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THE PREPARATION OF SOME BENZO[*a*]QUINOLIZINES, DIBENZO[*a,h*]QUINOLIZINES AND DIBENZO[*a,f*]QUINOLIZINES

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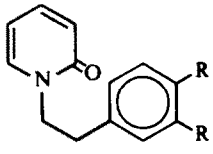
Abstract—Some further clarifications and corrections to the literature concerning the reactions between $POCl_3$ and certain heterocyclic amides are presented.

IN A previous paper[1] we confirmed earlier reports[2] that 1-β-arylethyl-2-pyridones (**1**) are not cyclized by $POCl_3$ to benzo[*a*]quinolizines (**2**) as originally reported by Sugasawa *et al.*,[3] and we also found that the reaction of 2-β-arylethylisocarbostyrils (**3**) with $POCl_3$ leads to the 1-chloro-2-β-arylethylisoquinolinium salts and not to the dibenzo[*a,h*]quinolizine structures (**4**).



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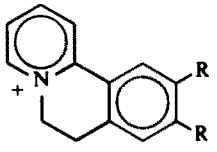

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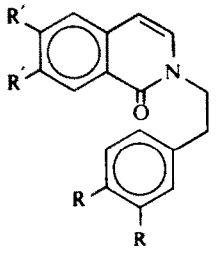

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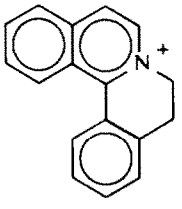

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It was with some interest that we learned of the claim[4] that during the formation of the 3,4-dihydroisoquinolinium salts **5**, (R = OMe, R′ = H and R = R′ = OMe) from the 3,4-dihydroisoquinolines and β-3,4-dimethoxyphenethyl bromide, small amounts of **6** (R = OMe, R′ = H and R = R′ = OMe) respectively were formed, particularly when the structural proof rested upon a comparison of the basic material with that obtained by Sugasawa and Kakemi.[5] Repetition[6] of the reactions as described[4] confirmed our suspicions that the basic products are not the dibenzo[*a,h*]-quinolizine products (**6**), but the tetrahydroisoquinolines **7**, (R = OMe, R′ = H and

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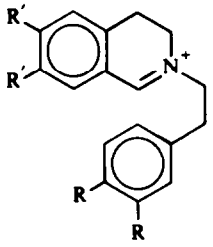
R = R′ = OMe) respectively, formed, presumably by disproportionation of the salts **5**. The fully aromatic compounds **8** (R = OMe, R′ = H and R = R′ = OMe) were also isolated.



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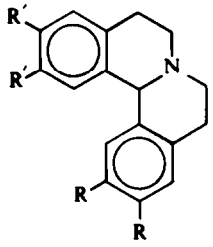

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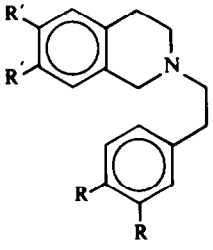

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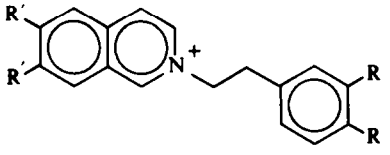

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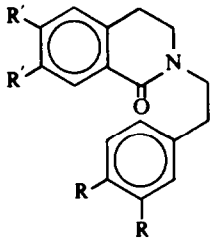

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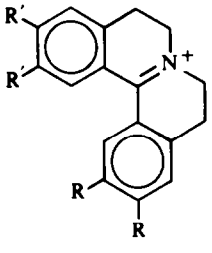

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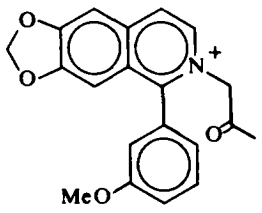
It has been reported[5] that oxidation of **5** (R = R′ = OMe) yields the dihydroisocarbostyril **9**, (R = R′ = OMe) which, with $POCl_3$ is cyclized to **10** (R = R′ = OMe), but we were able to show[1] that **9** (R = R′ = OMe) is not formed under the conditions used[5] and that the "cyclization" product is simply the tetrahydroisoquinoline **7**, (R = R′ = OMe). We have now[6] found that the dihydroisocarbostyril **9**, (R = R′ = OMe) can be prepared by the hydrogenation of the corresponding isocarbostyril **3**, (R = R′ = OMe). When **9** (R = R′ = OMe) is treated with $POCl_3$ under the usual conditions, a quaternary salt, characterized as the iodide, m.p. 222° is produced in 34% yield. The structure **10** (R = R′ = OMe) follows from analytical and spectral data. The NMR spectrum (measured in CD_3SOCD_3 soln) is, due to the symmetry of the molecule about the $>C=N^+<$ grouping, particularly simple; two singlets at 3·8 and 4·0 δ are attributed to the four OMe groups, whilst the aromatic protons resonate as two two-hydrogen singlets at 7·3 and 7·34 δ. When **10** (R = R′ = OMe)

was reduced with $NaBH_4$, 2,3,11,12-tetramethoxy-5,6,8,9-tetrahydro-13 H-dibenzo-[a,h]quinolizine (**6**, R = R′ = OMe) was formed. The entire sequence of reactions was repeated with **3** (R = OMe, R′ = H), leading ultimately to **6** (R = OMe, R′ = H) in good overall yield. The parent dihydroisocarbostyril (**9**, R = R′ = H) could not be cyclized with $POCl_3$, thus confirming an earlier observation of Perkin,[7] who prepared **9** (R = R′ = H) by the electrolytic reduction of N-β-phenethylhomophthalimide.

