510. *Carcinogenic Nitrogen Compounds. Part XX.* Benzacridines, Benzocarbazoles, and Benzophenarsazines with Hydrogenated Rings.*

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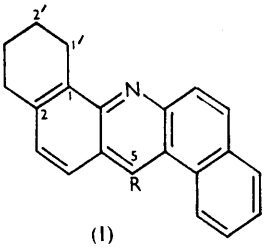
A number of 1 : 2-, 2 : 3-, and 3 : 4-benzacridines, 2 : 3- and 3 : 4-benzocarbazoles, and 1 : 2- and 3 : 4-benzophenarsazines, bearing one or two hydrogenated rings, together with similar indane derivatives, have been synthesised for studies in chemical carcinogenesis. *cis*-2-Decalone is shown to undergo Pfitzinger reactions with isatins to give mixtures of the corresponding linear and angular benzacridine derivatives, and *cis*-2-decalone phenylhydrazone to undergo Fischer indolisation to give a mixture of the linear and the angular benzocarbazole.

Hydrogenation products of carcinogenic hydrocarbons and analogous nitrogen compounds are important tools for research in chemical carcinogenesis, not only for the experimental control of the π-electron-density theory of carcinogenicity (according to which hydrogenation reduces or suppresses activity), but also for investigating their fixation by cell receptors competitively with the fully aromatic parent substances.[1] Such a competition can be expected to inhibit the carcinogenic effect of the fully conjugated compound by their partially hydrogenated derivatives, and this has recently been demonstrated experimentally.[2] Determination of the carcinogenic activity of hydrogenated molecules may also provide clues to the ability of cellular enzyme systems to carry out dehydrogenations. These considerations prompted the synthesis of various benzacridines, benzocarbazoles, and benzophenarsazines bearing one or two hydrogenated rings; as direct hydrogenation of polycyclic compounds generally leads to products of indeterminate constitution,[3] it was preferable to start from intermediates with hydrogenated rings.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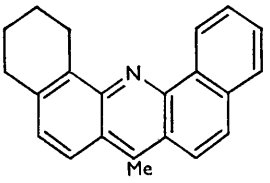
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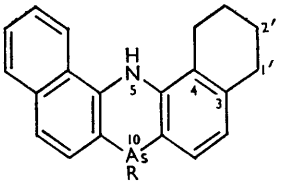
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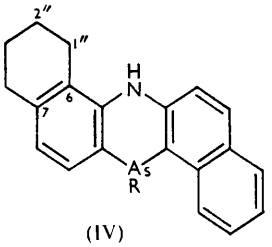
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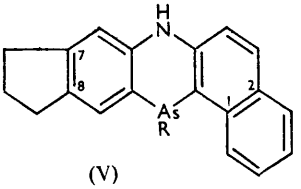
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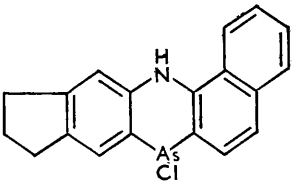

(VI)

1′ : 2′ : 3′ : 4′-Tetrahydro-1 : 2-6 : 7-dibenzacridine (I; R = H) was prepared by the action of paraformaldehyde[4] on a mixture of β-naphthol and 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine; its 5-methyl homologue (I; R = Me) was synthesised by the action of acetic anhydride[5] on 5 : 6 : 7 : 8-tetrahydro-*N*-β-naphthyl-1-naphthylamine, the latter being

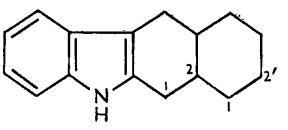
* Part XIX, *J.*, 1956, 2048.

