609. *Carcinogenic Nitrogen Compounds. Part XXII.** cyclo*Hexyl Derivatives of Benzacridines, Carbazole, and other Nitrogen Heterocycles.*

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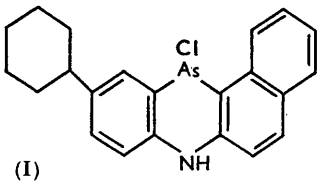
Several *cyclo*hexyl derivatives of angular benzacridines and of carbazole, pyrrocoline, and other nitrogen heterocycles have been synthesised and found to be non-carcinogenic.

The influence of *cyclo*hexyl radicals on carcinogenic activity has not yet been reported, although in angular benzacridines some phenyl derivatives have been found to be carcinogenic.[1] *p-cyclo*Hexylaniline, best prepared by Beckmann rearrangement of 4-*cyclo*hexylacetophenone oxime,[2] on iodine-catalysed Knoevenagel condensation [3] with β- and α-naphthol gave *N-p-cyclo*hexylphenyl-β- and -α-naphthylamine. Wieland–Rheinheimer condensation [4] with arsenic trichloride then led to 10-chloro-8-*cyclo*hexyl-5 : 10-dihydro-1 : 2- (I) and -3 : 4-benzophenarsazine. Modified Bernthsen cyclisation [5] of *N-p-cyclo*hexylphenyl-β-naphthylamine with acetic anhydride yielded 7-*cyclo*hexyl-5-methyl-3 : 4-benzacridine (II; R = Me); 5 : 7-di*cyclo*hexyl- (II; R = *cyclo*hexyl) and 7-*cyclo*hexyl-5-



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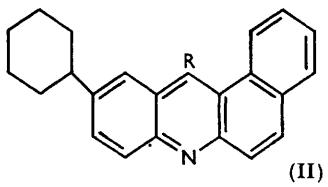

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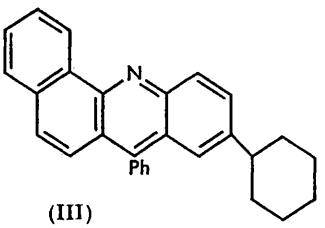

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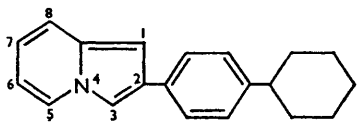


(IV)

phenyl-3 : 4-benzacridine (II; R = Ph) were prepared by a similar reaction with *cyclo*hexanecarboxylic and benzoic acid respectively. The 5-methyl-, 5-*cyclo*hexyl-, and 5-phenyl-derivatives of 7-phenyl-3 : 4-benzacridine were also prepared by Bernthsen reactions with *N*-4-diphenylyl-β-naphthylamine.[6] 7-*cyclo*Hexyl-3 : 4-benzacridine (II; R = H) was prepared by Ullmann condensation [7] of *p-cyclo*hexylaniline with β-naphthol and paraformaldehyde. 7-*cyclo*Hexyl-5-phenyl-1 : 2-benzacridine (III) was prepared from *N-p-cyclo*hexylphenyl-α-naphthylamine.

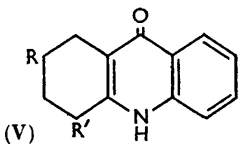
2-*p-cyclo*Hexylphenylindole was prepared by Fischer cyclisation of the phenylhydrazone of 4-*cyclo*hexylacetophenone; addition of the ω-bromo-derivative of this ketone to 2-picoline, 2 : 5- and 2 : 4-lutidine, and 5-ethyl-2-methylpyridine, afforded pyridinium

* Part XXI, Buu-Hoï, Jacquignon, and Long, *J.*, 1957, 505.