Remarkably few syntheses of the dibenzo[a,h]quinolizine skeleton have appeared in the literature, although Bradsher *et al.*[8] have developed a successful route from 1-arylisoquinolines such as **11**.



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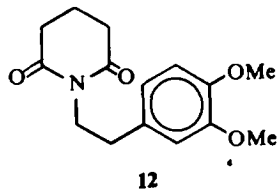

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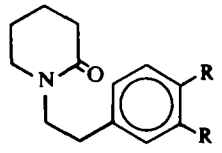

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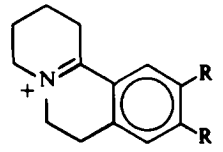

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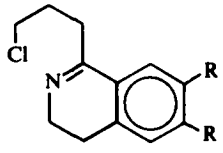

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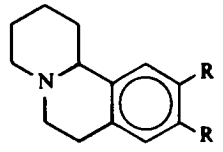

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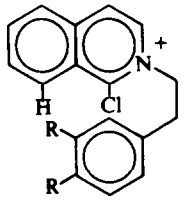
In 1939 Sugasawa *et al.*[9] reported that the N-β-arylethylpiperidone **13**, (R = OMe), obtained from the lactam **12**, is cyclized by $POCl_3$ to the benzo[a]quinolizine derivative **14** (R = OMe). The same product had previously[10] been prepared from **15** (R = OMe). Both groups of workers reduced their quaternary salts **14** to a base **16** (R = OMe), but there is some discrepancy in the descriptions of this material. We have now prepared **13** (R = OMe) by catalytic hydrogenation of the pyridone **1** (R = OMe), and have reacted it with $POCl_3$, thus obtaining a quaternary salt, isolated as the iodide, m.p. 206–207° (60% yield). Analytical and spectral data confirm that a cyclization to **14** (R = OMe) had occurred. Reduction of this product with $NaBH_4$ gave a gum the hydrochloride, picrate and methiodide of which closely resemble the salts described by Childs and Pyman[10] for their sample of **16** (R = OMe). We have repeated the entire reaction sequence from **1** (R,R = CH_2O_2), and **16** (R,R = CH_2O_2) has been obtained in good yield. As expected, the parent piperidone **13**, (R = H) was not cyclized by $POCl_3$, but when it was treated with PPA a small

amount of a quaternary salt was isolated which, when reduced with $NaBH_4$, yielded a base **16** (R = H) identical with that obtained from **15** (R = H).

There are numerous cyclization reactions of amides reported in the literature, especially by the Japanese workers and we chose to re-examine the quinoline series. It has been shown[11] that, although the reactivities of 1-chloroisoquinolinium salts and 2-chloroquinolinium salts towards nucleophiles are about the same, each is much more susceptible than 2-chloropyridinium ions to such reagents. However, it is possible that with ions such as **17** there is some steric repulsion to the approach of the bulky aromatic ring, but this should be absent in the quinolinium salt **18**.

The previously reported[12] reaction between the carbostyril **19** (R = H) and $POCl_3$ was repeated under the original conditions and a quaternary iodide was isolated, m.p. 180–181° (dec). Akahoshi reports m.p. 185–186°. Elemental analysis of our sample indicated the presence of both chlorine and iodine, but a better analytical derivative was obtained when ethanolic $HClO_4$ was added to an ethanol solution of the iodide. The product was identified as **20** (R = H, R′ = OEt, $X = ClO^{4-}$) by elemental and spectral analysis. Clearly the iodide m.p. 180–181° is **20** R = H, R′ = Cl, $X = I^{\ominus}$ and not the ring-closed material **21** (R = R′ = H) as claimed by Akahoshi. Further evidence for structure **20** was secured by showing that the product obtained from it by hydrogenation is identical with **22** (R = H) obtained by the hydrogenation of **18** (R = H).

When **19** (R,R = CH_2O_2) was similarly reacted with $POCl_3$ a quaternary iodide m.p. 187–189° was obtained, together with large proportions of **19** (R,R = CH_2O_2). Our analytical data are compatible with structure **20** (R,R = CH_2O_2, R′ = Cl, X = I) rather than the dibenzo[*af*]quinolizine **21**,(R,R = CH_2O_2, R′ = H) claimed by the Japanese workers. However, a second compound, m.p. 296–298° (d) was isolated from the reaction mixture by us to which we allocate the structure **21** (R,R = CH_2O_2, R′ = H), once again from the spectral data. The peak at highest *m/e* ratio in the mass spectrum of the compound corresponds to an ion of structure **23**; dehydrogenation of **21** (R,R = CH_2O_2, R′ = H) under these conditions is not surprising. Reduction of **21** (R,R = CH_2O_2, R′ = H) gave a base **24**, m.p. 128°, which was shown NOT to be identical with **22** (R,R = CH_2O_2) obtained by the reduction of **18** (R,R = CH_2O_2).



