930. *Chemical Constitution and Amœbicidal Activity. Part VI.* A New Synthesis of 2-Ketones and 2-Alcohols derived from 3-Alkyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizines.*

By J. M. Osbond.

Synthesis and cyclisation of the ketals (II; R = Et, Bu^n, and Bu^i) to the benzo[*a*]quinolizine derivatives (III and IV) are described. The reduction of these compounds by various reagents to the more saturated ketones (V) and alcohols (VII), and reconversion of the former by chloranil into the αβ-unsaturated ketones (IV), are reported. Dehydrogenation with mercuric acetate of the compounds (IV), (V), and (VII) has been investigated.

SEVERAL 2-ketones [1a,b] and 2-alcohols [1c] of the series 3-alkyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (cf. V and VII) have been described and shown to have important psycho-sedative properties [2] and have provided the intermediate

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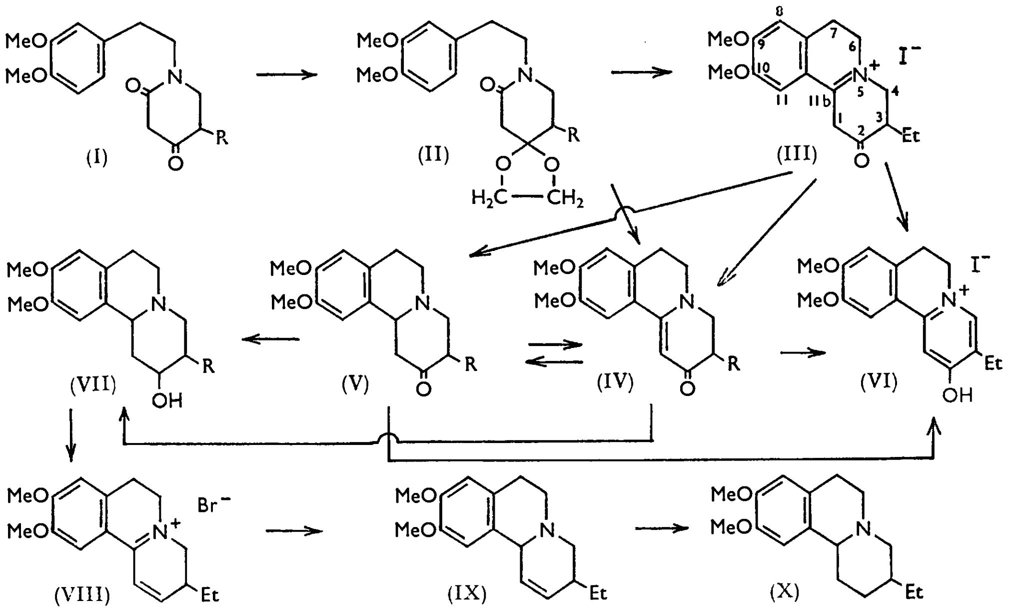
* Part V, *J.*, 1959, 3630.

[1] (*a*) Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1958, **41**, 119; (*b*) Battersby, Openshaw, and Wood, *J.*, 1953, 2463; (*c*) Brossi, Chopard, and Schnider, *Helv. Chim. Acta*, 1958, **41**, 1793.

[2] Pletscher, *Science*, 1957, **126**, 507; Pletscher, Besendorf, and Bachtold, *Arch. exp. Path. Pharmakol.*, 1958, **232**, 499.

compounds for the synthesis of emetine,[3a] dehydroemetine,[3b] and their isomers and analogues.

A new route to this type of compound is now described and involves the cyclisation of the ketals (II; R = Et, $\mathrm{Bu^n}$, or $\mathrm{Bu^i}$). Synthesis of the phenethylpiperidinedione (I; R = Et) and its ketal (II) was recorded first by Ban;[4a] both compounds have now



been obtained crystalline.[4b] In a similar way, *via* the Mannich base from 3,4-dimethoxyphenethylamine, formaldehyde, and a substituted malonic acid, we have prepared the compounds (I; R = $\mathrm{Bu^n}$ and $\mathrm{Bu^i}$) and the corresponding ketals (II). An attempt by Ban[4a] to cyclise the ethyl compound (II; R = Et) with phosphorus oxychloride was unsuccessful; after our work[5] had been completed, Itoh and Sugasawa[6] effected this cyclisation with phosphorus pentoxide, obtaining a benzo[*a*]quinolizinium salt. In our hands, treatment with phosphorus oxychloride in toluene gave, after brief acid hydrolysis and addition of potassium iodide, a quaternary iodide (III) in 73% yield.