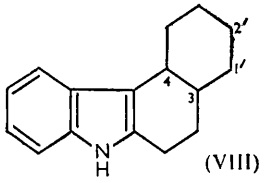
[1] Cf. Lacassagne, Buu-Hoï, and Rudali, *Brit. J. Exp. Pathol.*, 1945, **26**, 5.
[2] Kotin, Falk, Lijinsky, and Zechmeister, *Science*, 1956, **123**, 102.
[3] Cf. Lijinsky and Zechmeister, *J. Amer. Chem. Soc.*, 1953, **75**, 5495.
[4] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.
[5] Cf. Buu-Hoï, *J.*, 1946, 792; 1949, 670; 1950, 1146.

obtained by iodine-catalysed condensation of β-naphthol with 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine. 5 : 6 : 7 : 8-Tetrahydro-*N*-α-naphthyl-1-naphthylamine, similarly prepared by using α-naphthol, condensed with acetic anhydride to 1′ : 2′ : 3′ : 4′-tetrahydro-5-methyl-1 : 2-8 : 9-dibenzacridine (II). The fully aromatic compounds corresponding to these three tetrahydrodibenzacridines are carcinogenic.[6]

The condensation of 5 : 6 : 7 : 8-tetrahydro-*N*-α- and -*N*-β-naphthyl-1-naphthylamine with arsenic trichloride [7] readily yielded 10-chloro-5 : 10 : 1′ : 2′ : 3′ : 4′-hexahydro-3 : 4-6 : 7- (III; R = Cl) and 10-chloro-5 : 10 : 1″ : 2″ : 3″ : 4″-hexahydro-1 : 2-6 : 7-dibenzophenarsazine (IV; R = Cl); these reacted with methylmagnesium iodide [8] to give 10-methyl-5 : 10 : 1′ : 2′ : 3′ : 4′-hexahydro-3 : 4-6 : 7- (III; R = Me) and 10-methyl-5 : 10 : 1″ : 2″ : 3″ : 4″-hexahydro-1 : 2-6 : 7-dibenzophenarsazine (IV; R = Me). Similar compounds with a *cyclo*pentene ring were prepared from 5-aminoindane; this amine (which was obtained free from traces of the 4-isomer by Beckmann rearrangement of 5-acetylindane oxime) gave, with β- and α-naphthol, *N*-β- and -α-naphthyl-5-indanylamine, which were converted by arsenic trichloride into 10-chloro-5 : 10-dihydro-7 : 8-*cyclo*penteno-1 : 2-(V; R = Cl) and 10-chloro-5 : 10-dihydro-2 : 3-*cyclo*penteno-6 : 7-benzophenarsazine (VI); the former yielded with methylmagnesium iodide the 10-methyl compound (V; R = Me). In the various cyclisations reported, the possibility of ring-closure at the 3-position of the β-naphthyl moiety was not considered, in view of earlier results in similar cases.[5]

(VII)





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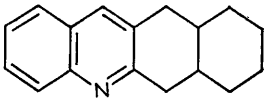
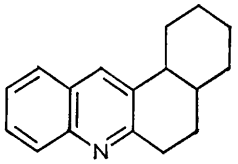


(IX)



(X)

A convenient route to heterocyclic compounds bearing two adjacent hydrogenated benzene rings was to start from decalones. Thus, *cis*-β-decalone phenylhydrazone underwent Fischer indolisation with hydrogen chloride to give a mixture of the linear (VII) and the angular octahydrobenzocarbazole (VIII) in a ratio of approximately 2 : 1; the constitution of these products was proved by their dehydrogenation with chloranil to 2 : 3- and 3 : 4-benzocarbazole respectively. Similarly, it was found that the Pfitzinger reaction of *cis*-β-decalone with isatin gave a mixture of cinchoninic acids which underwent thermal decarboxylation to a mixture of octahydrobenzacridines (IX) and (X), likewise in a 2 : 1 ratio; although these were destroyed when heated with selenium, the latter was smoothly dehydrogenated by chloranil to 3 : 4-benzacridine.

Experimental

1′ : 2′ : 3′ : 4′-*Tetrahydro*-1 : 2-6 : 7-*dibenzacridine* (I; R = H).—To a boiling mixture of 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (5 g.) and β-naphthol (5 g.), paraformaldehyde (1 g.) was added in small portions; when the vigorous reaction had subsided, boiling was continued for 5 more minutes, and the product fractionated *in vacuo*. The thick resin (3 g.; b. p. 300—320°/20 mm.) was treated in hot ethanol with ethanolic picric acid; 1′ : 2′ : 3′ : 4′-*tetrahydro*-1 : 2-6 : 7-*dibenzacridine picrate* formed deep yellow prisms, m. p. 274—275° (decomp.), from benzene

[6] Cf. Cook, *Proc. Intern. Congr. Cancer, Madrid*, 1933, **2**, 373; Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Lacassagne, Buu-Hoï, Zajdela, Royer, and Hubert-Habart, *ibid.*, 1955, **42**, 186, and unpublished results.