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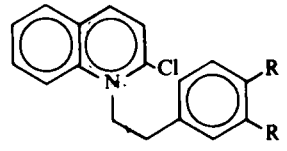

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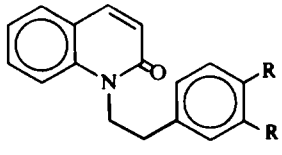

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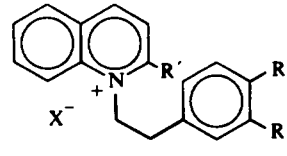

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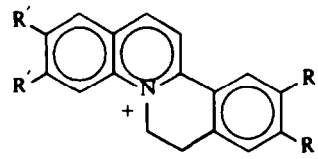
TABLE 1

Compound	m.p.	Mol. formula	% Yield	Analysis % Found C	H	N	Br	I	% Required C	H	N	Br	I
A	143–144°	$C_{13}H_{14}BrN$	85	59·2	5·5	5·2	30·1	—	59·1	5·3	5·3	30·25	—
B	194–196°	$C_{15}H_{18}BrNO_2$	70	55·35	5·7	4·2	24·9	—	55·6	5·6	4·3	24·65	—
C	227–228°	$C_{14}H_{14}BrNO_2$	68	54·4	4·5	4·5	26·0	—	54·6	4·6	4·5	25·9	—
1, R = H	103–105°	$C_{13}H_{13}NO$	75	78·6	6·8	6·8	—	—	78·3	6·6	7·0	—	—
1, R = OCH_3	78–79°	$C_{15}H_{17}NO_3$	60	69·55	6·75	5·7	—	—	69·5	6·6	5·4	—	—
1, RR = —OCH_2O—	145–147°[c]	$C_{14}H_{13}NO_3$	65	69·3	5·5	5·7	—	—	69·1	5·4	5·8	—	—
13, R = H	39–42°[c]	$C_{13}H_{17}NO$	95	76·7	8·6	6·8	—	—	76·8	8·4	6·9	—	—
13, R = OCH_3		$C_{15}H_{21}NO_3$	90	68·5	7·9	5·5	—	—	68·4	8·0	5·3	—	—
13, RR = —OCH_2O—	93–96°[c]	$C_{14}H_{17}NO_3$	95	68·2	6·9	5·7	—	—	68·0	6·9	5·7	—	—
14, R = H	173–174°[c]	$C_{13}H_{16}IN$	17	49·4	5·1	4·7	—	40·2	49·8	5·15	4·5	—	40·5
14, R = OCH_3	206–207°[c]	$C_{15}H_{20}INO_2$	56	47·3	5·3	3·4	—	33·2	47·4	5·9	3·45	—	33·3
14, RR = —OCH_2O—	216–220°[c]	$C_{14}H_{16}INO_2$	15	46·4	4·2	3·7	—	36·1	47·1	4·5	3·9	—	35·5
16, R = H	241–243°[c]	$C_{13}H_{17}N.HCl$	70	69·8	8·0	6·7	15·8	(Cl)	69·8	8·1	6·3	15·8	(Cl)
16, R = OCH_3	243–244°[c]	$C_{15}H_{21}NO_2.CH_3I$	55	49·6	6·25	3·4	—	32·9	49·6	6·2	3·6	—	32·6
16, R = OCH_3	232–233°	$C_{15}H_{21}NO_2.HCl$	68	63·3	7·7	4·9	12·8	(Cl)	63·5	7·8	4·9	12·5	(Cl)



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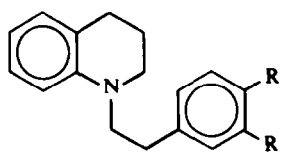

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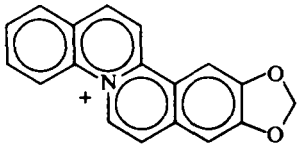

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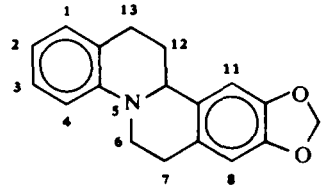

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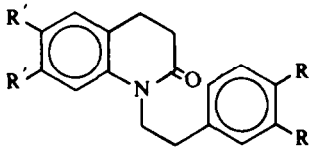

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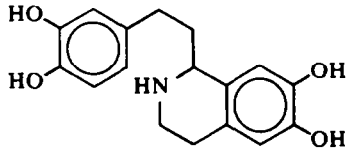

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The dihydroquinolone (**25**, RR = CH_2O_2, R′ = H), when reacted with $POCl_3$, gave the same product **21** (RR = CH_2O_2, R′ = H) as that obtained from **19** (RR = CH_2O_2). Sugasawa *et al.*[13] had previously shown that the product obtained from **25** (R = R′ = OMe) and $POCl_3$ was **21**, (R = R′ = OMe), this latter structure is secure by its alternative synthesis[14] from **26** via phenolic coupling and methylation.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH soln; IR spectra were measured as nujol mulls and chemical shifts are expressed in ppm downfield from TMS as an internal standard.

The reaction between 3,4-dihydroisoquinoline and β-(3,4-dimethoxyphenyl)ethyl bromide

The isoquinoline (1·8 g) and the bromide (1·8 g) were heated together for ¾ hr at 145°. The reaction mixture was triturated with hot benzene (2 × 25 ml) and the decanted benzene soln extracted with dil HCl. The acidic extract was made alkaline with 10% NaOH aq and the liberated base obtained as a brown oil by extraction with ether and evaporation of the dried extracts. The hydrochloride of the base was obtained by passing HCl gas through a soln of the base in ether. Recrystallization of the white solid so obtained yielded 2-β-(3,4-*dimethoxyphenyl)ethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride* (**7**, R′ = H, R = OMe) (0·45 g, 18%) as colourless prisms m.p. 218–219° (Lit[4] m.p. 212–214°) (Found: C, 68·35; H, 7·2; N, 4·3. $C_{19}H_{24}ClNO_2$ requires: C, 68·4; H, 7·2; N, 4·2%) [This material is identical in all respects with an authentic sample prepared by reduction of **5**, (R = H, R′ = OCH_3) with sodium borohydride.]

