68. *Carcinogenic Nitrogen Compounds. Part XXIX.*[1] *2,5-Diethylaniline and Benzacridines derived therefrom.*

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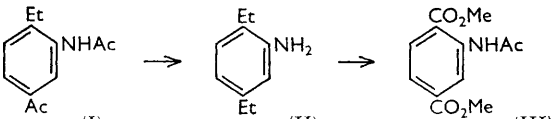
o-Ethylacetanilide is shown to undergo Friedel–Crafts acetylation with aluminium chloride and acetyl chloride in the position *para* to the ethyl group, thus providing a novel route to 2,5-diethylaniline; this last amine was used for the synthesis of new nitrogen-containing heterocyclic compounds, including several polysubstituted benzacridines. With acetic anhydride and zinc chloride, acetylation of *o*-ethylacetanilide took place in the position *meta* to the ethyl group.

In the Friedel–Crafts acetylation of *o*-methylacetanilide, using aluminium chloride as catalyst, the acetyl group enters the position *para* to the methyl group,[2] and as both theory and practice ascribe a lesser *ortho* : *para*-directing influence to the ethyl than to the methyl group,[3] it was of interest to investigate the behaviour of *o*-ethylacetanilide in the same reaction. The aluminium chloride-catalysed acetylation of *o*-ethylacetanilide with acetyl chloride was found to give, in low yield, 3-acetamido-4-ethylacetophenone (I), whose constitution was established by Huang-Minlon reduction of the corresponding amino-ketone to a substance identical with 2,5-diethylaniline (II) prepared from *p*-diethylbenzene

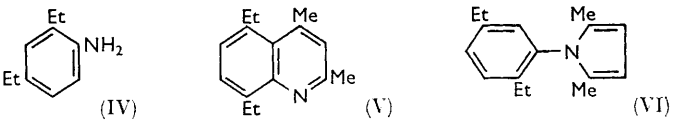
[1] Part XXVIII, Buu-Hoï, Périn, and Jacquignon, *J.*, 1960, 4500.
[2] Buu-Hoï, Ekert, and Royer, *Compt. rend.*, 1951, **233**, 627.
[3] See general discussion in Badger, "Structures and Reactions of the Aromatic Compounds," Cambridge Univ. Press, 1954.

by nitration and reduction. This amine gave an *N*-acetyl derivative, m. p. 158·5°, whereas Voswinkel [4] gave m. p. 99° for 2,5-diethylacetanilide; a similar discrepancy was noted between the m. p. of our *N*-benzoyl derivative (107°) and that reported by von Auwers,



(I) (II) (III)

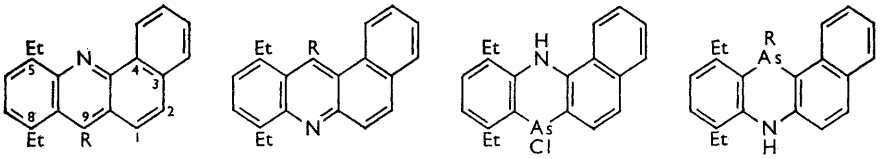
Lechner, and Bundesmann [5] for 2,5-diethylbenzanilide (*ca.* 130°). Hence it was thought useful to confirm the structure of our diethylaniline, and this was achieved by oxidising the *N*-acetyl derivative with potassium permanganate and working up the product to



(IV) (V) (VI)

dimethyl 2-acetamidoterephthalate (III), a substance already prepared by other routes.[6] Thus, the aluminium chloride-catalysed Friedel–Crafts acetylation of *o*-ethylacetanilide follows the same pattern as that of *o*-methylacetanilide. When, however, zinc chloride and acetic anhydride were used for the acetylation, substitution occurred, not in the position *para* to the ethyl group, but in the *meta* position, as Wolff–Kishner reduction yielded 2,4-diethylaniline (IV), identical with the amine obtained from *m*-diethylbenzene by nitration and reduction.[7] This is in line with Klingel's observation on the zinc chloride-catalysed acetylation of *o*-methylacetanilide by acetic anhydride.[8]

