Studies in the Indole Series. Part VII.[1] Indolo[1,7-*ab*][1]benzazepines and Related Compounds

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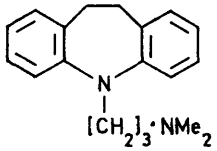
Methods of converting 10,11-dihydrodibenz[*b,f*]azepine into its *N*-amino-derivative are described, and the syntheses from the latter of indolo[1,7-*ab*][1]benzazepines by Fischer cyclisation of appropriate hydrazones are discussed. The polycyclic indoles have been converted into basic products by the Mannich reaction, and the indolic derivatives have been reduced with sodium and liquid ammonia to the corresponding indolines.

In earlier papers of this series we have discussed the chemistry of simple indole derivatives, such as the tryptamines and γ-carbolines, some of which possessed stimulant or anti-serotonin activities. The present paper concerns compounds which combine the features of an indole with those of the dihydrodibenz[*b,f*]azepine system found in the clinically useful anti-depressant imipramine (I).

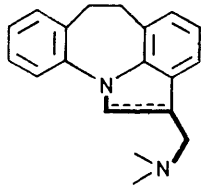


(I)

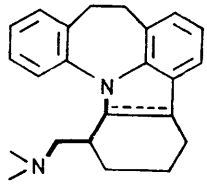
The structures (II)—(IV) indicate the manner in which the basic side-chain of imipramine could be incorporated into three polycyclic systems each containing the indole ring. Our main objectives have been to produce basic compounds of these types which might exhibit imipramine-like activity and/or other potentially useful pharmacological properties, and we consider here compounds of types (II) and (III). The synthesis and properties of a series of compounds of type (IV) will be reported in a further paper.‡

A few examples of polycyclic analogues of known tricyclic psychotropic drugs are to be found in the literature [2] but to our knowledge only those compounds represented by formula (V) have hitherto contained the indole nucleus, albeit in reduced form. They were made from the oxindoles (VII) by reduction with lithium aluminium hydride, and were claimed to have anti-allergic and spasmolytic activities.[3] The compounds (VI) are said to show anti-depressant properties,[4] as do some related oxindoles and indolines,[5] but these compounds do not have the two-carbon bridge between the phenyl rings shown in structures (II)—(V) and (VII).

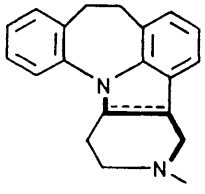
Since the desired polycyclic indoles were expected to be available through Fischer cyclisations of suitable hydrazones of the hitherto unknown hydrazine derivative (VIII), an immediate objective was the preparation



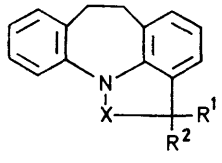
(II)†



(III)

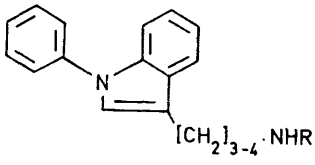


(IV)



(V) R^1 = alkyl,
R^2 = dialkylaminoalkyl,
X = CH_2

(VII) R^1, R^2 as above, X = CO



(VI) R = alkyl

† In formulae (II)—(IV) both the indolic and indolinic structures are to be considered as represented.

of considerable quantities of this compound. The first approach, reduction of the *N*-nitroso-compound (X), has been examined closely, and the reported preparation [6] of this latter compound has been greatly improved.

Reduction of diphenylnitrosamine (IX) by lithium aluminium hydride gives *NN*-diphenylhydrazine (XI).§ [8] Using suitably modified conditions we reduced the nitrosamine (X) and obtained 75% yields of the hydrazine (VIII) on scales of several hundred grams, a reduction

‡ These latter compounds were discussed briefly at the 3rd International Meeting of Chimie Therapeutique in Paris, July, 1967.

§ The influence of the quality of the metal hydride on the course of nitrosamine reductions has been noted.[7]

[1] Part VI, C. J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc.* (*C*), 1971, 359.

[2] *E.g.* E. Galantay, C. Hoffman, N. Paolella, J. Gogerty, L. Iorio, G. Leslie, and J. H. Trapold, *J. Medicin. Chem.*, 1969, **12**, 444; L. G. Humber, M. A. Davis, G. Beaulieu, and M.-P. Charest, *Canad. J. Chem.*, 1968, **46**, 2981; Dart Industries Inc., U.S.P. 3,493,567 (*Chem. Abs.*, 1970, **72**, 79,125n); Rexall Drug and Chemical Co., U.S.P. 3,544,558 (*Chem. Abs.*, 1971, **74**, 100,132r). Chemische Fabrik Promonta Gmbh., Belg.P. 762,366.

[3] J. R. Geigy A.-G., B.P. 936,782; 936,783.

[4] Pfizer, B.P. 1,220,628.

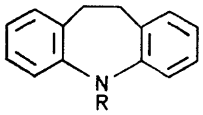
[5] A. Canas-Rodriguez and P. R. Leeming, *J. Medicin. Chem.*, 1972, **15**, 762; *cf.* S. Toyoshima, N. Hirose, K. Yamatsu, and S. Sohda, *J. Pharm. Soc. Japan*, 1970, **90**, 1524.

[6] J. Thiele and O. Holzinger, *Annalen*, 1899, **305**, 102.

[7] H. S. Broadbent, W. S. Burnham, R. K. Olsen, and R. M. Sheeley, *J. Heterocyclic Chem.*, 1968, **5**, 757.

[8] R. H. Poirier and F. Benington, *J. Amer. Chem. Soc.*, 1952, **74**, 3192.

apparently not achieved by Porai-Koshits.[9] The reduction was also successful with sodium aluminium hydride, but failed with sodium dihydrobis-(2-methoxyethoxy)-aluminate. Reduction with zinc and acetic acid, successful with diphenylnitrosamine,[10] gave erratic results with



(VIII) R = NH_2
(X) R = NO
(XII) R = H

Ph_2NR

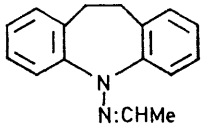
(IX) R = NO
(XI) R = NH_2

nitrosodihydrodibenz[*b,f*]azepine. Some hydrazine was obtained but there was always considerable cleavage to the parent system (XII).

