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SOME DERIVATIVES OF 5H-DIBENZ[b.f]AZEPINE

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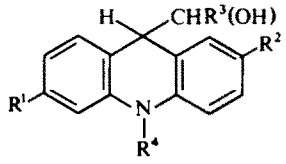
Abstract—By rearrangement of the corresponding 9,10-dihydroacridine derivates of type I, 5-methyl-10-phenyl- and 5-methyl-10-propyl-dibenz[b.f]azepine and 7-chloro-2-methoxy-5H-dibenz[b.f]azepine have been synthesized.

IT HAS been shown[1] that Wagner–Meerwein rearrangement of 9-hydroxymethyl-9,10-dihydroacridine (I) represents a satisfactory way into the 5H-dibenz[b.f]azepine (II) series. In view of the pharmaceutical interest in derivatives of II we have expanded this method. 10-Methyl-9,10-dihydroacridine (III) gave with butyl lithium the red 9-lithio derivative which reacted with benzaldehyde and butyraldehyde to give 9-(α-hydroxybenzyl)- and 9-(α-hydroxybutyl)-10-methyl-9,10-dihydroacridine (IV, R = Ph or Pr). These compounds show the strong absorption at about 290 mμ typical of 9,10-dihydroacridine derivatives and OH absorption in the IR. Treatment of IV (R = Ph) with phosphorus pentoxide in xylene proceeded with rearrangement and gave 5-methyl-10-phenyldibenz[b.f]azepine (V, R = Ph). The UV spectrum was in accord with the formula; *per exclusionem*, the structure also follows from the non-identity of the compound with the known[2] 9-benzylidene-10-methyl-9,10-dihydroacridine (VI). Equally, from IV (R = Pr), 5-methyl-10-propyldibenz[b.f]-azepine (V, R = Pr) was obtained; its UV spectrum was very similar to that of the phenyl analog.

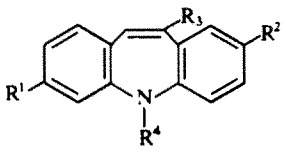
The method seemed particularly suitable for the synthesis of dibenz[b.f]azepine derivatives, substituted in the aromatic rings. We have thus prepared 7-chloro-2-methoxy-5H-dibenz[b.f]azepine (X), a compound similar in its skeleton to the anti-malarial drug atebrine, by the following route.

7-Chloro-9-formyl-2-methoxyacridine (VIII) prepared according to Perrine and Sargent,[3a] was reduced with LAH to 7-chloro-9-hydroxymethyl-2-methoxy-9,10-dihydroacridine (IX) and the latter treated with phosphorus pentoxide in xylene. The main product was the desired compound X, identified by its NMR (see below) and UV spectra. An isomeric by-product was identified as 7-chloro-2-methoxy-9-methylacridine (VII); its formation is undoubtedly due to the fact that IX is partly dehydrated *without* rearrangement, giving the 9-methylene-9,10-dihydroacridine derivative XI which isomerizes to VII. As expected, the isomers VII and X yield different dihydroderivatives. It is interesting that no analogous dehydration reaction was observed in the case of IV; here, the methylene dihydroacridine structure would have been stable. A similar formation of V from 9-iodomethyl-10-methylacridine has been observed by Whitlock.[3b]

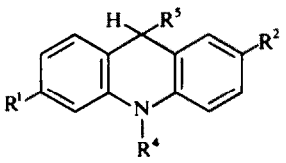
The imino group in X can be alkylated in the normal manner. Thus, e.g. by successive treatment of this compound with sodamide and 3-dimethylaminopropyl



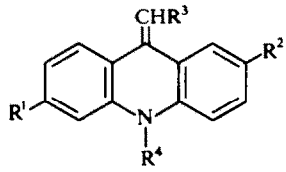
I $R^1 = R^2 = R^3 = R^4 = H$
IV $R^1 = R^2 = H$, $R^4 = Me$, $R^3 = Ph$ or Pr
IX $R^1 = Cl$, $R^2 = OMe$, $R^3 = R^4 = H$



