276. *The Synthesis of Emetine and Related Compounds. Part IV.* A New Synthesis of 3-Substituted* 1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-2-*oxo*-11b*H*-*benzo*[a]*quinolizines.*

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The compounds (I), named in the title, are produced by spontaneous cyclisation of the 2-(2-alkyl-3-oxobutyl)-3,4-dihydroisoquinolinium cations (II), which arise either by the mercuric acetate dehydrogenation of the related tetrahydroisoquinolines (III), prepared by a Mannich reaction, or more simply by amine interchange between the dihydroisoquinoline (V) and the quaternised Mannich bases (VI). The procedure has also been applied to the synthesis of 9,10-methylenedioxy- and 9,10-unsubstituted analogues of (I), and, less satisfactorily, to the related indoloquinolizines (XVII).

When the dihydroisoquinoline (V) was treated with formaldehyde and a methyl ketone, the benzoquinolizine (I) was not produced, but a more complex product which is assigned the structure (IX).

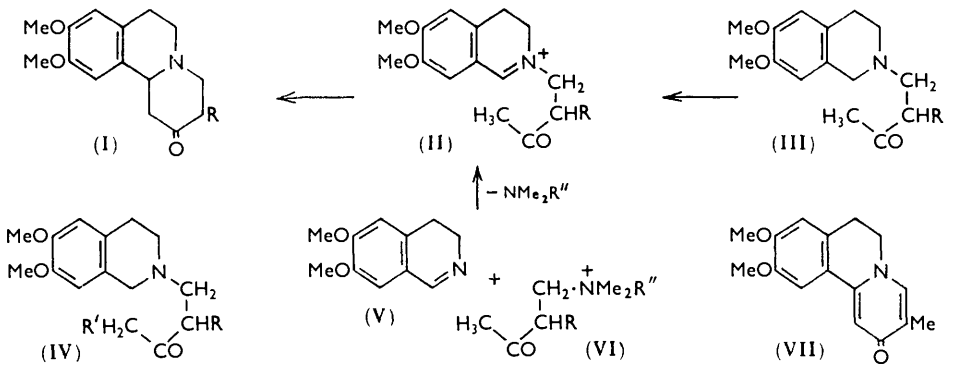
The 2-oxohexahydrobenzo[*a*]quinolizine (I; R = Et) has proved a useful starting material for the synthesis of rubremetine [1] and of emetine and 2-dehydroemetine.[2] It was first

* Part III, *J.*, 1961, 4939.

[1] Battersby and Openshaw, *Experientia*, 1950, **6**, 387.

[2] Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515; Brossi, Baumann, Chopard-dit-Jean, Würsch, Schneider, and Schnider, *ibid.*, p. 772.

described by Battersby and Openshaw,[1,3] and subsequently Brossi and his co-workers[4] developed a modified synthesis of this and related compounds. In both of these methods, the ketone (I) was produced by Dieckmann cyclisation of the appropriate diester, which was prepared from 3,4-dimethoxyphenethylamine by a four- or five-stage process. We now report a simpler synthesis of the ketone (I; R = Et) and its analogues, suitable for their large-scale manufacture.



By analogy with the condensation of cotarnine with acetone,[5] it seemed likely that a compound of the structure (II) would cyclise readily or spontaneously, to the benzo[*a*]quinolizine (I). The first method investigated for the production of an intermediate of type (II) was the oxidation by mercuric acetate of the corresponding tetrahydroisoquinoline (III). When 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride was heated under reflux with aqueous formaldehyde in an excess of methyl n-propyl ketone, a mixture containing approximately equal amounts of the isomeric Mannich bases (III; R = Et) and (IV; R = H, R′ = Et) resulted. These could be separated as the naphthalene-2-sulphonates. When the former was heated with mercuric acetate in aqueous acetic acid at 70—75°, then demercurated with hydrogen sulphide, basification of the reaction solution gave the benzo[*a*]quinolizine (I; R = Et); the isomeric Mannich base did not give a benzo[*a*]quinolizine under these conditions and was recoverable. To prepare the benzo[*a*]quinolizine (I; R = Et) by this route, the preliminary separation of the isomeric Mannich bases was therefore not essential, for the desired product could be readily isolated from the oxidation mixture. The use of α-ethylacetoacetic acid in place of methyl n-propyl ketone was preferable, however, since its reaction with 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline and formaldehyde gave only the desired Mannich base (III; R = Et), and oxidation of the crude base with mercuric acetate gave a 54% yield of the benzo[*a*]quinolizine (I; R = Et). From the residues, small quantities of 3,4-dihydro-6,7-dimethoxyisoquinoline and 6,7-dimethoxyisoquinoline were isolated by chromatography. The dihydroisoquinoline is probably formed by fission of the intermediate (II; R = Et), with the liberation of 3-ethylbut-3-en-2-one, for the odour of this is evident during the reaction. It has recently been shown by Brossi and his co-workers[6] that the latter reaction is reversible; the dihydroisoquinoline and the unsaturated ketone react to give the base (I; R = Et), though in small yield (14%).* The fully aromatic isoquinoline is not formed by further dehydrogenation of the dihydro-compound but perhaps arises through initial dehydrogenation of the Mannich base (III; R = Et) at the 2,3-positions

* *Added in proof.* Beke and Szántay (*Chem. Ber.*, 1962, **95**, 2132) report good yields when the reaction is conducted under acid conditions.

[3] Battersby, Openshaw, and Wood, *J.*, 1953, 2463.
[4] Brossi, Lindlar, Walter, and Schnider, *Helv. Chim. Acta*, 1958, **41**, 119.
[5] Liebermann and Kropf, *Ber.*, 1904, **37**, 211.
[6] Brossi, Chopard-dit-Jean, Würsch, and Schnider, *Helv. Chim. Acta*, 1960, **43**, 583.

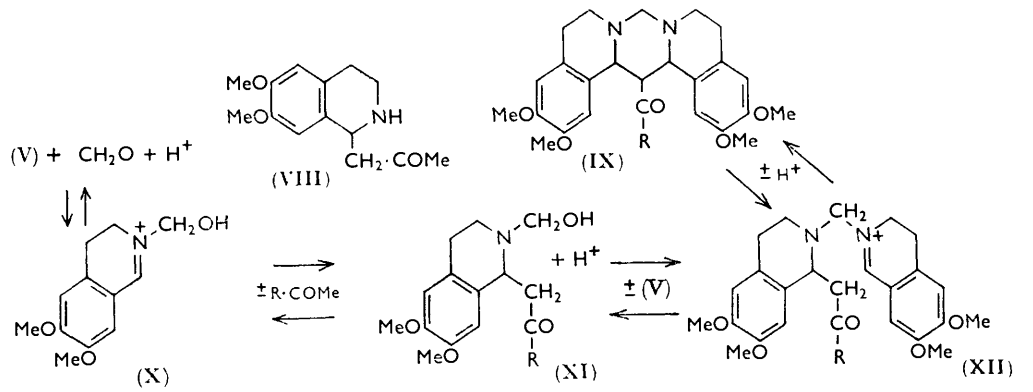
(cf. Knabe [7]), followed by re-arrangement to the Δ^3-dehydro-compound and subsequent aromatisation and reversal of the Mannich reaction. The benzo[*a*]quinolizines (I; R = Pr^n, Bu^n, and n-C_5H_{11}) were obtained from the appropriate α-substituted acetoacetic acids in the above manner.