[1] Zajdela and Buu-Hoï, *Acta Unio Intern. contra Cancrum*, 1950, **7**, 184.
[2] Mayes and Turner, *J.*, 1929, 500.
[3] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346.
[4] Cf. Buu-Hoï *et al.*, *Rev. sci.*, 1944, **82**, 453; 1945, **83**, 41; *J.*, 1951, 795; 1953, 3584.
[5] Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1946, 792; 1949, 670.
[6] Buu-Hoï, *J.*, 1950, 1146.
[7] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.

bromides which with alkali underwent the Tschitschibabin cyclisation [8] to 2-*p*-*cyclo*hexylphenylpyrrocoline (IV) and its 6-methyl, 7-methyl, and 6-ethyl homologues; with sodium nitrite and hydrochloric acid these gave the 3-nitroso-derivatives. 2-*p*-*cyclo*Hexylphenylquinoxaline was obtained by Hinsberg condensation [9] of ω-bromo-4-*cyclo*hexylacetophenone with *o*-phenylenediamine.

4- and 2-*cyclo*Hexyl*cyclo*hexanone readily underwent Tiedtke condensations with anthranilic acid [10] to 1- and 3-*cyclo*hexyl-1 : 2 : 3 : 4-tetrahydroacridone (V; R′ = C_6H_{11}, R = H; and *vice versa*). Fischer indolisation of the phenylhydrazones of these *cyclo*hexanones gave 1- and 3-*cyclo*hexyl-1 : 2 : 3 : 4-tetrahydrocarbazole (cf. VI), of which



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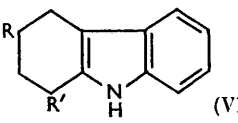

(VI)

only the former could be dehydrogenated with chloranil, to afford 3-*cyclo*hexylcarbazole. The same product is isolated in small yield in the Friedel–Crafts reaction of carbazole with *cyclo*hexene, which is known to give mostly a di*cyclo*hexylcarbazole,[11] and this establishes the structure of this mono*cyclo*hexyl product.

A number of these heterocyclic products proved non-carcinogenic by the skin-painting test on mice.

Experimental

p-cyclo*Hexylaniline*.—*cyclo*Hexylbenzene was acetylated by Mayes and Turner's method,[2] and the resulting 4-*cyclo*hexylacetophenone converted into its *oxime*, prisms, m. p. 117° (from ethanol) (Found: C, 77·3; H, 8·9. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%); Beckmann rearrangement with phosphorus pentachloride in ether gave in almost quantitative yield *p*-*cyclo*hexylacetanilide, which was hydrolysed to *p*-*cyclo*hexylaniline. This amine was characterised by its reaction (*a*) with 2 : 3-dichloro-1 : 4-naphthaquinone,[12] which furnished 2-*chloro*-3-p-cyclo*hexylanilino*-1 : 4-*naphthaquinone*, needles, m. p. 148° (from ethanol) (Found: C, 71·9; H, 5·3. $C_{22}H_{20}O_2NCl$ requires C, 72·2; H, 5·5%), and (*b*) with chloranil, to give 2 : 6-*dichloro*-3 : 5-*di*-p-cyclo*hexylanilino*-1 : 4-*benzoquinone*, dark brown needles, m. p. 303° (from benzene) (Found: N, 5·6. $C_{30}H_{32}O_2N_2Cl_2$ requires N, 5·5%).

1-p-cyclo*Hexylphenyl*-2 : 5-*dimethylpyrrole*.—A mixture of *p*-*cyclo*hexylaniline (7 g.) and hexane-2 : 5-dione (7 g.) was refluxed for 4 hr., and fractionated *in vacuo*; the *pyrrole* (8·5 g.), b. p. 205—206°/15 mm., formed prisms, m. p. 96°, from light petroleum (b. p. 35—75°) (Found: C, 85·0; H, 9·5. $C_{18}H_{23}N$ requires C, 85·3; H, 9·2%).

2-p-cyclo*Hexylphenylindole*.—Phenylhydrazine (4 g.) and 4-*cyclo*hexylacetophenone (6 g.) were heated at 120° until no more steam was given off; after cooling, freshly fused, powdered zinc chloride (8 g.) was added, and the mixture heated at 200° for a few minutes, then cooled. Water was added, and the product taken up in benzene, washed with dilute aqueous alkali, dried (Na_2SO_4), recovered, and distilled *in vacuo*. The portion boiling at 310—315°/20 mm. crystallised as leaflets, m. p. 206°, from ethanol–benzene (Found: C, 87·0; H, 7·7. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7%).