Reduction of the nitrosamine with aluminium and iodine in ethanol–tetrahydrofuran [11] gave a trace of hydrazine (t.l.c.), but this could not be isolated. Other chemical reductions either caused no reaction or caused cleavage to dihydrodibenz[*b,f*]azepine; similar failures in nitrosamine reductions have been noted by other workers.[12-14]

Catalytic hydrogenation of nitrosodihydrodibenz[*b,f*]-azepine led only to denitrosation. Conditions included hydrogenation over palladium–charcoal in neutral, alkaline, or acidic ethanol, in acetic acid, in acetic anhydride or over Raney nickel in methanolic ammonia. Hydrogenation of diphenylnitrosamine similarly gives diphenylamine and nitrogen as the sole products.[15]

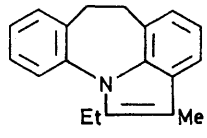
Direct conversion of the nitrosamine (X) into the hydrazone (XIII) was accomplished through the little known reaction of Wieland and Fressel.[16] Treatment with 2 equiv. of ethylmagnesium iodide gave 13% of a product which was identical with that made from the hydrazine (VIII) and acetaldehyde.



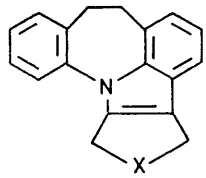
(XIII)

Finally we were able to obtain some of the hydrazine (VIII) by treatment of dihydrobenz[*b,f*]azepine conjugate base with ethereal chloramine solution. The yield was only 20% but since 74% of the dibenzazepine was recoverable, the actual conversion was good. No hydrazine could be obtained from dihydrodibenz[*b,f*] azepine itself on treatment with chloramine, probably because of the very low basicity of the starting material. In contrast to this, aliphatic hydrazines are known to be formed comparatively readily from strongly basic amines and chloramine.[17]

N-Aminodihydrodibenz[*b,f*]azepine was characterised readily by formation of its hydrochloride, and of aldehyde and ketone derivatives, and by the Fischer cyclisation of some of the latter with ethanolic hydrogen chloride. Thus with diethyl ketone the indolo[1,7-*ab*]-[1]benzazepine (XIV) was formed, and with carbocyclic ketones the pentacyclic compounds (XV) were obtained; 4-piperidones yielded the compounds (XVI) which, as mentioned earlier, will be discussed elsewhere.



(XIV)

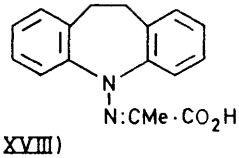


(XV) X = $[CH_2]_{1-3}$
(XVI) X = $CH_2 \cdot NR$, R = H, alkyl, *etc.*
(XVII) X = $CH_2 \cdot O$

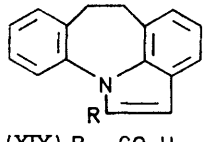
The oxygen analogue (XVII) was not readily obtained from tetrahydro-γ-pyrone and *N*-aminodihydrodibenz-[*b,f*]azepine by the ordinary Fischer cyclisation, but it could be made by treating the hydrazone (XIII) with tetrahydro-γ-pyrone in glacial acetic acid.

In contrast to these reactions, the acetone hydrazone of *N*-aminodihydrodibenz[*b,f*]azepine could not be cyclised to an identifiable indole derivative under any conditions.

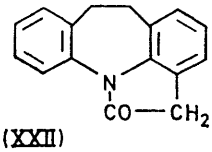
The hydrazine base (VIII) reacted with pyruvic acid in ethanol to yield the hydrazone (XVIII); however, when the hydrazine hydrochloride was used cyclisation took place, giving a mixture of the tetracyclic acid (XIX)



(XVIII)



(XIX) R = CO_2H
(XX) R = CO_2Et
(XXI) R = H



(XXII)

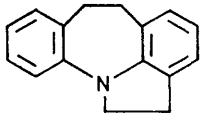
and its ethyl ester (XX). In the presence of excess of hydrogen chloride only the ester was formed. Decarboxylation of the acid (XIX) yielded the unsubstituted indolobenzazepine (XXI), and the structure of this was

[9] B. A. Porai-Koshits, E. N. Sof'ina, and I. Ya. Kvito, *J. Gen. Chem.* (*U.S.S.R.*), 1964, **34**, 2110.
[10] A. T. Balaban, P. T. Frangapol, M. Marculescu, and J. Bally, *Tetrahedron*, 1961, **13**, 266; National Cash Register Co., B.P. 883,803 (*Chem. Abs.*, 1962, **57**, 4638).
[11] VEB Arzneimittelwerk Dresden, G.P. 1,155,138 (*Chem. Abs.*, 1964, **60**, 2826).
[12] M. J. Kalm, *J. Medicin. Chem.*, 1964, **7**, 427.
[13] R. J. Hedrick and R. T. Major, *J. Org. Chem.*, 1964, **29**, 2486.
[14] H. H. Stroh, D. Henning, and J. Kandler, *Z. Chem.*, 1963, **3**, 426.
[15] C. Paal and W.-N. Yao, *Ber.*, 1930, **63**, 57.
[16] H. Wieland and H. Fressel, *Ber.*, 1911, **44**, 898.
[17] R. A. Rowe and L. F. Audrieth, *J. Amer. Chem. Soc.*, 1956, **78**, 563.

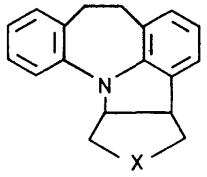
confirmed by an alternative preparation, in which the oxindole (XXII) was reduced with lithium aluminium hydride to give the same compound.

In Part V [18] it was shown that *N*-phenylindoles could be reduced easily to the corresponding indolines with sodium and ammonia. The foregoing tetra- and pentacyclic indoles could be reduced similarly giving the compounds (XXIII) and (XXIV). The u.v. spectra of these compounds were virtually identical with that of dihydrodibenzazepine (XII), showing that no change had occurred in the aromatic systems during the reductions.