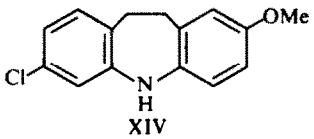
II $R^1 = R^2 = R^3 = R^4 = H$
V $R^1 = R^2 = H$, $R^4 = Me$, $R^3 = Ph$ or Pr
X $R^1 = Cl$, $R^2 = OMe$, $R^3 = R^4 = H$
XII $R^1 = Cl$, $R^2 = OMe$, $R^3 = H$
$R^4 = -(CH_2)_3NEt_2$



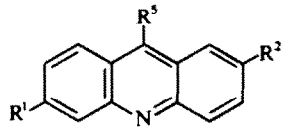
III $R^1 = R^2 = R^5 = H$, $R^4 = Me$
XIII $R^1 = Cl$, $R^2 = OMe$, $R^4 = H$, $R^5 = Me$



VI $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Me$
XI $R^1 = Cl$, $R^2 = MeO$, $R^3 = R^4 = H$



XIV



VII $R^1 = Cl$, $R^2 = OMe$, $R^5 = Me$
VIII $R^1 = Cl$, $R^2 = OMe$, $R^5 = CHO$

chloride, 7-chloro-5-(γ-dimethylaminopropyl)-2-methoxy-5H-dibenz[b.f]azepine (XII) was obtained.

The NMR spectrum of X deserves some comment. In dibenz[b.f]azepine (I), we had observed a sharp singlet at 6·25 ppm assigned to the vinylic hydrogen atoms of the central ring. In X, the respective hydrogens are no longer equivalent and appear as part of the aromatic multiplet, the aromatic protons being shielded by the methoxy and imino groups.

In the alternative structure XI, the exocyclic methylene hydrogen atoms should have appeared at much higher field (compare *cis*-stilbene which absorbs at 6·55 ppm and 1,1-diphenylethylene with an absorption at 5·40 ppm).

EXPERIMENTAL

10-Methyl-9,10-dihydroacridine (III) was prepared according to Agranat[4] from 9,10-dihydroacridine, NaH and MeBr in anisole, m.p. 96°; UV (EtOH): 286 mμ (ε, 4·20).

9-(α-Hydroxybutyl)-10-methyl-9,10-dihydroacridine (IV, R = Pr). At 0°, 10 g of the preceding compound was added to a soln of BuLi, prepared from 1·5 g Li and 12 g BuBr in 180 ml ether. The red soln was refluxed for 30 min and cooled at 0°, and 5 g of butyraldehyde in 20 ml ether was added. The reaction mixture was refluxed for 2 hr and decomposed with 200 g ice and 30 g NH_4Cl. The usual work-up gave an oil which crystallized upon cooling and was recrystallized from pet. ether as colourless crystals, m.p. 115°; yield, 8 g (63%); UV (EtOH): 285 mμ (ε, 4·03). IR(Nujol): 3360, 2950, 1600, 1470, 1370, 1350, 1265, 1130 cm^{-1}. (Found: C, 80·8; H, 8·2; N, 5·6. Calc. for $C_{18}H_{21}NO$: C, 80·9; H, 7·9; N, 5·2%.)

5-Methyl-10-propyl-5H-dibenz[b.f]*azepine* (V, R = Pr). The rearrangement was carried out with P_2O_5 in xylene (see below); the reaction time was 2 hr. After chromatography on alumina, the product was obtained as a yellowish oil; yield, 27%; UV (EtOH): 255 (ε, 4·28); 284° (3·84); 340° mμ (2·95); IR (Nujol): 1430, 1350, 1310, 1275, 1240, 1125, 1040 cm^{-1}. (Found: C, 86·7; H, 7·5; N, 5·1. Calc. for $C_{18}H_{19}N$: C, 86·8; H, 7·6; N, 5·6%.)

