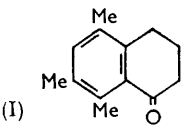
508. *Carcinogenic Nitrogen Compounds. Part XXXIV.*[1] *5,7,8-Trimethyl-1-tetralone and Benzocarbazoles and Dibenzocarbazoles Derived Therefrom.*

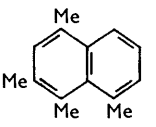
By N. P. Buu-Hoi and G. Saint-Ruf.

5,7,8-Trimethyl-1-tetralone has been synthesised from pseudocumene and its structure ascertained. From this ketone, polymethyl derivatives of 1,2-benzocarbazole and 1,2:5,6- and 1,2:7,8-dibenzocarbazole have been prepared as potential carcinogens.

With the aim of enhancing the carcinogenicity of 1,2-benzocarbazole and 1,2:5,6- and 1,2:7,8-dibenzocarbazole [2] by polymethyl substitution, the synthesis was investigated of several such carbazoles bearing at least three methyl groups. One convenient intermediate was 5,7,8-trimethyl-1-tetralone (I), which was readily prepared from pseudocumene by succinoylation,[3,4] reduction of the keto-acid, and cyclisation of the resulting γ-2,4,5-trimethylphenylbutyric acid. Succinoylation was best effected in methylene chloride, and gave a single keto-acid, melting at 109°; the excellent yield for the keto-acid shows that no rearrangement or Jacobsen degradation of pseudocumene had occurred in the present experiments. Proof of the structure of 5,7,8-trimethyl-1-tetralone, and hence



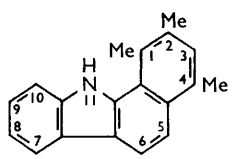
(I)



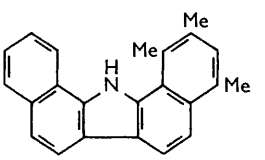
(II)

of the succinoylation product, was provided by reaction with methylmagnesium iodide and dehydration of the alcohol thus obtained to a hydrocarbon, which underwent dehydrogenation to 1,2,4,8-tetramethylnaphthalene (II), already synthesised in a different way.[5]

1,2,4-Trimethylbenzo[*a*]carbazole (III) was prepared by conversion of the phenylhydrazone of the tetralone (I) into the 5,6-dihydro-derivative followed by dehydrogenation over palladium–charcoal, an agent that was found far superior to chloranil (which



(III)



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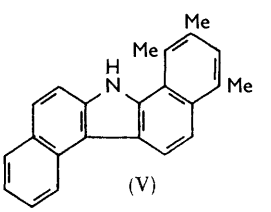

(V)

had been used in similar syntheses [6]) in respect both of yields and of the purity of the final products. Six more highly methylated analogues were similarly prepared and are listed in Tables 1 and 2.

The pentacyclic carbazoles (IV) and (V) were prepared from the tetralone (I) and α- and β-naphthylhydrazine by the same reaction sequence.

[1] Part XXXIII, Buu-Hoï, Jacquignon, and Marty, *J.*, 1962, 1056.
[2] Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Boyland and Mawson, *Biochem. J.*, 1938, **32**, 1460; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Assoc. franç. Étude Cancer*, 1955, **42**, 3; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635.
[3] Claus, *Ber.*, 1887, **20**, 1374.
[4] Muhr, *Ber.*, 1895, **28**, 3215.
[5] Ruzicka, Ehmann, and Mörgeli, *Helv. Chim. Acta*, 1933, **16**, 314.
[6] See, *inter alia*, Barclay and Campbell, *J.*, 1945, 530; Buu-Hoï *et al.*, *J. Org. Chem.*, 1949, **14**, 492, 802.

TABLE 1.

5,6-Dihydrobenzo[*a*]carbazoles.