The residual solid after trituration was dissolved in hot water (40 ml) and the mixture filtered through Kieselguhr. The soln was made just alkaline (pH 8) with $NaHCO_3$ aq and treated with a slight excess of 10% NaCN aq to precipitate the 3,4-dihydroisoquinoline as its pseudocyanide. The solid was filtered and to the filtrate was added a few drops of 60% $HClO_4$ when a small amount of a yellow oil separated. Treatment of the oil with acetone produced a yellow solid which was crystallized from EtOH to give 2-β-(3,4-*dimethoxyphenyl)ethyl-isoquinolinium* (**8**, R′ = H, R = OMe) perchlorate (70 mg) as yellow needles m.p. 213–214. This material is identical in all respects with an authentic sample prepared by treating **8** as its bromide salt in EtOH with 60% $HClO_4$.

The reaction between 6,7-*dimethoxy*-3,4-*dihydroisoquinoline and* β-(3,4-*dimethoxyphenyl*)*ethyl bromide*

A similar procedure to the above using the isoquinoline (4·1 g), the bromide (4·7 g) and a 50% $CHCl_3$: benzene soln as triturant yielded 2β-(3,4-*dimethoxyphenyl*)*ethyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline hydrochloride* (**7**, R′ = R = OCH_3) as white needles (0·3 g) m.p.[1] 233–234 also isolated from the reaction was 2-β-(3,4-dimethoxyphenyl)ethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide, m.p. 199–201° and a small quantity of the fully aromatic isoquinolinium iodide, m.p. 183–184°. Both of these compounds were compared with authentic specimens, with which they were found to be identical.

Preparation of the dibenzo[a,h]*quinolizinium salts*

2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-3,4-*dihydroisocarbostyril* (**9**, R′ = H, R = OCH_3) was prepared by treatment of the corresponding isocarbostyril **3**, (2·2 g) in MeOH (100 ml) with Raney Ni (0·25 g) and H_2 (1350 lbs/sq in) at 150° for 2 hr. Evaporation of the filtered (Kieselguhr) reaction mixture yielded a solid which on recrystallization from EtOH gave **9** (R′ = H, R = OCH_3) as long colourless needles (2·2 g), m.p. 109–110°; λ_{max} (ε)nm, 231 (13,900, 281 (4,400); ν_{max} cm^{-1}, 1637, 1613, 1602; NMR ($CDCl_3$) ppm, 2·7–3·0 (4H, m) and 3·2–3·9 (4H, m), (methylenic protons); 3·8 (6H, s), (2x-OCH_3); 6·8 (3H, s), (C_6H_3≡); 7·1–7·45 (3H, m), (—C_5H, —C_6H, —C_7H;; 8·1 (1H, q), (—C_8H). (Found: C, 73·3; H, 6·5; N, 4·3 $C_{19}H_{21}NO_3$ requires: C, 73·3; H, 6·8; N, 4·5%).

Similarly prepared were

(a) 2-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6,7-*dimethoxy*-3,4-*dihydroisocarbostyril* (**9**, R′ = R = OCH_3) as colourless needles (96%), m.p. 128–129° from EtOH/pet. ether (60–80°); λ_{max} (ε)nm, 273 (8,500), 299 (6,800). ν_{max} cm^{-1}, 1644, 1600, 1589; NMR ($CDCl_3$) ppm, 2·4–3·1 (6H, m) and 3·4 (2H, m), (methylenic protons); 3·85 (6H, s) and 3·90 (3H, s) and 3·95 (3H, s), (4x —O CH_3); 6·6 (1H, s), (—C_5H); 6·8 (3H, s), (C_6H_3≡); 7·66 (1H, s), (—C_8H). (Found: C, 67·7; H, 7·2; N, 3·75. $C_{21}H_{25}NO_5$ requires: C, 67·9; H, 6·8; N, 3·8%).

(b) 2-β-*Phenylethyl*-3,4-*dihydroisocarbostyril* (**9**, R′ = R = H) as colourless prisms (98%) from EtOH/light petroleum (60–80°) m.p. 76–77° (Lit.[7] m.p. 77–78°); λ_{max} (ε)nm, 230 (15,000), 252 (11,200), 264 sh (8,800), 279 sh (4,100); NMR ($CDCl_3$) ppm, 2·80 (2H, t, J = 6·0 Hz) and 2·92 (2H, t, J = 7·5 Hz), (2x $ArCH_2$—); 3·32 (2H, t, J = 6·0 Hz) and 3·77 (2H, t, J = 7·5 Hz), (2x—CH_2N=); 7·1–7·4 (3H, m), (—C_5H, —C_6H and —C_7H); 7·26 (5H, s), (C_6H_5—); 8·1 (1H, m), (—C_8H). (Found: C, 81·0; H, 6·9; N, 5·6. Calc. for $C_{17}H_{17}NO$: C, 81·2; H, 6·8; N, 5·6%).

2,3-*Dimethoxy*-5,6,8,9-*tetrahydrodibenzo*[a,h]*quinozinium iodide* (**10**, R′ = H, R = OCH_3) was obtained by heating on an oil bath, at 130°, for 2½ hr, a mixture of **9** (R′ = H, R = OCH_3), (1·1 g) and $POCl_3$ (7 ml). The cooled mixture was shaken with successive portions (15 ml) of light petroleum (60–80°), the residue dissolved in water, the soln extracted with benzene (15 ml) and filtered (Kieselguhr). Addition of aqueous KI precipitated a pure yellow solid (1·25 g). Recrystallization from EtOH yielded the quaternary iodide m.p. 215–216° as yellow prisms; λ_{max} (ε)nm, 268 (13,700), 298 (11,800), 317 (11,300), 388 (8,300); ν_{max} cm^{-1}, 1619, 1600, 1557, 1517; NMR (DMSO.D_6) ppm, 3·0–3·4 (4H, m), ($ArCH_2$—); 3·5–4·3 (4H, m), (2x—$CH_2\overset{+}{N}$≡); 3·8 (3H, s), (—OCH_3); 4·0 (3H, s), (—OCH_3); 7·17 (1H, s), (—C_4H); 7·33 (1H, s), (—C_1H); 7·7 (4H, m), (—$C_{10}H$, —$C_{11}H$, —$C_{12}H$, —$C_{13}H$). (Found: C, 54·0; H, 4·7; N, 3·5; I, 30·2. $C_{19}H_{20}NO_2I$ requires: C, 54·2; H, 4·8; N, 3·3; I, 30·1%).