Reaction of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride with formaldehyde and ethyl methyl ketone, or benzyl methyl ketone, gave in each case (in contrast with methyl n-propyl ketone) only one Mannich base (III; R = Me or Ph), and acetone and diethyl ketone gave the bases (III; R = H) and (IV; R = R′ = Me), respectively. Similarly, when 1,2,3,4-tetrahydroisoquinoline or its 6,7-methylenedioxy-analogue was heated with formaldehyde and ethyl methyl ketone, reaction occurred exclusively at the methylene carbon atom of the ketone. When the base (III; R = Me) was heated with 2 mol. of mercuric acetate in aqueous acetic acid at 70—75°, the reaction mixture gave, after demercuration, mainly unchanged starting material together with a small yield of the benzo[*a*]quinolizine (I; R = Me). At reflux temperature 13% of the benzo[*a*]quinolizine (I; R = Me) was obtained, together with 15% of the tetradehydro-compound (VII). Increasing the proportion of mercuric acetate to 4 mol. gave 30% of the benzo[*a*]quinolizine (I; R = Me) but, surprisingly, only a trace of the tetradehydro-compound (VII) was formed. It is suggested that with 4 mol. of mercuric acetate the intermediate dihydroisoquinolinium cation (II; R = Me) is largely converted by mercuration into a stabilised complex, and that ring-closure to the benzo[*a*]quinolizine (I; R = Me) occurs only when the reaction mixture is subsequently demercurated with hydrogen sulphide. With 2 mol. of mercuric acetate, however, complex-formation is less complete and some benzo[*a*]quinolizine (I; R = Me) is probably produced directly during the reaction and is further oxidised to the tetradehydro-compound (VII) by the mercurous acetate present; it has been shown that mercurous acetate will perform this oxidation. Other analogues of the Mannich base (III) similarly gave hexahydro-2-oxobenzo[*a*]quinolizines in 15—25% yield, with the following exceptions. The base (III; R = H) gave only a 6% yield of compound (I; R = H), the main product being 3,4-dihydro-6,7-dimethoxyisoquinoline (V), and the latter was the sole product of oxidation of the base (IV; R = H, R′ = Et). In these two examples the absence of an alkyl group β to the nitrogen facilitates the Hofmann-type elimination of the side-chain from the intermediate dihydroisoquinolinium cation (*e.g.*, II; R = H).

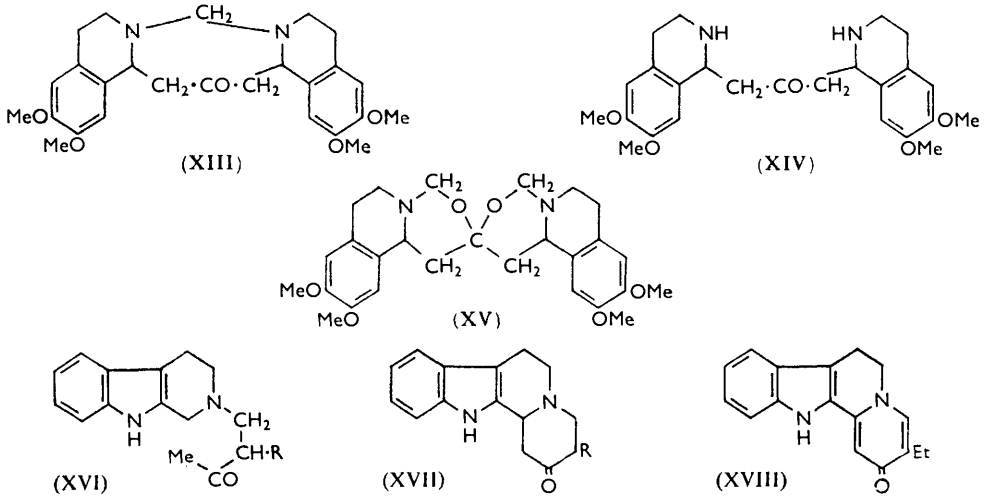
In a later approach to the synthesis of hexahydro-2-oxobenzo[*a*]quinolizines it was considered that 3,4-dihydro-6,7-dimethoxyisoquinoline (V) might react with a Mannich base cation (VI; R″ = H or Me), by amine interchange,[8] to give the intermediate (II), with subsequent ring-closure to the benzo[*a*]quinolizine (I). This possibility was realised, for when the dihydroisoquinoline (V) and the Mannich base methiodide (VI; R = Et, R″ = Me) were heated together in alcohol under reflux, a 75% yield of the benzo[*a*]quinolizine (I; R = Et) resulted. This procedure has proved convenient for the preparation of kilogram quantities of this compound, and is considered to be superior to other known methods of synthesis. The protonated Mannich base (VI; R = Et, R″ = H) and its diethylamino-analogue also reacted with 3,4-dihydro-6,7-dimethoxyisoquinoline (V) in a similar manner. The scope of the reaction has been further exemplified by the preparation of the benzo[*a*]quinolizines (I; R = Bu^n) and (I; R = Et; H for MeO).

According to Chapman *et al.*,[9] the dihydroisoquinoline (V) reacts with acetone in the presence of acid to give a ketone (VIII), and it appeared to us that the dihydroisoquinoline (V) might react with a ketone in the presence of formaldehyde to give a benzo[*a*]quinolizine (I) directly. Although the desired end was not achieved, some novel compounds resulted. When the dihydroisoquinoline (V) was heated with formaldehyde and methyl n-propyl ketone in alcohol, in a sealed tube at 100°, a solid of the formula $C_{28}H_{36}N_2O_5$ was produced.

[7] Knabe, *Arch. Pharm.*, 1959, **292**, 416, 652.
[8] Schöpf and Thesing, *Angew. Chem.*, 1951, **63**, 377.
[9] Chapman, Holton, Ritchie, Walker, Webb, and Whiting, *J.*, 1962, 2471.



The liquors did not contain a detectable quantity of the benzo[*a*]quinolizine (I; R = Et), for when they were heated with alcoholic hydroxylamine hydrochloride none of the characteristic, sparingly soluble oxime hydrochloride was obtained. Some 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride was produced, however, but it was shown that this also arises when the product of reaction of the dihydroisoquinoline (V) with formaldehyde was heated with hydroxylamine hydrochloride. In the presence of acid, neither the desired benzo[*a*]quinolizine nor the C_{28} compound was produced. The C_{28} compound absorbed at 1690 cm.$^{-1}$ (C=O), but not in the N–H stretching region, and it liberated formaldehyde and the dihydroisoquinoline (V) on being heated with dilute aqueous mineral acid; it was assigned the polycyclic structure (IX; R = Pr^n). Analogous compounds (IX; R = Me, Ph, or Bu^t) were obtained on reaction of the dihydroisoquinoline (V) with formaldehyde and acetone, acetophenone, or methyl t-butyl ketone, but not from diethyl ketone. The scheme shown, involving the transient intermediates (X), (XI), and (XII), is a possible mechanism of formation of the polycyclic compounds (IX). At one stage it was thought that the product derived from acetone might have the structure (XIII) and confirmation of this was sought by its attempted synthesis from the known [9] *meso*- and racemic compounds (XIV) and formaldehyde. Surprisingly, both isomers yielded the same compound, which was not identical with the above product. It did not contain a carbonyl group and is formulated as the spiroketal (XV).