Compound	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
1,2,4-Trimethyl-	195°	$C_{19}H_{19}N$	87·2	7·5	5·4	87·3	7·3	5·4
1,2,4,8-Tetramethyl-	223	$C_{20}H_{21}N$	87·0	7·6	5·2	87·3	7·6	5·1
1,2,4,10-Tetramethyl-	177	$C_{20}H_{21}N$	87·6	7·5	5·2			
1,2,4,7,10-Pentamethyl-	200	$C_{21}H_{23}N$	86·9	7·9	4·9			
1,2,4,8,9-Pentamethyl-	236	$C_{21}H_{23}N$	87·1	7·9	4·8	87·2	8·0	4·8
1,2,4,8,10-Pentamethyl-	166	$C_{21}H_{23}N$	87·3	7·6	5·1			
1,2,4,9,10-Pentamethyl-	163	$C_{21}H_{23}N$	87·2	7·8	5·0			
picrate	184	$C_{27}H_{26}N_4O_7$	—	—	11·0	—	—	10·8

TABLE 2.

Benzo[*a*]carbazoles.

Compound	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
1,2,4-Trimethyl-	236°	$C_{19}H_{17}N$	87·8	6·7	5·7	88·0	6·6	5·4
picrate	191	$C_{25}H_{20}N_4O_7$	—	—	11·7	—	—	11·5
1,2,4,8-Tetramethyl-	241	$C_{20}H_{19}N$	88·0	7·0	5·2	87·9	7·0	5·1
1,2,4,10-Tetramethyl-	225	$C_{20}H_{19}N$	88·1	7·0	5·2			
picrate	183	$C_{26}H_{22}N_4O_7$	—	—	10·9	—	—	11·1
1,2,4,7,10-Pentamethyl-	259	$C_{21}H_{21}N$	88·1	7·2	5·0	87·8	7·3	4·9
picrate	206	$C_{27}H_{24}N_4O_7$	—	—	10·8	—	—	10·9
1,2,4,8,9-Pentamethyl-	251	$C_{21}H_{21}N$	87·5	7·5	5·0	87·8	7·3	4·9
picrate	213	$C_{27}H_{24}N_4O_7$	—	—	11·0	—	—	10·9
1,2,4,8,10-Pentamethyl-	232	$C_{21}H_{21}N$	87·5	7·4	5·0	87·8	7·3	4·9
picrate	200	$C_{27}H_{24}N_4O_7$	—	—	11·2	—	—	10·9
1,2,4,9,10-Pentamethyl-	222	$C_{21}H_{21}N$	87·5	7·3	5·1	87·8	7·3	4·9
picrate	192	$C_{27}H_{24}N_4O_7$	—	—	11·0	—	—	10·9

All the carbazoles are being tested for sarcoma-inducing activity, by subcutaneous injections in mice, and results will be reported later.

EXPERIMENTAL

Succinoylation of Pseudocumene.—To an ice-cooled, stirred solution of pseudocumene (60 g.) and succinic anhydride (55 g.) in methylene chloride (250 c.c.), aluminium chloride (86 g.) was added in small portions, and the mixture left overnight at room temperature. After treatment with dilute hydrochloric acid and evaporation of the solvent, the solid obtained was collected, dissolved in aqueous sodium carbonate and precipitated with dilute hydrochloric acid. After recrystallisation from cyclohexane, β-2,4,5-trimethylbenzoylpropionic acid was obtained in 80% yield as prisms, m. p. 109° (lit.,[3] 105°,[4] 98°) (Found: C, 70·6; H, 7·1. Calc. for $C_{13}H_{16}O_3$: C 70·9; H, 7·3%).

γ-2,4,5-Trimethylphenylbutyric Acid.—A solution of the foregoing acid (41 g.) and 98% hydrazine hydrate (20 g.) in diethylene glycol (300 c.c.) was heated at 100° for a few minutes; potassium hydroxide (34 g.) was added, and the mixture heated at 250° until evolution of nitrogen had ceased (*ca.* 8 hr.). After cooling, dilution with water, and acidification with hydrochloric acid, the solid formed was taken up in benzene, the solution dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*; the portion boiling at 250°/19 mm. formed needles (34 g.), m. p. 122°, from cyclohexane (Found: C, 75·7; H, 8·5%; *M*, 208. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%; *M*, 206).