The non-basic tetracyclic indole (XXI) was readily converted into tertiary basic products (XXV) by the Mannich reaction with formaldehyde and secondary amines. Secondary bases could not be made conveniently by this method but compound (XXVII) could be obtained by catalytic debenzylation of the *N*-methyl-*N*-benzyl derivative (XXV). Sodium–ammonia reduction of these indoles gave basic indolines

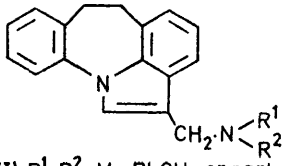


(XXIII)



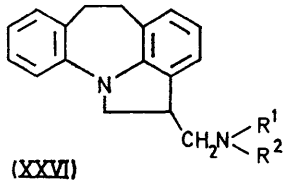
(XXIV) X = $[CH_2]_{1-2}$

(XXVI). In these compounds the imipramine side-chain is fused to the aromatic system as shown in formula (II). In order to obtain compounds of type



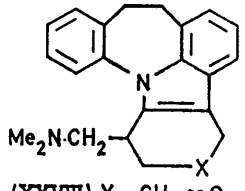
(XXV) R^1, R^2 = Me, $PhCH_2$, or part of a ring

(XXVII) R^1 = H, R^2 = Me

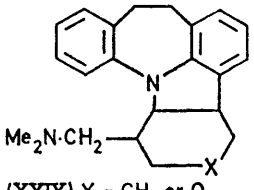


(XXVI)

(III) the pentacyclic indoles (XV; X = $[CH_2]_2$) and (XVII) were subjected to the modified Mannich reaction of Thesing and Semler [19] in which the components were heated for several hours instead of carrying out the reaction at room temperature. This yielded products which by analogy with the above report should have the structures (XXVIII). They gave the indolines (XXIX) on reduction.



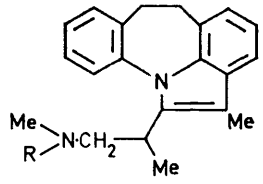
(XXVIII) X = CH_2 or O



(XXIX) X = CH_2 or O

Similar reactions of the tetracyclic compound (XIV) yielded the tertiary bases (XXX) and (XXXI), of which the former may be considered a ring-opened version of (XXVIII; X = CH_2); catalytic debenzylation of the benzylic base yielded the secondary amine (XXXII).

In the case of compound (XXX) the structure was confirmed by the n.m.r. spectrum, which showed a singlet for the methyl group attached to the tertiary carbon, a doublet for the methyl group attached to the secondary carbon, and a singlet for the *N*-methyl groups.

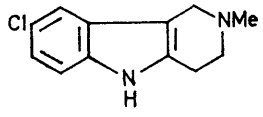


(XXX) R = Me

(XXXI) R = $PhCH_2$

(XXXII) R = H

The basic products described were submitted to a variety of pharmacological tests. Compound (XXV; $R^1 = R^2$ = Me) showed anti-serotonin activity equal to half that of the γ-carboline (XXXIII); [20] and compounds (XXVI; R^1 = H, R^2 = Me) and (XXVI; $R^1 = R^2$ = Me) showed sedative properties, but only at very high dosage. None of the compounds showed imipramine-like activity in the normal pharmacological tests.



(XXXIII)

EXPERIMENTAL

The solvents, spectroscopic instruments, chromatographic conditions, and other general details were as described in Parts IV and VI, unless otherwise stated. Tetrahydrofuran was fresh peroxide-free material, and was dried either by molecular sieve or by distillation from sodium.

10,11-*Dihydro*-5-*nitroso*-5H-*dibenz*[b,f]*azepine* (X).—10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine (390·5 g, 2 mol) in dimethylformamide (3·9 l) was treated with powdered sodium nitrite (152 g, 2·2 mol). The mixture was stirred and cooled to 3—10° and 2N-hydrochloric acid (2 l, 4 mol) was added during 1 h. A precipitate formed during this period. Stirring was continued for 30 min without cooling and the mixture was poured into water (6—7 l). After stirring for a further 15 min the product was filtered off and washed with water (3 l) and ice-cold ethanol (500 ml). The crude nitrosamine, dried *in vacuo* at 35°, formed a yellow-brown solid (427 g, 95%), m.p. *ca.* 113° (lit.,[6] for recrystallised material, 120°).

5-*Amino*-10,11-*dihydro*-5H-*dibenz*[b,f]*azepine* (VIII).—A suspension of lithium aluminium hydride (65·5 g, 1·15 × 1·5 mol) in dry ether (1·35 l) was stirred under nitrogen at 27° and a solution of the preceding nitrosamine (336 g, 1·5 mol) in dry tetrahydrofuran (1·35 l) was added during 1—1½ h, the temperature being kept at 27—30° throughout.

[18] B. Heath-Brown, *Chem. and Ind.*, 1969, 1595.
[19] J. Thesing and G. Semler, *Annalen*, 1964, **680**, 52.
[20] Part IV, C. J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc.* (*C*), 1968, 1235.

