*]quinolizinium salts prepared by us. The ultraviolet absorption spectra of the benzo[*a*]quinolizinium salts are recorded in Fig. 1 and of the benzo[*c*]quinolizinium salts in Fig. 2.

We have been unable to find an analogous synthesis in which a cyclic ketone is converted into an aromatic ring system by a " dehydration " reaction. It seems likely that the first stage is enolisation, probably with formation of the enol acetate; subsequent shift of the 1 : 2-double bond to the 2 : 3-position and 1 : 4-elimination of acetic acid gives

[13] Reppe, *Annalen*, 1953, **582**, 1.
[14] Schinz and Hinder, *Helv. Chim. Acta*, 1947, **30**, 1349.
[15] Bradsher and Beavers, *Chem. and Ind.*, 1954, 1394.
[16] *Idem*, *J. Amer. Chem. Soc.*, 1955, **77**, 453.

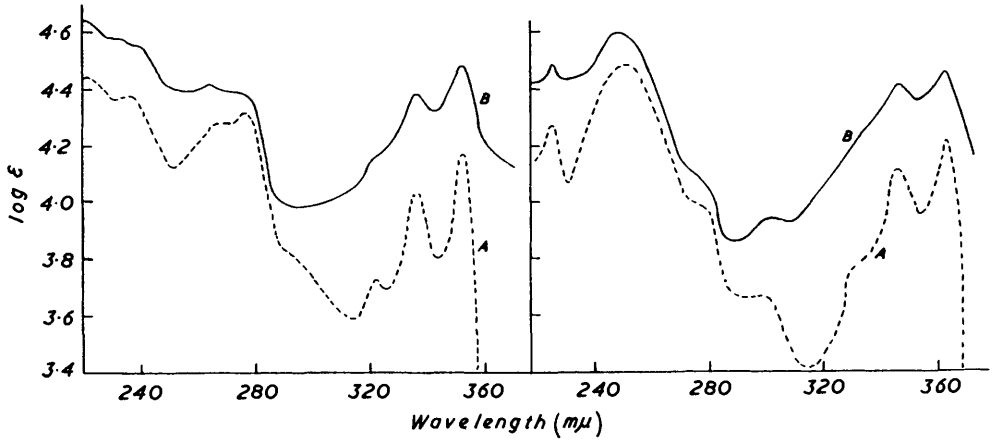
the quinolizinium cation as shown below. We have not yet performed any quantitative experiments to test this hypothesis.



[*Added June 30th*, 1958.—Prasad and Swan (*J.*, 1958, 2024) reported the synthesis of the oxo-compound (IV) and isolated as their intermediate, not the ketone (III), but the corresponding imine. We have examined compounds (IV), (XVII), and (XXVIII) with this possibility in mind, and all are free from significant infrared absorption in the

FIG. 1. *A, Benzo*[a]*quinolizinium perchlorate. B, Benzo*[a]*quinolizinium picrate.*

FIG. 2. *A, Benzo*[c]*quinolizinium perchlorate. B, Benzo*[c]*quinolizinium picrate.*



3400 cm.$^{-1}$ (NH) region; in addition, nitrogen analyses of these compounds are concordant with the ketonic structure. We conclude that under our conditions of hydrolysis the pyridyl ketones are formed, and not the imines.]

EXPERIMENTAL

M. p.s were determined on a Kofler block.

Quinolizinium Bromide (I; X = Br).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide [8] (1·28 g.) in acetic anhydride (20 ml.) was boiled under reflux for 1·5 hr. The solution was cooled, the acetic anhydride hydrolysed with an equal volume of water, and the resulting solution evaporated to dryness under reduced pressure. The solid residue was precipitated from its solution in absolute ethanol by dry ether, giving quinolizinium bromide, m. p. 260—261° (1·13 g., 96%). Recrystallization from ethyl acetate–alcohol gave colourless prisms, m. p. 262—264°, $\lambda_{max.}$ 2250, 2740, 2840, 3100, 3170, 3240 Å ($\log_{10}$ ε 4·23, 3·42, 3·43, 4·00, 3·95, 4·16) in H_2O.