The sequence of reactions leading to ring-addition in the isoquinoline series has also been applied to the carboline series. The Mannich bases (XVI; R = Me and Et), obtained

from 1,2,3,4-tetrahydro-β-carboline, were oxidised with 3 mol. of mercuric acetate, but poor yields of the octahydro-oxoindolo[2,3-*a*]quinolizines (XVII; R = Me or Et) resulted, together with some β-carboline. With 3·5 mol. of mercuric acetate, the base (XVI; R = Et) also gave the tetrahydro-oxoindolo[2,3-*a*]quinolizine (XVIII). A somewhat better yield of the product (XVII; R = Et) was obtained when 3,4-dihydro-β-carboline was condensed with the quaternary base (VI: R = Et, R″ = Me).

Experimental

Synthesis of the Isoquinoline Mannich Bases (III) *and* (IV).—(A) *The reaction of* 1,2,3,4-*tetrahydroisoquinolines with ketones and formaldehyde.* (*a*) A mixture of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (20 g.), methyl n-propyl ketone (111 ml.), and 38·8% w/v aqueous formaldehyde (7·4 ml.) was heated to the b. p. during 10 min. and refluxed for 40 min., with stirring throughout. The resulting solution was cooled, the crystals produced were treated with sufficient water to dissolve them, and the supernatant layer of ketone was evaporated *in vacuo*. The residual aqueous solution was diluted with water to 200 ml., treated with a solution of naphthalene-2-sulphonic acid (18·5 g.) in water (50 ml.), and seeded. The

Table 1.

Reaction of 1,2,3,4-tetrahydroisoquinoline hydrochlorides with formaldehyde and ketones.

No.	6,7-Subst.	Ketone	Reaction time (min.)	Product	Salt	(Yield %)	M. p. (efferv.)
1	$(MeO)_2$	Me·CO·Pr^n	40	(III; R = Et)	Naphthalene-2-sulphonate	(14)	144—145°
2				(IV; R = H, R′ = Et) *	,,	(30)	145—146
3	,,	Et·CO·Et	40	(IV; R = R′ = Me)	,,	(95)	184—185
4	,,	Me·CO·Me	25	(III; R = H)	,,	(92)	167—168
5	,,	Me·CO·Et	30	(III; R = Me) †	,,	(93)	172—173
6	None	Me·CO·Et	20	(III; R = Me; H for MeO)	Hydrochloride	(70)	154—155
7	CH_2O_2	Me·CO·Et	20	[III; R = Me; CH_2O_2 for $(MeO)_2$]	,,	(74)	165—166

	Found (%)					Required (%)			
No.	C	H	N	S	Formula	C	H	N	S
1	64·2	6·3	2·75	6·05	$C_{27}H_{33}NO_6S$	64·9	6·65	2·8	6·4
2	64·9	6·6	2·85	5·95	$C_{27}H_{33}NO_6S$	,,	,,	,,	,,
3	64·85	6·95	2·8	6·25	$C_{27}H_{33}NO_6S$	,,	,,	,,	,,
4	63·8	6·3	3·05	6·7	$C_{25}H_{29}NO_6S$	63·65	6·2	2·95	6·8
5	64·2	6·45	2·95	6·7	$C_{26}H_{31}NO_6S$	64·3	6·4	2·9	6·6
6	—	—	5·45	14·15 ‡	$C_{14}H_{20}ClNO$	—	—	5·5	14·0 ‡
7	—	—	4·7	12·4 ‡	$C_{15}H_{20}ClNO_3$	—	—	4·7	11·95 ‡

* The *hydrochloride* has m. p. 183—184° (efferv.) (Found: N, 4·45; Cl, 11·3. $C_{17}H_{26}ClNO_3$ requires N, 4·3; Cl, 10·85%), and the free *base* has m. p. 37·5—38·5° (Found: C, 70·05; H, 8·1; N, 4·85. $C_{17}H_{25}NO_3$ requires C, 70·05; H, 8·65; N, 4·8%). † The free *base* has m. p. 97—98° (Found: C, 69·4; H, 8·3; N, 5·2. $C_{16}H_{23}NO_3$ requires C, 69·3; H, 8·35; N, 5·05%). ‡ Chlorine.

mixture was shaken for 3 hr., then set aside overnight, and the resulting mixture of crystals and gum was collected, washed with water, and dissolved in hot acetone (75 ml.). The acetone solution was cooled to 0°, giving crystals of 1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-3′-*oxohexyl*-*isoquinoline* (IV; R = H, R′ = Et) *naphthalene*-2-*sulphonate* (12·84 g.), m. p. 138—141°. Recrystallisation from acetone afforded the pure salt, m. p. 145—146° (see Table 1).

The aqueous filtrate from the above crude product was made alkaline with potassium hydroxide and extracted with chloroform (2 × 150 ml.), and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residual gum was dissolved in acetone, neutralised with a solution of naphthalene-2-sulphonic acid in acetone, seeded, and set aside at 0° for several days. The resulting crystals of 2-(2-*ethyl*-3-*oxobutyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (III; R = Et) *naphthalene*-2-*sulphonate* (6·1 g.) had m. p. 136—140°, raised to m. p. 144—145° on recrystallisation from acetone (see Table 1). Admixture with the naphthalene-2-sulphonate of the above isomeric base depressed the m. p. to 129—141°.

(*b*) The general method of reaction of other ketones was to heat the tetrahydroisoquinoline

hydrochloride with 1·05 mol. of concentrated aqueous formaldehyde and 12 mol. of ketone at 100°. With acetone and ethyl methyl ketone a sealed vessel was used. Since only one product resulted in each case, the procedure for its isolation was simplified as follows. With 1,2,3,4-tetrahydroisoquinoline and its 6,7-methylenedioxy-derivative the reaction mixture was evaporated and the residue treated with acetone, whereupon the hydrochloride crystallised. In the other experiments the reaction mixture was treated with water and, after removal of the excess of ketone, the aqueous solution of Mannich base hydrochloride was basified with aqueous potassium hydroxide and extracted with chloroform. The extract was evaporated and the residual base was converted to the naphthalene-2-sulphonate in acetone. Samples for analysis were crystallised from alcohol or acetone. The results are summarised in Table 1.

(B) *The reaction of* 1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline with* β-*keto-acids and formaldehyde.* (*a*) Ethyl acetoacetate (5·67 g.) and ice-cold 0·92N-aqueous potassium hydroxide (52·2 ml.) were shaken together for 1 hr., and the resulting solution was set aside at 0° overnight. With ice-water cooling and stirring, the solution was brought to pH 7 with concentrated hydrochloric acid and treated with 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (10 g., 1 mol.), 38·8% w/v aqueous formaldehyde (3·37 ml., 1 mol.), and then dropwise, during 1 hr., with concentrated hydrochloric acid (4·2 ml. minus that required above). The solution was kept at 0° for a further hour and allowed to come to room temperature overnight, then traces of acetone formed in the reaction were evaporated *in vacuo*. The solution was basified with aqueous potassium hydroxide and extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residual gummy base in acetone was evaporated, and the gum, which began to crystallise spontaneously, was taken up in ether (*ca.* 50 ml.) and set aside at 0°. The resulting crystals (2·99 g.), m. p. 128—135°, were recrystallised from alcohol, yielding colourless plates, m. p. 149—150°, of the di-Mannich base 2-*acetyl*-1,3-*bis*-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*isoquinolyl*)*propane* (Found: C, 69·4; H, 7·7; N, 5·7. $C_{27}H_{36}N_2O_5$ requires C, 69·2; H, 7·75; N, 6·0%). The ethereal liquors were evaporated, and the residual gum was dissolved in acetone (15 ml.) and neutralised with a solution of naphthalene-2-sulphonic acid in acetone, giving crystals (8·36 g.), m. p. 156—164° (effervescence). Recrystallisation from alcohol gave the pure Mannich base (III; R = H) naphthalene-2-sulphonate, m. p. 166—167° (effervescence) alone and in admixture with the product prepared from acetone (see Table 1). From the acetone liquors more crystals (1·01 g.), m. p. 187—189°, separated. These had m. p. 190—191° after recrystallisation from alcohol and consisted of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline naphthalene-2-sulphonate.