[*Caution:* The reaction was slightly exothermic; initially about 50 ml of the nitrosamine solution was added then no more was added until the exothermic reaction had been observed. Thereafter the addition was continued, alternately allowing the temperature to rise to 30° and then cooling to 27°]. The exothermic reaction ceased at the end of the addition, after which the mixture was kept at 30° for 20—30 min and then cooled to 0°. It was decomposed by cautious addition of water (65·5 ml) in tetrahydrofuran (131 ml) followed by N-sodium hydroxide (262 ml), and then filtered. The inorganic residue was extracted thoroughly with tetrahydrofuran and the combined extracts were evaporated *in vacuo*. The residue was dissolved in ether (750 ml) and stirred under nitrogen at 0° during addition of 2N-hydrochloric acid (1·5 l). The crude hydrazine hydrochloride was collected after 15 min, washed twice with 2N-hydrochloric acid, then with ether, and finally dried *in vacuo* at 50°. It formed a grey solid, m.p. *ca.* 130° (275 g, 74·3%). The two layers of the filtrate were separated, the ether layer yielding 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine, m.p. 105°, after evaporation and crystallisation from benzene–light petroleum (yield 18·8 g, 6·4%). The aqueous layer was made alkaline and extracted with ether. The latter contained a base which was distilled to give the *hydrazine* (10·7 g, 3·4%), b.p. 145—148° at 0·08 mmHg. It crystallised from light petroleum (b.p. 40—60°) with m.p. 54—55° (Found: N, 13·5. $C_{14}H_{14}N_2$ requires N, 13·3%).[21] The *hydrochloride* had m.p. *ca.* 140° (Found: Cl, 14·2; N, 11·2. $C_{14}H_{14}N_2$,HCl requires Cl, 14·4; N, 11·4%). The *acetyl derivative* had m.p. 268° (from ethanol) (Found: C, 76·0; H, 6·4. $C_{16}H_{16}N_2O$ requires C, 76·2; H, 6·4%). The *acetaldehyde hydrazone* had m.p. 68° (from methanol or light petroleum) (Found: C, 81·2; H, 7·0; N, 11·9. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8; N, 11·9%). The *acetone hydrazone* had m.p. 88—89° (from light petroleum) (Found: C, 81·3; H, 7·3. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·25%). The *cyclohexanone hydrazone* had m.p. 100° (from ethanol) (Found: C, 82·6; H, 7·7. $C_{20}H_{22}N_2$ requires C, 82·7; H, 7·6%).

5-*Ethylidenamino*-10,11-*dihydro*-5H-*dibenz*[b,f]*azepine* (XIII).—A Grignard solution [from ethyl iodide (13·9 g, 0·089 mol) and magnesium (2·15 g, 0·089 mol) in ether (120 ml)] was stirred at 25° and a solution of the nitroso-derivative (X) (5 g, 0·022 mol) in dry tetrahydrofuran (80 ml) was added during 0·75 h. After a further 1 h, the mixture was decomposed with ice and dilute acetic acid and extracted with ether, and the extracts were washed with sodium hydrogen carbonate solution, dried, and evaporated. After separation of some 10,11-dihydro-5*H*-dibenz[*b*,*f*]-azepine by crystallisation, the residue was purified by chromatography (benzene–alumina) to yield the hydrazone (0·7 g, 13%), m.p. 65° (from methanol), identical with the acetaldehyde derivative just described except that the m.p. was slightly lower. Further elution of the column yielded more 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (total 2·05 g, 47%).

Treatment of 10,11-*Dihydro*-5H-*dibenz*[b,f]*azepine with Chloramine*.—(By C. E. Smithen). Sodium hydride dispersion (50%; 5·3 g, 0·11 mol) and dry dimethyl sulphoxide (60 ml) were stirred at 65—70° under nitrogen. After 1·5 h, hydrogen evolution had ceased; the mixture was cooled to 30—40°, and treated with a solution of 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (19·5 g, 0·1 mol) in dry dimethyl sulphoxide (60 ml). After 1 h at 40° the mixture was cooled to 20° and treated with a dry ethereal solution of chloramine (0·1 mol in 500 ml) added in 50 min, during which the original orange colour faded. The mixture was stirred overnight and treated cautiously with water (300 ml). The separated aqueous layer was re-extracted with ether, and the combined extracts were washed with saturated brine, cooled to 0°, and treated with cold 5N-hydrochloric acid (100 ml) with vigorous stirring. Filtration yielded 5-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine hydrochloride, which was washed with ether and dried. A further small crop was obtained on treating the acid filtrate with brine (total 5·0 g, 20·4%). This product was identical with that obtained by reducing the nitrosamine.

Evaporation of the ether layers yielded starting material, which was crystallised from light petroleum; m.p. 106—107°; yield 14·5 g (74%).

1-*Ethyl*-6,7-*dihydro*-2-*methylindolo*[1,7-ab][1]*benzazepine* (XIV).— 5-Amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine hydrochloride (49·4 g, 0·2 mol) and diethyl ketone (17·2 g, 0·2 mol) were boiled in ethanol (200 ml) for 1 h with stirring. Ammonium chloride was deposited. The mixture was cooled and filtered and the solid portion was washed with water yielding a product (40 g). A further portion (1·3 g) was obtained by evaporating the liquors, dissolving in ether, washing the ether layer with dilute acid, and then evaporating. The combined products were purified by column chromatography (benzene–alumina) and crystallised from ethanol or acetone to yield the *indole*, m.p. 93—95° (38·2 g, 73%) (Found: C, 87·5; H, 7·4; N, 5·5. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3; N, 5·4%); $\lambda_{max.}$ 207, 267, and 312; $\lambda_{min.}$ 248 and 292 nm (log ε 4·49, 4·12, and 4·09; 3·90 and 3·95); τ *ca.* 2·6—3·1 (7H, m, ArH), 6·83 (4H, s, $CH_2{\cdot}CH_2$), 7·05 (2H, q, *J* 7·5 Hz, CH_2Me), 7·69 (3H, s, Me), and 8·97 (3H, t, *J* 7·5 Hz, $CH_2{\cdot}CH_3$).

When acetone was substituted for diethyl ketone in this preparation, indolic material could not be isolated.

1,2,3,4,8,9-*Hexahydro*[1]*benzazepino*[3,2,1-jk]*carbazole* (XV; X = $[CH_2]_2$).—A mixture of 5-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (5 g, 0·024 mol) and cyclohexanone (2·34 g, 0·024 mol) in ethanol (20 ml) was boiled for 1 h. Ethanolic 3N-hydrogen chloride (20 ml, 0·06 mol) was added to the hot solution and the whole was then heated under reflux for 1 h. Ammonium chloride was filtered off, the solution was evaporated to dryness, and the crude product was extracted with chloroform. After washing with water, the dried solution was evaporated finally at 0·1 mmHg, and the product was purified (benzene–alumina) to give the *carbazole* (5·6 g, 86·2%). This could be distilled, b.p. 230° (air-bath) at $2{\cdot}3 \times 10^{-7}$ mmHg, forming an amorphous solid, m.p. *ca.* 50° (Found: C, 87·3; H, 7·1; N, 4·9. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0; N, 5·1%); $\lambda_{max.}$ 210, 265, and 311 nm (log ε 4·43, 4·14, and 4·16); $\lambda_{min.}$ 245 and 289 nm (log ε 3·92 and 3·93).