2-p-cyclo*Hexylphenylquinoxaline*.—4-*cyclo*Hexylacetophenone (10 g.) was treated in chloroform with bromine (10 g.) in the presence of a few drops of hydrobromic acid, and the product washed with cooled, dilute aqueous sodium carbonate and dried (Na_2SO_4); the chloroform was distilled off, and the crude ω-bromo-ketone (3 g.) refluxed in ethanol for 4 hr. with *o*-phenylenediamine (2 g.) and sodium acetate (1 g.). After cooling, water was added, and the precipitate recrystallised from ethanol, giving prisms (2 g.), m. p. 137°, of the *quinoxaline* (Found: C, 83·7; H, 7·3. $C_{20}H_{20}N_2$ requires C, 83·3; H, 7·0%).

[8] Tschitschibabin, *Ber.*, 1927, **60**, 1607; Borrows, Holland, and Kenyon, *J.* 1946, 1069, 1083; Buu-Hoï *et al.*, *Rec. Trav. chim.*, 1949, **68**, 441; *J. Org. Chem.*, 1954, **19**, 1370.

[9] Hinsberg, *Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim. France*, 1950, **17**, 753.

[10] Tiedtke, *Ber.*, 1909, **42**, 621.

[11] Cf. Buu-Hoï and Cagniant, *Ber.*, 1944, **77**, 121.

[12] Cf. Buu-Hoï *et al.*, *Bull. Soc. chim. France*, 1944, **11**, 578; *Rec. Trav. chim.*, 1952, **71**, 1059.

2-p-cyclo*Hexylphenylpyrrocoline* (IV).—The ω-bromo-ketone (2 g.) and 2-picoline (1 g.) were heated in ethanol (10 c.c.) for 30 min. at 60°; after cooling, water (100 c.c.) was added, and the water-insoluble impurities removed by ether-extraction. The aqueous layer was brought to the b. p. with sodium hydrogen carbonate (5 g.), and the precipitate which formed on cooling was collected, washed with water, and recrystallised from ethanol, giving the *pyrrocoline* as leaflets (1·3 g.), m. p. 208° (Found: C, 87·5; H, 7·6. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7%). It gave a 3-*nitroso-derivative* when treated (1 g.) in hydrochloric acid with sodium nitrite (0·6 g., in water) (subsequent basification with sodium carbonate [13]), as dark green leaflets, m. p. 188° (from ethanol) (Found: N, 9·0. $C_{20}H_{20}ON_2$ requires N, 9·2%).

2-p-cyclo*Hexylphenyl*-6-*methylpyrrocoline* (IV).—Prepared from 2 : 5-lutidine (1·2 g.), this *compound* (1·2 g.) formed leaflets, m. p. 207°, from ethanol (Found: C, 86·8; H, 7·9. $C_{21}H_{23}N$ requires C, 87·2; H, 8·0%); the 3-*nitroso-derivative* formed dark green needles, m. p. 190°, from ethanol (Found: N, 8·8. $C_{21}H_{22}ON_2$ requires N, 8·8%). Similar reactions gave 2-p-cyclo*hexylphenyl*-7-*methyl*-, leaflets, m. p. 226° (from ethanol–benzene) (Found: C, 87·3; H, 8·1%) [3-*nitroso-derivative*, bluish-green prisms, m. p. 196° (Found: N, 8·5%)], and 6-*ethyl*-2-p-cyclo*hexylphenyl-pyrrocoline*, needles, m. p. 159° (from ethanol) (Found: C, 86·8; H, 8·2. $C_{22}H_{25}N$ requires C, 87·1; H, 8·2%) [3-*nitroso-derivative*, dark green leaflets, m. p. 148° (Found: N, 8·2. $C_{22}H_{24}ON_2$ requires N, 8·4%)].

N-p-cyclo*Hexylphenyl*-α-*naphthylamine*.—*p-cyclo*Hexylaniline (20 g.), α-naphthol (25 g.), and iodine (0·2 g.) were refluxed for 18 hr.; after cooling, the product was washed in benzene with 10% aqueous sodium hydroxide, recovered, and fractionated *in vacuo*. The *arylamine* (25 g.), b. p. 252—254°/0·8 mm., crystallised as needles, m. p. 115°, from ethanol (Found: C, 87·4; H, 7·9. $C_{22}H_{23}N$ requires C, 87·7; H, 7·7%).

