951. *Carcinogenic Nitrogen Compounds. Part XXXI.*[1] *Benzacridines and Other Nitrogen-heterocyclic Derivatives of* m-*Ethylaniline.*

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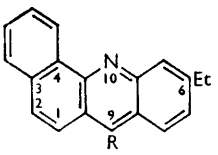
A number of substituted angular 1,2- and 3,4-benzacridines and 1,2- and 3,4-benzophenarsazines have been synthesised from *m*-ethylaniline for evaluation of carcinogenic activity, together with other nitrogen-containing heterocyclic derivatives of this amine.

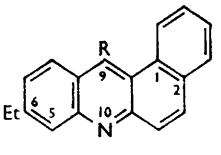
Introduction of an ethyl radical into the molecule of polycyclic aromatic hydrocarbons such as 1,2-benzanthracene and similar nitrogen-bearing heterocycles such as 1,2-benzacridine, either enhances or decreases the carcinogenic activity of the basic molecule, depending on the site of the substitution. Thus, 5- and 10-ethyl-1,2-benzanthracene are considerably more active than 1,2-benzanthracene itself, whereas the 8-isomer is completely inactive;[2] in the 3,4-benzacridine series,* the 7-ethyl-9-methyl derivative is less carcinogenic than the non-ethylated substance.[3] We have already reported syntheses of 5-, 7-, and 9-ethyl derivatives of 1,2- and 3,4-benzacridine,[4] and to extend these studies 6-ethylbenzacridines have now been prepared.

* The numbering of the benzacridines in this paper follows the recommendations of the I.U.P.A.C. which was used by us in Part XXIX (*J.*, 1961, 384), but differs from that used in some earlier papers in this series.

[1] Part XXX, Buu-Hoï and Saint-Ruf, *J.*, 1961, 2258.
[2] Cf. Shubik and Hartwell, "Compounds which have been tested for Carcinogenic Activity," National Cancer Institute, Bethesda, 1957.
[3] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[4] Buu-Hoï and Jacquignon, *J.*, 1959, 3095.

The starting material, *m*-ethylaniline, was conveniently prepared by reduction of 3-nitroacetophenone to 3-aminoacetophenone, followed by Wolff–Kishner reduction; this procedure ensures a product that is free from *ortho*- and *para*-isomers. The reaction of paraformaldehyde and *m*-ethylaniline with α- or with β-naphthol [5] yielded 6-ethyl-3,4- (I; R = H) and 1,2-benzacridine (II; R = H), respectively. 6-Ethyl-9-methyl- (I; R = Me) and 6,9-diethyl-3,4-benzacridine (I; R = Et) were prepared by a modified


(I)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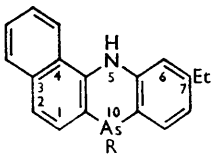
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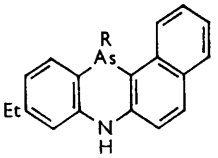
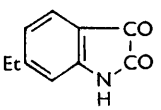
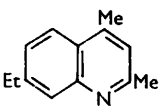

(IV)

Bernthsen reaction,[6] from *N*-*m*-ethylphenyl-1-naphthylamine with acetic and propionic anhydride, and 6,9-diethyl-1,2-benzacridine (II; R = Et) was similarly obtained from *N*-*m*-ethylphenyl-2-naphthylamine. The secondary diarylamines were prepared from *m*-ethylaniline and α- or β-naphthol; [7] their condensation with arsenic trichloride gave 10-chloro-7-ethyl-5,10-dihydro-3,4- (III; R = Cl) and -1,2-benzophenarsazine (IV; R = Cl). Replacement of the halogen by a methyl group, to give 7-ethyl-5,10-dihydro-10-methyl-3,4- (III; R = Me) and -1,2-benzophenarsazine (IV; R = Me), was achieved by means of methylmagnesium iodide.[8]

(V)



(VI)