Treatment of this iodide (III) with sodium hydroxide gave the yellow base (IV; R = Et) which was characterised as hydrochloride, hydrobromide, and hydriodide which on basification regenerated the same base. From the ultraviolet absorption spectra in ethanol or water it appeared that the base (IV; R = Et) and its salts had similar structures (see Table, nos. 2—4) but were different from the quaternary iodide (III) (no. 1). Indeed the hydriodide and quaternary iodide differed in melting point, infrared and ultraviolet spectra, and chemical reactions (see below). Conversion of the quaternary iodide into the non-crystalline chloride and treatment of this with 48% hydrobromic acid also gave the hydrobromide of base (IV; R = Et). The greater stability of the tertiary (IV) than of the quaternary structure (III) was also illustrated by the cyclisation of the ketals (II; R = $\mathrm{Bu^n}$ and $\mathrm{Bu^i}$). Several attempts to isolate structures corresponding to (III) were made but only salts of the tertiary type (IV) were isolated and attempts to convert these into the quaternary derivatives (III; R = $\mathrm{Bu^n}$ or $\mathrm{Bu^i}$) under various conditions

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[3] (*a*) Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515; (*b*) Brossi, Baumann, Chopard, Würsch, Schneider, and Schnider, *ibid.*, 1959, **42**, 772; Osbond, B.P. Spec. 835,489.

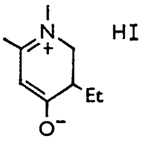
[4] (*a*) Ban, *Pharm. Bull.* (*Japan*), 1955, **3**, 53; (*b*) Barash, Osbond, and Wickens, *J.*, 1959, 3530.

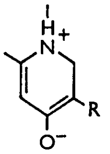
[5] Osbond, B.P. Spec. 861,524, (1957), 861,525 (1957).

[6] Itoh and Sugasawa, *J. Org. Chem.*, 1959, **24**, 2042.

were unsuccessful. This behaviour is unusual in the sense that normally enamines with acid give the immonium salt;[7] presumably in this case the keto-group stabilises the structure (IV). Nevertheless, although the ultraviolet absorption of the bases (IV; R = Et, $\mathrm{Bu^n}$, and $\mathrm{Bu^i}$) and their salts in ethanol and water (Table; compare nos. 1, 7, and 9 with 3, 4, 6, and 10) differed from that of the quaternary salt (III), yet in dilute acid these salts all had ultraviolet absorption similar to that of the quaternary iodide (III) in water (compare nos. 5, 8, 11, and 12 with 1). The structure of the quaternary iodide (III) and

(IIIa)





(IVa)

the bases (IV) could probably be more accurately formulated as polar forms such as (IIIa) and (IVa) on the basis of their ultraviolet and infrared spectra. The ultraviolet spectrum of salt (III) shows a more complex chromophoric system than is present in the simple 1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium compounds,[8] and the infrared spectrum shows no hydroxyl band and a ketone band at 1630 $\mathrm{cm.^{-1}}$ (for $\nu_{\mathrm{max.}}$ of this and other compounds see the Experimental section). Similarly the bases and salts (IV; R = Et and $\mathrm{Bu^i}$) showed no hydroxyl band; the bases had only weak bands in the carbonyl region (1640—1698 $\mathrm{cm.^{-1}}$), and the salts showed bands of medium intensity at ~1635 $\mathrm{cm.^{-1}}$ (cf. infrared spectrum of 4-hydroxypyridine;[9] C=O band at 1638 $\mathrm{cm.^{-1}}$).

The iodide (III) undergoes two reactions not given by the bases (IV; R = Et, $\mathrm{Bu^n}$, or $\mathrm{Bu^i}$) or their salts: (1) The melting point of the quaternary iodide [III; m. p. 171—172·5°, followed by resolidification at ~180° and finally melting at 240—241° (decomp.)] was interpreted as due to aromatisation of the heterocyclic ring by disproportionation; thus pyrolysis of this salt at 180° gave 3-ethyl-6,7-dihydro-2-hydroxy-9,10-dimethoxybenzo[*a*]quinolizinium iodide (VI) whose structure was confirmed by the ultraviolet absorption spectrum (no. 14; cf. the bromide [1a]) and by conversion into the pyridone form (m. p. 227—230°), identical with an authentic specimen [1a] (see below). By contrast, the hydriodide of the base (IV; R = Et) was thermally stable, although treatment of

Ultraviolet absorption spectra.