2,3,11,12-*Tetramethoxy*-5,6,8,9-*tetrahydrodibenzo*[a,h]*quinolizinium iodide* (**10**, R′ = R = OCH_3) was similarly prepared from the corresponding amide (1·7 g) as yellow rosettes (0·75 g) from MeOH m.p. 221–222°; ν_{max} cm^{-1}, 1604, 1568, 1552, 1524. NMR (DMSO.D_6), 3·0–3·5 (4H, m) (2x $ArCH_2$—); 3·8–4·2 (4H, m); (2x —CH_2N≡); 3·83 (6H, s), (2x —OCH_3); 4·0 (6H, s), (2x —OCH_3); 7·28 (2H, s), (—C_4H, —$C_{10}H$); 7·34 (2H, s), (—C_1H, —$C_{13}H$). (Found: C, 52·1; H, 5·5; N, 2·8; I, 25·8. $C_{21}H_{24}INO_4$ requires: C, 52·4; H, 5·0; N, 2·9; I, 26·4%).

The parent compound **10** (R′ = R = H) could not be prepared by this procedure. Reduction of the salts **10** under normal conditions with sodium borohydride yielded:

(a) 2,3-*Dimethoxy*-5,6,8,9-*tetrahydro*-13bH-*dibenzo*[a,h]*quinolizine* (**6**, R′ = H, R = OCH_3) as a white solid (93·5%) m.p. 126–127° which was characterized as its hydrochloride (ppted from a soln of the base in dry ether by anhyd HCl) m.p. 227–228° from EtOH as small colourless needles; ν_{max} cm^{-1}, 2300, 1610, 1515; NMR ($CDCl_3$) ppm, 1·9 (4H, m) (2x $ArCH_2$—), 3·0–3·5 (5H, m), (=NH and 2x —CH_2N≡); 3·79 (3H, s) and 3·81 (3H, s), (2x —OCH_3), 5·53 (1H, s), (13b —H); 6·67 (1H, s), (—C_4H), 6·77 (1H, s), (—C_1H); 7·2–7·5 (4H, m), (—$C_{10}H$, —$C_{11}H$, —$C_{12}H$, —$C_{13}H$). (Found: C, 68·6; H, 6·7; N, 4·3; Cl, 11·0. $C_{19}H_{22}ClNO_2$ requires: C, 68·75; H, 6·7; N, 4·2; Cl, 10·7%). The methiodide was obtained as small yellow needles from acetone m.p. 242–243°. (Found: C, 54·7; H, 5·5; N, 3·0; I, 29·3. $C_{20}H_{24}INO_2$ requires: C, 54·9; H, 5·5; N, 3·2; I, 29·0%).

(b) 2,3,11,12-*Tetramethoxy*-5,6,8,9-*tetrahydro*-13bH-*dibenzo*[a,h]*quinolizine* (**6**, R' = R = OCH_3) as white crystals (95%) m.p. 161–162°. The hydrochloride gave colourless prisms from EtOH m.p. 225–226°; ν_{max} cm^{-1} 2500, 2350, 1609, 1511; NMR ($CDCl_3$) ppm, 2·8–3·8 (8H, m), 3·78 (6H, s, 2x $OC\underline{H}_3$); 3·89 (6H, s), (2x $OC\underline{H}_3$): 5·54 (1H, s), (—C(—H)—); 6·72 (2H, s), (C_4H and $C_{10}H$); 6·77 (2H, s), (—C_1H, —$C_{13}H$). (Found: C, 64·2; H, 6·2; N, 3·6; Cl, 9·1. $C_{21}H_{26}ClNO_4$ requires: C, 64·7; H, 6·2; N, 3·6; Cl, 9·1%).

Preparation of the benzo[a]*quinolizines*

The pyridinium salts A, B and C* were prepared by heating, for 8 hr, a soln of the appropriate β-phenethylbromide (1 mole) in dry acetone and pyridine (3 mole). After cooling the solid colourless products were collected and recrystallized from EtOH.

*A = 1-β-*Phenylethylpyridinium bromide*; B = 1-β-(2,3-*dimethoxyphenyl*)*ethyl pyridinium bromide*; C = 1-β-(2,3-*methylenedioxyphenyl*)*ethyl pyridinium bromide*.

Preparation of the 2-pyridones

1-(β-*Phenylethyl*)-2-*pyridone* (**1**, R = H) was prepared by the method of Sugasawa[5] (Table 1).