2,3,7,8-*Tetrahydro*-1H-[1]*benzazepino*[3,2,1-hi]*cyclopent*-[b]*indole* (XV; X = CH_2).—This was prepared similarly from cyclopentanone (yield 57%); it formed *crystals*, m.p. 120° (from ethanol) (Found: C, 87·9; H, 6·8; N, 5·3. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6; N, 5·4%).

2,3,4,5,9,10-*Hexahydro*-1H-[1]*benzazepino*[3,2,1-hi]*cyclo-hept*[b]*indole* (XV; X = $[CH_2]_3$).—Prepared in the same way from cycloheptanone (yield 68·5%), this formed *crystals*, m.p. 133° (from ethanol) (Found: C, 87·7; H, 7·5; N, 5·0. $C_{21}H_{21}N$ requires C, 87·75; H, 7·4; N, 4·9%).

[21] This compound was originally described in our B.P. 1,035,449/1966; R. W. Woodard, K. Baldzer, and D. W. Boykin, *J. Medicin. Chem.*, 1971, **14**, 1131 give m.p. 52—53°.

1,4,8,9-*Tetrahydro*-2H-[1]*benzazepino*[3,2,1-hi]*pyrano*-[4,3-b]*indole* (XVII).—A solution of 5-ethylidenamino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (4·72 g, 0·02 mol) in glacial acetic acid (30 ml) was treated with tetrahydro-γ-pyrone (2·0 g, 0·02 mol), and heated at 100° for 0·75 h. After evaporation of the acetic acid, the residue was treated with 2N-ammonium hydroxide and extracted with chloroform. The crude product was dissolved in the minimum amount of ethyl acetate and treated with light petroleum, which precipitated an impurity. Evaporation of the solution yielded the *pyranoindole* (1·2 g, 21·8%) as an off-white solid, m.p. 132—135° (from ethanol) (Found: C, 82·5; H, 6·4; N, 4·9. $C_{19}H_{17}NO$ requires C, 82·9; H, 6·2; N, 5·1%); $\lambda_{max.}$ 210, 263, and 308 nm (log ε 4·45, 4·15, and 4·17); $\lambda_{min.}$ 243 and 287 nm (log ε 3·89 and 3·91) [Found: *M* (mass spec.), 275. $C_{19}H_{17}NO$ requires *M*, 275·3].

5-(1-*Carboxyethylidenamino*)-10,11-*dihydro*-5H-*dibenz*-[b,f]*azepine* (XVIII).—5-Amino-10,11-dihydro-5*H*-dibenz-[*b*,*f*]azepine base (4·2 g, 0·02 mol) and pyruvic acid (1·94 g, 1·1 × 0·02 mol) in ethanol (12·6 ml) containing acetic acid (2 drops) were boiled for 0·5 h and evaporated *in vacuo*. Crystallisation from benzene–light petroleum yielded the pale yellow *hydrazone* (4·07 g, 72·6%), m.p. 113—114° (Found: C, 72·9; H, 6·0; N, 10·0. $C_{17}H_{16}N_2O_2$ requires C, 72·85; H, 5·75; N, 10·0%).

6,7-*Dihydroindolo*[1,7-ab][1]*benzazepine*-1-*carboxylic Acid* (XIX) *and its Ethyl Ester* (XX).—5-Amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine hydrochloride (24·6 g, 0·1 mol) and pyruvic acid (8·8 g, 0·1 mol) were boiled in ethanol (100 ml). Ammonium chloride separated, and after 1 h this was filtered off. The filtrate was evaporated, the residue was treated with ether and a little 2N-hydrochloric acid, and the mixture was filtered. The ether layer was extracted three times with ammonia solution (1 part *d* 0·880: 1 part water), washed with water, dried, and evaporated to yield a syrup which was distilled, b.p. (air-bath) *ca.* 110—130° at 10^{-3} mmHg. The distillate was crystallised from light petroleum, and gave the *ethyl ester*, m.p. 90—92° (3·8 g, 13·0%) (Found: C, 77·9; H, 6·0; N, 4·6. $C_{19}H_{17}NO_2$ requires C, 78·3; H, 5·9; N, 4·8%).

The ammonia solution was made acid, and was extracted with ether. Evaporation of the latter yielded a solid which was crystallised from methanol to give the *acid* (10·0 g, 37·9%), m.p. 221—223° (decomp.) (Found: C, 77·4; H, 4·9; N, 5·6. $C_{17}H_{13}NO_2$ requires C, 77·5; H, 4·8; N, 5·3%).

When the cyclisation was repeated with the addition of some ethanolic 5N-hydrogen chloride the ester was the only product. Alkaline hydrolysis yielded the free acid.

6,7-*Dihydroindolo*[1,7-ab][1]*benzazepine* (XXI).—The acid (XIX) (0·5 g), quinoline (4 ml), and copper chromite (0·05 g) were heated at 220° for 30 min; decarboxylation was then complete. The cooled mixture was treated with ether and filtered, and the filtrate was washed successively with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water. The residue from evaporation (0·3 g, 72%) was purified by alumina chromatography of a benzene solution, followed by crystallisation from ethanol to give the *indole*, m.p. 96—97° (Found: C, 87·7; H, 5·9; N, 6·5. $C_{16}H_{13}N$ requires C, 87·6; H, 6·0; N, 6·4%); $\lambda_{max.}$ 210, 259, 298, and 307; $\lambda_{min.}$ 239, 274, and 302 nm (log ε 4·50, 4·10, 4·17, and 4·17; 3·73, 3·92, and 4·16). For another preparation see later.