No.	Compound	Solvent	$\lambda_{\mathrm{max.}}$ (mμ)	log ε
1	(III)	H_2O	225, 249, 330—335	4·26, 4·06, 4·22
2	(IV; R = Et)	EtOH	237, 284, 360—363	4·33, 3·96, 4·30
3	(IV; R = Et), HCl	H_2O	239, 288, 360	4·28, 3·89, 4·27
4	(IV; R = Et), HBr	H_2O	237·5, 288, 360	4·30, 3·91, 4·26
5	(IV; R = Et), HCl	0·2N-HCl	250, 341	4·15, 4·31
6	(IV; R = Et), HI	H_2O	232, 288, 360	4·39, 3·86, 4·24
7	(IV; R = $\mathrm{Bu^n}$)	EtOH	237, 286, 361—362	4·26, 3·90, 4·14
8	(IV; R = $\mathrm{Bu^n}$), HBr	0·2N-HCl	250, 335	4·20, 4·30
9	(IV; R = $\mathrm{Bu^i}$)	EtOH	238, 284—285, 362	4·29, 3·91, 4·23
10	(IV; R = $\mathrm{Bu^i}$), HI	H_2O	229—230, 282—283, 360	4·40, 3·93, 4·21
11	(IV; R = $\mathrm{Bu^i}$), HBr	0·2N-HCl	250, 335	4·22, 4·30
12	(IV; R = $\mathrm{Bu^i}$), HCl	0·2N-HCl	250, 340	4·18, 4·29
13	(V; R = Et), HCl	H_2O	225, 282	3·94, 3·9
14	(VI)	H_2O	230, 260, 312	4·48, 4·39, 4·20
15	(VIII)	H_2O	277, 355	4·27, 4·23
16	(VIII)	0·1N-NaOH	277, 355	4·20, 4·16
17	(IX)	H_2O	226, 282	3·87, 3·56

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[7] Leonard and Gash, *J. Amer. Chem. Soc.*, 1954, **76**, 2781; Witkop, *ibid.*, 1956, **78**, 2873.

[8] Ban and Yonemitsu, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 653.

[9] Mason, *J.*, 1957, 4874.

the base with mercuric acetate [10,1a] readily gave the salt (as VI). (2) Potassium borohydride [11] reduced the salt (III) in methanol to ketone (V; R = Et), rapidly and in 94% yield. Comparison, by mixed melting point and infrared spectra, of this product and its hydrochloride and hydrobromide with authentic specimens [1a] showed them to be identical. By contrast, similar attempts to reduce the bases (IV; R = Et, Bu^n, or Bu^i) and their salts under a variety of conditions failed, only unchanged material being obtained. This ready reduction of the salt (III) supports the immonium structure proposed for this iodide (cf. ref. 11).

Reduction of the bases (IV; R = Et, Bu^n, and Bu^i) was, however, effected by three reagents: (1) Lithium aluminium hydride in boiling tetrahydrofuran gave the saturated ketones in fair yield. The retention of the ketone group was unexpected; selective reduction of the double bond of an αβ-unsaturated ketone or ester is rare [12a] although complete reduction to the saturated alcohol is well known.[12b] (2) Reduction of the base (IV; R = Et) with lithium [13] in ammonia also gave the saturated ketone (V; R = Et) in 30% yield. (3) The same base in presence of palladised charcoal absorbed 2 mol. of hydrogen, giving the alcohol (VII; R = Et), identical with a specimen obtained from ketone (V; R = Et) by hydrogenation [1b] with Adams catalyst.

Dehydrogenation of the αβ-saturated ketones (V; R = Et, Bu^n, and Bu^i) has been effected with two reagents. (1) It was hoped that treatment of the ethyl derivative with a limited quantity of mercuric acetate would give the unsaturated ketone (IV). However, treatment with one mol. gave only unchanged starting material, and use of 2 mol. gave a 60% yield of the quaternary bromide (VI) together with mercury but no mercurous acetate. (2) Chloranil [14] in benzene, however, readily dehydrogenated all three ketones (V) to their unsaturated derivatives (IV) in good yield. In the butyl case, the primary product was a 2 : 1 adduct [15] of ketone (IV; R = Bu^n) and tetrachloroquinol that appeared to be stable to base but with acid gave the required salt of (IV).

The alcohol (VII; R = Et) with mercuric acetate (2 mol.) gave the quaternary salt (VIII) in 30% yield, mercurous acetate, and a little mercury. With an excess of the reagent the yield of salt (VIII) was 92%. This formulation (enamine) was based on analysis and the ultraviolet absorption spectrum (Table, no. 15); in 0·1N-sodium hydroxide the maxima were unchanged (no. 16) and this suggests the alternative arrangement of double bonds (enamine form) for (VIII). However, the ready reduction of this product by potassium borohydride to the base (IX) (the spectrum of which shows only the dimethoxybenzene chromophore) supports structure (VIII). The presence of one isolated double bond was proved by hydrogenation of product (IX) with Adams catalyst (1 mol. absorbed) to 3-ethyl-1,3,4,6,7,11*b*-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (X).