1-[β-(2,3-*Dimethoxyphenyl*)*ethyl*]-2-*pyridone* (**1**, R = OCH_3) was prepared by treating a soln of A (13·6 g) in water (50 ml) rapidly with a soln $K_3Fe(CN)_6$ (60 g) in water (140 ml) under N_2. The dark soln was stirred for ½ hr. KOH (73 g) in water (60 ml) was then added dropwise so that the temp of the soln remained below 40°. After the addition the temp was raised to 65° for 1 hr after which time the cooled reaction mixture was shaken with benzene (200 ml), filtered and the aqueous phase separated and further extracted with benzene (2 × 100 ml). The combined extracts were dried and on evaporation gave an oil which solidified on standing and was recrystallized from benzene: light petroleum (60–80°) (Table 1); λ_{max} (ε)nm, 230 (13,900), 287 (5,800), 306 (5,700); ν_{max} cm^{-1}, 1663, 1582, 1510; NMR (CF_3COOH), 3·1 (2H, t, J = 7·0 Hz), (Ar—CH_2—), 4·5 (2H, t, J = 7·0 Hz) (—CH_2N═); 3·75 (6H, s), (2 × —OCH_3); 6·5 (3H, s), (C_6H_3≡); 6·5–8·0 (4H, m), (C_6H_4═).

1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-2-*pyridone* (**1**, R, R = —OCH_2O—) was prepared and recrystallized by the above method (Table 1). ν_{max} cm^{-1}, 1665, 1582.

Preparation of the piperidones

The piperidones were prepared by reduction of the corresponding pyridones (2·0 g) in MeOH (100 ml) over Raney Ni (0·25 g) at 85 atms and 140°. After filtration and evaporation oily products were obtained which solidified on standing, these were recrystallized from benzene: light petroleum (60–80°) mixtures (Table 1) to give

(a) 1-(β-*Phenylethyl*)-2-*piperidone* (**13**, R = H), ν_{max} cm^{-1}, 1647, 1488, 747, 695. NMR ($CDCl_3$) ppm, 1·65 (4H, m), (—CH_2CH_2— at C_4 and C_5); 2·3 (2H, broad s), (—$C\underline{H}_2CO$—); 2·9 (2H, t, J = 7·0 Hz), (Ph—$C\underline{H}_2$—); 3·1 (2H, broad s) (—CH_2N—); 3·5 (2H, t, J = 7·0 Hz), (Ph$CH_2C\underline{H}_2$—); 7·23 (5H, s), (C_6H_5—).

(b) 1-[β-(3,4-*Dimethoxyphenyl*)*ethyl*]-2-*piperidone* (**13**, R = OCH_3), ν_{max} cm^{-1}, 1620, 1587, 1508; NMR ($CDCl_3$) ppm, 1·6 (4H, m), (—CH_2CH_2— at C_4 and C_5), 2·2 (2H, broad s), (—$C\underline{H}_2CO$—); 2·6 (2H, t, J = 7·0 Hz), ($ArCH_2$—); 2·9 (2H, broad m), (—CH_2N═); 3·3 (2H, t, J = 7·0 Hz), ($ArCH_2C\underline{H}_2$N═); 6·4 (3H, s), (C_6H_3≡).

(c) 1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-2-*piperidone* (**13**, R, R = —OCH_2O—), ν_{max} cm^{-1}, 1616, 1500, 1480; NMR ($CDCl_3$) ppm, 1·7 (4H, m) (—CH_2CH_2— at C_4 and C_5); 2·35 (2H, m), (—CH_2CO—); 2·75 (2H, t, J = 7·5 Hz), ($ArCH_2$—); 3·1 (2H, m), (—CH_2N═); 3·5 (2H, t, J = 7·5 Hz) ($ArCH_2C\underline{H}_2$N═); 5·9 (2H, s), (—O CH_2 O—) 6·7 (3H, s), (C_6H_3≡).

Preparation of the quinolizinium salts (**14**)[15]

(a) 1,2,3,4,6,7-*Hexahydrobenzo*[a]*quinolizinium iodide* (**14**, R = H) as a yellow crystalline solid from EtOH (Table 1). Picrate as dark brown needles from EtOH m.p. 137–139° (Lit.[15] 139–140°); ν_{max} cm^{-1}, 1663, 1602, 1570; NMR (DMSO.D_6) ppm, 2·3 (4H, m), (—CH_2CH_2— at C_2 and C_3); 3·2–3·4 (4H, m), (2 × CH_2— at C_1 and C_7); 4·0–4·2 (4H, m), (2 × —CH_2— N^+≡); 7·0–7·3 (4H, m), (C_6H_4═).

(b) 1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizinium iodide* (**14**, R = OCH_3) as brown shiny needles from EtOH (Table 1); λ_{max} (ε)nm, 246 (15,600), 304 (8,200), 355 (8,900); ν_{max} cm^{-1}, 1648, 1607, 1574, 1522; NMR ($CDCl_3$) ppm, 2·0 (4H, m) (—CH_2CH_2— at C_2 and C_3); 3·2 (4H, 2 × —CH_2— at C_1 and C_7); 3·9 (10H, broad s), (2 × —OCH_3 and 2 × —CH_2N^+≡); 6·65 (1H, s), (—C_8H); 7·0 (1H, s), (—$C_{11}H$).

(c) 1,2,3,4,6,7-*Hexahydro*-9,10-*methylenedioxybenzo*[a]*quinolizinium iodide* (**14**, R, R = —OCH_2O—) as yellow prisms from EtOH (Table 1); λ_{max} (ε)nm, 249 (14,700), 296 (7,800), 362 (6,900); ν_{max} cm^{-1}, 1648, 1603, 1500; NMR ($CDCl_3$) ppm, 2·0 (4H, broad s) (—CH_2CH_2— at C_2 and C_3); 3·02 (4H, broad s), (2 ×

—CH_2— at C_1 and C_7); 3·9 (4H, broad s), (2× —CH_2—$\overset{+}{N}\equiv$); 6·0 (2H, s), (—OCH_2O—); 6·6 (1H, s), (—C_8H); 7·0 (1H, s), (C_{11}—H).