[7] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1.

(Found : N, 10·5. $C_{27}H_{20}O_7N_4$ requires N, 10·9%), which gave on basification with aqueous ammonia the free *acridine*, pale yellow needles, m. p. 162° (from ethanol) (Found : C, 88·7; H, 6·2. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%).

5 : 6 : 7 : 8-*Tetrahydro*-N-2-*naphthyl*-1-*naphthylamine*.—A mixture of 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (25 g.), β-naphthol (25 g.), and iodine (0·5 g.) was refluxed for 24 hr.; the product was then taken up in benzene, washed with aqueous sodium hydroxide, and dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The secondary *amine* (20 g.; b. p. 312—317°/65 mm.) formed colourless needles, m. p. 59°, from light petroleum (Found : C, 87·9; H, 7·3. $C_{20}H_{19}N$ requires C, 87·9; H, 7·0%).

1′ : 2′ : 3′ : 4′-*Tetrahydro*-5-*methyl*-1 : 2-6 : 7-*dibenzacridine* (I; R = Me).—A mixture of the foregoing amine (5 g.), acetic anhydride (6 g.), and fused zinc chloride (5 g.) was refluxed for 24 hr.; after cooling, the mixture was treated with hot aqueous sodium hydroxide and benzene, the benzene layer dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The thick orange resin (3 g.; b. p. 308—312°/15 mm.) was converted into a *picrate*, crystallising as deep yellow prisms, m. p. 249—250° (decomp.), from benzene (Found : N, 10·3. $C_{28}H_{22}O_7N_4$ requires N, 10·6%); the free *base* formed yellowish leaflets, m. p. 170°, from ethanol (Found : C, 88·6; H, 6·3. $C_{22}H_{19}N$ requires C, 88·9; H, 6·4%).

5 : 6 : 7 : 8-*Tetrahydro*-N-α-*naphthyl*-1-*naphthylamine*.—Prepared as for the β-isomer, this *amine* (10 g.) formed a yellow, viscous oil, b. p. 279—281°/30 mm. (Found : C, 87·7; H, 7·1%), which gave a picrate, crystallising as dark violet needles, m. p. 96° (decomp.), from ethanol.

1′ : 2′ : 3′ : 4′-*Tetrahydro*-5-*methyl*-1 : 2-8 : 9-*dibenzacridine* (II).—Obtained from the foregoing amine (5 g.) as for the isomeric compound (I; R = Me), this *acridine*, b. p. 310—315°/18 mm., was purified *via* its picrate (deep yellow prisms, m. p. 230—231°, from benzene), and formed yellowish needles, m. p. 152°, from ethanol (Found : C, 88·6; H, 6·2%).

10-*Chloro*-5 : 10 : 1′ : 2′ : 3′ : 4′-*hexahydro*-3 : 4-6 : 7-*dibenzophenarsazine* (III; R = Cl).—A solution of 5 : 6 : 7 : 8-tetrahydro-*N*-α-naphthyl-1-naphthylamine (5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed with arsenic trichloride (3 g.) for 30 min. The precipitate (5 g.) which was formed on cooling crystallised as greenish-yellow needles, m. p. 268° (decomp. >252°), from xylene, giving a blood-red halochromy in sulphuric acid (Found : C, 62·5; H, 4·5. $C_{20}H_{17}NClAs$ requires C, 62·9; H, 4·5%).

5 : 10 : 1′ : 2′ : 3′ : 4′-*Hexahydro*-10-*methyl*-3 : 4-6 : 7-*dibenzophenarsazine* (III; R = Me).—The foregoing *chloro-derivative* (2 g.) was added portionwise with stirring to an excess of ethereal methylmagnesium iodide, and the mixture refluxed for a few minutes. After treatment with aqueous ammonium chloride and evaporation, the residue was crystallised from ethanol, giving colourless prisms (1·5 g.), m. p. 173° (Found : C, 69·5; H, 5·3. $C_{21}H_{20}NAs$ requires C, 69·8; H, 5·5%).