2,5-Diethylaniline was converted into various nitrogen-bearing heterocyclic compounds, for testing as potential carcinogens or cocarcinogens. A Combes–Beyer reaction [9] with acetylacetone, followed by cyclisation of the product with sulphuric acid, led to 5,8-diethyl-2,4-dimethylquinoline (V); condensation with hexane-2,5-dione yielded 1-(2,5-diethylphenyl)-2,5-dimethylpyrrole (VI). In the benzacridine series, 5,8-diethyl-3,4-benzacridine (VII; R = H) was synthesised by reaction with α-naphthol in the presence of paraformaldehyde; [10] and a similar reaction with β-naphthol afforded 5,8-diethyl-1,2-benzacridine (VIII; R = H). Knoevenagel condensation of α-naphthol with the amine (II)



(VII) (VIII) (IX) (X)

in the presence of iodine [11] furnished *N*-(2,5-diethylphenyl)-α-naphthylamine; modified Bernthsen reactions [12] of this secondary amine with acetic and propionic anhydride gave respectively 5,8-diethyl-9-methyl- (VII; R = Me) and 5,8,9-triethyl-3,4-benzacridine (VII; R = Et), whose structures resembled those of homologues already found carcinogenic.[13]

[4] Voswinkel, *Ber.*, 1889, **22**, 315.
[5] von Auwers, Lechner, and Bundesmann, *Ber.*, 1925, **58**, 48.
[6] Ullmann and Uzbachian, *Ber.*, 1903, **36**, 1804.
[7] Copenhaver and Emmet Reid, *J. Amer. Chem. Soc.*, 1927, **49**, 3161.
[8] Klingel, *Ber.*, 1885, **18**, 2696.
[9] Combes, *Compt. rend.*, 1888, **106**, 1536; Beyer, *Ber.*, 1887, **20**, 1767.
[10] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029; Buu-Hoï, *J.*, 1950, 1146.
[11] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17.
[12] Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1946, 792.
[13] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

When β-naphthol was used in the Knoevenagel condensation of the amine (II), *N*-(2,5-diethylphenyl)-β-naphthylamine was obtained, from which 5,8-diethyl-9-methyl- (VIII; R = Me) and 5,8,9-triethyl-1,2-benzacridine (VIII; R = Et) were prepared.

In the phenarsazine series, 10-chloro-6,9-diethyl-5,10-dihydro-3,4- (IX) and -1,2-benzophenarsazine (X; R = Cl) were prepared by the Wieland–Rheinheimer reaction [14] of arsenic trichloride and the appropriate secondary amines; a dimethyl homologue of (IX) had already been found to produce papillomas of the skin in mice.[15] With methylmagnesium iodide, compound (X; R = Cl) yielded 6,9-diethyl-5,10-dihydro-10-methyl-1,2-benzophenarsazine (X; R = Me).

The results of biological investigation of these various compounds will be reported later.

Experimental

Aluminium Chloride-catalysed Acetylation of o-*Ethylacetanilide.*—This compound (199 g.), b. p. 178°/12 mm., m. p. 110°, was prepared from *o*-ethylaniline (b. p. 110°/12 mm.; 160 g.) and acetic anhydride (141·5 g.) in benzene (300 c.c.) by one hour's refluxing. To a suspension of this amide (100 g.) in anhydrous carbon disulphide (750 c.c.) and acetyl chloride (48 g.), powdered aluminium chloride (122·5 g.) was added in small portions, and the mixture refluxed for 10 hr. on a water-bath. After cooling and treatment with cold dilute hydrochloric acid, the product was taken up in chloroform, the organic layer was washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvents were distilled off, and the residue was fractionated *in vacuo*. 3-*Acetamido*-4-*ethylacetophenone* (I) (33·5 g.) formed yellow crystals (from cyclohexane), m. p. 97°, b. p. 220°/15 mm. (Found: C, 70·0; H, 7·4. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·3%). The 25% yield thus obtained was the highest in a series of experiments using various solvents and different periods of heating; with methylene chloride as solvent, no reaction took place, and only an 8% yield was recorded when light petroleum was used.

3-*Amino*-4-*ethylacetophenone.*—A mixture of the foregoing acetamido-ketone (37 g.) and hydrochloric acid (300 c.c.) was refluxed for 75 min.; after cooling and basification with aqueous sodium hydroxide, the *product* was taken up in ether and worked up in the usual way, giving a viscous yellow oil (18 g.), b. p. 187°/15 mm. (Found: N, 8·6. $C_{10}H_{13}NO$ requires N, 8·5%).

