Synthesis of 7,10- and 7,8-Dimethylbenz[*c*]acridine

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7,10-Dimethylbenz[*c*]acridine, commonly used in experimental cancerology, is shown to be a mixture with 7,8-dimethylbenz[*c*]acridine. Unambiguous syntheses of these two dimethylbenz[*c*]acridines are described.

SOME thirty years ago, the carcinogenic activity of benzo[*c*]acridine in mice was shown. Among derivatives of this system, 7,10-dimethylbenz[*c*]acridine (1) has proved the most sarcomatogenic.[1] A relatively large number of papers [2-7] have dealt with this compound, often taken as a typical example of a nitrogen analogue of carcinogenic methylated polycyclic hydrocarbons.

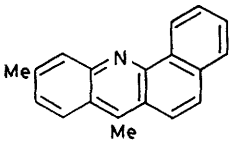
Recently, we have shown the transforming effect of this compound on hamster embryo cells in tissue culture.[8] The sample we used was prepared according to the published method,[9] and was therefore comparable with the samples used in all previous studies. This permitted us to compare efficiently the transforming effect in tissue culture with the sarcomatogenic properties *in vivo*.

However the n.m.r. spectrum of our sample (m.p. 141°) showed that it was a mixture of 7,10- (1) and 7,8-dimethylbenz[*c*]acridine (2) in the ratio 85 : 15. All attempts to separate the isomers by crystallisation or column chromatography were unsuccessful. It is not surprising that both isomers (1) and (2) are formed when the Bernthsen reaction is applied to *N*-*m*-tolyl-1-naphthylamine, since either of the two positions *ortho* to the

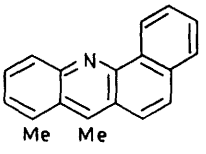
[1] A. Lacassagne, N. P. Buu-Hoï, R. Daudel, and F. Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315, and references therein.
[2] P. Daudel, B. Chenon, N. P. Buu-Hoï, P. Jacquignon, A. Lacassagne, G. Prodi, G. Vallee, R. Vasquez, and F. Zajdela, *Bull. Soc. Chim. biol.*, 1960, **42**, 135.
[3] E. W. Chan and J. K. Ball, *Biochim. Biophys. Acta*, 1971, **31**, 238.
[4] N. P. Buu-Hoï, M. Orley, M. Mangane, and P. Jacquignon, *J. Heterocyclic Chem.*, 1965, **2**, 236.
[5] P. Bothorel, A. Unanue, C. Gondere, N. P. Buu-Hoï, P. Jacquignon, and F. Perin, *Bull. Soc. chim. France*, 1966, 2920.
[6] C. R. Engel and E. Sawicki, *J. Chromatog.*, 1967, **31**, 149.
[7] C. Liberman, P. Lazar, I. Chouroulinkov, and M. Guerin, *Compt. rend. Soc. biol.*, 1968, **162**, 835.
[8] P. Markovits, J. Coppey, D. Papadopoulo, A. Mazabraud, and M. Hubert-Habart, *Internat. J. Cancer*, 1974, **14**, 215.
[9] N. P. Buu-Hoï and J. Lecocq, *Compt. rend.*, 1944, **218**, 792.

amine function of the tolyl ring can be involved in the condensation reaction.

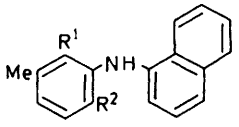
Owing to the strong carcinogenic and transforming activities of the mixture, we wished to synthesise both compounds in an unambiguous way, to characterize them, and to attempt to define what part each plays in



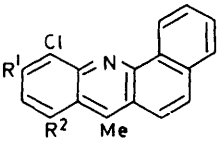
(1)



(2)



(3) R^1 = Cl, R^2 = H
(4) R^1 = H, R^2 = Cl



(5) R^1 = Me, R^2 = H
(6) R^1 = H, R^2 = Me

the biological activity of the mixture. We therefore condensed the hydrochlorides of 2-chloro-3-methyl- [10] and 2-chloro-5-methyl-aniline [11] with 1-naphthol to give the naphthylamines (3) and (4), respectively. Subjection of these two amines to the Bernthsen reaction gave, respectively, 11-chloro-7,10- (5) and 11-chloro-7,8-dimethylbenz[*c*]acridine (6). Dechlorination [12] then led to the benz[*c*]acridines (1) and (2).