Reduction of the benzoquinolizinium salts

Ethanolic solutions of the salts **14** were reduced by the addition of an excess of aqueous $NaBH_4$ in the usual way giving: (a) 1,2,3,4,6,7-*Hexahydro*-11b*H*-*benzo*[a]*quinolizine* (**16**, R = H) as an oil which was characterized as its *hydrochloride*; ν_{max} cm^{-1}, 2520, 2470, 1602. The Methiodide had a m.p. 226–229° from EtOH. (b) 1,2,3,4,6,7-*Hexahydro*-9,10-*dimethoxy*-11b*H*-*benzo*[a]*quinolizine* (**16**, R = CH_3O) as a colourless gum which was characterized as its *methiodide*; ν_{max} cm^{-1} 1612, 1516, 1463.

1-[β-(3,4-*Methylenedioxyphenyl*)*ethyl*]-3,4-*dihydrocarbostyril* (**25**, R, R = —OCH_2O—).

The carbostyril, **19** (R,R = —OCH_2O—), (1·4 g) was hydrogenated as the pyridones **13** yielding the dihydro-compound (1·3 g) as colourless needles m.p. 92–93°; λ_{max} (ε)nm, 245 (7,700), 286 (3,700); ν_{max} cm^{-1}, 1665, 1657, 1600; NMR ($CDCl_3$) ppm, 2·5–3·0 (6H, m); 4·15 (2H, m), (—CH_2CO—; 5·94 (2H, s), (—OCH_2O—); 6·76 (3H, broad s), (≡C_6H_3); 7–7·25 (4H, m), ($C_5C_6C_7$ and C_8 H's). (Found: C, 73·2; H, 5·9; N, 4·9; $C_{18}H_{17}NO_3$ requires: C, 73·2; H, 5·8; N, 4·7%).

The reaction of **19** (RR = —OCH_2O—) *with* $POCl_3$

A soln of the carbostyril (2·0 g) in $POCl_3$ (13 ml) was heated in an oil bath 2 hr at 140°. Excess $POCl_3$ was removed by distillation and the residue triturated with portions of light petroleum (60–80°), (15 ml). The residue was treated with warm water (2 × 30 ml) and insoluble material removed by filtration. The addition of KI precipitated a yellow solid (2·5 g). The crude product was divided into two. (i) The crude material (1·25 g) was triturated with several portions of warm EtOH and the residue (0·45 g) was 1-[β-(3,4-*methylenedioxyphenyl*)*ethyl*]-2-*chloroquinolinium iodide* (**20**, RR = —OCH_2O—, R' = Cl) m.p. 187–189°; λ_{max} 242, 290, 332; ν_{max} cm^{-1}, 1610, 1582, 1569; NMR (CF_3COOH) ppm, 3·45 (3H, t, J = 7·5 Hz), ($ArCH_2$···), 5·6 (2H, t, J = 7·5 Hz), (=$\overset{+}{N}$—CH_2); 5·98 (2H, s), (—OCH_2O—); 6·78 (3H, m); 8·0–8·6 (4H. m), (C_5,C_6,C_7,C_8-H's); 8·64 (2H, s), (C_3 and C_4-H's). (Found: Cl, 9·3; I, 25·8. $C_{18}H_{15}NO_2ClI$ requires: Cl, 8·1; I, 28·1%). (ii) The crude material (1·25 g) was dissolved in MeOH (25 ml) and filtered. On standing for some days the crystalline 9,10-*methylenedioxy*-6,7-*dihydrobenzo*[a,f]*quinolizinium iodide* (**21**, R,R = OCH_2O, R' = H), (0·12 g) m.p. 296–298° d. separated; λ_{max} (ε)nm 257 (12,000), 290 (14,600), 342 (5,600), 414 (14,500); ν_{max} cm^{-1}, 1605, 1572; NMR (DMSO . D_6) ppm, 3·38, (2H, t, J = 7·0 Hz), (—C_7H_2—); 5·16, (2H, t, J = 7·0 Hz), (—C_6H_2—), 6·32 (2H, s), (—OCH_2O—); 7·3, (1H, s), (C_8H); 7·63–8·82, (5H, m), (C_1, C_2, C_3, C_4 and C_{13}Hs), 8·06, (1H, s) (C_{11}-H), 9·23 (1H, d, J = 9·0 Hz), (C_{12}-H). (Found: C, 53·8; H, 3·2; N, 3·3; I, 31·7. $C_{18}H_{14}INO_2$ requires: C, 53·6; H, 3·5; N, 3·5; I, 31·5%); M/S (70 eV). P. *m/e* = 401. Starting material **9** (RR = —OCH_2O—), (1·2 g) was recovered from the combined mother liquors of (i) and (ii).