9-(α-*Hydroxybenzyl*)-10-*methyl*-9,10-*dihydroacridine* (IV, R = Ph). In the manner described above, this product was obtained in 65% yield (10 g) from 10 g of III and 20 g benzaldehyde, m.p. 154°. UV ($CHCl_3$): 293 (ε, 4·08); 384 (2·40); 402 mμ (2·49); IR (Nujol): 3330, 3030, 2900, 1610, 1470, 1330, 1270, 1140, 1040, 1025 cm^{-1}. (Found: C, 80·6; H, 602; N, 5·0. Calc. For $C_{21}H_{19}NO$: C, 80·4; H, 6·3; N, 4·7%.)

5-Methyl-10-phenyl-5H-dibenz[b.f]*azepine* (V, R = Ph). From 8 g of the foregoing compound, by reaction with P_2O_5 in xylene for 22 hr, an oil was obtained which solidified spontaneously and was purified by chromatography on alumina, benzene serving as solvent and eluent. The product was recrystallized from pet. ether, yield 2 g (26%); m.p. 200–200·5°. UV ($CHCl_3$): 264 (ε, 4·30); 290° (4·08); 370° mμ (2·70); IR (Nujol): 2950, 1600, 1470, 1370, 1270, 1130 cm^{-1}. (Found: C, 88·8; H, 6·1; N, 5·1. Calc. for $C_{21}H_{17}N$: C, 89·0; H, 6·0; N, 5·0%).

9-*Benzylidene*-10-*methyl*-9,10-*dihydroacridine* was prepared according to Decker and Pschorr[2] from N-methylacridone and benzylmagnesiumchloride. The reaction product was decomposed with NH_4Cl; even so, the dehydrated product was obtained directly. After recrystallization from MeOH or isopropyl alcohol, it melted at 143°. UV ($CHCl_3$): 294 (ε, 4·05), 400 mμ (4·16).

6-*Chloro*-2-*methoxy*-9-*methylacridine* (VII) was prepared according to Campbell,[5] but with slight modifications, Li from EtOH or BuOH, m.p. 169–170°; (yield, 74%). UV (EtOH): 263 (ε, 5·04); 320 (3·40); 335 (3,70); 352 (3,84); 382 (3,80); 402 mμ (3,80).

6-*Chloro*-9-*hydroxymethyl*-2-*methyl*-9,10-*dihydroacridine* (IX). A suspension of 5 g LAH in 100 ml ether was added to a suspension of 12 g of VIII, prepared from the foregoing compound according to Perrine and Sargent,[3] in 500 ml ether. The suspension of the acridine derivative was cooled with an ice-salt mixture. The mixture was refluxed for 5 hr and cooled, the excess of the hydride destroyed by addition of AcOEt, and the colloidal suspension formed abolished by addition of 8 g sodium potassium tartrate in 100 ml water. The aqueous layer was extracted 3 times with 100 ml ether and the combined solns were dried and concentrated *in vacuo*. The residue was recrystallized from CCl_4 and formed colourless crystals (11·2 g; 85%), m.p. 153–154°. UV (EtOH): 290 (ε, 4,20); 325° mμ (3,60); IR (Nujol): 3350, 2900 cm^{-1}. (Found: C, 65·5; H, 5·5; Cl, 13·5. Calc. for $C_{15}H_{14}ClNO_2$: C, 65·4; H, 5·1; Cl, 12·9%).

7-*Chloro*-2-*methoxy*-5H-*dibenz*[b,f]*azepine* (X). In an atmosphere of N_2 and with stirring, a soln of 11 g of the foregoing compound in 100 ml xylene was added slowly (4·5 hr) to a suspension of 30 g P_2O_5 in 500 ml xylene, which had been dried and distilled over CaH_2. After refluxing the mixture for 0·5 hr, it was treated with 2 l. water and the aqueous layer extracted twice with 100 ml benzene. The combined organic solns were concentrated *in vacuo* at a temp not exceeding 60°. The oily residue was best chromatographed on alumina, although it sometimes crystallized spontaneously and could then be purified by recrystallization from pet. ether.

