## 58. *The Chemistry of Carcinogenic Nitrogen Compounds. Part X.* The Pfitzinger Reaction in the Synthesis of* 1 : 2-*Benzacridines.*

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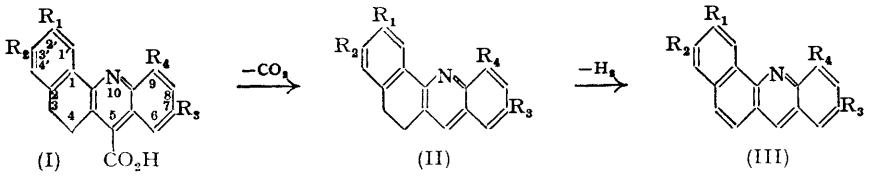
The Pfitzinger–Borsche condensation of isatins with diversely substituted 1-tetralones, followed by decarboxylation of the cinchoninic acids and dehydrogenation of the 3 : 4-dihydro-1 : 2-benzacridines by chloranil, has been successfully employed for the synthesis of several 1 : 2-benzacridines containing methoxy- and halogeno-substituents.

The use of the Pfitzinger–Borsche reaction (Pfitzinger, *J. pr. Chem.*, 1897, **56**, 283; Borsche and Rottsieper, *Annalen*, 1910, **377**, 70) for preparation of 1 : 2-benzacridines was initiated by von Braun and Wolff (*Ber.*, 1922, **55**, 3685; cf. von Braun and Stuckenschmidt, *Ber.*, 1923, **56**, 1727; von Braun, *Annalen*, 1927, **451**, 1), who prepared 3 : 4-dihydro-1 : 2-benzacridine and several of its derivatives by decarboxylation of the corresponding 5-carboxylic acids. Dehydrogenation of the 3 : 4-dihydrobenzacridines was effected by these authors by means of lead oxide at a high temperature, which readily gave 1 : 2-benzacridine itself but brought about the loss of mobile substituents such as chlorine atoms; these observations have recently been confirmed and extended by one of us (Buu-Hoï, *J.*, 1946, 792).

The present work reports the preparation, by the same sequence of reactions, of several new 1 : 2-benzacridines bearing halogen atoms and methoxy-groups, and a modification of the dehydrogenation method, in which chloranil in xylene is used in place of lead oxide. As with carbazole derivatives (Barclay and Campbell, *J.*, 1945, 530) and more complex compounds of the same type (Buu-Hoï, Hoán, Khôi, and Xuong, *J. Org. Chem.*, 1949, **14**, 492; 1950, **15**, 511, 957; 1951, **16**, 315), all the substituents were retained during the dehydrogenation. Thus, 2′-chloro-7-methyl-1 : 2-benzacridine-5-carboxylic acid (I; $R_1$ = Cl, $R_2$ = $R_4$ = H, $R_3$ = Me), obtained from 7-chloro-1-tetralone and 5-methylisatin,




(I) (II) (III)

gave on decarboxylation 2′-chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine (II; $R_1$ = Cl, $R_2$ = $R_4$ = H, $R_3$ = Me), and this was smoothly converted by chloroanil into 2′-chloro-7-methyl-1 : 2-benzacridine (III; $R_1$ = Cl, $R_2$ = $R_4$ = H, $R_3$ = Me); from the same ketone and 5 : 7-dimethylisatin, 2′-chloro-7 : 9-dimethyl-1 : 2-benzacridine (III; $R_1$ = Cl, $R_2$ = H, $R_3$ = $R_4$ = Me) was similarly synthesised. That both chlorine and bromine atoms are retained in this method is demonstrated by the successful preparation of 7-bromo-2′-chloro-1 : 2-benzacridine (III; $R_1$ = Cl, $R_2$ = $R_4$ = H, $R_3$ = Br) from 7-chloro-1-tetralone and 5-bromoisatin.

In the group of benzacridines containing methoxy-groups, the present synthesis is a useful alternative to the modified Ullmann–Fettvadjian method (Buu-Hoï, *J.*, 1950, 2096). Thus, 2′-methoxy-1 : 2-benzacridine was readily obtained from 3 : 4-dihydro-2′-methoxy-1 : 2-benzacridine-5-carboxylic acid (I; $R_1$ = OMe, $R_2$ = $R_3$ = $R_4$ = H) *via* its decarboxylation product. Condensation of 7-methoxy-1-tetralone with isatin had already been performed by von Braun (*loc. cit.*), but the m. p. 123° given for the reaction product was erroneous; dehydrogenation of 3 : 4-dihydro-2′-methoxy-1 : 2-benzacridine could also be effected through the lead monoxide method. When, however, alkyl groups were present simultaneously, the chloranil method was far superior, as in the case of 2′-methoxy-3′ : 7-dimethyl-1 : 2-benzacridine (III; $R_1$ = OMe, $R_2$ = $R_3$ = Me, $R_4$ = H), prepared from 7-methoxy-6-methyl-1-tetralone and 5-methylisatin.