6,7-*Dihydroindolo*[1,7-ab][1]*benzazepin*-1(2H)-*one* (XXII).—This compound was made in a manner similar to that of ref. 22. 10,11-Dihydro-5*H*-dibenz[*b*,*f*]azepine (58·5 g, 0·3 mol), chloroacetyl chloride (28 ml; slight excess), and dry benzene (180 ml) were boiled for 3 h; the mixture was filtered, evaporated to smaller volume, and treated with light petroleum, giving the *chloroacetyl derivative*, m.p. 97—98° (78 g, 95%) (Found: Cl, 13·2. $C_{16}H_{14}ClNO$ requires Cl, 13·0%). This material was mixed with powdered anhydrous aluminium chloride (78 g) and heated slowly to 150°; a vigorous reaction occurred with liberation of hydrogen chloride. After 15 min this reaction had ceased. The mixture was cooled and decomposed with ice and ether. Insoluble lumps were dissolved in warm benzene. The combined ether–benzene layers were washed with sodium hydrogen carbonate solution and water. Evaporation yielded the *oxindole*, which crystallised from benzene–light petroleum (59·5 g, 84·5% overall); m.p. 96—98° (not 198° as stated in the patent) (Found: C, 82·0; H, 5·4; N, 5·8. $C_{16}H_{13}NO$ requires C, 81·7; H, 5·6; N, 5·95%).

6,7-*Dihydroindolo*[1,7-ab][1]*benzazepine* (XXI).—The oxindole derivative (XXII) (23·5 g, 0·1 mol) in dry tetrahydrofuran (235 ml) was added during 15 min to a stirred suspension of lithium aluminium hydride (3·8 g, 0·1 mol) in dry ether (100 ml) in a nitrogen atmosphere. A slight exothermic reaction occurred but the temperature did not exceed 33°. The mixture was stirred and boiled for 3 h, cooled to 0°, and decomposed with water (3·8 ml), tetrahydrofuran (7·6 ml), and N-sodium hydroxide (15·2 ml) as described for 5-amino-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine. The mixture was filtered, the filtrate was evaporated, and the crude product, dissolved in benzene, was passed through a column of alumina (grade II). Evaporation of the first eluates followed by crystallisation from ethanol yielded the indole, m.p. 100—102° (16·2 g, 73·9%), identical (t.l.c., and u.v. spectrum) with the product obtained by decarboxylation of 6,7-dihydroindolo[1,7-*ab*][1]benzazepine-1-carboxylic acid (the m.p. was slightly higher).

1,2,3,4,4a,8,9,14a-*Octahydro*[1]*benzazepino*[3,2,1-jk]*carbazole* (XXIV; X = $[CH_2]_2$).—The hexahydrocarbazole (XV; X = $[CH_2]_2$) (3·3 g, 0·012 mol) was dissolved in a mixture of dry tetrahydrofuran (30 ml) and liquid ammonia (70 ml), and was treated with sodium (0·55 g, 0·024 mol), added in small pieces during 10—15 min. The blue colour became permanent on the addition of the last piece. After a further 10 min the mixture was treated with excess of ammonium chloride, and allowed to evaporate; the residue was treated with water and ether. The ether layer yielded the *octahydro-derivative* (2·4 g, 72%), which crystallised from light petroleum with m.p. 103° (Found: C, 87·3; H, 7·6; N, 5·3. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7; N, 5·1%); $\lambda_{max.}$ 210 and 300 nm (log ε 4·46 and 4·24); $\lambda_{min.}$ 253 nm (log ε 3·57).

2,3,3a,7,8,13a-*Hexahydro*-1H-[1]*benzazepino*[3,2,1-hi]-*cyclopent*[b]*indole* (XXIV; X = CH_2).—This was obtained similarly from the tetrahydro-compound (XV; X = CH_2) (yield 83%) as a viscous *oil*, b.p. 250—260° (air-bath) at $2·3 \times 10^{-6}$ mmHg (Found: C, 87·3; H, 7·1; N, 5·4. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3; N, 5·4%).

1,2,6,7-*Tetrahydroindolo*[1,7-ab][1]*benzazepine* (XXIII).—6,7-Dihydroindolo[1,7-*ab*][1]benzazepine (2·19 g, 0·01 mol) was dissolved in dry tetrahydrofuran (44 ml) and liquid ammonia (44 ml) and was treated with sodium (0·51 g, 2·2 × 0·1 mol) as just described. After the appearance of a blue colour lasting 5—10 min, the mixture was treated with a slight excess of ammonium chloride and worked up as before. The residue from the ether layer crystallised from

[22] J. R. Geigy, A. G., B.P. 897,052.

ethanol or light petroleum to give the *indoline* (1·88 g, 85%), m.p. 79—81° (Found: C, 87·1; H, 6·8; N, 6·15. $C_{16}H_{15}N$ requires C, 86·8; H, 6·8; N, 6·3%); $\lambda_{max.}$ 211 and 294; $\lambda_{min.}$ 252 nm (log ε 4·43 and 4·27; 3·40). For 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine: $\lambda_{max.}$ 212 and 291; $\lambda_{min.}$ 250 nm (log ε 4·40 and 4·27; 3·32); τ 2·7—3·3 (7H, m, ArH), 6·03 (2H, t, *J ca.* 8 Hz, ArCH_2), and 6·95 (6H, t + s, N·CH_2 + CH_2·CH_2).