(*b*) Ethyl α-methylacetoacetate (6·27 g.) was substituted for ethyl acetoacetate in the reaction described in (*a*) above. The chloroform solution of the resulting base was evaporated and the residual crude product was converted in acetone into the naphthalene-2-sulphonate (15·31 g.), m. p. 162—165° (effervescence), raised to m. p. 171—172° (effervescence) on recrystallisation from alcohol. A solution of this salt in hot water (300 ml.) was cooled and made alkaline with concentrated aqueous ammonia, giving colourless crystals (6·03 g.), m. p. 97—98°, of the Mannich base (III; R = Me).

(*c*) When ethyl α-ethylacetoacetate (6·9 g.) was substituted for ethyl acetoacetate in procedure (*a*), and the resulting base was dissolved in acetone and neutralised with naphthalene-2-sulphonic acid, crystals of the tetrahydroisoquinoline naphthalene-2-sulphonate (1·56 g.), m. p. 188—191°, first separated. The acetone liquors were concentrated, seeded, and set aside, to give the Mannich base (III; R = Et) naphthalene-2-sulphonate (7·35 g.), m. p. 140—142° raised to m. p. 144—145° on recrystallisation from acetone. The acetone liquors contained more of the above compounds, but it was not possible to isolate them in a pure state.

When ethyl α-n-propylacetoacetate (7·5 g.) was used in place of ethyl α-ethylacetoacetate, the reaction mixture gave in addition to some of the tetrahydroisoquinoline naphthalene-2-sulphonate (2·16 g.), a mixture (13·33 g.), m. p. 81—93°, containing the Mannich base (III; R = Pr^n) naphthalene-2-sulphonate. It was not possible to separate this mixture into its constituents by crystallisation, but a solution in alcohol (80 ml.), treated with concentrated aqueous hydrogen bromide (3 ml.), gave crystals of the Mannich base (III; R = Pr^n) *hydrobromide* (5·39 g.), m. p. 191—192° (effervescence) (Found: C, 56·0; H, 7·45; N, 3·6; Br, 20·2. $C_{18}H_{28}BrNO_3$ requires C, 55·95; H, 7·3; N, 3·65; Br, 20·7%).

Because of the difficulty of resolving the mixtures resulting from the use of ethyl α-ethylacetoacetate and its higher homologues, it was preferable not to isolate the Mannich bases (III; R = Et ⟶ C_5H_{11}) before their conversion into the desired benzo[*a*]quinolizines, but to

oxidise the total reaction base directly with mercuric acetate, as described in paragraph (*b*) below.

Preparation of 2-*Oxobenzo*[a]*quinolizines by Mercuric Acetate Oxidation.*—3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11b*H*-*benzo*[a]*quinolizine* (I; R = Et). (*a*) 1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (100 g.) was treated with methyl n-propyl ketone (555 ml.) and 38·8% w/v aqueous formaldehyde (37·0 ml.) in the manner described above. After removal of unchanged ketone the aqueous solution (1500 ml.) of the resulting mixture of products was treated with glacial acetic acid (200 ml.) and mercuric acetate (277·5 g., 2 mol.) and stirred at 70° for 30 min. The suspension of mercury salts was cooled, saturated with hydrogen sulphide, and filtered (Hyflo), and the aqueous filtrate was concentrated, basified with aqueous potassium hydroxide, and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and evaporated, and a solution of the residual mixture of bases in acetone (500 ml.) was neutralised with a solution of naphthalene-2-sulphonic acid (*ca.* 80 g.) in acetone (200 ml.) and set aside for 2 days. The resulting mixture (58·5 g.) of naphthalene-2-sulphonates was collected and the acetone liquors were concentrated, giving a further 29·8 g. of mixture. The combined solids were refluxed with acetone (2200 ml.) for 30 min. and the hot suspension was filtered, yielding 28·9 g. of the *benzo*[a]*quinolizine* (I; R = Et) *naphthalene*-2-*sulphonate*, m. p. 198—199° (effervescence) unchanged by recrystallisation from alcohol (Found: C, 64·7; H, 6·15; N, 2·8. $C_{27}H_{31}NO_6S$ requires C, 65·2; H, 6·25; N, 2·8%). The free base (I; R = Et) had m. p. 109·5—110·5° (lit.,[3] 109—109·5°). The acetone liquors were evaporated and the residue was crystallised from water (2000 ml.), giving unchanged 1,2,3,4-tetrahydro-6,7-dimethoxy-2-3′-oxohexylisoquinoline naphthalene-2-sulphonate (35·5 g.), m. p. 140—143°. The aqueous liquors were evaporated *in vacuo* and the residual solid was refluxed with acetone (500 ml.), cooled, and filtered to give a further 12·2 g., m. p. 198—199° (effervescence), of the benzo[*a*]quinolizine salt.

(*b*) The chloroform solution of crude Mannich base (III; R = Et), prepared from ethyl α-ethylacetoacetate (345 g.), 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (500 g.), and 38·8% w/v aqueous formaldehyde (168·4 ml.) in the manner described above, was concentrated and treated with water (5 l.) and glacial acetic acid (250 ml.). The resulting aqueous solution of Mannich base was freed from residual chloroform by evaporation *in vacuo*, diluted with water to 7·5 l., treated with glacial acetic acid (875 ml.) and mercuric acetate (1388 g.), stirred at 70—75° for 30 min., cooled, saturated with hydrogen sulphide, filtered (Hyflo), and evaporated *in vacuo*. A stirred solution of the residue in water (9·6 l.) and glacial acetic acid (100 ml.) was brought to pH 11—12 by slow addition of concentrated aqueous potassium hydroxide, with addition of seeds of the benzo[*a*]quinolizine (I; R = Et) when the solution became turbid. The resulting suspension of solid was set aside at 0° for 2 hr. and the sticky solid was collected and washed with water (2 l.), the filtrate and washings being retained ("filtrate A"). A solution of the solid in chloroform (750 ml.) was filtered from sediment, washed with water, dried (Na_2SO_4), and evaporated, and the residue was freed from traces of chloroform by evaporating a solution in alcohol. Crystallisation of the residue from alcohol (500 ml.), with cooling to 0°, gave 211 g. (33·5%), **m. p. 110—112°**, of the benzo[*a*]quinolizine (I; R = Et). The alcoholic liquors were concentrated to *ca.* 400 ml., heated with hydroxylamine hydrochloride (30 g.) on the steam-bath for 10 min., and cooled, yielding 37·4 g. (5%), m. p. 225—226° (effervescence), of the insoluble 2-hydroxyiminobenzo[*a*]quinolizine hydrochloride. "Filtrate A" was extracted with chloroform (2 × 1 l.), and the extract was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residual base in alcohol (1 l.), neutralised with alcoholic hydrogen chloride and kept at 0°, gave 109·5 g. (22%), m. p. 256—258°, of unchanged 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride. From the alcoholic liquors 25·7 g. (3·5%), m. p. 231—232° (effervescence), of the 2-hydroxyiminobenzo[*a*]quinolizine hydrochloride were derived.