The picrate crystallized from absolute ethanol as yellow needles, m. p. 179° (Found: C, 50·6; H, 3·3. Calc. for $C_{15}H_{10}O_7N_4$: C, 50·3; H, 2·8%), $\lambda_{max.}$ 2270, 2850, 2880, 3120, 3190, 3250 Å ($\log_{10}$ ε 4·84, 3·64, 3·62, 4·18, 4·18, 4·4), in EtOH. A mixed m. p. with quinolizinium picrate supplied by Professor Boekelheide showed no depression. The perchlorate, obtained from the picrate by anionic exchange on Amberlite I.R.A.-400 had m. p. 287° (lit.,[1] m. p. 287°).

3-*Ethoxypropionaldehyde*.—A mixture of 3-ethoxypropionaldehyde diethyl acetal [10] (70 g.) and 3% aqueous hydrochloric acid (300 ml.) was stirred at room temperature until homogeneous. The solution was shaken several times with ether, and the ethereal solution washed with a saturated aqueous solution of calcium chloride, dried (Na_2SO_4), and distilled, giving 3-ethoxypropionaldehyde (29·5 g., 58%), b. p. 40°/16 mm.

4-*Ethoxybutan*-2-*ol* (V).—A solution of 3-ethoxypropionaldehyde (29·5 g.) in ether (50 ml.) was added dropwise to the Grignard reagent from methyl iodide (35 g.) in dry ether (400 ml.). After the addition the mixture was stirred for 1 hr., then hydrolyzed with saturated aqueous ammonium chloride. The ether layer was separated, dried (Na_2SO_4), and distilled. The yield of 4-ethoxybutan-2-ol, b. p. 69°/24 mm., n_D^{25} 1·4125, was 22·5 g. (66%).

3-*Bromo*-1-*ethoxybutane*.—Phosphorus tribromide (24 g.) was added dropwise to 4-ethoxybutan-2-ol (21 g.), the temperature being kept below 60°. The whole was then heated at 60° for 1 hr., cooled, and poured on ice, and the organic layer was washed with aqueous sodium hydrogen carbonate and with water. The crude product was dried ($MgSO_4$) and then distilled, giving 3-bromo-1-ethoxybutane, b. p. 160°/744 mm., n_D^{25} 1·4475 (22 g., 68%).

2-γ-*Ethoxy*-α-*methylbutyrylpyridine* (VII).—A stirred solution of 2-cyanopyridine (12 g.) in dry ether (100 ml.) was treated with the Grignard reagent from 3-bromo-1-ethoxybutane (21 g.) in dry ether (240 ml.), and the mixture kept overnight at room temperature. After addition of ice-cold 5N-hydrochloric acid the aqueous layer was separated and basified with aqueous ammonia (*d* 0·88), and the base extracted with ether. The ethereal extract was dried ($MgSO_4$), and distilled, giving 2-γ-ethoxy-α-methylbutyrylpyridine, b. p. 146—148°/13 mm. (13 g., 54%), $\lambda_{max.}$ 2270, 2660 Å ($\log_{10}\varepsilon$ 4·21, 3·96) in EtOH. The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from aqueous ethanol as yellow prisms, m. p. 141° (Found: C, 56·2, H, 5·2. $C_{18}H_{21}O_5N_5$ requires C, 55·8; H, 5·5%).

1 : 2 : 3 : 4-*Tetrahydro*-2-*methyl*-1-*oxoquinolizinium Bromide* (IX).—A solution of the ketone (VII) (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then evaporated to dryness under reduced pressure. The residue was dissolved in the minimum quantity of water and treated dropwise with aqueous sodium carbonate, and the liberated bromo-amine was extracted by chloroform. The chloroform extract was dried ($MgSO_4$) and boiled under reflux till an oil separated, then the chloroform was evaporated. The residual bromide would not solidify, but gave a 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, which crystallized from aqueous ethanol as yellow needles, m. p. 182° (decomp.) (Found: C, 43·6; H, 3·9. $C_{16}H_{16}O_4N_5Br,H_2O$ requires C, 43·6; H, 4·1%).