10-*Chloro*-5 : 10 : 1″ : 2″ : 3″ : 4″-*hexahydro*-1 : 2-6 : 7-*dibenzophenarsazine* (IV; R = Cl).—Prepared from 5 : 6 : 7 : 8-tetrahydro-*N*-2-naphthyl-1-naphthylamine (5 g.) as for the isomer, this *phenarsazine* (5 g.) formed deep yellow needles, m. p. 290° (decomp. >266°), from xylene (Found : C, 62·6; H, 4·3%). 5 : 10 : 1″ : 2″ : 3″ : 4″-*Hexahydro*-10-*methyl*-1 : 2-6 : 7-*dibenzophenarsazine* (IV; R = Me) formed colourless prisms, m. p. 179°, from ethanol, giving a red halochromy in sulphuric acid (Found : C, 69·6; H, 5·3%).

Fischer Cyclisation of cis-β-*Decalone Phenylhydrazone*.—*cis*-β-Decalone was prepared by chromic acid oxidation of *cis*-β-decalol (a product, m. p. 18°, obtained by hydrolysis of the acetate and fractional crystallisation from light petroleum, was used) according to Leroux's procedure.[9] A mixture of this ketone (10 g.) and phenylhydrazine (10 g.) was heated at 120° until evolution of steam had ceased, and the crude phenylhydrazone was boiled for a few seconds with an acetic acid solution of hydrogen chloride, then diluted with water; the product was taken up in benzene, washed with water, and dried (Na_2SO_4), the solvent distilled off, and the residue fractionated *in vacuo*. The portion boiling at 250—255°/20 mm. (12 g.) solidified partly on treatment with light petroleum and recrystallised from ethanol. cis-1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*Octahydro*-2 : 3-*benzocarbazole* (VII) formed colourless leaflets (7·8 g.), m. p. 188°, whose solutions showed a strong violet fluorescence (Found : C, 85·0; H, 8·3. $C_{16}H_{19}N$ requires C, 85·3; H, 8·4%); this compound gave a brown-violet picrate which decomposed on recrystallisation from benzene, but with tetrachlorophthalic anhydride in acetic acid a stable vermilion addition-compound, m. p. 174—175°, was obtained.[10] A solution of compound (VII) (3 g.) and chloranil

[8] Aeschlimann, *J.*, 1927, 413.
[9] Leroux, *Ann. Chim.*, 1910, **21**, 458; Zelinsky and Turowa-Pollak, *Ber.*, 1925, **58**, 1293.
[10] Cf. Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056.

(9 g.) in dry xylene (30 c.c.), refluxed for 16 hr., yielded 2 : 3-benzocarbazole (1 g.), crystallising as colourless, sublimable prisms, m. p. 333°, from benzene.[11]

Evaporation of the mother-liquor from the crystallisation of compound (VII) afforded cis-1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*octahydro*-3 : 4-*benzocarbazole* (VIII) (3·8 g.), b. p. 251—252°/20 mm. (Found : C, 85·2; H, 8·2%), whose picrate formed brown-red prisms, m. p. 135—136° (decomp.), from benzene. Dehydrogenation with chloranil yielded 3 : 4-benzocarbazole, m. p. 135°, whose picrate formed ruby-red needles, m. p. 175° (decomp.), from benzene.[12]

Pfitzinger Condensation of cis-β-*Decalone with Isatin.*—A mixture of *cis*-β-decalone (10 g.), isatin (11 g.), and potassium hydroxide (12 g.) in ethanol (75 c.c.) was gently refluxed for 12 hr., the solvent then distilled off *in vacuo*, and water added. The neutral impurities were removed by ether-extraction, the aqueous layer was acidified with acetic acid, and the precipitate collected, washed with water, and dried. This cinchoninic acid mixture (14 g.) was heated above the m. p., and the residue distilled *in vacuo*, giving a thick yellow oil (10 g.; b. p. 290—300°/17 mm.), which solidified partly on trituration with light petroleum. cis-1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*Octahydro*-2 : 3-*benzacridine* (IX) formed colourless needles (5 g.), m. p. 171°, from ethanol, giving a yellow halochromy in sulphuric acid (Found : C, 86·0; H, 7·8. $C_{17}H_{19}N$ requires C, 86·1; H, 8·0%), and a *picrate*, deep yellow prisms (from ethanol), m. p. 227—228° (decomp.) (Found : N, 11·7. $C_{23}H_{22}O_7N_4$ requires N, 12·0%).