N-p-cyclo*Hexylphenyl*-β-*naphthylamine* (32 g.), similarly prepared, formed needles, m. p. 102°, from ethanol (Found: C, 87·5; H, 8·0%).

10-*Chloro*-8-cyclo*hexyl*-5 : 10-*dihydro*-1 : 2-*benzophenarsazine* (I).—A solution of *N-p-cyclo*hexylphenyl-β-naphthylamine (3 g.) and arsenic trichloride (1·8 g.) in *o*-dichlorobenzene (15 c.c.) was refluxed for 4 hr.; the precipitate which was formed after cooling was recrystallised from xylene, giving orange-yellow prisms (3 g.), m. p. 220° (decomp. >211°), whose halochromy in sulphuric acid was brown-red (Found: C, 64·7; H, 4·9. $C_{22}H_{21}NClAs$ requires C, 64·5; H, 5·1%).

10-*Chloro*-8-cyclo*hexyl*-5 : 10-*dihydro*-3 : 4-*benzophenarsazine*, similarly prepared from the α-naphthylamine, formed, from toluene, deep yellow prisms, m. p. 234° (decomp. >213°), giving a red halochromy in sulphuric acid (Found: C, 64·5; H, 5·2%).

7-cyclo*Hexyl*-3 : 4-*benzacridine* (II; R = H).— To a mixture of *p-cyclo*hexylaniline (10 g.) and β-naphthol (10 g.) heated at 250°, paraformaldehyde (2 g.) was added in small portions; after the vigorous reaction had subsided, the product was boiled for 5 min., and purified by distillation and conversion into a picrate, which crystallised as dark yellow prisms, m. p. 233—234° (decomp.), from benzene. Basification with aqueous ammonia afforded the *base* (3 g.), forming yellowish needles, m. p. 95°, from acetone (Found: C, 88·4; H, 6·9. $C_{23}H_{21}N$ requires C, 88·7; H, 6·8%).

7-cyclo*Hexyl*-5-*phenyl*-1 : 2-*benzacridine* (III).—*N-p-cyclo*Hexylphenyl-α-naphthylamine (10 g.), benzoic acid, and freshly fused zinc chloride were heated at 200—210° for 24 hr.; after cooling and addition of 20% aqueous sodium hydroxide, the product was washed in benzene with water, dried (Na_2SO_4), recovered, distilled *in vacuo*, and purified *via* the picrate. The free *base* formed yellowish needles, m. p. 148°, from acetone (Found: C, 89·6; H, 6·2. $C_{29}H_{25}N$ requires C, 89·9; H, 6·5%). The 3 : 4-*benzacridines* tabulated were similarly prepared.

			Found (%)		Required (%)	
3 : 4-Benzacridines	M. p.	Formula	C	H	C	H
7-*cyclo*Hexyl-5-methyl-	111°	$C_{24}H_{23}N$	88·4	7·0	88·6	7·1
7-*cyclo*Hexyl-5-phenyl-	147	$C_{29}H_{25}N$	89·6	6·5	89·9	6·5
5-*cyclo*Hexyl-7-phenyl-	114	$C_{29}H_{25}N$	89·7	6·3	89·9	6·5
5 : 7-Di*cyclo*hexyl-	109	$C_{29}H_{31}N$	88·3	7·6	88·5	7·9
5-Methyl-7-phenyl-	135	$C_{24}H_{17}N$	90·0	5·6	90·3	5·4
5 : 7-Diphenyl-	232	$C_{29}H_{19}N$	91·5	5·3	91·3	5·0

2- *and* 4-cyclo*Hexyl*cyclo*hexanone*.—2- and 4-*cyclo*Hexyl*cyclo*hexanol, obtained by hydrogenation of 2- and 4-hydroxydiphenyl, were oxidised to the ketones [14] by chromic acid in acetic

[13] Cf. Burrows, Holland, and Kenyon, *J.*, 1946, 1075.