2-*Methylquinolizinium Picrate* (XI; X = *Picrate*).—Treatment of the crude bromide (IX) with acetic anhydride for 1 hr. and treatment of the product with aqueous sodium picrate gave 2-*methylquinolizinium picrate*, recrystallized from absolute ethanol as yellow needles, m. p. 162° [65% overall yield from the ketone (VII)] (Found: C, 52·0; H, 3·5. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·25%), $\lambda_{max.}$ 2270, 2850, 3120, 3200, 3255 Å ($\log_{10}\varepsilon$ 4·54, 3·81, 4·29, 4·29, 4·61) in H_2O. The *perchlorate*, obtained by anionic exchange, crystallised from absolute ethanol as buff needles, m. p. 110·5° (Found: C, 49·1; H, 4·1. $C_{10}H_{10}O_4NCl$ requires C, 49·3; H, 4·1%), $\lambda_{max.}$ 2260, 2855, 3120, 3200, 3260 Å ($\log_{10}\varepsilon$ 4·32, 3·5, 4·1, 4·03, 4·3) in H_2O.

3-*Ethoxy*-1-*phenylpropan*-1-*ol* (VI).—Slow addition of 3-ethoxypropionaldehyde (28 g.) in dry ether (50 ml.) to the stirred Grignard reagent from bromobenzene (50 g.) in dry ether (600 ml.) with subsequent stirring for 1 hr. and working up as for the alcohol (V) gave 3-*ethoxy*-1-*phenylpropan*-1-*ol*, b. p. 147°/15 mm. (39·5 g., 79·5%), n_D^{25} 1·5075 (Found: C, 73 7; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%).

1-*Bromo*-3-*ethoxy*-1-*phenylpropane*.—Treatment of the alcohol (VI) (30 g.) with phosphorus tribromide (20 g.) as described above gave the bromopropane, b. p. 81—83°/0·15 mm. (23 g., 57%).

2-γ-*Ethoxy*-α-*phenylbutyrylpyridine* (VIII).—2-Cyanopyridine (10 g.), stirred in dry ether (100 ml.), was treated with the Grignard reagent from 1-bromo-3-ethoxy-1-phenylpropane (23 g.) in dry ether (250 ml.), and the mixture kept overnight at room temperature. Working up as described above gave, after distillation, 2-cyanopyridine (3 g.) and 2-γ-*ethoxy*-α-*phenylbutyrylpyridine*, b. p. 152°/0·5 mm. (11·5 g., 63·5% on 2-cyanopyridine used) (Found: C, 75·6; H, 7·15. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxo*-2-*phenylquinolizinium Bromide* (X).—A solution of the ketone (VIII) (1·38 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 30 min. Cyclization in chloroform as described above gave the bromide as pale green prisms, m. p. 196° (1·06 g., 72%), $\lambda_{max.}$ 2460, 2860, 3770 Å ($\log_{10}\varepsilon$ 3·95, 3·86, 3·92) in EtOH. The *picrate* crystallized from aqueous ethanol as yellow needles, m. p. 152° (Found: C, 56·0; H, 3·3. $C_{21}H_{16}O_8N_4$ requires C, 55·8; H, 3·6%).

2-*Phenylquinolizinium Picrate* (XII; X = *Picrate*).—Acetic anhydride treatment of the bromide (X) for 30 min. gave 2-phenylquinolizinium picrate (88·4%) which crystallized from absolute ethanol as yellow needles, m. p. 168° (lit.,[6] m. p. 168—170°) (Found: C, 57·8; H, 3·4.

Calc. for $C_{21}H_{14}O_7N_4$: C, 58·05; H, 3·25%), $\lambda_{max.}$ 2500, 3420 Å ($\log_{10}\varepsilon$ 4·36, 4·54) in H_2O. The perchlorate crystallized from absolute ethanol as colourless needles, m. p. 168° (lit.,[6] m. p. 168—169·5°) (Found: C, 58·6; H, 4·3. Calc. for $C_{15}H_{12}O_4NCl$: C, 58·95; H, 4·0%), $\lambda_{max.}$ 2630, 3420 ($\log_{10}\varepsilon$ 4·18, 4·37) in H_2O.

Methyl β-*Methoxy*isobutyrate (XIII).—Methyl methacrylate (100 g., freshly distilled from 1 g. of quinol) was added to a solution of sodium (1 g.) in dry methanol (400 ml.), and the mixture boiled under reflux for 30 min. The methanol was removed by distillation and ether (200 ml.) was added to the residue. The ethereal solution was shaken with cold dilute hydrochloric acid, then with aqueous sodium hydroxide, and finally with water. After drying ($MgSO_4$) the ethereal solution was distilled, giving the methyl ester, b. p. 147°/746 mm. (39 g., 30%). Prolonged boiling of the reaction mixture led to a considerable decrease in the yield.