The reaction of **25** (RR = —OCH_2O—) *with* $POCl_3$

The dihydrocarbostyril (0·9 g) was treated with $POCl_3$ in the usual way yielding 9,10-*methylenedioxy*-6,7-*dihydrodibenzo*[a,f]*quinolizinium iodide* (**21**; 0·65 g, 53%) m.p. 296–298° as yellow garnets from EtOH. This material was identical (IR, UV, NMR) with, and did not depress, on admixture, the m.p. of the salt m.p. 296–298° obtained from the previous reaction. 9,10-*Methylenedioxy*-6,7,12,13-*tetrahydro*-11b *H*-*dibenzo*-[a,f]*quinolizine* (**24**, RR = —OCH_2O—). To the corresponding quinolizinium salt **23**, (0·4 g) dissolved in 20% aqueous EtOH (20 ml) was added a soln (5 ml) of $NaBH_4$ in the same solvent. The stirred soln deposited a white solid (0·25 g) which crystallized from EtOH as small colourless prisms m.p. 132–133° which became yellow on exposure to air; λ_{max} (ε)nm 263 (9,300), 300 (6,100); ν_{max} cm^{-1}, 1605, 1568; NMR ($CDCl_3$) ppm, 2·0–3·3 (8H, m); 3·8 (1H, m), (C_{11b}-H); 5·93 (2H, s), (—OCH_2O—); 6·63 (1H, s), (C_8-H); 6·79 (1H, s), $C_{(11}$-H), 6·55–7·25 (4H, m), (C_1,C_2,C_3 and C_4-Hs). The methiodide was obtained from EtOH as bright yellow garnets m.p. 221–223°. (Found: C, 54·4; H, 4·5; N, 2·9; I, 30·1. $C_{19}H_{20}INO_2$ requires: C, 54·2; H, 4·8; N, 3·3; I, 30·1%).

1-[β-(3,4-*Methylenedioxyphenyl*]-1,2,3,4-*tetrahydroisoquinoline*. **18**, RR = —OCH_2O—) was reduced with $NaBH_4$ as in the previous case; no solid material separated from the reaction mixture. The usual dilution and extraction procedure yielded solid product (70%) which recrystallized from EtOH as clumps of needles m.p. 124–125°. A mixed m.p. determination carried out with the base obtained in the previous reduction reaction showed a marked depression; λ_{max} (ε)nm, 233 (16,400), 292 (3,500). ν_{max} cm^{-1}, 1610, 1580; NMR ($CDCl_3$) ppm, 2·6–3·6 (8H, m), 4·1 (2H, m), (Ar—CH_2—N=), 5·94 (2H, s), (—OCH_2O—), 6·77 (3H, s), ($C_6\underline{H}_3\equiv$), 6·2–7·2 (4H, m), (C_6H_4=). (Found: C, 76·8; H, 7·1; N, 4·8. $C_{18}H_{19}NO_2$ requires: C, 76·8; H, 6·8; N, 5·0%).

The reaction of 1-β-*phenylethylcarbostyril* (**19**, R = H) *with* $POCl_3$

The literature method[12] was employed. From **19** (R = H; 0·7 g) yellow needles (0·6 g) m.p. 180–181° were obtained, and crystallized by the addition of ether (3 vol) to an ethanolic soln of the salt (1 vol). (Lit.[12] 185–186); λ_{max} (ε)nm, 247 (18,700), 331 (8,400); ν_{max} cm^{-1}, 1620, 1610, 1595; NMR (DMSO.D_6) ppm, 2·8 (2H, t, J = 7·5 Hz), (—$C\underline{H}_2$Ar); 4·5 (2H, t, J = 7·5 Hz), (—CH_2—$\overset{+}{N}$≡) 6·65 (1H, d, J = 7·0 Hz); (C_4—H); 7·5 (5H, s), (C_6H_5—); 7·4, 7·8 (4H, m). (C_6H_4=); 7·95 (1H, d, J = 7·0 Hz), (—C_3H). (Found: Cl, 5·95; I, 44·8. $C_{17}H_{15}I$ NCl requires: Cl, 9·0; I, 32·1%). A soln of the iodide in a minimum of EtOH was treated with a few drops of 60% $HClO_4$, and 2-*ethoxy*-1-β-*phenylethylquinolinium perchlorate* (**20**, R = H, R′ = OCH_2CH_3, X = ClO_4) crystallized as grey needles m.p. 209–210°; NMR (DMSO.D_6) ppm, 1·5 (3H, t, J = 8·0 Hz), ($\underline{CH}_3CH_2$—); 3·2 (2H, t, J = 7·5 Hz), ($ArCH_2$—); 4·7 (2H, q, J = 8·0 Hz), ($CH_3C\underline{H}_2$—); 5·0 (2H, t, J = 7·5 Hz), (—CH_2—N≡); 7·35 (5H, s), (C_6H_5—); 7·6–8·5 (4H, m), (C_6H_4=); 7·9 (1H, d, J = 7·0 Hz), (—C_3H); 9·15 (1H, d, J = 7·0 Hz), (—C_4H). (Found: C, 58·0; H, 5·15; N, 3·85; Cl, 9·85. $C_{19}H_{20}ClNO_5$ requires: C, 60·5; H, 5·3; N, 3·7; Cl, 9·6%).

The catalytic reduction of **20** (R = H, R′ = Cl, X = I) *and* (R = R′ = H, X = Br)

The quaternary salt (1·0 g) dissolved in air free EtOH (200 ml) was reduced in the presence of Adams catalyst at 45 lb/sq in for 16 hr. The catalyst was filtered off, the filtrate evaporated to low bulk and a few drops of conc HI aq added to it. On standing EtOH soln from the reduction of bromide salt deposited the hydroiodide of 1-β-*phenylethyl*-1,2,3,4-*tetrahydroquinoline* (**22**, R = H) as pale yellow cubes (0·6 g) m.p. 209–211°; λ_{max} (ε)nm, 266 (1,050); ν_{max} cm^{-1}, 2730, 2680, 1600, 750, 710. The EtOH soln obtained by reduction of the chloro-iodide salt deposited pale yellow cubes (0·2 g) m.p. 208–210°, identical in all respects with the authentic 1-β-phenylethyl-1,2,3,4-tetrahydroquinoline hydroiodide.

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