EXPERIMENTAL

Spectroscopic data for compounds marked * are shown in Table 1. The infrared spectra were determined for Nujol mulls by Dr. A. Wagland.

Butyl-3,4-*dimethoxyphenethylaminomethylmalonic Acid*.—To a solution of 3,4-dimethoxyphenethylamine (163 g.) and n-butylmalonic acid (160·5 g.) in ethanol (500 c.c.) and water (1050 c.c.), 40% aqueous formaldehyde (121 c.c.) was added at 0°. After 16 hr. at 0° the *acid* (247 g.) was filtered off, dried, and washed with hot ethanol; it had m. p. 150° (decomp.) (Found: C, 60·7; H, 7·8; N, 3·8. $C_{18}H_{27}NO_6$ requires C, 61·2; H, 7·7; N, 4·0%).

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[10] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.

[11] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1953, **75**, 4474; Brook and Karrer, *Helv. Chim. Acta*, 1957, **40**, 260.

[12] (*a*) Lutz and Hinkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4091; (*b*) Micovic and Mihailovic, " Lithium Aluminium Hydride in Organic Chemistry," Monograph Serbian Acad. Sciences, 1955, Vol. IX, p. 1937.

[13] Djerassi and Thomas, *J. Amer. Chem. Soc.*, 1957, **79**, 3838.

[14] Cf. Braude, Brook, and Linstead, *J.*, 1954, 3569; Agnello and Laubach, *J. Amer. Chem. Soc.*, 1957, **79**, 1257; Campbell and Kidd, *J.*, 1954, 2154.

[15] Cf. Braude, Hanah, and Linstead, *J.*, 1960, 3249; Latif, Fathy, Mishriky, and Atallah, *J. Org. Chem.*, 1960, **25**, 1618.

(3,4-*Dimethoxyphenethylaminomethyl*)*isobutylmalonic Acid*.—Similarly isobutylmalonic acid (176 g.) gave the corresponding *acid* (295 g.), m. p. 148° (decomp.) (Found: C, 60·7; H, 7·7; N, 3·8%).

2-(3,4-*Dimethoxyphenethylaminomethyl*)*hexanoic Acid*.—The n-butylmalonic acid (175 g.) in 60% acetic acid (1800 c.c.) was boiled under reflux for 10 hr. The solvent was removed and the *hexanoic acid* crystallised from ethanol–ether, forming plates (76 g.), m. p. 147—149° (Found: C, 66·1; H, 9·0; N, 4·7. $C_{17}H_{27}NO_4$ requires C, 66·0; H, 8·8; N, 4·5%).

2-(3,4-*Dimethoxyphenethylaminomethyl*)-4-*methylpentanoic Acid*.—Similarly, decarboxylation of the isobutylmalonic acid (175 g.) gave the *pentanoic acid* (76 g.) as prisms (from ethanol–ether), m. p. 162—163° (Found: C, 66·0; H, 8·9%).

1-(3,4-*Dimethoxyphenethyl*)-5-*ethyl*-2-*oxopiperidine*-4-*spiro*-2′-(1′,3′-*dioxolan*) (II).—The ketal was prepared according to the directions of Ban [4a] from compound (I; R = Et) (12·6 g.) as a gum (12·2 g.) which crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave prisms, m. p. 65—68° (Found: C, 65·4; H, 7·8; N, 4·0. Calc. for $C_{19}H_{27}NO_5$: C, 65·3; H, 7·8; N, 4·0%).

3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxobenzo*[a]*quinolizinium Iodide* (III).—The ketal (II; R = Et) (7·9 g.), dry toluene (30 c.c.), and phosphorus oxychloride (20 c.c.) were heated in a boiling-water bath for 3 hr. The solution was taken to dryness under reduced pressure and the residue warmed with 2N-hydrochloric acid (30 c.c.) for 5 min. at 50—60°. The filtered, cooled solution was treated with potassium iodide solution, and the oily iodide was extracted into chloroform. This iodide * crystallised from methanol–ether as yellow prisms (6·86 g.; 73%), m. p.s 171—172·5° (decomp.) (resolidifies at 180°), 240—241° (decomp.) (Found: C, 48·6, 48·35, 48·3; H, 5·4, 5·2, 5·4; N, 3·2, 2·9, 3·35; I, 29·7. $C_{17}H_{22}INO_3,0{\cdot}5H_2O$ requires C, 48·1; H, 5·5; N, 3·3; I, 29·9%), $\nu_{max.}$ 1630s, 1610m, 1560s, and 1530s cm.$^{-1}$.