The hydroxyiminobenzo[*a*]quinolizine hydrochloride can be converted back into the oxobenzo[*a*]quinolizine (I; R = Et) hydrochloride in high yield by treatment with formaldehyde in aqueous hydrochloric acid at room temperature.

By essentially similar methods the following 1,2,3,4,6,7-hexahydro-9,10-dimethoxy-2-oxo-3-alkyl-11b*H*-benzo[*a*]quinolizines were obtained:

3-n-Propyl- (I; R = Pr^n), m. p. 107—108° (lit.,[4] 102—103°) (Found: C, 71·3; H, 8·1; N, 4·6. Calc. for $C_{18}H_{25}NO_3$: C, 71·25; H, 8·3; N, 4·6%) [*naphthalene*-2-*sulphonate*, m. p. 186—187° (effervescence) (Found: C, 65·85; H, 6·9; N, 2·85; S, 5·75. $C_{28}H_{33}NO_6S$ requires C,

65·7; H, 6·5; N, 2·75; S, 6·25%)], 3-n-butyl- (I; R = Bu^n), m. p. 111—112° (lit.,[4] 114°) [*naphthalene-2-sulphonate*, m. p. 208—209° (effervescence) (Found: C, 66·15; H, 6·7; N, 2·8; S, 6·1. $C_{29}H_{35}NO_6S$ requires C, 66·25; H, 6·7; N, 2·65; S, 6·1%)], and 3-n-pentyl- (I; R = n-C_5H_{11}), m. p. 121—122·5° (lit.,[4] 122°) [*naphthalene-2-sulphonate*, m. p. 200—202° (effervescence) (Found: C, 66·6; H, 6·85; N, 2·6; S, 5·9. $C_{30}H_{37}NO_6S$ requires C, 66·75; H, 6·9; N, 2·6; S, 5·95%)].

1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-3-*methyl*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I; R = Me). A mixture of the Mannich base (III; R = Me) (2 g.), mercuric acetate (4·6 g., 2 mol.), water (30 ml.), and glacial acetic acid (5 ml.) was refluxed for 20 min. Crystals separated from the solution first formed, but these soon gave place to a suspension of mercury. The product was isolated in the manner of (*a*) above, but with chloroform in place of ether-extraction, and the resulting mixture of bases was heated with a little acetone, giving a suspension of crystals. After cooling to 0°, the crystals (0·45 g.), m. p. 188—238°, were collected, digested with a little hot benzene, cooled, and collected again. A solution of the crystals (0·30 g.), m. p. 246—252°, in hot acetone was concentrated, giving colourless crystals, m. p. 255—257°, of 6,7-*dihydro*-9,10-*dimethoxy*-3-*methyl*-2-*oxo*-2H-*benzo*[a]*quinolizine* (VII) (Found: C, 70·75; H, 6·4; N, 5·3. $C_{16}H_{17}NO_3$ requires C, 70·85; H, 6·3; N, 5·15%). The acetone liquors from the above 0·45 g. of crude product were evaporated, the residue was chromatographed (Al_2O_3) in benzene, and the eluted (benzene) base was dissolved in acetone and neutralised with naphthalene-2-sulphonic acid, yielding the *benzo*[a]*quinolizine* (I; R = Me) *naphthalene-2-sulphonate* (0·44 g.), m. p. 202—203° (effervescence) (Found: C, 64·15; H, 6·1; N, 2·9; S, 6·35. $C_{26}H_{29}NO_6S$ requires C, 64·6; H, 6·0; N, 2·9; S, 6·65%). From the liquors the Mannich base (III; R = Me) naphthalene-2-sulphonate (0·14 g.) was obtained. The benzo[*a*]quinolizine base (I; R = Me) had m. p. 137·5—138·5° (lit.,[10] 139°) (Found: C, 70·2; H, 7·6; N, 5·25. Calc. for $C_{16}H_{21}NO_3$: C, 69·8; H, 7·7; N, 5·1%).

When the Mannich base (III; R = Me) (2 g.) was treated with 4 mol. of mercuric acetate in the above manner, no mercury was formed. A solution of the derived crude base in hot petroleum (b. p. 80—100°) (300 ml.) was cooled, filtered from a trace of compound (VII), and evaporated, and, without chromatography, the residue was dissolved in acetone and neutralised with naphthalene-2-sulphonic acid, yielding the benzo[*a*]quinolizine (I; R = Me) naphthalene-2-sulphonate (1·04 g.), m. p. 202—203° (effervescence). The liquors were concentrated and seeded, giving 3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (V) *naphthalene-2-sulphonate* (0·32 g.), m. p. 165—172°. After recrystallisation from alcohol it had the double m. p. 170—171° and 174—175° (Found: C, 63·1; H, 5·35; N, 3·3; S, 7·75. $C_{21}H_{21}NO_5S$ requires C, 63·15; H, 5·3; N, 3·5; S, 8·0%).

1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-2-*oxo*-3-*phenyl*-11bH-*benzo*[a]*quinolizine* (I; R = Ph). The crude Mannich base (III; R = Ph), derived from the product of reaction of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (15 g.) with 1·05 mol. of formaldehyde and 5 mol. of benzyl methyl ketone during 30 min. at 100°, was dissolved in water (270 ml.) containing glacial acetic acid (45 ml.) and heated with mercuric acetate (41·7 g., 2 mol.) at 70—75° for 30 min. The product was isolated in the manner of (*a*) above, but with chloroform in place of ether-extraction, and the resulting crude base was digested with hot alcohol (50 ml.), giving a suspension of crystals. After cooling, the crystals (5·09 g.), m. p. 162—164°, were collected and recrystallised by evaporating a hot solution in chloroform with simultaneous addition of alcohol, giving colourless needles (4·5 g.) of the *benzo*[a]*quinolizine* (I; R = Ph) which lost alcohol at *ca.* 125° and melted at 169—170° (Found: C, 73·05; H, 7·15; N, 3·75; loss on drying, 6·3. $C_{21}H_{23}NO_3,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 73·35; H, 7·2; N, 3·9; loss 6·4%).

1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-1,3-*dimethyl*-2-*oxo*-11bH-*benzo*[a]*quinolizine*. The Mannich base (IV; R = R′ = Me) naphthalene-2-sulphonate (2 g.) was heated with mercuric acetate (5·12 g., 4 mol.), water (35 ml.), and glacial acetic acid (6 ml.) under reflux for 20 min. The derived crude base was purified in the manner described for the benzo[*a*]quinolizine (I; R = Me) (2nd experiment), and yielded a naphthalene-2-sulphonate (0·53 g.), m. p. 150—170°. Recrystallisation from alcohol gave colourless prisms of the pure *benzo*[a]*quinolizine naphthalene-2-sulphonate* (0·3 g.), m. p. 185—187° (effervescence) (Found: C, 65·15; H, 6·3; N, 3·1; S, 6·2. $C_{27}H_{31}NO_6S$ requires C, 65·15; H, 6·3; N, 2·8; S, 6·45%). The *benzo*[a]*quinolizine* base had m. p. 103—104° (Found: C, 70·45; H, 7·9; N, 4·8. $C_{17}H_{23}NO_3$ requires C, 70·55; H, 8·0; N, 4·85%).