The low overall yield in the preparation of the benzacridines (1) and (2) is mainly due to the difficulty of condensing acetic acid with the amines (3) and (4); the *N*-acetyl derivatives of the amines are formed rather than compounds (5) and (6). Another difficulty arose in defining the best conditions to dechlorinate compounds (5) and (6) without reducing the benz[*c*]acridine ring.

To our knowledge 7,8-dimethylbenz[*c*]acridine has never been prepared before. The description of its spectrum [4] is apparently that of either 7,9- or 7,11-dimethylbenz[*c*]acridine.[13]

EXPERIMENTAL

The ^{1}H n.m.r. spectra were recorded at 100 MHz with a Varian XL-100 spectrometer (concentrations in $CDCl_3$ down to 10^{-3}M with Me_4Si as internal standard). U.v. spectra were recorded with a Varian-Techtron 635 instrument for ethanolic solutions. T.l.c. was carred out on Merck silica gel 60F-254 (0.25 mm thick).

Preparation of 7,10-*Benz*[c]*acridine according to Reference* 9.—A mixture of *N*-*m*-tolyl-1-naphthylamine [9] (10 g), acetic anhydride (10 g), acetic acid (5 g), and powdered anhydrous zinc chloride (15 g) was kept at 260 °C for 16 h. The solid was then stirred with warm aqueous sodium hydroxide and extracted with benzene. This treatment was repeated several times. The organic phase was collected, washed with water, and dried (Na_2SO_4). The benzene was distilled off at atmospheric pressure. The residue was distilled at 0.4 mm Hg and the fraction boiling between 200 and 230° collected (yield 8.4 g). This material crystallized from benzene as yellow needles (m.p. 141°). On t.l.c. it moved as a major spot [R_F 0.85 (pentane–ether 9 : 1); R_F 0.53 (benzene)] with two other spots of very low fluoresence intensity; the latter were eliminated by chromatography on a silica gel column and elution with benzene. The material corresponding to R_F 0.53 melts at 146° (yield 3.9 g, 29%) (Found: C, 88.8; H, 6.1; N, 5.45. Calc. for $C_{19}H_{15}N$: C, 88.7; H, 5.9; N, 5.45%).

The n.m.r. spectrum of the material of m.p. 146° is a superimposition of those of compounds (1) and (2) (see later) in the ratio 85 : 15 as measured by integration of the methyl resonances.

N-(2-*Chloro*-3-*methylphenyl*)- (3) *and* N-(2-*Chloro*-5-*methylphenyl*)-1-*naphthylamine* (4).—1-Naphthol (10 g) and the hydrochloride of 2-chloro-3-methyl- or 2-chloro-5-methylaniline (10 g) were maintained at 230 °C for 6—8 h with stirring. After cooling at room temperature, the residue was extracted with chloroform. The solution was successively washed with dilute aqueous sodium hydroxide and water. Chloroform was distilled off under reduced pressure and the remaining solid was distilled under high vacuum. *Compound* (3), b.p. 193° at 0.6 mmHg, was chromatographed on a silica gel column and eluted with cyclohexane; it crystallized from pentane as yellow crystals, m.p. 74° (yield 3.6 g, 24%) (Found: C, 76.55; H, 5.55; Cl, 13.25; N, 5.6. $C_{17}H_{14}ClN$ requires C, 76.25; H, 5.25; Cl, 13.25; N, 5.25%). *Compound* (4) b.p. 165° at 0.05 mmHg, was crystallized from pentane without chromatographic treatment, as needles, m.p. 65° (yield 7 g, 47%) (Found: C, 76.1; H, 5.15; Cl, 13.2; N, 5.2%). Each amines [(3) or (4)] moved as one spot on t.l.c. (R_F 0.85 in pentane–ether, 9 : 1).