3-*Ethyl*-3,4,6,7-*tetrahydro*-9,10-*dimethoxy*-2-*oxo*-2H-*benzo*[a]*quinolizine* (IV; R = Et).—(*a*) Cyclisation of the ketal was carried out as described above; after the acid hydrolysis the solution was made alkaline with an excess of 2N-sodium hydroxide, and the precipitated *base* * was extracted with benzene. It crystallised from ethyl acetate as yellow prisms (45%), m. p. 169—171·5° (Found: C, 70·9; H, 7·4; N, 5·0. $C_{17}H_{21}NO_3$ requires C, 71·0; H, 7·4; N, 4·9%), $\nu_{max.}$ 1698w, 1685w, 1670w, 1615s, 1585s, and 1545s cm.$^{-1}$.

The *hydrochloride* * separated from methanol–ether as pale yellow prisms, m. p. 222·5—224° (decomp.) (Found: C, 62·8; H, 6·85; Cl, 11·55. $C_{17}H_{21}NO_3,HCl$ requires C, 63·1; H, 6·85; Cl, 10·95%). The hydriodide,* crystallised similarly, had m. p. 215—217° (decomp.), $\nu_{max.}$ 1640s, 1615m, 1580sh, 1570s, and 1530 cm.$^{-1}$. Comparison of this spectrum with the spectrum of compound (III) also showed many differences in the " finger-print region."

(*b*) Cyclisation of the ketal (6·1 g.) as described above, and subsequent treatment with an excess of 20% aqueous hydrobromic acid and concentration to dryness, gave, after crystallisation, the *hydrobromide* * (3·30 g.), m. p. 225—228°, of base (IV) (Found: C, 55·6; H, 6·1; N, 3·85; Br, 21·0. $C_{17}H_{21}NO_3,HBr$ requires C, 55·4; H, 6·0; N, 3·8; Br, 21·7%), $\nu_{max.}$ 1635m, 1610s, 1565s, and 1515 cm.$^{-1}$.

(*c*) Treatment of the quaternary iodide (III) in methanol with 2N-sodium hydroxide, followed by extraction with benzene and crystallisation of the base from ethyl acetate, gave the base (IV), m. p. and mixed m. p. 168—170°.

(*d*) 3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-oxo-2*H*-benzo[*a*]quinolizine (0·578g.) in benzene (15 c.c.) was refluxed with chloranil (0·49 g.) for 2·5 hr. The benzene solution was washed 3 times with 2N-sodium hydroxide, then with water, and dried (Na_2SO_4). The product crystallised from ethyl acetate, to give the base (IV) (0·38 g., 65%), m. p. and mixed m. p. 167·5—170·5°; the hydrochloride had m. p. 225—228°, $\lambda_{max.}$ 239, 288, and 360 mμ.

3-*Butyl*-3,4,6,7-*tetrahydro*-9,10-*dimethoxy*-2-*oxo*-2H-*benzo*[a]*quinolizine* (IV; R = Bu).—(*a*) The ketal (II; R = Bu^n) [non-crystalline; 4·37 g.; prepared (cf. refs. 4) in 56% overall yield from 2-(3,4-dimethoxyphenethylaminomethyl)hexanoic acid without characterisation of the intermediates] was heated in toluene (20 c.c.) and phosphorus oxychloride (10 c.c.) at 95° for 3 hr. Isolation of the *base* * as described above and crystallisation from ethyl acetate gave yellow needles (1·5 g., 41%), m. p. 181—183° (Found: C, 72·2; H, 8·0; N, 4·7. $C_{19}H_{25}NO_3$ requires C, 72·35; H, 8·0; N, 4·4%). Comparison with the specimen prepared as in (*b*) below, by mixed m. p. and infrared spectra, showed the two to be identical.