2-*Dimethylaminomethyl*-6,7-*dihydroindolo*[1,7-ab][1]*benzazepine* (XXV; $R^1 = R^2 =$ Me).—Aqueous dimethylamine solution (5·26N; 0·76 ml, 0·004 mol) was added below the surface of glacial acetic acid (4 ml) with cooling, and then 40% formaldehyde solution (0·3 ml, 0·004 mol) was added, followed by 6,7-dihydroindolo[1,7-*ab*][1]benzazepine (0·88 g, 0·004 mol). No reaction occurred until dioxan (7 ml) had been added to bring the indole into solution; the reaction was completed by warming at 40° for 48 h and the mixture was poured into water. Some neutral material was extracted with ether, and the aqueous portion was made alkaline and extracted with ether. Evaporation yielded a base (0·4 g, 36%), which was converted into a *hydrochloride* and crystallised from water containing a little hydrochloric acid; m.p. 135—137° (Found: C, 73·0; H, 7·1; Cl, 11·2. $C_{19}H_{20}N_2$,HCl requires C, 72·9; H, 6·8; Cl, 11·3%).

2-N-*Benzyl*-N-*methylaminomethyl*-6,7-*dihydroindolo*[1,7-ab][1]*benzazepine* (XXV; R^1 = Me, R^2 = $PhCH_2$).—This was prepared similarly from *N*-benzylmethylamine (6·65 g, 1·1 × 0·05 mol), acetic acid (25 ml), formaldehyde (4·1 ml, 1·1 × 0·05 mol), the indole derivative (11·0 g, 0·05 mol), and dioxan (25 ml). After 65 h at 40° the mixture was poured into water and ether. Very little basic material was found in the aqueous layer but when the ether was shaken with 2N-hydrochloric acid a gummy hydrochloride was precipitated. This was washed several times with ether and then made alkaline and extracted with fresh ether. The dried ether solution was treated with a slight excess of dry ethereal hydrogen chloride, and yielded the base hydrochloride (16·0 g, 82%), which was used directly for the following catalytic debenzylation.

2-*Methylaminomethyl*-6,7-*dihydroindolo*[1,7-ab][1]*benzazepine* (XXVII).—The foregoing crude hydrochloride (15·9 g, 0·041 mol) in methanol (100 ml) was treated with charcoal and filtered. The solution was hydrogenated (20°; 1 atm) over 5% palladium–charcoal (2 g) (uptake 800 ml in 3 days). The catalyst and precipitate were filtered off and extracted with boiling methanol. Evaporation of the combined methanol extracts yielded three crops of solid (total 7·5 g, 61%). A portion recrystallised from methanol yielded the *hydrochloride*, m.p. 266—268° (Found: C, 72·1; H, 6·2; Cl, 11·8. $C_{18}H_{18}N_2$,HCl requires C, 72·3; H, 6·5; Cl, 11·9%). The remainder was converted into an oily base and then into a *methanesulphonate*, m.p. 177—178° (from methanol–ether) (Found: C, 63·8; H, 5·9; N, 7·8. $C_{18}H_{18}N_2$,CH_4O_3S requires C, 63·7; H, 6·2; N, 7·8%).

6,7-*Dihydro*-2-*piperidinomethylindolo*[1,7-ab][1]*benzazepine* (XXV; $R^1R^2 = [CH_2]_5$).—This was prepared as for the dimethylaminomethyl derivative. The crude basic product (81%) was converted into a *maleate*, m.p. 228—230° (from methanol) (Found: C, 72·6; H, 6·6; N, 6·5. $C_{22}H_{24}N_2$,$C_4H_4O_4$ requires C, 72·2; H, 6·5; N, 6·5%). The *base* obtained from the maleate crystallised from light petroleum (b.p. 40—60°) with m.p. 77—78° (Found: N, 8·8. $C_{22}H_{24}N_2$ requires N, 8·8%).

6,7-*Dihydro*-2-(4-*methylpiperazin*-1-*yl*)*methylindolo*[1,7-ab][1]*benzazepine* (XXV; $R^1R^2 = [CH_2]_2$·NMe·$[CH_2]_2$).—This was prepared similarly in 59·5% yield. The *base* crystallised from light petroleum with m.p. 128° (Found: C, 79·7; H, 7·6. $C_{22}H_{25}N_3$ requires C, 80·0; H, 7·6%). The *dihydrochloride* crystallised from methanol with m.p. 242° (decomp.) (Found: Cl, 17·4; N, 10·2. $C_{22}H_{25}N_3$,2HCl requires Cl, 17·5; N, 10·4%).

2-*Dimethylaminomethyl*-1,2,6,7-*tetrahydroindolo*[1,7-ab]-[1]*benzazepine* (XXVI; $R^1 = R^2 =$ Me).—The free base of the foregoing dihydro-derivative (2·87 g, 0·0104 mol) was dissolved in a mixture of dry tetrahydrofuran (29 ml) and liquid ammonia (58 ml) and treated with sodium (0·53 g, 2·2 × 0·0104 mol) as described earlier. After removal of the ammonia the residue was treated with 2N-sodium hydroxide and ether. The ether layer yielded a base which was converted into a *hydrochloride*, m.p. 208—210° (2·1 g, 73%) (Found: C, 72·3; H, 7·3; Cl, 11·2. $C_{19}H_{22}N_2$,HCl requires C, 72·5; H, 7·4; Cl, 11·3); $\lambda_{max.}$ 212·5 and 294; $\lambda_{min.}$ 250 nm (log ε 4·38 and 4·27; 3·43).

The hydrochlorides of the following analogous compounds were obtained in the same way: 2-*methylaminomethyl*-, m.p. *ca.* 268° (Found: C, 72·2; H, 7·0; Cl, 11·8. $C_{18}H_{20}N_2$,HCl requires C, 71·9; H, 7·0; Cl, 11·8%); 2-*piperidinomethyl*-, m.p. 229—231° (Found: C, 74·5; H, 7·7; Cl, 9·9. $C_{22}H_{26}N_2$,HCl requires C, 74·45; H, 7·7; Cl, 10·0%); 2-(4-*methylpiperazin*-1-*ylmethyl*)-, m.p. *ca.* 280° (Found: C, 63·1; H, 7·3; Cl, 16·7. $C_{22}H_{27}N_3$,2HCl,0·6H_2O requires C, 63·3; H, 7·3; Cl, 17·0%).