5,7,8-Trimethyl-1-tetralone.—A solution of the foregoing acid (33 g.) and one drop of pyridine in anhydrous benzene (500 c.c.) was treated portionwise with thionyl chloride (38 g.); the mixture was refluxed for 1 hr. on the water-bath, the solvent and thionyl chloride in excess were distilled off, and the residue dissolved in methylene chloride (500 c.c.). To this solution, aluminium chloride (24 g.) was added portionwise and the mixture was left for 12 hr. at room

temperature. After the usual treatment and fractionation *in vacuo* the *tetralone* crystallised as prisms (14 g., 46%), m. p. 64°, b. p. 175—178°/21 mm. (Found: C, 83·4; H, 8·5. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%); nitrobenzene was a poor cyclisation medium, as a yield of only 14% was recorded, even when the mixture was left for 48 hr. The *oxime* formed needles, m. p. 173°, from cyclohexane (Found: N, 6·7. $C_{13}H_{17}NO$ requires N, 6·9%), and the *semicarbazone* needles, m. p. 204°, from ethanol (Found: N, 16·8. $C_{14}H_{19}N_3O$ requires N, 17·1%).

1,2-*Dihydro*-4,5,6,8-*tetramethylnaphthalene*.—To an ethereal solution of methylmagnesium iodide (prepared from 6 g. of methyl iodide and 0·5 g. of magnesium), the above ketone (4 g.) was added in small portions, and the mixture refluxed for 15 min. on the water-bath; after decomposition with ice-cold dilute sulphuric acid, the organic layer was collected, the ether distilled, and the crude alcohol heated for a few minutes with formic acid (10 c.c.). After dilution with water, the dehydration product was taken up in benzene, dried (Na_2SO_4), recovered, and fractionated *in vacuo*. The *dihydro-compound* (3 g.) had b. p. 170°/20 mm., n_D^{23} 1·5663 (Found: C, 90·5; H, 9·6. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%). This compound, when refluxed and then distilled over 5% palladium–charcoal, gave 1,2,4,8-tetramethylnaphthalene, b. p. 178°/20 mm., n_D^{23} 1·5902 (Ruzicka *et al.*[5] give b. p. 150°/10 mm.); the picrate formed vermilion needles, m. p. 147° (lit.,[5] m. p. 145·5°) (Found: N, 10·1. Calc. for $C_{20}H_{19}N_3O_7$: N, 10·2%).

Preparation of Benzocarbazoles.—The crude arylhydrazones (1 part) of the tetralone (I), prepared in boiling ethanol (30 minutes' refluxing), were heated for 1 min. in acetic acid saturated with hydrogen chloride (10 parts); the precipitate obtained on cooling and dilution with water recrystallised from ethanol. All the 3,4-dihydro-1,2-benzocarbazoles thus obtained in 80—95% yields, were colourless needles or leaflets. Their dehydrogenation was effected in all cases, with almost quantitative yields, by repeated sublimation *in vacuo* over 5% palladium–charcoal and recrystallisation from ethanol–benzene; in some instances, dehydrogenation was also achieved by refluxing a solution of the dihydro-compound (1 mol.) and chloranil (1·2 mol.) in anhydrous xylene, but the yields were lower (*ca.* 40%) and the products difficult to purify. All the benzocarbazoles were prisms or leaflets, and the picrates crystallised from benzene as reddish-brown to dark brown needles.

1,2,4-*Trimethyldibenzo*[a,i]*carbazole*.—The 5,6-*dihydro-derivative*, prepared from the α-naphthylhydrazone of the tetralone (I), formed needles, m. p. 220°, from ethanol (Found: N, 4·5. $C_{22}H_{21}N$ requires N, 4·7%). Dehydrogenation over palladium–charcoal gave *compound* (IV), crystallising as prisms, m. p. 223°, from ethanol–benzene (Found: C, 89·3; H, 6·2; N, 4·6. $C_{23}H_{19}N$ requires C, 89·3; H, 6·2; N, 4·5%); the *picrate* formed brown-red prisms, m. p. 208°, from ethanol (Found: N, 10·9. $C_{29}H_{22}N_4O_7$ requires N, 10·4%).

8,9,11-*Trimethyldibenzo*[a,g]*carbazole*.—The 12,13-*dihydro-derivative*, obtained from β-naphthylhydrazine, formed sublimable needles, m. p. 252°, from ethanol (Found: N, 4·6%). Dehydrogenation gave *compound* (V), leaflets, m. p. 223° (from ethanol–benzene) (Found: C, 81·1; H, 6·2; N, 4·7%); *picrate*, brown needles, m. p. 218° (decomp. >200°), from ethanol (Found: N, 10·7%).

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