[10] Mizukami, *Chem. and Pharm. Bull.*, 1958, **6**, 312.

1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I; R = H). The Mannich base (III; R = H) naphthalene-2-sulphonate (2 g.) was oxidised with 4 mol. of mercuric acetate in the manner of the preceding experiment, and the derived crude base was heated with petroleum (b. p. 60—80°) (100 ml.), and cooled. The petroleum solution was filtered and evaporated, and the residual gum was treated with ether (4 ml.), giving crystals (0·06 g.), m. p. 146—150°, of the benzo[*a*]quinolizine (I; R = H). Recrystallisation from light petroleum (b. p. 60—80°) gave the pure compound, m. p. 152—153° (lit.,[4] 150—151°) (Found: C, 69·1; H, 7·25; N, 5·35. Calc. for $C_{15}H_{19}NO_3$: C, 68·95; H, 7·35; N, 5·35%). From the ethereal liquors 3,4-dihydro-6,7-dimethoxyisoquinoline (V) naphthalene-2-sulphonate (0·3 g.), m. p. 170—171°, was derived.

1,2,3,4,6,7-*Hexahydro*-3-*methyl*-2-*oxo*-11bH-*benzo*[a]*quinolizine*. The Mannich base (III; R = Me; H for MeO) hydrochloride (5 g.) was heated with mercuric acetate (25·2 g., 4 mol.), water (164 ml.), and glacial acetic acid (27 ml.) under reflux for 10 min., and the derived mixture of bases was boiled with petroleum (b. p. 60—80°) (200 ml.) and filtered, the filtrate being retained (" Filtrate A "). The filtered solid was heated with a little acetone, and then cooled, and the resulting crystals (0·26 g.), m. p. 204—222°, were converted in hot acetone into the hydrochloride, m. p. 306—308° (decomp.). A solution of the hydrochloride in hot water was basified with ammonia and cooled to 0°, and the resulting crystals of base were recrystallised from acetone, giving 6,7-*dihydro*-3-*methyl*-2-*oxo*-2H-*benzo*[a]*quinolizine* (VII; H for MeO), m. p. 227—228° (Found: C, 79·4; H, 6·15; N, 6·55. $C_{14}H_{13}NO$ requires C, 79·6; H, 6·2; N, 6·65%), $\lambda_{max.}$ 253, 279 mμ (ε 35,200, 16,200) in 0·1N-aqueous NaOH, and 243, 271, 295 mμ (ε 28,100, 9300, 15,900) in 0·1N-HCl–EtOH. " Filtrate A " was evaporated, and a solution of the residual oil in acetone (20 ml.) was neutralised with naphthalene-2-sulphonic acid and kept at 0°, giving crystals (0·23 g.), m. p. 122—130°, of a naphthalene-2-sulphonate. The derived base gave a hydrochloride, m. p. 256—258°, which is formulated as 3,4,6,7-*tetrahydro*-3-*methyl*-2-*oxo*-2H-*benzo*[a]*quinolizine hydrochloride* (Found: C, 67·2; H, 6·0; N, 5·6; Cl, 14·45. $C_{14}H_{16}ClNO$ requires C, 67·35; H, 6·4; N, 5·6; Cl, 14·25%). This compound had $\lambda_{max.}$ 254, 266, 295, 364 mμ (ε 16,800, 14,000, 7540, 12,100) in 0·1N-aqueous NaOH, and 243, 290, 340 mμ (ε 7080, 15,400, 6080) in 0·1N-HCl–EtOH. The acetone liquors from the above naphthalene-sulphonate were evaporated, and the base recovered from the residue was purified by chromatography on alumina in benzene and conversion, in acetone, into the hydrochloride (0·69 g.), m. p. 248° (effervescence), which gave 1,2,3,4,6,7-*hexahydro*-3-*methyl*-2-*oxo*-11bH-*benzo*[a]*quinolizine*, m. p. 95—96° (Found: C, 77·9; H, 7·85; N, 6·4. $C_{14}H_{17}NO$ requires C, 78·1; H, 7·95; N, 6·5%).

1,2,3,4,6,7-*Hexahydro*-3-*methyl*-9,10-*methylenedioxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine*. The corresponding Mannich base hydrochloride (4 g.) was oxidised with 4 mol. of mercuric acetate, the derived crude base was digested with hot ether (20 ml.), then cooled to 0°, and the resulting crystals (0·7 g.), m. p. 154—158°, were recrystallised from alcohol, giving colourless needles of the *benzo*[a]*quinolizine*, m. p. 157—158° (Found: C, 69·75; H, 6·6; N, 5·45. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%).

3-*Dialkylaminomethylalkan*-2-*ones and their Methiodides*.—The following general procedure was found to give a yield of 3-dimethylaminomethylpentan-2-one superior to that recorded in the literature.[6,11] 3-*Dimethylaminomethylpentan*-2-*one*. Ethyl α-ethylacetoacetate (100 g.) and ice-cold 0·93N-aqueous potassium hydroxide (748 ml.) were shaken together at room temperature for 4½ hr. With stirring, the resulting solution was brought to pH 7 with concentrated hydrochloric acid and treated with anhydrous dimethylamine hydrochloride (52 g.), 38·8% w/v aqueous formaldehyde (49 ml.), and then dropwise, during 1 hr., with concentrated hydrochloric acid (60·3 ml., less that required above). The solution was kept at room temperature overnight, washed with ether (500 ml.), cooled in ice–water, treated with sodium chloride (250 g.) and ether (1 l.), stirred vigorously, and treated with an ice-cold solution of potassium hydroxide (52 g.) in water (100 ml.) during 15 min. The ethereal layer was separated, the aqueous layer was extracted with more ether (1 l.), and the combined ethereal solution was dried (Na_2SO_4) and distilled. The crude product (50·5 g.), b. p. 72—80°/20 mm., was distilled fractionally, yielding 3-dimethylaminomethylpentan-2-one (46·4 g., 51%), b. p. 67—70°/17 mm., n_D^{24} 1·4270. The methiodide had m. p. 146—148°. When the above Mannich reaction was performed at 0°, a poor yield of the product resulted.

In a similar manner the following were obtained: 3-diethylaminomethylpentan-2-one

[11] Mannich and Bauroth, *Ber.*, 1924, **57**, 1108.

(36%), b. p. 87·5—89·5°/17 mm., n_D^{22} 1·4338 (lit.,[12] b. p. 86—87°/15 mm., n_D^{18} 1·4385), and 3-*dimethylaminomethylheptan*-2-*one* (49%), b. p. 90—92°/12·5 mm., n_D^{22} 1·4339 (Found: C, 69·75; H, 11·95; N, 7·8. $C_{10}H_{21}NO$ requires C, 70·1; H, 12·35; N, 8·2%), which, in ethyl acetate, gave a quantitative yield of the *methiodide*, m. p. 141—142° (Found: N, 4·35; I, 40·45. $C_{11}H_{24}INO$ requires N, 4·5; I, 40·5%).