3-*Methoxy*-2-*methylpropan*-1-*ol* (XIV).—To a stirred solution of lithium aluminium hydride (10 g.) in ether (300 ml.) was added the ester (XIII) (39 gm.) in ether (350 ml.); the mixture was boiled for 1 hr., then set aside overnight. Excess of lithium aluminium hydride was decomposed with ethyl acetate, and the mixture treated with water. The ethereal solution was separated, dried ($MgSO_4$), and distilled, giving the alcohol, b. p. 154—155°/733 mm. (25 g., 95%) (lit.,[12] b. p. 154—155°).

1-*Chloro*-3-*methoxy*-2-*methylpropane* (XVI).—This was prepared from the alcohol (XIV) as described by Elderfield, Pitt, and Wempen.[12]

2-γ-*Methoxy*-β-*methylbutyrylpyridine* (XVII).—A stirred solution of 2-cyanopyridine (20 g.) in dry ether (150 ml.) was treated with the Grignard reagent from the chloropropane (XVI) (27·5 g.) in ether (300 ml.), and kept overnight at room temperature. Working up as described for the compound (VII) gave the *pyridyl ketone*, b. p. 140—142°/13 mm. (33 g., 64·6%) (Found: C, 68·4; H, 7·95. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%). The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from ethanol as yellow needles, m. p. 125° (Found: C, 54·6; H, 4·85. $C_{17}H_{19}O_5N_5$ requires C, 54·7; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro*-3-*methyl*-1-*oxoquinolizinium Bromide* (XVIII).—2-γ-Methoxy-β-methylbutyrylpyridine (2 g.) was cyclized as described above. The *bromide* separated from the hot chloroform solution as a solid which recrystallized from ethyl acetate–ethanol as colourless prisms, m. p. 205° (decomp.) (1·8 g., 73·5%) (Found: C, 46·1; H, 5·1. $C_{10}H_{12}ONBr,H_2O$ requires C, 46·2; H, 5·4%), $\lambda_{max.}$ 2750 Å ($\log_{10}\varepsilon$ 3·93) in EtOH. The *picrate* crystallized from absolute ethanol as yellow needles, m. p. 157° (Found: C, 49·2; H, 3·8. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%), $\lambda_{max.}$ 2750 Å ($\log_{10}\varepsilon$ 3·98) in EtOH.

3-*Methylquinolizinium Bromide* (XIX).—Acetic anhydride treatment of the bromide (XVIII) for 30 min. gave a quantitative yield of 3-*methylquinolizinium bromide*, which crystallized from ethyl acetate–ethanol as colourless prisms, m. p. 189° (Found: C, 49·7; H, 5·3. $C_{10}H_{10}NBr,H_2O$ requires C, 49·6; H, 5·0%), $\lambda_{max.}$ 2300, 2860, 3140, 3200, 3280 Å ($\log_{10}\varepsilon$ 4·28, 3·41, 4·03, 3·96, 4·25) in H_2O. The *picrate* crystallized from absolute ethanol as yellow needles, m. p. 182° (Found: C, 51·45; H, 3·3. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·25%), $\lambda_{max.}$ 2300, 3140, 3210, 3280 Å ($\log_{10}\varepsilon$ 4·53, 4·26, 4·26, 4·48) in H_2O.

3-*Ethoxybutan*-1-*ol* (XXI).—Ethyl β-ethoxybutyrate [14] (25 g.) in ether (50 ml.) was added slowly to lithium aluminium hydride (6 g.) in ether (250 ml.), and the mixture kept overnight. Excess of lithium aluminium hydride was decomposed with ethyl acetate, the mixture hydrolyzed, and the ether layer separated, and dried ($MgSO_4$). Distillation gave the butanol, b. p. 163—166°/748 mm. (17 g., 92%), n_D^{25} 1·4155.

1-*Bromo*-3-*ethoxybutane*.—Phosphorus tribromide (30 g.) was added slowly to 3-ethoxybutan-1-ol (35·5 g.), the temperature being kept below 60° for 1 hr. The cooled mixture was poured on ice, and the separated organic layer shaken with aqueous sodium hydrogen carbonate, followed by water. The dried ($MgSO_4$) liquid was distilled, giving the bromide, b. p. 159°/747 mm. (41 g., 75%), n_D^{25} 1·4450.