1-[1-(*Dimethylaminomethyl*)*ethyl*]-6,7-*dihydro*-2-*methylindolo*[1,7-ab][1]*benzazepine* (XXX).—Aqueous 8N-dimethylamine solution (12·5 ml, 0·1 mol) was added to glacial acetic acid (80 ml) with cooling, and this was followed by 40% aqueous formaldehyde (7·5 ml, 0·1 mol). 1-Ethyl-6,7-dihydro-2-methylindolo[1,7-*ab*][1]benzazepine (13·0 g, 0·05 mol) was added and the mixture was heated at 90° for 7 h. It was next evaporated *in vacuo*, and treated with a mixture of water and ether. The aqueous layer was made alkaline, and extracted with ether. Evaporation of the ether yielded a syrup which was distilled [b.p. (air-bath) 200° at 0·006 mmHg] to yield the *base* (11 g, 69·2%) (Found: C, 82·9; H, 8·3; N, 8·8. $C_{22}H_{26}N_2$ requires C, 83·0; H, 8·2; N, 8·8%), τ ($CDCl_3$ + trace CF_3·CO_2H) 7·60 (s, CMe), *ca.* 7·8 (s, NMe_2), and 8·30 (d, *J* 7 Hz, CH*Me*); the singlet for the NMe_2 group shifted downfield on adding more trifluoroacetic acid; the other bands were not appreciably altered.

The *oxalate* had m.p. 191—193° (Found: C, 70·1; H, 7·0; N, 6·6. $C_{24}H_{28}N_2O_4$ requires C, 70·55; H, 6·9; N, 6·85%).

1-[1-(N-*Benzyl*-N-*methylaminomethyl*)*ethyl*]-6,7-*dihydro*-2-*methylindolo*[1,7-ab][1]*benzazepine* (XXXI).—A mixture prepared from *N*-benzylmethylamine (18·5 g, 2 × 0·0765 mol), glacial acetic acid (130 ml), 40% formaldehyde (11·5 ml, 2 × 0·0765 mol), and 1-ethyl-6,7-dihydro-2-methylindolo[1,7-*ab*][1]benzazepine (20 g, 0·0765 mol) was heated at 90° for 15 h, then evaporated *in vacuo* and treated with water and ether. The basic product was found in the ether layer, and was extracted with 2N-hydrochloric acid. The acid extract was made alkaline and extracted with chloroform, evaporation of which gave the crude base (21·3 g, 70·5%). The *oxalate* had m.p. 196—198° (Found: C, 74·6; H, 6·9; N, 5·8. $C_{30}H_{32}N_2O_4$ requires C, 74·4; H, 6·7; N, 5·8%).

6,7-*Dihydro*-2-*methyl*-1-[1-(*methylaminomethyl*)*ethyl*]-*indolo*[1,7-ab][1]*benzazepine* (XXXII).—The foregoing free base (7·9 g, 0·02 mol) in ethanol (60 ml) containing hydrogen chloride (0·02 mol) was hydrogenated over 5% palladium–

charcoal (2 g) at 20° and 1 atm (uptake 470 ml in 24 h). Filtration and evaporation gave material which was treated with ether and 2N-acetic acid. The acid layer was made alkaline and extracted with chloroform, which yielded a base (5·7 g, 82·6%). The *oxalate* had m.p. 179—181° (Found: C, 70·0; H, 6·8; N, 6·9. $C_{23}H_{26}N_2O_4$ requires C, 70·0; H, 6·6; N, 7·1%).

1-[(*Dimethylamino*)*methyl*]-1,4,4a,8,9,14a-*hexahydro*-2H-[1]*benzazepino*[3,2,1-hi]*pyrano*[4,3-b]*indole* (XXIX; X = O).—Aqueous 25% dimethylamine (2·54 ml, 0·014 mol) in glacial acetic acid (12 ml) was treated with formaldehyde (40%; 1·08 ml, 0·014 mol). The solution was added to a stirred suspension of the foregoing pyranoindole (3·55 g, 0·013 mol) in glacial acetic acid (20 ml), and the mixture was heated for 6 h at 100°. The solution was evaporated to dryness under reduced pressure, and the residue was treated with an excess of dilute ammonia solution. The crude base was extracted with ether and isolated as a viscous gum (2·8 g) which could not be crystallised ($\lambda_{max.}$ 212, 265, and 309 nm; $\lambda_{min.}$ 249 and 292 nm).

The crude base (2·8 g, 0·0084 mol) was dissolved in a mixture of dry tetrahydrofuran (60 ml) and liquid ammonia (150 ml), and treated with sodium (0·43 g, 0·019 mol) during 0·5 h; a permanent blue colour was then obtained. After addition of a slight excess of ammonium chloride, the mixture was evaporated to dryness. Water was added, and the product was extracted with benzene to give the *hexahydro-compound* (2·0 g, 46·1%), which distilled at 180° (air-bath) and 10^{-3} mmHg, forming a glass, m.p. *ca.* 55—60° (Found: C, 79·1; H, 8·2; N, 7·8. $C_{22}H_{26}N_2O$ requires C, 79·0; H, 7·8; N, 8·4%), $\lambda_{max.}$ 213 and 295 nm (log ε 4·40 and 4·16); $\lambda_{min.}$ 252 nm (log ε 3·74).

1-[(*Dimethylamino*)*methyl*]-1,2,3,4,4a,8,9,14a-*octahydro*-[1]*benzazepino*[3,2,1-jk]*carbazole* (XXIX; X = CH_2).—The hexahydrocarbazole (XV; X = $[CH_2]_2$) (13·8 g, 0·05 mol) was subjected to a Mannich reaction with dimethylamine and formaldehyde as described for the preparation of the foregoing pyrano[4,3-*b*]indole. After purification, in benzene solution on an alumina column, the basic product (4·4 g, 26%) was reduced with sodium and ammonia to give the octahydro-base. This was purified (benzene–alumina) and converted into a *hydrochloride*, m.p. 250—255° (Found: C, 74·7; H, 7·9; Cl, 9·5. $C_{23}H_{28}N_2$,HCl requires C, 74·9; H, 7·9; Cl, 9·6%).

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