2,5-*Diethylaniline* (II).—A solution of the foregoing amino-ketone (25 g.) and hydrazine hydrate (15 g.) in diethylene glycol (300 c.c.) was refluxed for 6 hr. with potassium hydroxide (25 g.) under removal of water. After cooling and dilution with water, the product was taken up in benzene, the benzene solution dried (Na_2SO_4), the solvent distilled, and the residue fractionated *in vacuo*, giving a pale yellow oil (17 g.), b. p. 122°/15 mm., $n_D^{26·8}$ 1·5418. Acetylation with acetic anhydride in benzene yielded 2,5-diethylacetanilide, m. p. 158·5° (from benzene) (Found: C, 75·3; H, 8·7. Calc. for $C_{12}H_{17}NO$: C, 75·4; H, 8·9%); Gaudion, Hook, and Plant [16] gave m. p. 154°, and Voswinkel [4] gave m. p. 99°. The *N*-benzoyl derivative of 2,5-diethylaniline crystallised from hexane as prisms, m. p. 107° (Found: C, 80·5; H, 7·8; N, 5·5. Calc. for $C_{17}H_{19}NO$: C, 80·6; H, 7·6; N, 5·5%) (lit.,[5] m. p. 130°). The *toluene*-p-*sulphonyl derivative* formed needles, m. p. 103°, from hexane (Found: N, 4·7. $C_{17}H_{21}NO_2S$ requires, N4·6%); the *methanesulphonyl derivative* formed leaflets, m. p. 76°, from hexane (Found: N, 5·9. $C_{11}H_{17}NO_2S$ requires N, 6·2%). The derivatives prepared from a sample of 2,5-diethylaniline synthesised by nitration of *p*-diethylbenzene and subsequent reduction had the same properties.

Oxidation of 2,5-*Diethylacetanilide.*—To a suspension of this compound (10 g.) in water (750 c.c.), potassium permanganate (70 g.) was added in small portions with stirring, and the mixture heated at 95° for 8 hr. and filtered. Acidification of the filtrate with hydrochloric acid furnished a precipitate of acetamidoterephthalic acid, which was deacetylated with hot hydrochloric acid; neutralisation gave aminoterephthalic acid, m. p. 325°, from water.[17] Esterification of this acid with methanol and sulphuric acid afforded dimethyl aminoterephthalate, crystallising as yellowish prisms, m. p. 135°, from ethanol (lit.,[18] m. p. 134°),

[14] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1.
[15] Lacassagne, Buu-Hoï, Royer, and Rudali, *Compt. rend. Soc. biol.*, 1951, **145**, 1451.
[16] Gaudion, Hook, and Plant, *J.*, 1947, 1631.
[17] Wegscheider, Perndanner, and Auspitzer, *Monatsh.*, 1910, **31**, 1299.
[18] Cahn-Speyer, *Monatsh.*, 1907, **28**, 805.

which with acetic anhydride in benzene gave dimethyl acetamidoterephthalate, prisms, m. p. 168°, from benzene (lit.,[18] m. p. 167°).

Zinc Chloride-catalysed Friedel–Crafts Acetylation of o-Ethylaniline.—To a mixture of this amine (26 g.) and anhydrous zinc chloride (52 g.), acetic anhydride (104 g.) was cautiously added, and after 14 hours' refluxing the mixture was heated with hydrochloric acid for 90 min. After cooling and filtration, the filtrate was basified with sodium hydroxide, and the product taken up in benzene, washed with water and dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The crude 4-amino-3-ethylacetophenone thus obtained as a yellow viscous oil (5·5 g.) was reduced with hydrazine hydrate and potassium hydroxide in diethylene glycol in the usual conditions, giving 2,4-diethylaniline (3 g.), b. p. 118—120°/24 mm.; the *N*-acetyl and the *N*-benzoyl derivative melted at 112° and 176° respectively (lit.,[7] 112—113·5° and 176·5°).