11-*Chloro*-7,10- (5) *and* 11-*chloro*-7,8-*dimethylbenz*[c]*acridine* (6).—The amine (3) or (4) (20 g), acetic anhydride (20 g), acetic acid (10 g), and powdered anhydrous zinc chloride (30 g) were kept at 200 °C for 6 h with stirring. After cooling the mixture was treated with concentrated aqueous potassium hydroxide (25%) and extracted with chloroform. The treatment was repeated until all the solid was in solution. The organic solutions was then decanted, washed with water, dried (Na_2SO_4), and distilled. The fraction boiling at 200—220° and 0.05 mmHg was isolated and dissolved in benzene. This solution was passed through a silica gel column; further addition of benzene allowed recovery of the benzacridines which remained on the column. The *benz*[c]*acridine* (5) crystallized from benzene as yellow needles, m.p. 234° (yield 1.5 g, 7%) (Found: C, 78.35; H, 4.9; Cl, 12.25; N, 4.85. $C_{19}H_{14}ClN$ requires C, 78.2; H, 4.85; Cl, 12.15; N, 4.8%). The *benz*[c]*acridine* (6) crystallized from cyclohexane as yellow needles, m.p. 208° (yield 800 mg, 4%) (Found: C, 78.3; H, 4.85; Cl, 12.25; N, 4.85%). Compounds (5) and (6) have the same R_F value (0.85) on t.l.c. (solvent benzene).

Reduction of the Chlorobenz[c]*acridines* (5) *and* (6).—Compound (5) or (6) was dissolved in ethanol (50 ml), and hydrazine hydrate (85%; 2 ml) and palladium–charcoal (10%; 100 mg) were added. The mixture was kept under reflux with stirring for 15 min. The palladium–charcoal was filtered off and washed several times with boiling chloroform. The organic solution was distilled and the residue taken up with water and extracted with benzene. The benzenic solution was washed with water, dried (Na_2SO_4),

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[12] M. L. Mosby, *J. Org. Chem.*, 1959, **24**, 421.
[13] P. Jacquignon, personal communication.

and concentrated. Chromatography on a silica gel column and elution with benzene gave first the starting material, followed by the expected pure benzacridine, which was crystallized from either cyclohexane or pentane. 7,10-*Dimethylbenz*[c]*acridine* (1) formed yellow needles, m.p. 152° (yield 150 mg, 57%) (Found: C, 88.7; H, 5.95; N, 5.45. $C_{19}H_{15}N$ requires C, 88.7; H, 5.9; N, 5.45%), $\lambda_{max.}$ (EtOH) 278 nm (ε 13 150); δ 9.52 (H-1), 8.16 (H-8), 8.15 (H-11), 8.04 (H-6), 7.75—7.85 (H-2, -3, and -4), 7.72 (H-5), 7.45 (H-9), 3.09 (7-Me), and 2.64 (10-Me), $J_{1,5}$ 0.6, $J_{5,6}$ 9.3, $J_{8,9}$ 8.8, $J_{8,11}$ 0.5, $J_{9,11}$ 1.7, $J_{9,10}$ 0.5, $J_{10,11}$ 0.8 Hz. 7,8-*Dimethylbenz*[c]*acridine* (2) afforded bright yellow needles, m.p. 147° (yield 130 mg, 50%) (Found: C, 88.75; H, 5.9; N, 5.5%); $\lambda_{max.}$ (EtOH) 281 nm (ε 5 400); 9.52 (H-1), 8.22 (H-11), 8.09 (H-6), 7.75—7.85 (H-2, -3, and -4), 7.73 (H-5), 7.625 (H-10), 7.37 (H-9), 3.30 (7-Me), and 3.05 (8-Me), $J_{1,5}$ 0.6, $J_{5,6}$ 9.6, $J_{9,10}$ 7.3, $J_{9,11}$ 1.7, $J_{10,11}$ 8.6, $J_{8,9}$ 0.8, $J_{8,11}$ 0.7 Hz.

This work was supported by the Ministère de la Qualité de la Vie.

[6/853 *Received, 4th May,* 1976]