* Part IX, *J.*, 1951, 2964.

During this work, several other 3 : 4-dihydro-1 : 2-benzacridine-5-carboxylic acids were also prepared from 1-tetralones, and some of the decarboxylation products were isolated, but further study was discontinued because the 1 : 2-benzacridines were not carcinogenic.

## Experimental

*2'-Chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine-5-carboxylic Acid.*—7-Chloro-1-tetralone, m. p. 96°, was prepared from chlorobenzene by the standard succinic anhydride method; von Braun (*loc. cit.*) prepared it by a Sandmeyer reaction from the diazo-compound from 7-aminotetralone and gave m. p. 94°. A solution of 7-chloro-1-tetralone (2 g.), 5-methylisatin (2 g.), and potassium hydroxide (2 g. in 2 c.c. of water) in ethanol (10 c.c.) was refluxed for 24 hours on a water-bath. After dilution with water (50 c.c.), removal of neutral impurities by ether-extraction, and acidification with acetic acid, an *acid* (3·5 g.) was precipitated, crystallising as fine, pale yellow needles, shrinking above 200°, m. p. 269°, from toluene (Found : C, 70·1; H, 4·5. $C_{19}H_{14}O_2NCl$ requires C, 70·5; H, 4·3%).

The pale yellow *acids* recorded in the table were similarly prepared.

| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield, % | M. p. | Crystal form | Solvent | Formula | Found, % C | H | N | Required, % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Substituted* 3 : 4-*dihydro*-1 : 2-*benzacridine*-5-*carboxylic acids* (I). | | | | | | | | | | | | | | |
| Cl | — | Me | Me | 70 | 246° | Needles | PhMe | $C_{20}H_{16}O_2NCl$ | 70·8 | 4·5 | — | 71·1 | 4·7 | — |
| Cl | — | Br | — | 90 | 319 | Prisms | EtOH | $C_{18}H_{11}O_2NBrCl$ | 55·2 | 3·0 | — | 55·6 | 2·8 | — |
| MeO | — | — | — | 90 | 229 | Prisms | MeOH | $C_{19}H_{15}O_3N$ | — | — | 4·6 | — | — | 4·6 |
| MeO | Me | Me | — | — | 256 | Needles | EtOH | $C_{21}H_{19}O_3N$ | 75·4 | 5·6 | — | 75·7 | 5·7 | — |
| MeO | Me | — | — | — | 264 [a] | Needles | EtOH | $C_{20}H_{17}O_3N$ | 75·0 | 5·4 | — | 75·4 | 5·3 | — |
| MeO | MeO | — | — | — | 263–264 | — | EtOH | $C_{20}H_{17}O_4N$ | 71·4 | 5·0 | — | 71·6 | 5·1 | — |
| — | MeO | — | — | 95 | 329 | Needles | Xylene | $C_{19}H_{15}O_3N$ | — | — | 4·4 | — | — | 4·6 |
| — | MeO | Me | — | 90 | 319 | — | — | $C_{20}H_{17}O_3N$ | — | — | 4·3 | — | — | 4·4 |
| — | MeO | Br | — | 80 | 308 | Prisms | AcOH | $C_{19}H_{14}O_3NBr$ | 59·1 | 3·4 | — | 59·4 | 3·6 | — |
| *Substituted* 3 : 4-*dihydro*-1 : 2-*benzacridines* (II). | | | | | | | | | | | | | | |
| Cl | — | Me | Me | — | 99° | Prisms [1] | EtOH–$C_6H_6$ | $C_{19}H_{16}NCl$ | 77·4 | 5·7 | — | 77·6 | 5·4 | — |
| Cl | — | Br | — | — | 122 | Needles [2] | EtOH | $C_{17}H_{11}NBrCl$ | 59·1 | 3·1 | — | 59·2 | 3·2 | — |
| MeO | — | — | — | — | 82 | Leaflets [3] | EtOH | $C_{18}H_{15}ON$ | 82·4 | 5·9 | — | 82·7 | 5·7 | — |
| MeO | Me | Me | — | — | 129 | Needles [4] | EtOH | $C_{20}H_{19}ON$ | 83·1 | 6·9 | — | 83·0 | 6·6 | — |
| MeO | Me | — | — | — | 109 | Needles [5] | EtOH | $C_{19}H_{17}ON$ | 82·6 | 6·4 | — | 82·9 | 6·2 | — |
| MeO | MeO | — | — | — | 114–115 | Needles [6] | EtOH | $C_{19}H_{17}O_2N$ | — | — | 4·7 | — | — | 4·8 |
| — | MeO | — | — | — | 90 | Needles [7] | EtOH | $C_{18}H_{15}ON$ | 82·5 | 6·0 | — | 82·7 | 5·7 | — |
| — | MeO | Me | — | — | 107 | Needles [8] | EtOH | $C_{19}H_{17}ON$ | 82·5 | 6·2 | — | 82·9 | 6·2 | — |
| — | MeO | Br | — | — | 151 | Prisms [9] | $C_6H_6$ | $C_{18}H_{14}ONBr$ | 63·2 | 4·2 | — | 63·5 | 4·1 | — |
| MeO | — | Br | — | — | 158 | Needles | EtOH | $C_{18}H_{14}ONBr$ | — | — | 4·0 | — | — | 4·1 |