Among the other nitrogen heterocycles prepared from *m*-ethylaniline, 6-ethylisatin (V) was obtained in low yields by a Martinet reaction involving diethyl oxomalonate; [9] it is worth mention that this cyclisation led to an apparently homogeneous product, whereas in the more usual Sandmeyer isatin synthesis as applied to *m*-substituted anilines mixtures of the two possible cyclisation products are obtained.[10] Similarly, a Combes reaction [11] with acetylacetone afforded 7-ethyl-2,4-dimethylquinoline (VI), which must have contained none (or very little) of the isomeric 5-ethyl-2,4-dimethylquinoline as the liquid base gave a sharp-melting picrate; with hexane-2,5-dione, *m*-ethylaniline furnished 1-*m*-ethylphenyl-2,5-dimethylpyrrole.

Preliminary biological tests carried out in this Institute show 6-ethyl-9-methyl-3,4-benzacridine to be appreciably carcinogenic.

Experimental

Preparation of m-*Ethylaniline.*—*m*-Nitroacetophenone, m. p. 76°, was best prepared by nitrating acetophenone (60 g.) in solution in sulphuric acid (300 g.), cooled in ethanol–solid carbon dioxide, by means of nitric acid (*d* 1·4134; 55 g.) in sulphuric acid (165 g.); reduction to *m*-aminoacetophenone, m. p. 97°, was effected by iron powder and hydrochloric acid, this procedure being more convenient than that using iron and acetic acid.[12] A solution of the

[5] For similar reactions with *m*-toluidine, see Buu-Hoï, Royer, and Hubert-Habart, *J.*, 1955, 1082.
[6] Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1946, 792.
[7] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346.
[8] Seide and Gorski, *Ber.*, 1929, **62**, 2186; Buu-Hoï, Hiong-Ki-Wei, and Royer, *Rev. Sci.*, 1944, **82**, 3237.
[9] Martinet, *Ann. Chim.* (*France*), 1919, **11**, 15.
[10] Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234.
[11] Combes, *Compt. rend.*, 1888, **106**, 1536; Buu-Hoï and Guettier, *Rec. Trav. chim.*, 1946, **65**, 502.
[12] Rupe, Braun, and von Zembruski, *Ber.*, 1901, **34**, 3522.

amino-ketone (15 g.) in diethylene glycol (38 g.) was refluxed with hydrazine hydrate (15 g.) and potassium hydroxide (15 g.) for 8 hr., with removal of water; after cooling and dilution with water, the product was taken up in ether, washed with water, dried (Na_2SO_4), recovered, and fractionated, giving *m*-ethylaniline (11 g., 80%), b. p. 214°/760 mm. This amine (1 g.) and tetrachlorophthalic anhydride (1 g.) in acetic acid (20 c.c.), when refluxed for 10 min., yielded *tetrachloro*-N-m-*ethylphenylphthalimide*, leaflets (from acetic acid) (1·2 g.), m. p. 192°, giving orange solutions in *NN*-dimethylaniline (Found: C, 49·1; H, 2·5. $C_{16}H_9Cl_4NO_2$ requires C, 49·4; H, 2·3%).

1-m-*Ethylphenyl*-2,5-*dimethylpyrrole*.—Hexane-2,5-dione (2 g.) and *m*-ethylaniline (2 g.) were refluxed for 1 hr. with one drop of acetic acid, and the product then distilled, giving the *pyrrole* (2·5 g.), b. p. 261—262°/755 mm., n_D^{24} 1·5586 (Found: C, 84·0; H, 8·5; N, 7·3. $C_{14}H_{17}N$ requires C, 84·4; H, 8·6; N, 7·0%).

7-*Ethyl*-2,4-*dimethylquinoline* (VI).—Acetylacetone (5 g.) and *m*-ethylaniline (6 g.) were refluxed for 5 hr., and the crude anil formed was heated for 1 hr. on the water-bath with sulphuric acid (50 c.c.). After cooling and basification with aqueous ammonia, the product was taken up in benzene, washed with water, dried (Na_2SO_4), recovered, and distilled; the oil obtained gave a *picrate*, orange needles, m. p. 210° (from ethanol) (Found: N, 13·1. $C_{19}H_{18}N_4O_7$ requires N, 13·4%). Basification with ammonia yielded the free *quinoline* (6 g.), b. p. 298°/751 mm., $n_D^{22·5}$ 1·5951 (Found: C, 84·0; H, 8·5. $C_{13}H_{15}N$ requires C, 84·3; H, 8·2%).