5,8-*Diethyl*-2,4-*dimethylquinoline* (V).—A mixture of 2,5-diethylaniline (4 g.) and acetylacetone (2·6 g.) was refluxed for 1 hr. with 1 drop of acetic acid, and the crude anil obtained was cyclised by sulphuric acid (3 parts) in 30 min. on a water-bath. After cooling, the mixture was basified with dilute aqueous sodium hydroxide, and the product taken up in ether, dried (Na_2SO_4), recovered, and fractionated *in vacuo*, giving the *quinoline* as a pale yellow oil (3·3 g.), b. p. 178—180°/15 mm., n_D^{21} 1·5792 (Found: N, 6·6. $C_{15}H_{19}N$ requires N, 6·6%); the *picrate* crystallised as golden-yellow leaflets, m. p. 133°, from ethanol (Found: N, 12·8. $C_{21}H_{22}N_4O_7$ requires N, 12·7%).

1-(2,5-*Diethylphenyl*)-2,5-*dimethylpyrrole* (VI).—A mixture of 2,5-diethylaniline (3 g.) and hexane-2,5-dione (3 g.) was refluxed for 2 hr. with 1 drop of acetic acid, then fractionated *in vacuo*, giving the *pyrrole* as a pale yellow oil (3·5 g.), b. p. 156°/20 mm. (Found: N, 5·9. $C_{16}H_{21}N$ requires N, 6·2%).

5,8-*Diethyl*-3,4-*benzacridine* (VII; R = H).—To a mixture of 2,5-diethylaniline (10 g.) and α-naphthol (10·6 g.), heated at *ca.* 250°, paraformaldehyde (7·2 g.) was cautiously added in small portions, and the product brought to the b. p. at atmospheric pressure, then fractionated *in vacuo*. The yellow resin obtained, b. p. >260°/20 mm., was dissolved in ethanol and converted into a *picrate*, which recrystallised from ethanol–benzene as yellow prisms, m. p. 141° (Found: N, 10·6. $C_{27}H_{22}N_4O_7$ requires N, 10·9%). Decomposition of this picrate with aqueous ammonia afforded the free *base* (0·8 g.), yellowish needles, m. p. 71° (from ethanol) (Found: C, 88·2; H, 6·7; N, 5·0. $C_{21}H_{19}N$ requires C, 88·4; H, 6·7; N, 4·9%).

5,8-*Diethyl*-1,2-*benzacridine* (VIII; R = H).—Similarly prepared from 2,5-diethylaniline (12 g.) and β-naphthol (12·7 g.) with paraformaldehyde (8·7 g.), this *acridine* crystallised as yellowish needles (1 g.), m. p. 109°, from ethanol (Found: C, 88·4; H, 6·6; N, 4·7%); the addition compound with picric acid formed golden-yellow needles, m. p. 245° (decomp. >208°), from ethanol–benzene.

N-(2,5-*Diethylphenyl*)-α-*naphthylamine*.—A mixture of 2,5-diethylaniline (7·5 g.) and α-naphthol (9·5 g.) was refluxed for 18 hr. with a few crystals of iodine; after cooling and treatment with aqueous sodium hydroxide, the *product* was taken up in ether, dried (Na_2SO_4), recovered, and fractionated *in vacuo*, giving a pale yellow oil (6 g.), b. p. 249—250°/13 mm. (Found: C, 87·1; H, 7·6; N, 5·2. $C_{20}H_{21}N$ requires C, 87·3; H, 7·6; N, 5·1%).

5,8-*Diethyl*-9-*methyl*-3,4-*benzacridine* (VII; R = Me).—A mixture of the foregoing secondary amine (13 g.), acetic anhydride (7·5 g.), and freshly fused zinc chloride (8 g.) was gently refluxed for 40 hr. After cooling and treatment with aqueous sodium hydroxide, the product was taken up in benzene, washed with water, dried (Na_2SO_4), recovered, and fractionated *in vacuo*, giving a yellow resin (8 g.), b. p. >260°/20 mm., which was dissolved in ethanol and converted into a *picrate*; this crystallised as deep yellow needles, m. p. 205° (decomp. >180°), from ethanol–benzene (Found: C, 63·9; H, 4·6. $C_{28}H_{24}N_4O_7$ requires C, 63·6; H, 4·5%). Basification with aqueous ammonia afforded the free *base*, as yellowish prisms, m. p. 88° (from hexane) (Found: C, 88·6; H, 6·9; N, 4·5. $C_{22}H_{21}N$ requires C, 88·3; H, 7·0; N, 4·7%).