[a] Solvated crystals melt at <200°.

[1] Picrate, m. p. 143°. [2] Picrate, m. p. 236°. [3] Picrate, m. p. 231°. [4] Pale yellow; picrate, m. p. 254°. [5] Yellow; *picrate*, prisms (from EtOH), m. p. 242° (Found : N, 11·4. $C_{25}H_{20}O_8N_4$ requires N, 11·1%). [6] Pale yellow; picrate, m. p. 227°. [7] Picrate, m. p. 211°. [8] Picrate, m. p. 216°. [9] Yellow.

*2'-Chloro-3 : 4-dihydro-7-methyl-1 : 2-benzacridine.*—The well-dried corresponding carboxylic acid (2 g.) was heated above its m. p. in a vacuum, and the residue distilled. The distillate (1·2 g.) formed fine shiny, colourless needles, m. p. 129°, from ethanol (Found : C, 77·0; H, 5·1. $C_{18}H_{14}NCl$ requires C, 77·2; H, 5·0%), and gave a picrate crystallising as fine shiny yellow prisms, m. p. 233°, from ethanol. Decarboxylation of the other acids gave yields ranging from 60% (for the halogen-containing acids) to 90%.

The *dihydro*-compounds tabulated were similarly prepared.

*2'-Chloro-7-methyl-1 : 2-benzacridine.*—A solution of the corresponding dihydro-compound (0·5 g.) and chloranil (1 g.) in dry xylene (10 c.c.) was refluxed for 48 hours. After cooling and filtration, and repeated washing of the filtrate with dilute aqueous sodium hydroxide, then with water, the xylene was evaporated, and the residue crystallised as silky pale yellow needles (0·3 g.), m. p. 141°, from ethanol (Found : N, 4·9. $C_{18}H_{12}NCl$ requires N, 5·0%); the corresponding *picrate* crystallised as fine, deep yellow needles, m. p. 247°, from ethanol (Found : N, 11·2. $C_{24}H_{15}O_7N_4Cl$ requires N, 11·0%). All the other dehydrogenations gave the following products in excellent yield ranging from 70 to 90% (pure) :

*2'-Chloro-7 : 9-dimethyl-1 : 2-benzacridine* formed pale yellow shiny leaflets, m. p. 162°, from benzene (Found : N, 4·6. $C_{19}H_{14}NCl$ requires N, 4·8%). *7-Bromo-2'-chloro-1 : 2-benz-*

*acridine* formed almost colourless needles, m. p. 192°, from benzene (Found : N, 4·0. $C_{17}H_9NBrCl$ requires N, 4·1%); the orange-yellow picrate had m. p. 235°. *2'-Methoxy*-1 : 2-*benzacridine* formed pale yellow prisms, m. p. 128°, from ethanol (Found : C, 83·3; H, 5·0. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·0%). *2'-Methoxy*-3' : 7-*dimethyl*-1 : 2-*benzacridine* crystallised as silky, almost colourless needles, m. p. 159°, from ethanol (Found : N, 4·8. $C_{20}H_{17}ON$ requires N, 4·9%).

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