Preparation of 2-*Oxobenzo*[a]*quinolizines from Dihydroisoquinolines.*—3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I; R = Et). (*a*) A solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (265 g.) in alcohol (2650 ml.) was treated with 3-dimethylaminomethylpentan-2-one methiodide (397 g., 1 mol.) and refluxed for 1 hr. The cooled mixture was diluted with water (2200 ml.), the alcohol was evaporated *in vacuo*, the residual aqueous suspension of solid was shaken with chloroform (550 ml.) and an aqueous solution of potassium hydroxide (150 g.), and the mixture was filtered (Hyflo) from a little sediment. The chloroform solution was separated, the aqueous solution was extracted with more chloroform (550 ml.), and the total chloroform extract was washed with water, dried (Na_2SO_4) and evaporated. Traces of chloroform were removed from the residue by evaporation of a solution in hot alcohol, and the resulting sticky crystals were crystallised from alcohol (550 ml.), with cooling to 0°, in two crops (250·8 g., m. p. 110—111°, and 35·8 g., m. p. 109—110°). The combined product was recrystallised from alcohol (500 ml.), yielding colourless needles (273·6 g., 68·4%), m. p. 111—112°, of the benzo[*a*]quinolizine (I; R = Et). The combined alcoholic liquors were refluxed with hydroxylamine hydrochloride (45 g.) for 20 min., and set aside, to give 31·7 g. (6·7%), m. p. 227—228° (effervescence), of the 2-hydroxyiminobenzo[*a*]quinolizine hydrochloride.

(*b*) A solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (10 g.) in alcohol (100 ml.) was treated with 3-dimethylaminomethylpentan-2-one (7·5 g.) and glacial acetic acid (3·46 g.), set aside for 2 hr., and refluxed for 1 hr. The product was isolated and purified in the manner of (*a*) above, yielding 4·2 g. (28%), m. p. 108—110°, of the benzo[*a*]quinolizine (I; R = Et).

3-*n*-*Butyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-2-*oxo*-11bH-*benzo*[a]*quinolizine* (I; R = Bu^n). A solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (20 g.) in alcohol (200 ml.) was refluxed with 3-dimethylaminomethylheptan-2-one methiodide (32·8 g.) for 1 hr., and the product was isolated in the manner of (*a*) preceding. A solution of the resulting crude base in hot petroleum (b. p. 60—80°) (750 ml.) was filtered from resin and evaporated; the residual solid crystallised from alcohol (*ca.* 40 ml.) as plates (21·2 g., 64%), m. p. 112—113°, of the benzo[*a*]quinolizine (I; R = Bu^n).

3-*Ethyl*-1,2,3,4,6,7-*hexahydro*-2-*oxo*-11bH-*benzo*[a]*quinolizine*. A solution of 3,4-dihydroisoquinoline (10 g.) in alcohol (100 ml.) was refluxed with 3-dimethylaminomethylpentan-2-one methiodide (21·8 g.) for 1¼ hr., and the product was isolated and purified in the manner of the preceding experiment, giving the *benzo*[a]*quinolizine* (7·6 g., 44%), m. p. 99—100·5° (Found: C, 78·5; H, 8·1; N, 5·8. $C_{15}H_{19}NO$ requires C, 78·55; H, 8·35; N, 6·1%). From the liquors, 2-hydroxyiminobenzo[*a*]quinolizine hydrochloride (0·52 g.), m. p. 230—231° (effervescence), was derived by treatment with hydroxylamine hydrochloride.

Reaction of 3,4-*Dihydro*-6,7-*dimethoxyisoquinoline* (V) *with Formaldehyde and Ketones.*—The general method of reaction is exemplified by the following experiment; the results are summarised in Table 2.

TABLE 2.

Reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline with formaldehyde and ketones.

R in Product (IX)	Yield (%)	M. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Pr^n	26	217—219°	70·0	7·25	5·65	$C_{26}H_{36}N_2O_5$ *	69·95	7·55	5·85
Me	35	224—226	69·1	7·3	5·95	$C_{26}H_{32}N_2O_5$	69·0	7·15	6·2
Ph	76	210—211	72·4	6·6	5·2	$C_{31}H_{34}N_2O_5$	72·35	6·65	5·45
Bu^t	10	247—248	70·1	7·55	5·75	$C_{29}H_{38}N_2O_5$	70·4	7·75	5·65

* *M*, Found (ebull.): 536. Reqd., 480.

3,4-Dihydro-6,7-dimethoxyisoquinoline (10 g.), paraformaldehyde (1·6 g., 1 mol.), methyl n-propyl ketone (5·6 ml., 1 mol.), and ethanol (10 ml.) were heated together in a sealed tube at 100° for 1½ hr., with cooling at intervals of 30 min. The crystals which resulted after 1 hr. did

[12] Heilmann, de Gaudemaris, and Arnaud, *Compt. rend.*, 1952, **234**, 1177.

not dissolve on further heating. The suspension of crystals was diluted with alcohol (50 ml.), set aside for 1 hr., and filtered, yielding 3·3 g. of 16-*butyroyl*-5,6,10,11,16,16*a*-*hexahydro*-2,3,13,14-*tetramethoxy*-8H,15bH-*pyrimido*[6,1-a : 4,3-a']*di-isoquinoline* (IX; R = Pr^n), m. p. 217—219° unchanged by recrystallisation from alcohol. The alcoholic filtrate was concentrated, neutralised with glacial acetic acid, boiled with hydroxylamine hydrochloride, and set aside to give crystals, m. p. 252—253°, of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride. Seeding the liquors with the oxime hydrochloride of the benzo[*a*]quinolizine (I; R = Et) failed to give any of that product. The yield of the polycyclic compound (IX; R = Pr^n) was reduced when ethanol was omitted from the above reaction.

Reaction of 1,3-*Bis*-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*acetone* (XIV) *with Formaldehyde.*—The *meso*-compound [9] (XIV) (0·5 g.) was heated with paraformaldehyde (0·068 g.) in ethanol (2 ml.) in a sealed tube at 100° for 1 hr. After cooling, the resulting crystals (0·3 g.), m. p. 206—211°, were collected and twice recrystallised from alcohol, giving colourless plates of 2,2'-*spirobi*-(1,2,7,11b-*tetrahydro*-9,10-*dimethoxy*-4H,6H-[1,3]-*oxazino*[4,3-a]*isoquinoline*) (XV), m.p. 221—222·5° (Found: C, 67·15; H, 6·85; N, 5·75. $C_{27}H_{34}N_2O_6$ requires C, 67·2; H, 7·1; N, 5·8%). This product showed no infrared carbonyl absorption. An identical product (m. p., infrared spectrum) was obtained from similar treatment of the racemic [9] compound (XIV).

1,2,3,4-*Tetrahydro*-2-(2-*methyl*-3-*oxobutyl*)-β-*carboline* (XVI; R = Me).—1,2,3,4-Tetrahydro-β-carboline [13] hydrochloride (10·45 g.), ethyl methyl ketone (54·5 ml.), and 38·8% w/v aqueous formaldehyde (4·08 ml.) were heated together in a sealed tube at 100°, with occasional shaking, for 12 min. As the resulting solution cooled, crystallisation took place. After 24 hr. at room temperature, the crystals (6·05 g.), which darkened at *ca.* 200° with evolution of 3-methylenebutan-2-one and then decomposed at 280°, were collected and dissolved in water (450 ml.). The aqueous solution was stirred with ether (25 ml.) and gradually basified with an excess of concentrated aqueous ammonia, the ether was removed in a current of nitrogen, and the resulting aqueous suspension of crystals was filtered, yielding the Mannich *base* (XVI; R = Me) (5·05 g.), m. p. 111—113° (Found: C, 74·95; H, 7·55; N, 10·95. $C_{16}H_{20}N_2O$ requires C, 74·95; H, 7·85; N, 10·95%).