(*b*) 3-Butyl-1,3,4,6,7,11*b*-hexahydro-9,10-dimethoxy-2-oxo-2*H*-benzo[*a*]quinolizine [1a] (3·17 g.) and chloranil (2·6 g.) in benzene (100 c.c.) were boiled under reflux for 2·5 hr. The yellow crystals, m. p. 181—182·5° (2·14 g.), were filtered off, washed with 2N-sodium hydroxide and water and crystallised from methanol. An *adduct* composed of the tetrahydro-base (IV; R = Bu^{n}) and the quinol (2 : 1) separated; it had m. p. 183—185° [Found: C, 60·65, 60·4; H, 5·95, 6·1; N, 3·1, 3·2. $(C_{19}H_{25}NO_3)_2,C_6H_2Cl_4O_2$ requires C, 60·1; H, 5·8; N, 3·2%). The *hydrobromide* * of base (IV; R = Bu^{n}) crystallised from ethanol–ether as yellow prisms, m. p. 217—219° (Found: C, 58·0; H, 6·65; N, 3·5. $C_{19}H_{25}NO_3,HBr$ requires C, 57·6; H, 6·6; N, 3·5%). The base from the hydrobromide separated from ethyl acetate as needles, m. p. 180—182·5° (Found: C, 71·7; H, 7·7; N, 4·7%). The *hydrochloride*, crystallised from methanol–ether and air-dried, had m. p. 187—190° (decomp.) (Found: C, 61·4; H, 7·4; N, 3·9; Cl, 9·7. $C_{19}H_{25}NO_3,HCl,H_2O$ requires C, 61·9; H, 7·4; N, 3·8; Cl, 9·6%).

3,6,7,11*b*-*Tetrahydro*-3-*isobutyl*-9,10-*dimethoxy*-2-*oxo*-2H-*benzo*[a]*quinolizine* (IV; R = Bu^{i}).—(*a*) The ketal (II; R = Bu^{i}) [non-crystalline; 5·0 g.; prepared (cf. refs. 4) in 57% overall yield from 2-(3,4-dimethoxyphenethylaminomethyl)-4-methylpentanoic acid] was cyclised as in (*a*) above to the *quinolizine* * (IV) which crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as yellow prisms (1·8 g., 43%), m. p. 156—158° (Found: C, 72·7; H, 7·39; N, 4·4. $C_{19}H_{25}NO_3$ requires C, 72·35; H, 8·0; N, 4·4%), $\nu_{\max.}$ 2350w, 1695w, 1640m, 1615s, 1585s, 1550s cm.$^{-1}$. A mixed m. p. with a specimen from (*b*) below, gave no depression.

When the product was processed as described above for the iodide (III), the corresponding quaternary iodide was not isolated. Instead the hydriodide, m. p. 203·5—205° (decomp.) (from methanol–ether), of the base (IV; R = Bu^{i}) was obtained, identical with that described below (mixed m. p., ultraviolet and infrared spectra). It resisted reduction by potassium borohydride.

(*b*) 1,3,4,6,7,11*b*-Hexahydro-3-isobutyl-9,10-dimethoxy-2-oxo-2*H*-benzo[*a*]quinolizine [1a] (3·17 g.) and chloranil (2·6 g.) in benzene (100 c.c.) were boiled under reflux for 2·5 hr., and the solution was washed with 2N-sodium hydroxide and water and dried. The product (1·44 g.) had m. p. 158—160° (from ethyl acetate–light petroleum). The *hydrobromide* * crystallised from ethanol–ether as yellow prisms, m. p. 220—222° (decomp.) (Found: C, 57·85; H, 6·5; N, 3·5. $C_{19}H_{25}NO_3,HBr$ requires C, 57·6; H, 6·6; N, 3·5%). The *hydrochloride*,* air-dried, had m. p. 202—204° (Found: C, 61·45; H, 7·2; N, 3·8; Cl, 10·0. $C_{19}H_{25}NO_3,HCl,H_2O$ requires C, 61·9; H, 7·4; N, 3·8; Cl, 9·6%). The *hydriodide* * had m. p. 210° (decomp.) (Found: C, 51·4; H, 5·9; N, 3·25; I, 28·1. $C_{19}H_{25}NO_3,HI$ requires C, 51·5; H, 5·9; N, 3·2; I, 28·6%), $\nu_{\max.}$ 2480w, 1635s, 1600m, 1555—1570s, 1530 cm.$^{-1}$.

