Carcinogenic Nitrogen Compounds. Part LIV.[1] Some Limitations to the Bernthsen Synthesis of *meso*-Substituted Benzacridines

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The Bernthsen reaction of trialkylacetic acids with *N*-arylnaphthylamines leads to benzacridines having no substituent in the *meso*-position; further, an indirect limitation to the applicability of the Bernthsen synthesis is the impossibility of using the Knoevenagel method for preparing *N*-arylnaphthylamines bearing alkylthio groups, these being split off in the course of the reaction.

The great majority of benzacridines and dibenzacridines bearing an alkyl group in the *meso*-position have been prepared by the Bernthsen reaction, which consists of heating carboxylic acids or their anhydrides with the appropriate diarylamine in the presence of zinc chloride;[2] for this, not only straight-chain aliphatic acids but also α-alkylacetic acids (such as isobutyric and diethylacetic acid[3]) gave been used with success. With the aim of preparing, for cancer research, benzacridines and dibenzacridines bearing tertiary alkyl groups in the *meso*-position, we have investigated the behaviour of various trialkylacetic acids in the Bernthsen reaction.

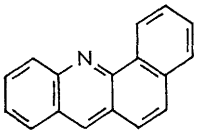
We found that heating, under reflux, of pivalic acid with *N*-phenyl-1-naphthylamine and zinc chloride yielded benz[*c*]acridine (I) as the main product; with *N*-phenyl-2-naphthylamine and with di-2-naphthylamine, benz[*a*]acridine (II) and dibenz[*a*,*j*]acridine (III) were obtained, respectively. These non-substituted

[1] Part LIII, N. P. Buu-Hoï, A. Martani, A. Ricci, M. Dufour, P. Jacquignon, and G. Saint-Ruf, preceding Paper.

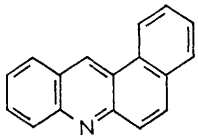
[2] A. Bernthsen, *Annalen*, 1884, **224**, 1; N. P. Buu-Hoï, *J. Chem. Soc.*, 1946, 792.

[3] N. P. Buu-Hoï, *J. Chem. Soc.*, 1949, 670; N. P. Buu-Hoï, R. Royer, B. Eckert, and P. Jacquignon, *ibid.*, 1952, 4867.

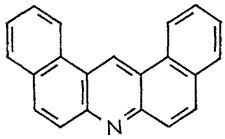
acridines, of which the yields were 8—12%, were obviously the result of the cleavage of the t-butyl group which had occupied the *meso*-position, under the influence of the catalyst. In spite of the poor yields in pure acridines, this reaction is useful for preparing compounds like (I) which are not easily accessible by more conventional methods. It is interesting to note that benzacridines bearing t-alkyl groups in sites other



(I)



(II)



(III)

than *meso* have successfully been prepared,[4] which suggests the particular lability of a *meso*-located t-butyl radical. The influence of the structure of, on the one hand, the trialkylacetic acid, and of the diarylamine on the other, was illustrated by an unsuccessful attempt to prepare dibenz[*c*,*h*]acridine from pivalic acid and di-1-naphthylamine, and by the decreasing reactivity observed with higher homologues of pivalic acid {dibenz[*a*,*j*]acridine was obtained in only 3% yield from αα-dimethylvaleric acid, and none of the three acridines (I), (II), or (III) could be obtained with 2,2-dimethyloctanoic acid}; in these negative cases, the diarylamine could be totally or almost totally recovered. This points to the acylation of the diarylamines, which is subject to steric hindrance, as being the limiting factor in our synthesis.

Another, this time indirect, limitation to the generalisation of the Bernthsen reaction was encountered in an attempt to prepare benz[*c*]acridines bearing a methylthio substituent; *N*-(4-methylthiophenyl)-1-naphthylamine, necessary for this preparation, could not be obtained by applying the Knoevenagel condensation reaction of naphthols with primary arylamines in the presence of iodine[5] to *p*-thioanisidine; heating of this amine with 1-naphthol in the presence of even catalytic amounts of iodine resulted, surprisingly, in extensive cleavage of the methylthio group, the main reaction product being *N*-phenyl-1-naphthylamine itself. This cleavage of the methylthio group, which also occurred when *p*-thioanisidine was heated alone in the presence of small amounts of iodine, was accompanied by evolution of gases, among which methanethiol was present. In the absence of iodine, this cleavage did not occur, and the intrinsic stability of *p*-thioanisidine was manifest in successful Ullmann–Fetvadjian reactions with naphthols and paraformaldehyde. Thus, 9-methylthiobenz[*c*]acridine, 5-methyl-9-methylthiobenz[*c*]acridine, and 10-methylthiobenz[*a*]acridine were easily obtained from 1- and 4-methyl-1-naphthol and 2-naphthol, respectively.