2-γ-*Ethoxyvalerylpyridine* (XXII).—A stirred solution of 2-cyanopyridine (16 g.) in ether (150 ml.) was treated with the Grignard reagent from 1-bromo-3-ethoxybutane (30 g.), in ether (350 ml.). The yellow complex formed was kept overnight at room temperature. Working up as described above gave the valerylpyridine, b. p. 156—158°/16 mm. (19 g., 55%). The 2 : 4-*dinitrophenylhydrazone* crystallized from 95% ethanol as yellow prisms, m. p. 137° (Found: C, 55·5; H, 5·3. $C_{18}H_{21}O_5N_5$ requires C, 55·8; H, 5·5%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*methyl*-1-*oxoquinolizinium Bromide* (XXIII).—A solution of the valerylpyridine (XXII) (2 g.) in 35% hydrobromic acid was boiled under reflux for 10 min.

(longer boiling led to side reactions and tars were obtained). Worked up as before, the bromide (1·1 g., 47%) had m. p. 170—171° (from ethanol–ether), $\lambda_{max.}$ 2750 Å ($\log_{10}\varepsilon$ 3·75) in EtOH. The *picrate* crystallised from absolute ethanol as yellow buffers, m. p. 146° (Found: C, 48·9; H, 3·9. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%).

4-*Methylquinolizinium Picrate* (XXIV; X = *Picrate*).—Acetic anhydride treatment of the bromide (XXIII) for 30 min. gave 4-methylquinolizinium picrate (65%), m. p. 135° (lit.,[2] m. p. 135—135·5°), $\lambda_{max.}$ 2310, 2910, 3170, 3300, 3560 Å ($\log_{10}\varepsilon$ 4·53, 3·83, 4·27, 4·45, 4·26) [lit.,[2] $\lambda_{max.}$ 2300, 2900, 3170, 3300, 3330 Å ($\log_{10}\varepsilon$ 4·49, 3·77, 4·23, 4·4, 4·18)] in H_2O.

2-γ-*Ethoxybutyrylquinoline* (XXV).—1-Benzoyl-2-cyano-1 : 2-dihydroquinoline [17] was converted into 2-cyanoquinoline [18] in 30% yield. The cyanoquinoline (21 g.) stirred in ether (200 ml.) was treated slowly with the Grignard reagent from the 3-ethoxypropyl bromide (30 g.) in ether (350 ml.), and the mixture kept overnight at room temperature. Worked up as described above, the butyrylquinoline was obtained as an oil, b. p. 144—146°/0·05 mm. (28·5 g., 86%). The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from 95% ethanol as orange yellow prisms, m. p. 137° (Found: C, 59·6; H, 4·85. $C_{21}H_{21}O_5N_5$ requires C, 59·6; H, 5·0%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*oxobenzo*[c]*quinolizinium Bromide* (XXVIII).—A solution of 2-γ-ethoxybutyrylquinoline (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then concentrated under reduced pressure to 5 ml. The solution was cooled and diluted, and the precipitated bromo-amine was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and boiled under reflux. Concentration of the chloroform solution gave the crystalline bromide, m. p. 188—189° (1·72 g., 75%). The picrate crystallized from absolute alcohol containing a trace of picric acid as yellow prisms, m. p. 151°. The *phenylhydrazone iodide* was obtained by heating together the bromide and phenylhydrazine in glacial acetic acid, diluting the mixture, and precipitating the insoluble iodide by addition of aqueous sodium iodide; it crystallized from absolute ethanol as red needles, m. p. 264° (Found: C, 54·6; H, 4·5. $C_{19}H_{18}N_3I$ requires C, 54·95; H, 4·4%).

Benzo[c]*quinolizinium Picrate* (XXXI).—Acetic anhydride treatment of the bromide (XXVIII) for 30 min. gave *benzo*[c]*quinolizinium picrate* (63%) which crystallized from absolute ethanol as yellow needles, m. p. 188—189° (Found: C, 56·0; H, 3·3. $C_{19}H_{12}O_7N_4$ requires C, 55·9; H, 3·0%), $\lambda_{max.}$ 2270, 2500, 3050, 3480, 3640 Å ($\log_{10}\varepsilon$ 4·48, 4·59, 3·93, 4·41, 4·46) in H_2O. The *perchlorate* crystallized from absolute ethanol as buff needles, m. p. 188—189° (Found: C, 55·4; H, 3·45. $C_{13}H_{10}O_4NCl$ requires C, 55·8; H, 3·6%), $\lambda_{max.}$ 2270, 2525, 3000, 3470, 3640 Å ($\log_{10}\varepsilon$ 4·27, 4·48, 3·67, 4·11, 4·2) in H_2O.