6-*Ethylisatin* (V).—A solution of *m*-ethylaniline (10 g.) and diethyl oxomalonate (13 g.) in acetic acid (50 c.c.) was refluxed for 1 hr.; after cooling, dilute hydrochloric acid was added, the precipitate of crude ethyl dioxindole-3-carboxylate obtained was suspended in 15% aqueous potassium hydroxide (30 c.c.), and the suspension boiled until a homogeneous solution was obtained. This was left to cool, then filtered, and acidified with acetic acid. Recrystallisation of the precipitate from acetic acid afforded 6-*ethylisatin* as orange needles (1 g.), m. p. 185° (Found: C, 68·6; H, 5·5. $C_{10}H_9NO_2$ requires C, 68·6; H, 5·2%).

6-*Ethyl*-3,4-*benzacridine* (I; R = H).—To a boiling mixture of *m*-ethylaniline (10 g.) and α-naphthol (15 g.), paraformaldehyde (10 g.) was added in small portions; after the violent evolution of water had subsided, the mixture was refluxed for 1 min., then fractionated *in vacuo*. The portion of b. p. >260°/17 mm. was converted into a *picrate* which recrystallised from ethanol–benzene as orange needles (3 g.), m. p. 245° (decomp. >230°) (Found: C, 61·9; H, 3·6; N, 11·6. $C_{25}H_{18}N_4O_7$ requires C, 61·7; H, 3·7; N, 11·6%). Basification with aqueous ammonia gave the free *base*, crystallising as yellowish needles, m. p. 90°, from light petroleum (Found: C, 88·4; H, 6·0. $C_{19}H_{15}N$ requires C, 88·7; H, 5·9%).

6-*Ethyl*-1,2-*benzacridine* (II; R = H).—A similar Ullmann reaction, performed with β-naphthol, furnished an orange-red oil, b. p. 260—270°/14 mm., which was converted into a *picrate* (5 g.), crystallising as yellow needles, m. p. 225° (decomp. >205°), from xylene (Found: N, 11·3. $C_{25}H_{18}N_4O_7$ requires N, 11·6%). The free *base* crystallised from ethanol as almost colourless needles, m. p. 123° (Found: C, 88·6; H, 5·9; N, 5·5. $C_{19}H_{15}N$ requires C, 88·7; H, 5·9; N, 5·3%).

N-m-*Ethylphenyl*-1-*naphthylamine*.—A mixture of *m*-ethylaniline (15 g.), α-naphthol (20 g.), and iodine (1 g.) was refluxed for 20 hr.; after cooling, the product was taken up in benzene, washed with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The secondary *amine* was a viscous yellow oil (17 g.), b. p. 244—245°/23 mm., n_D^{27} 1·6655 (Found: C, 87·3; H, 7·1; N, 5·8. $C_{18}H_{17}N$ requires C, 87·4; H, 6·9; N, 5·7%); the violet picrate decomposed on recrystallisation from methanol.

N-m-*Ethylphenyl*-2-*naphthylamine*.—Prepared from *m*-ethylaniline (15 g.), β-naphthol (20 g.), and iodine (1 g.) as above, this *amine*, b. p. 249—250°/17 mm., crystallised as needles (13 g.), m. p. 44°, from heptane (Found: C, 87·2; H, 7·2%); its *picrate* formed deep violet leaflets, m. p. 90°, from methanol (Found: N, 11·7. $C_{24}H_{20}N_4O_7$ requires N, 11·7%).