5,8,9-*Triethyl*-3,4-*benzacridine* (VII; R = Et).—This was prepared as above from *N*-(2,5-diethylphenyl)-α-naphthylamine (15 g.), propionic anhydride (9·5 g.), and zinc chloride (9·2 g.); after the usual treatment, the portion of b. p. 270—278°/14 mm. (10·7 g.) was converted into a *picrate*, which formed deep yellow needles, m. p. 231°, from benzene (Found: C, 63·9; H, 4·5; N, 10·6. $C_{29}H_{26}N_4O_7$ requires C, 64·2; H, 4·8; N, 10·3%). The free *base* crystallised from hexane as yellowish needles, m. p. 92° (Found: C, 87·4; H, 7·0; N, 4·7. $C_{23}H_{23}N$ requires C, 87·2; H, 7·3; N, 4·5%).

N-(2,5-*Diethylphenyl*)-β-*naphthylamine*.—A mixture of 2,5-diethylaniline (20 g.) and β-naphthol (25 g.) was refluxed for 24 hr. with iodine (1 g.), and the product worked up in the usual

way, giving a viscous yellow oil (13 g.), b. p. 253°/23 mm. (Found: C, 87·2; H, 7·5%); the corresponding picrate crystallised as violet-brown needles, m. p. 90°, from cyclohexane.

5,8-*Diethyl*-9-*methyl*-1,2-*benzacridine* (VIII; R = Me).—Prepared from the foregoing secondary amine (13 g.), acetic anhydride (7·5 g.), and zinc chloride (8·7 g.), this *acridine*, b. p. 276°/18 mm., formed cream-coloured needles (2 g.), m. p. 144°, from ethanol (Found: C, 88·1; H, 5·7; N, 4·8%). Its *picrate* crystallised as golden-yellow needles, m. p. 242° (decomp. >205°), from benzene (Found: N, 10·9%).

5,8,9-*Triethyl*-1,2-*benzacridine* (VIII; R = Et).—Prepared from the secondary amine (11 g.), propionic anhydride (6·8 g.), and zinc chloride (6·5 g.), this *acridine*, even after purification *via* its picrate, did not crystallise and formed a yellow, viscous oil (2 g.), b. p. 275—280°/22 mm. (Found: C, 87·0; H, 7·5%).

10-*Chloro*-6,9-*diethyl*-5,10-*dihydro*-3,4-*benzophenarsazine* (IX).—A solution of *N*-(2,5-diethylphenyl)-α-naphthylamine (2 g.) and arsenic trichloride (1·3 g.) in dry *o*-dichlorobenzene (8 c.c.) was gently refluxed for 90 min.; the precipitate formed on concentration and cooling was recrystallised from chlorobenzene, giving golden-yellow leaflets (1·8 g.), m. p. 223° (decomp. >160°) (Found: N, 3·6. $C_{20}H_{19}AsClN$ requires N, 3·6%. No satisfactory carbon value could be obtained).

10-*Chloro*-6,9-*diethyl*-5,10-*dihydro*-1,2-*benzophenarazine* (X; R = Cl).—Similarly prepared from *N*-(2,5-diethylphenyl)-β-naphthylamine (4 g.) and arsenic trichloride (2·7 g.), this *compound* formed golden-yellow leaflets (4 g.), m. p. 229° (decomp. >200°), from chlorobenzene, giving brown-red solutions in sulphuric acid (Found: C, 62·6; H, 5·0; N, 3·8. $C_{20}H_{19}AsClN$ requires C, 62·6; H, 5·0; N, 3·6%). 6,9-*Diethyl*-5,10-*dihydro*-10-*methyl*-1,2-*benzophenarsazine* (X; R = Me), prepared from the foregoing chloro-derivative (1 g.) with a slight excess of methylmagnesium iodide in anhydrous ether, formed colourless needles (0·7 g.), m. p. 86°, from methanol and gave red solutions in sulphuric acid (Found: C, 69·1; H, 6·1. $C_{21}H_{22}AsN$ requires C, 69·4; H, 6·1%).

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