1,2,3,4,6,7,12,12b-*Octahydro*-3-*methyl*-2-*oxoindolo*[2,3-a]*quinolizine* (XVII; R = Me).—The foregoing base (XVI; R = Me) (11·77 g.) was heated with mercuric acetate (43·9 g., 3 mol.), water (283 ml.), and glacial acetic acid (47 ml.) under reflux for 10 min. The resulting suspension of mercury was saturated with hydrogen sulphide at 90°, cooled, filtered (Hyflo), concentrated, basified with potassium hydroxide, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residual crude base was heated with ether (800 ml.) and cooled, and the ethereal solution was decanted from crude 1,2,3,4-tetrahydro-β-carboline (3·4 g.) and poured through a column of activated alumina, the column being eluted with ether and then with chloroform. The ethereal eluate was evaporated and the residual solid was converted in acetone (30 ml.) into a naphthalene-2-sulphonate (1·07 g.), m. p. 240° (effervescence), which was boiled with alcohol (20 ml.), cooled, and collected again, yielding 0·84 g., m. p. 242—243° (effervescence), of the indolo[2,3-*a*]quinolizine (XVII; R = Me) naphthalene-2-sulphonate. The derived base, m. p. 205—207°, crystallised from alcohol giving colourless plates, m. p. 208—209° (lit.,[14] 209—211°) of the indolo[2,3-*a*]quinolizine (XVII; R = Me) (Found: C, 75·55; H, 7·1; N, 10·65. Calc. for $C_{16}H_{18}N_2O$: C, 75·55; H, 7·15; N, 11·0%), $\nu_{max.}$ 1703 and 1724 $cm.^{-1}$ (C=O). The above chloroform eluate was evaporated and from the residual gum some crude β-carboline (0·18 g.), m. p. 192—195°, was derived. Crystallisation from water gave colourless needles of β-carboline, m. p. and mixed m. p. 199—200° (Found: C, 79·05; H, 4·95; N, 16·65. Calc. for $C_{11}H_8N_2$: C, 78·55; H, 4·8; N, 16·65%).

2-(2-*Ethyl*-3-*oxobutyl*)-1,2,3,4-*tetrahydro*-β-*carboline* (XVI; R = Et).—The crude base derived from 1,2,3,4-tetrahydro-β-carboline hydrochloride (40 g.) and equimolecular quantities of α-ethylacetoacetic acid and formaldehyde in the usual manner, was heated with ether (500 ml.) and set aside at room temperature overnight, giving the Mannich *base* (XVI; R = Et) (14·7 g.), m. p. 130—135°, raised to 135—137° by recrystallisation from alcohol (Found: C, 75·1; H, 8·0; N, 10·05. $C_{17}H_{22}N_2O$ requires C, 75·5; H, 8·2; N, 10·35%), $\nu_{max.}$ 1694w and 1706 $cm.^{-1}$ (C=O). The ethereal liquors were evaporated, and a solution of the residue in acetone (*ca.* 400 ml.) was neutralised with naphthalene-2-sulphonic acid, yielding 1,2,3,4-tetrahydro-β-carboline naphthalene-2-sulphonate (14·2 g.), m. p. 286—288° (decomp.). Concentration of the acetone liquors

[13] Abramovitch and Shapiro, *J.*, 1956, 4589.
[14] Philpott, B.P. 840,267.

gave crystals (15·2 g.) of the Mannich base (XVI; R = Et) naphthalene-2-sulphonate, m. p. 186—190° (effervescence), from which a further 6·9 g., m. p. 134—136°, of the base (XVI; R = Et) was obtained.

3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-2-oxoindolo[2,3-a]quinolizine (XVII; R = Et).—(*a*) *From base* (XVI; R = Et). The base (XVI; R = Et) (6 g.) was heated with mercuric acetate (21·24 g., 3 mol.), water (138 ml.), and glacial acetic acid (23 ml.) under reflux for 15 min. and the product was isolated in the manner described above for the methyl analogue. The resulting crude base was heated with acetone (20 ml.) and cooled, giving impure 1,2,3,4-tetrahydro-β-carboline (1·25 g.), m. p. 188—198°. The acetone liquors were evaporated and the residual mixture of bases was resolved by fractional elution from activated alumina with ether, and conversion of the resulting bases in acetone into the naphthalene-2-sulphonates. In this way the following were obtained: (1) The crude indolo[2,3-*a*]quinolizine (XVII; R = Et) naphthalene-2-sulphonate (1·41 g.), m. p. 238° (effervescence), which was heated with alcohol (20 ml.), cooled, collected, and converted into the base (0·53 g.), m. p. 197—201°. Crystallisation from alcohol afforded colourless needles (0·44 g.) of the *indolo[2,3-a]quinolizine* (XVII; R = Et), m. p. 206—207° (Found: C, 76·05; H, 7·45; N, 10·45. $C_{17}H_{20}N_2O$ requires C, 76·1; H, 7·5; N, 10·45%), $\nu_{max.}$ 1706 cm.$^{-1}$ (C=O). (2) Some Mannich base (XVI; R = Et) naphthalene-2-sulphonate (0·28 g.), m. p. 191° (effervescence). (3) β-Carboline naphthalene-2-sulphonate (0·41 g.), m. p. 182—184°, which yielded β-carboline base, m. p. 200—201°.

When the base (XVI; R = Et) (7·2 g.) was oxidised with 3·5 mol. of mercuric acetate (29·8 g.) in the above manner, and the derived crude base was heated with acetone (30 ml.) and cooled, crystals (0·52 g.) of m. p. *ca.* 280° were obtained. This product was converted, in alcohol, into the hydrochloride, m. p. 320—324°, and then back to the base which was crystallised from alcohol, giving pale yellow crystals of *3-ethyl-2,6,7,12-tetrahydro-2-oxoindolo[2,3-a]quinolizine* (XVIII), m. p. >350° (Found: C, 76·75; H, 6·25; N, 10·5. $C_{17}H_{16}N_2O$ requires C, 77·25; H, 6·1; N, 10·6%), $\nu_{max.}$ 1646 cm.$^{-1}$ (C=O, modified). From the acetone liquors the indolo[2,3-*a*]quinolizine (XVII; R = Et) and β-carboline were also obtained.

(*b*) *From 3,4-dihydro-β-carboline.* A solution of 3,4-dihydro-β-carboline [15] (1 g.) in alcohol (12 ml.) was heated with 3-dimethylaminomethylpentan-2-one methiodide (1·68 g., 1 mol.) under reflux for 2 hr. The resulting suspension of crystals was diluted with water, the alcohol was evaporated *in vacuo*, the residue was shaken with chloroform and aqueous potassium hydroxide, and the mixture was filtered. The chloroform solution of product was washed with water, dried (Na_2SO_4), and evaporated. The residue was freed from traces of chloroform by distillation with petroleum (b. p. 60—80°) and extracted with hot benzene (50 ml.). The benzene solution was filtered from amorphous material and evaporated. The residual crystalline base recrystallised from alcohol; the resulting pale yellow-brown plates (0·43 g.), m. p. 200—202°, on further recrystallisation from alcohol gave colourless flat needles (0·29 g., 18%) of the indolo[2,3-*a*]quinolizine (XVII; R = Et), m. p. 205—206°, undepressed by the product of (*a*) above.

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[15] Schöpf and Steuer, *Annalen*, 1947, **558**, 124.