The mother-liquor from the crystallisation of the product (IX) yielded, on evaporation and distillation *in vacuo*, cis-1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-*octahydro*-3 : 4-*benzacridine* (X) (2·5 g.), b. p. *ca.* 290°/15 mm. (Found : C, 85·7; H, 8·3%), whose *picrate* formed bright yellow prisms, m. p. 209—210° (decomp.) (Found : N, 11·7%). Dehydrogenation of this product (X) by chloranil[13] readily gave 3 : 4-benzacridine, m. p. 131° (picrate m. p. 238—240°).

Preparation of 5-*Aminoindane.*—5-Acetamidoindane (22 g.; b. p. 213°/18 mm.), obtained by a Beckmann rearrangement of 5-acetylindane oxime (29 g.; b. p. 180—185°/13 mm., m. p. 115—116°) with phosphorus pentachloride (36 g.) in cold ether (250 c.c.), was hydrolysed by refluxing hydrochloric acid (100 c.c.), to give, after basification, the free amine, b. p. 135—136°/13 mm., m. p. 35° (from light petroleum). 2-*Chloro*-3-5′-*indanylamino*-1 : 4-*naphthaquinone*, prepared by briefly refluxing an ethanolic solution of equimolecular amounts of this amine and 2 : 3-dichloro-1 : 4-naphthaquinone with sodium acetate,[14] formed red-violet needles, m. p. 196°, from ethanol (Found : C, 70·1; H, 4·3. $C_{19}H_{14}O_2NCl$ requires C, 70·5; H, 4·3%).

N-α-*Naphthyl*-5-*indanylamine.*—5-Aminoindane (4 g.), α-naphthol (5 g.), and iodine (0·1 g.) were refluxed for 36 hr., and the product was worked up in the usual way. The *amine* (4 g.), b. p. 266—267°/15 mm., formed colourless needles, m. p. 59°, from light petroleum (Found : C, 87·8; H, 6·5. $C_{19}H_{17}N$ requires C, 88·0; H, 6·6%).

10-*Chloro*-5 : 10-*dihydro*-2 : 3-cyclo*penteno*-6 : 7-*benzophenarsazine* (VI).—Prepared from the foregoing amine (2 g.) and arsenic trichloride (1·5 g.) in *o*-dichlorobenzene, this *compound* (2 g.) formed yellow leaflets, m. p. 278° (charring >260°), giving a brown-red halochromy in sulphuric acid (Found : C, 61·7; H, 4·0. $C_{10}H_{19}NClAs$ requires C, 62·0; H, 4·1%).

N-β-*Naphthyl*-5-*indanylamine.*—This *amine* (6 g.), prepared from 5-aminoindane (4 g.), β-naphthol (4·8 g.), and iodine (0·1 g.), formed colourless needles, m. p. 110°, from ethanol (Found : C, 87·9; H, 6·6%).

10-*Chloro*-5 : 10-*dihydro*-7 : 8-cyclo*penteno*-1 : 2-*benzophenarsazine* (V; R = Cl).—This *compound* formed from *o*-dichlorobenzene orange-yellow leaflets, m. p. 290° (charring >270°), giving a brown-red halochromy in sulphuric acid (Found : C, 61·8; H, 3·9%). 5 : 10-*Dihydro*-10-*methyl*-7 : 8-cyclo*penteno*-1 : 2-*benzophenarsazine* (V; R = Me), prepared with methylmagnesium iodide in the usual way, formed colourless prisms, m. p. 207°, from ethanol (Found : C, 68·9; H, 5·3. $C_{20}H_{18}NAs$ requires C, 69·2; H, 5·2%).

This work is part of a cancer research scheme (Professor A. Lacassagne), undertaken with the financial aid of the U.S. Dept. of Health, Education, and Welfare; the authors thank the authorities concerned.

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[11] Graebe and Knecht, *Annalen*, 1880, **202**, 16; Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 131.
[12] Japp and Maitland, *J.*, 1903, **83**, 270.
[13] Buu-Hoï, Hoán, and Xuong, *J.*, 1952, 279.
[14] Buu-Hoï, Royer, and Eckert, *Rec. Trav. chim.*, 1952, **71**, 1059.