[4] N. P. Buu-Hoï, *J. Chem. Soc.*, 1950, 1146.
[5] E. Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1, 17; N. P. Buu-Hoï, *J. Chem. Soc.*, 1952, 4346.
[6] F. Ullmann and A. La Torre, *Ber.*, 1904, **37**, 2924; F. Ullmann, *Annalen*, 1907, **355**, 349.

EXPERIMENTAL

Benz[c]*acridine* (I).—A mixture of *N*-phenyl-1-naphthylamine (2·2 g.), pivalic (trimethylacetic)acid (1·1 g.), and freshly fused zinc chloride (1 g.) was heated under reflux for 20 hr.; after cooling, the mixture was triturated with warm 25% aqueous sodium hydroxide in the presence of toluene; the organic later was washed with water and dried (Na_2SO_4), the solvent removed, and the residue distilled *in vacuo*. The resinous material obtained was dissolved in ethanol and treated with picric acid, to give a picrate, prisms, m. p. 222° (from ethanol); this was decomposed by means of aqueous ammonia, to furnish benz[*c*]acridine, prisms (0·25 g.), m. p. 108° (from ethanol). Identification was by comparison with an authentic sample prepared according to the literature [6] (a mixture of the 2 samples showed no depression of the m. p.), and by mass spectrometry (Found: *M*, 229. Calc. for $C_{17}H_{11}N$: *M*, 229).

Benz[a]*acridine* (II).—Similarly prepared with *N*-phenyl-2-naphthylamine, pivalic acid, and zinc chloride, this acridine formed needles (0·3 g.), m. p. 131° (lit.,[6] 131°) (from ethanol) (Found: C, 88·8; H, 5·0; N, 6·1%; *M*, 229. Calc. for $C_{17}H_{11}N$: C, 89·0; H, 4·8; N, 6·1%; *M*, 229).

Dibenz[a,j]*acridine* (III).—(a) *With pivalic acid.* Treatment of a mixture of di-2-naphthylamine (2·7 g.), pivalic acid (1·5 g.), and zinc chloride (1·5 g.) as above afforded the acridine (III), faintly yellow needles (0·45 g.), m. p. 216° (lit.,[7] 216°) (from ethanol) (Found: C, 90·2; H, 4·6; N, 5·0. Calc. for $C_{21}H_{13}N$: C, 90·3; H, 4·7; N, 5·0%).

(b) *With αα-dimethylvaleric acid.* The acid (2 g.) yielded 3% of the same acridine, m. p. 216°; picrate, m. p. 322° (lit., 323°).

Condensations Attempted with Various Secondary Diarylamines.—(a) *Pivalic acid and di-1-naphthylamine.* Dibenz[*c*,*h*]acridine, if indeed it were formed, could not be isolated, and most of the amine was recovered unchanged along with a resin which could not be distilled *in vacuo*.

(b) *Pivalic acid and* N-o-*tolyl- and* N-o-*fluorophenyl-1-naphthylamine.* These attempts, both negative, were made in view of difficulties previously encountered in preparing 11-methyl- and 11-fluoro-benz[*c*]acridine by the Ullmann–Fetvadjian method.

(c) *αα-Dimethylvaleric acid and 2,2-dimethyloctanoic acid.* These were negative with all the diarylamines except di-2-naphthylamine and the valeric acid (see above).

(d) *Pivalic acid and diphenylamine.* Refluxing (20 hr.) of equimolar quantities of these two reagents with zinc chloride resulted in 8—10% of acridine, m. p. 111° (from hexane); picrate, m. p. 207—208°. The de-t-butylation mechanism leading to the acridine is evidenced by an earlier observation [8] that, under less drastic conditions, 9-t-butylacridine could be isolated.