6-*Ethyl*-9-*methyl*-3,4-*benzacridine* (I; R = Me).—A mixture of *N*-*m*-ethylphenyl-1-naphthylamine (7 g.), acetic anhydride (7 g.), and freshly fused zinc chloride (7 g.) was refluxed for 48 hr.; after cooling, the mixture was treated with 20% aqueous sodium hydroxide, and the acridine was taken up in benzene, dried (Na_2SO_4), recovered, and distilled *in vacuo*. The portion of b. p. 280—286°/20 mm. crystallised from ethanol as yellowish needles (2 g.), m. p. 91° (Found: C, 88·5; H, 6·6; N, 5·3. $C_{20}H_{17}N$ requires C, 88·6; H, 6·3; N, 5·2%). The *picrate* formed golden-yellow needles, m. p. 234° (decomp. >190°), from toluene (Found: N, 10·9. $C_{26}H_{20}N_4O_7$ requires N, 11·2%).

6,9-*Diethyl*-3,4-*benzacridine* (I; R = Et).—Prepared as above from *N*-*m*-ethylphenyl-1-naphthylamine (6 g.), propionic anhydride (6 g.), and zinc chloride (6 g.), this *acridine*, b. p. 275—277°/16 mm., formed yellowish prisms (1·8 g.), m. p. 83°, from heptane (Found: C, 88·2; H, 6·5. $C_{21}H_{19}N$ requires C, 88·5; H, 6·7%) [*picrate*, orange-yellow prisms, m. p. 239° (decomp. >210°), from xylene (Found: N, 10·6. $C_{27}H_{22}N_4O_7$ requires N, 10·8%)].

6,9-*Diethyl*-1,2-*benzacridine* (II; R = Et).—Similarly prepared from *N*-*m*-ethylphenyl-2-naphthylamine, this *acridine*, b. p. 271—273°/15 mm., crystallised as yellowish needles, m. p. 121°, from cyclohexane (Found: C, 88·3; H, 6·3%) [*picrate*, orange-yellow prisms, m. p. 248° (decomp. >210°), from xylene (Found: N, 10·5%)].

10-*Chloro*-7-*ethyl*-5,10-*dihydro*-3,4-*benzophenarsazine* (III; R = Cl).—A solution of *N*-*m*-ethylphenyl-1-naphthylamine (2·5 g.) and arsenic trichloride (2 g.) in dry *o*-dichlorobenzene (10 c.c.) was gently refluxed for 90 min.; after cooling, the precipitate formed was collected and recrystallised from xylene, giving golden-yellow needles (2 g.) of the *phenarsazine*, m. p. 232° (decomp. >220°), whose solutions in sulphuric acid were red (Found: C, 60·5; H, 4·3. $C_{18}H_{15}AsClN$ requires C, 60·8; H, 4·2%).

10-*Chloro*-7-*ethyl*-5,10-*dihydro*-1,2-*benzophenarsazine* (IV; R = Cl), similarly prepared from *N*-*m*-ethylphenyl-2-naphthylamine, formed deep yellow prisms, m. p. 272° (decomp. >258°), from xylene (Found: C, 60·5; H, 4·5%), giving red solutions in sulphuric acid.

7-*Ethyl*-5,10-*dihydro*-10-*methyl*-3,4-*benzophenarsazine* (III; R = Me).—To a Grignard reagent (2 mol.), prepared from methyl iodide and magnesium in ether, compound (III; R = Cl) was added in small portions (1 mol.), and after the vigorous reaction had subsided, the solution was refluxed for 10 min.; after cooling and addition of ice-cold aqueous ammonium chloride, the ethereal layer was collected and dried (Na_2SO_4), the solvent removed, and the residual *phenarsazine* recrystallised from methanol, giving shiny colourless prisms (0·4 g.), m. p. 128°, whose solutions in sulphuric acid were yellow (Found: C, 67·9; H, 5·3. $C_{19}H_{18}AsN$ requires C, 68·1; H, 5·4%).

7-*Ethyl*-5,10-*dihydro*-10-*methyl*-1,2-*benzophenarsazine* (IV; R = Me), prepared from compound (IV; R = Cl), formed colourless prisms, m. p. 132°, from methanol (Found: C, 67·8; H, 5·5%).

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