3-*Ethyl*-1,3,4,6,7,11*b*-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-2H-*benzo*[a]*quinolizine* (V; R = Et).—(1) The quaternary iodide (III) (2·3 g.) in methanol (100 c.c.) was treated with potassium borohydride (0·2 g.) in two portions at 20°. After 12 hr. the methanol was removed and the residue extracted with a mixture of aqueous sodium carbonate and ether. After drying, the ether was concentrated and the keto-base (V) separated as colourless prisms (1·5 g., 94%); the m. p. and mixed m. p. with an authentic specimen [1a] (111—112°) was 111—112·5° (Found: C, 70·6; H, 7·7; N, 4·9. Calc. for $C_{17}H_{23}NO_3$: C, 70·6; H, 8·0; N, 4·8%), $\nu_{\max.}$ 1715 cm.$^{-1}$. The hydrochloride * (from ethanol–ether) had m. p. 201·5—202·5° (lit.,[1a] m. p. 198—200°) (Found: C, 61·1; H, 7·8; N, 4·1; Cl, 10·7. Calc. for $C_{17}H_{23}O_3N,HCl,0{\cdot}5H_2O$: C, 61·1; H, 7·55; N, 4·2; Cl, 10·6%). The hydrobromide had m. p. 216·5—217·5° (lit.,[1a] m. p. 216—217·5°), $\nu_{\max.}$ 3550s, 3450s, 2730s, 1725s, 1630m, 1620m. Attempts to reduce the base, hydrochloride, or hydriodide under the same conditions were ineffective. Similarly, the n-butyl and isobutyl quaternary chloride and iodide and the bases were resistant to reduction by potassium borohydride under various conditions.

(2) The base (IV; R = Et) (1·43 g.) was suspended in dry tetrahydrofuran (25 c.c.), treated portionwise with lithium aluminium hydride (0·3 g.), and refluxed on a water bath for 3 hr. After addition of ethyl acetate, ether, and water, the ethereal extract was dried; it gave a basic residue which was converted into the hydrobromide (0·72 g.), prisms (from methanol–ether), m. p. 220° (decomp.). The base (V) crystallised from light petroleum (b. p. 80—100°), then having m. p. and mixed m. p. 111—113°. An infrared spectrum confirmed that a ketone group was present.

(3) The base (IV; R = Et) (1·43 g.) was suspended in ether (40 c.c.) and added to a solution of lithium (0·16 g.) in liquid ammonia (300 c.c.) at −40°. After 15 minutes' stirring the blue colour had not been discharged, ammonium chloride (1·5 g.) was added, and the yellow solution allowed to evaporate to dryness. Water was added and the basic residue was extracted with

ether and converted into the hydrobromide which separated as nodules (0·55 g.), m. p. 208—209°. The keto-base (V) crystallised from isopropyl ether as needles, m. p. and mixed m. p. [1a] 109—110°.

1,3,4,6,7,11b-*Hexahydro*-3-*isobutyl*-9,10-*dimethoxy*-2-*oxo*-2H-*benzo*[a]*quinolizine* (V; R = Bu^i).—The tetrahydro-base (IV; R = Bu^i) (1·58 g.) was boiled in tetrahydrofuran (25 c.c.) with lithium aluminium hydride (0·34 g.) for 3 hr. The solution was cooled and decomposed with ethyl acetate and water. The product was taken into ether and gave a hydrobromide, prisms (0·9 g.) (from methanol–ether), m. p. 202—204·5° (Found: C, 56·3; H, 7·45. Calc. for $C_{19}H_{27}NO_3,HBr,0{\cdot}5H_2O$: C, 56·1; H, 7·4%), $\lambda_{max.}$ (in 95% EtOH) 232, 284—285 mμ (log ε 3·89, 3·56), $\nu_{max.}$ 2700m, 2580m, 1732s, 1615m, 1525s cm.$^{-1}$. The base from this salt separated from methanol as prisms, m. p. 126—129°. Comparison with an authentic sample [1a] (m. p. 128—130°) by mixed m. p. and infrared absorption showed their identity.

3-*Butyl*-1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-2-*oxo*-1H-*benzo*[a]*quinolizine* (V; R = Bu^n).—Similarly, the n-butyl base (IV) (1·0 g.) was reduced with lithium aluminium hydride. The product was isolated as the hydrochloride which crystallised from 2N-hydrochloric acid as prisms (0·2 g.), m. p. and mixed m. p. [1a] 198—199°.

3-*Ethyl*-1,3,4,6,7,11b-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-2H-*benzo*[a]*quinolizine* (VII; R = Et).—The keto-base (IV; R = Et) (0·6 g.) in methanol (15 c.c.) was hydrogenated with palladised charcoal (1 g.) at 20°/atm. (uptake of 2 mol. fairly rapid). After filtration, the methanol was removed. The alcohol crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles (0·2 g.), m. p. 155—157°, $\nu_{max.}$ 3160s, 1615w cm.$^{-1}$. A mixed melting point with an authentic specimen [1b] (m. p. 156—158°) gave no depression. The hydrobromide had m. p. 231·5—233° (lit.,[1b] m. p. 231—233°).

Catalytic reduction of the ketone (V) with Adams catalyst in methanol gave the same alcohol, m. p. 151—152°, in good yield.