Knoevenagel Reaction of p-*Thioanisidine with* 1-*Naphthol.*—A mixture of *p*-thioanisidine (20 g.) and 1-naphthol (20 g.) was refluxed for 10 hr. with iodine (0·2 g.); along with the formation of steam, there was a considerable evolution of fetid gases, among them methanethiol, which was identified by its characteristic smell and its reducing effect on hydrogen peroxide. The thick reaction product obtained on cooling was mostly insoluble in both toluene and aqueous sodium hydroxide; the toluene-soluble

[7] G. T. Morgan, *J. Chem. Soc.*, 1898, **73**, 542.
[8] N. P. Buu-Hoï and J. Lecocq, *Rec. Trav. chim.*, 1945, **64**, 250.

portion (6 g.) consisted almost entirely of *N*-phenyl-1-naphthylamine, which was characterised as follows. A solution of this product (1 g.) and arsenic trichloride (0·7 g.) in dry *o*-dichlorobenzene (5 c.c.) was refluxed for 20 min., and the precipitate obtained on cooling was recrystallised from toluene, to give 10-chloro-5,10-dihydro-3,4-benzophenarsazine,[9] yellow needles, m. p. 219° (Found: C, 58·3; H, 3·2. Calc. for $C_{16}H_{11}AsClN$: C, 58·6; H, 3·4%).

Iodine-catalysed Decomposition of p-*Thioanisidine.*—*p*-Thioanisidine (10 g.) was boiled in the presence of iodine (0·1 g.); again there was abundant evolution of fetid gases, among them methanethiol, and after 18 hr. the product was a brown tar, which was distilled *in vacuo*, giving *ca.* 5 g. of volatile material, and leaving a solid which was insoluble in benzene. The portion boiling at 70—80°/12 mm. (2 g.) gave, with acetic anhydride, acetanilide, m. p. 112° (cyclohexane), and was therefore aniline; the higher-boiling fraction (80—130°/12 mm.; 5 g.) yielded on acetylation a mixture of acetanilide and *p*-methylthioacetanilide, m. p. 126°.

10-*Methylthiobenz*[a]*acridine.*—To a boiling mixture of *p*-thioanisidine (5·6 g.) and 2-naphthol (6 g.), paraformaldehyde (1·9 g.) was added in small portions, and the mixture then heated for a few more min. and distilled *in vacuo*. The portion boiling at 270—280°/1 mm. (5 g.) solidified on treatment with ethanol; recrystallisation from the same solvent furnished the *benzacridine* as faintly yellow needles, m. p. 153° (Found: C, 78·8; H, 4·9; N, 5·2. $C_{18}H_{13}NS$ requires C, 78·5; H, 4·8; N, 5·1%); *picrate*, prisms, m. p. 256° (from toluene) (Found: N, 10·9. $C_{24}H_{16}N_4O_7S$ requires N, 11·1%).

9-*Methylthiobenz*[c]*acridine.*—Prepared similarly (20%) from 1-naphthol, and purified through its picrate, this *benzacridine* formed pale yellow prisms, m. p. 119° (from ethanol–benzene), giving, in sulphuric acid, yellow solutions which turned green (Found: C, 78·4; H, 5·0; N, 5·0%); *picrate*, microprisms, m. p. 266° (from toluene) (Found: N, 10·9%).

5-*Methyl*-9-*methylthiobenz*[c]*acridine.*—Prepared (40%) from *p*-thioanisidine (5·8 g.), 4-methyl-1-naphthol (6·2 g.), and paraformaldehyde (1·8 g.), this *benzacridine*, b. p. 280°/0·5 mm., was purified through its picrate, prisms, m. p. 256° (from toluene) (Found: N, 10·7. $C_{25}H_{18}N_4O_7S$ requires N, 10·8%); the *base* formed cream-coloured needles, m. p. 135° (from ethanol) (Found: C, 78·7; H, 5·1; N, 4·4. $C_{19}H_{15}NS$ requires C, 78·9; H, 5·2; N, 4·8%).

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[9] L. Lewis, *J. Amer. Chem. Soc.*, 1921, **43**, 2218.