acid. 4-*cyclo*Hexyl*cyclo*hexanone formed an iso*nicotinoylhydrazone*, prisms, m. p. 180° (from ethanol) (Found : C, 71·9; H, 8·6; N, 13·9. $C_{18}H_{25}ON_3$ requires C, 72·2; H, 8·4; N, 14·1%), and, on treatment (1 mol., in ethanol) with 2-thenaldehyde (2 mol.) in the presence of aqueous sodium hydroxide, gave 4-cyclo*hexyl*-2 : 6-*di*-(2-*thenylidene*)cyclo*hexanone*, yellow prisms, m. p. 172° (from ethanol) (Found : C, 71·4; H, 6·5. $C_{22}H_{24}OS_2$ requires C, 71·7; H, 6·5%). 2 : 6-*Di*-p-*anisylidene*-4-cyclo*hexyl*-, yellow needles, m. p. 126° (from ethanol) (Found : C, 80·5; H, 7·8. $C_{28}H_{32}O_3$ requires C, 80·7; H, 7·7%), 4-cyclo*hexyl*-2 : 6-*di*-(1-*naphthylidene*)-, yellow prisms, m. p. 166° (from ethanol) (Found : C, 89·1; H, 7·2. $C_{34}H_{32}O$ requires C, 89·4; H, 7·1%), and 2-*benzylidene*-6-cyclo*hexyl*-cyclo*hexanone*, colourless prisms, m. p. 102° (from ethanol) (Found : C, 84·7; H, 8·7. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%), were also prepared.

3-*cyclo*Hexyl-1 : 2 : 3 : 4-*tetrahydroacridone* (V; R = H, R′ = *cyclo*hexyl).—A mixture of 2-*cyclo*hexyl*cyclo*hexanone (10 g.) and anthranilic acid (10 g.) was heated at 160° for 1 hr., and at 250° for 30 min. with removal of water; after cooling, ethanol was added, and the solid *acridone* obtained was recrystallised twice from ethanol, giving prisms (10 g.), m. p. 358° (Found : C, 81·1; H, 8·2; N, 5·0. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2; N, 5·0%). 1-*cyclo*Hexyl-1 : 2 : 3 : 4-*tetrahydroacridone* (V; R = *cyclo*hexyl, R′ = H), similarly prepared, formed prisms (8 g.), m. p. 306°, from *o*-dichlorobenzene (Found : C, 81·0; H, 7·9%).

1-cyclo*Hexyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (VI; R = H, R′ = *cyclo*hexyl).—2-*cyclo*Hexyl*cyclo*hexanone (6 g.) and phenylhydrazine (4 g.) were heated at 120° for 10 min. with removal of water; the crude phenylhydrazone was then treated with a boiling solution of hydrogen chloride in acetic acid. After addition of water, the product was washed in benzene with water, dried ($CaCl_2$), recovered, and distilled *in vacuo*. The *carbazole* formed colourless prisms (4 g.), m. p. 69°, from light petroleum (b. p. 35—75°) (Found : C, 85·0; H, 9·3. $C_{18}H_{23}N$ requires C, 85·3; H, 9·2%).

3-cyclo*Hexyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (VI; R = *cyclo*hexyl, R′ = H).—Prepared as above from 4-*cyclo*hexyl*cyclo*hexanone, this *compound* (5 g.) formed needles, m. p. 97°, from light petroleum (Found : C, 85·2; H, 8·8%); dehydrogenation (of 1 g.) with chloranil (2 g.) in xylene afforded 3-cyclo*hexylcarbazole* (0·3 g.) as needles, m. p. 158° (Found : C, 86·4; H, 7·4. $C_{18}H_{19}N$ requires C, 86·7; H, 7·7%). The same compound was obtained by repeated recrystallisation of the product of Friedel–Crafts *cyclo*hexylation of carbazole (1 mol.) with *cyclo*hexene (1 mol.) in the presence of aluminium chloride.

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[14] Schrauth and Görig, *Ber.*, 1923, **56**, 1905; Vavon and Mitchovitch, *Compt. rend.*, 1928, **186**, 704.