The adsorbed product was eluted with benzene and obtained as brownish-yellow crystals from pet. ether (3·1 g; 29%), m.p. 176°. UV (EtOH): 265 (ε, 4,60); 303 (3,60); 370° mμ (2,90); IR (Nujol): 3340, 2900, 1600, 1510, 1470, 1370, 1320, 1250, 1230, 1175, 1090, 1045 cm^{-1}. (Found: C, 70·1; H, 4·8; Cl, 13·7; N, 5·8; OMe, 12·2. Calc. for $C_{15}H_{12}ClNO$: C, 69·9; H, 4·7; Cl, 13·6; N, 5·4; OMe, 12·0%.) NMR spectrum: multiplet at 6·9–6·2δ (centered at 6·45δ) and singlet at 3·7δ (OMe hydrogen atoms) in the ratio 1:3.

When the column was eluted further with ether, 2-methoxy-6-chloro-9-methylacridine was isolated, identified by mixed m.p. and the superimposability of the UV and IR spectra. A further quantity was isolated from the aqueous layer after it was made alkaline with ammonia, and had been extracted with benzene; m.p. 169–170°, mixed m.p. with the above product 140°.

6-*Chloro*-2-*methoxy*-9-*methyl*-9,10-*dihydroacridine* (XIII). A suspension of 1 g LAH in 50 ml dry ether was added to a suspension of 1 g of VII in 50 ml dry toluene and the mixture refluxed for 18 hr. Then water was added, in order to destroy the excess of hydride and the whole mass treated with 100 g $MgSO_4$. Thus, the colloidal $Al(OH)_3$ was precipitated and a clear soln obtained. The solvents were evaporated *in vacuo* and the yellow solid residue was dissolved in pet. ether and chromatographed on alumina. The colourless product (0·35 g; 34%) was recrystallized from heptane, m.p. 128–129°. UV (EtOH): 291 (ε, 4,20); 325° (3,60); IR (Nujol): 3360, 2900, 1600, 1480, 1380, 1290, 1250, 1160, 1095, 1040 cm^{-1}. (Found: C, 69·1; H, 5·6; Cl, 14·0. Calc. for $C_{15}H_{14}ClNO$: C, 69·4; H, 5·4; Cl, 13·7%.)

7-*Chloro*-2-*methoxy*-10,11-*dihydro*-5H-*dibenz*[b.f]*azepine* (XIV). A soln of 100 mg of X in 100 ml EtOH

was hydrogenated at ordinary press and temp in the presence of PtO_2. The product was an oil which crystallized when its soln in pet. ether was cooled in a dry ice-acetone bath; colourless crystals, m.p. 70°. The UV spectrum (290 mμ in EtOH) showed that the desired compound had been formed.

2-Methoxy-5-(γ-dimethylaminopropyl) 7-chloro-5H-dibenz[b.f]*azepine* (XII). Sodamide, freshly prepared from 0·5 g Na in liquid ammonia, was suspended in 100 ml toluene, and in an atmosphere of N_2, 1 g 2-methoxy-7-chloro-5H-dibenz[b.f]azepine in 50 ml dry toluene was added. The mixture was refluxed for 4 hr, and 15 g 3-dimethylaminopropyl chloride[6] in 50 ml toluene added at room temp. After 17 hr of refluxing, 200 ml water was added. The soln obtained in the usual work-up was evaporated *in vacuo* at a temp not exceeding 40° and the remaining brownish oil chromatographed on alumina, benzene being used as a solvent and eluent. Thus, a solid product was obtained (0·35 g; 26%) which was recrystallized from pet. ether, and melted at 88°. UV (EtOH): 260 (ε, 4,60); 291[a] (3·90); 357[a] mμ (3,20); IR (Nujol): 2930; 1590, 1460, 1270, 1130, 1085, 1035 cm^{-1}. (Found: C, 70·3; H, 6·8; Cl, 10·6. Calc. for $C_{20}H_{23}ClN_2O$: C, 70·1; H, 6·7; Cl, 10·2%.)

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