3-*Ethyl*-6,7-*dihydro*-2-*hydroxy*-9,10-*dimethoxybenzo*[a]*quinolizinium iodide* (VI).—The iodide (III) (1·0 g.) was heated at 180° for 10 min.; it frothed and then resolidified. The residue crystallised from methanol, the quaternary *iodide* * (VI) separating as yellow prisms (0·5 g.), m. p. 248° (Found: C, 49·5; H, 4·9; N, 3·4. $C_{17}H_{20}INO_3$ requires C, 49·3; H, 4·9; N, 3·4%), $\nu_{max.}$ 3550m, 1640m, and 1610m cm.$^{-1}$.

Treatment of the iodide in water and methanol with 2N-sodium carbonate gave the dihydrobenzo[*a*]quinolizine base, m. p. 227—230° alone or mixed with an authentic specimen [1a] (m. p. 229—231°). When the hydriodide of the αβ-unsaturated ketone (IV; R = Et) was treated in a similar manner, the salt was recovered unchanged.

(2) 3-Ethyl-1,3,4,6,7,11*b*-hexahydro-2-oxo-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (V; R = Et) (1·45 g., 1 mol.) was heated in 10% acetic acid (100 c.c.) with mercuric acetate (3·18 g., 2 mol.) at 90—95° for 3 hr., during which mercury separated but no mercurous acetate appeared to be formed. Hydrogen sulphide was passed into the hot solution, charcoal was added, and after filtration the filtrate was treated with an excess of hydrobromic acid. The benzo[*a*]quinolizinium bromide (1·10 g., 60%) separated as needles, m. p. 257—258°. The filtrate after removal of this salt was examined for the αβ-unsaturated ketone (IV; R = Et); none could be isolated. Use of only 1·59 g. (1 mol.) of mercuric acetate at 60° gave only unchanged starting material.

(3) When the αβ-unsaturated ketone (IV; R = Et) was treated with an excess of mercuric acetate in acetic acid, as described in (2), the quaternary bromide (VI) was isolated as before, having m. p. and mixed m. p. 257—258°.

3-*Ethyl*-3,4,6,7-*tetrahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium Bromide* (VIII).—Mercuric acetate (4 g.) and 3-ethyl-1,3,4,6,7,11*b*-hexahydro-2-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine (VII; R = Et) (1·45 g.) were heated in 10% acetic acid (75 c.c.) at 95° for 3 hr. The solution became yellow and after 0·5 hr. mercurous acetate and some mercury were precipitated. The product was worked up as in the above experiment and isolated as the *bromide* * (1·62 g., 92%) which separated from methanol–ether as yellow needles, m. p. 265—266° (decomp.) (Found: C, 58·2; H, 5·9; N, 3·9; Br, 22·0. $C_{17}H_{22}BrNO_2$ requires C, 57·95; H, 6·3; N, 4·0; Br, 22·7%). The infrared spectra in Nujol and hexachlorobutadiene showed no NH^+ band in the 2600 cm.$^{-1}$ region.

3-*Ethyl*-3,6,7,11*b*-*tetrahydro*-9,10-*dimethoxy*-4H-*benzo*[a]*quinolizine Hydrobromide* (cf. IX).—Potassium borohydride (0·25 g.) was added to a solution of the above quaternary bromide (VIII) (1·0 g.) in methanol (30 c.c.) at 20°. The yellow-green fluorescence rapidly disappeared and after 0·5 hr. 2N-sodium carbonate was added and the base extracted with ether. The *hydrobromide* * crystallised from methanol–ether as colourless needles (0·85 g.), m. p. 234—235° (Found: C, 57·5; H, 6·9; N, 3·7. $C_{17}H_{23}NO_2$,HBr requires C, 57·6; H, 6·8; N, 3·95%), $\nu_{max.}$ 2690s, 2600s, 1615m, 1525m cm.$^{-1}$.

3-*Ethyl*-1,3,4,6,7,11*b*-*hexahydro*-9,10-*dimethoxy*-2H-*benzo*[a]*quinolizine Hydrobromide* (cf. X).—The hydrobromide (0·37 g.) of base (IX) was hydrogenated in methanol (30 c.c.) at 20° and 1 atm. in the presence of Adams catalyst (0·05 g.). After an uptake of 26 c.c. ($1H_2$ = 24 c.c) the filtered solution yielded the *hydrobromide* (IX) as colourless prisms (from methanol–ether), m. p. 249—250° (Found: C, 57·1; H, 7·2; N, 3·8. $C_{17}H_{25}NO_2$,HBr requires C, 57·3; H, 7·35; N, 3·9%), $\nu_{max.}$ 2700s, 2640s, 2580s, 1615m, and 1525 cm.$^{-1}$.

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