1-γ-*Ethoxybutyryl*iso*quinoline* (XXVI).—2-Benzoyl-1-cyano-1 : 2-dihydroisoquinoline [19] was converted into 1-cyanoisoquinoline as described by Hoste and Gillis.[20] A stirred solution of 1-cyanoisoquinoline (11 g.) in ether (120 ml.) was treated with the Grignard reagent from 3-ethoxypropyl bromide (15 gm.) in ether (200 ml.) and kept overnight at room temperature. Working up as described above gave the butyrylisoquinoline, b. p. 137—139°/0·1 mm. (10·5 g., 60·5%). The 2 : 4-*dinitrophenylhydrazone* crystallized from 95% ethanol as yellow prisms, m. p. 139° (Found: C, 60·0; H, 5·0. $C_{21}H_{21}O_5N_5$ requires C, 59·6; H, 5·0%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxobenzo*[a]*quinolizinium Bromide* (XXIX).—A solution of 1-γ-ethoxybutyrylisoquinoline (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then concentrated to 5 ml. Dilution precipitated the bromo-amine which was extracted with chloroform, dried ($MgSO_4$), and boiled under reflux. The solid bromide separated as yellow prisms, m. p. 210° (decomp.) (1·9 g., 79·6%). The *picrate* crystallized from water as yellow prisms, m. p. 146° (Found: C, 53·8; H, 3·3. $C_{19}H_{14}O_8N_4$ requires C, 3·5; H, 3·3%). The *phenylhydrazone iodide*, prepared as described above, crystallized from absolute alcohol as orange-red prisms, m. p. 258—259° (Found: C, 55·0; H, 4·6. $C_{19}H_{18}N_3I$ requires C, 54·95; H, 4·4%).

Benzo[a]*quinolizinium Picrate* (XXXII; X = *Picrate*).—Acetic anhydride treatment of the bromide (XXIX) for 20 min. gave *benzo*[a]*quinolizinium picrate* (66·4%), yellow needles (from absolute ethanol), m. p. 178° (Found: C, 56·0; H, 3·3. $C_{19}H_{12}O_7N_4$ requires C, 55·9;

[17] Reissert, *Ber.*, 1905, **38**, 610.
[18] Kaufmann and Dändliker, *Ber.*, 1913, **46**, 2924.
[19] Reissert, *Ber.*, 1905, **38**, 3415.
[20] Hoste and Gillis, *Mededel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Klasse Wetenschap.*, 1951, **13**, 3; *Chem. Abs.*, 1952, **46**, 5474.

H, 3·0%), $\lambda_{max.}$ 2400, 2650, 3370, 3530 Å ($\log_{10}\varepsilon$ 4·56, 4·41, 4·39, 4·49) in H_2O. The *perchlorate* crystallized from absolute ethanol as colourless needles, m. p. 197° (Found: C, 55·4; H, 3·3. $C_{13}H_{10}O_4NCl$ requires C, 55·8; H, 3·6%), $\lambda_{max.}$ 2360, 2770, 3230, 3370, 3530 Å ($\log_{10}\varepsilon$ 4·38, 4·32, 3·75, 4·04, 4·17) in H_2O.

Benzo[b]*quinolizinium Picrate* (XXXIII; X = *Picrate*).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxobenzo[*b*]quinolizinium bromide [8] (0·133 g.) in acetic anhydride (20 ml.) containing a drop of concentrated sulphuric acid was boiled under reflux for 3 hr. The solution was cooled, an equal volume of water added, and the bulk of the solvent removed under reduced pressure. The remaining solution was treated with aqueous sodium picrate, giving benzo[*b*]quinolizinium picrate, which crystallized from 95% ethanol as yellow prisms, m. p. 215° (decomp.) (0·073 g., 62%) (lit.,[15] m. p. 214—216°).

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