1036. *Carcinogenic Nitrogen Compounds. Part XLII.*[1] *The Succinoylation of Hemimellitene and Some Synthetic Applications Thereof.*

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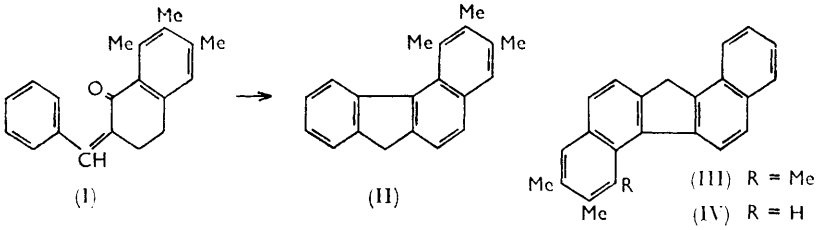
Hemimellitene undergoes Friedel–Crafts succinoylation mostly in position 5 and partly in position 4, giving ready access to 6,7,8- and 5,6,7-trimethyl-1-tetralone, and these have been used for the synthesis of polymethylated benzo[*c*]carbazoles and other polycyclic compounds.

Hemimellitene (1,2,3-trimethylbenzene), a little-investigated hydrocarbon, could be expected to undergo substitution preferentially in position 4, since this site is activated both by the *para*- and by the *ortho*-methyl group. However, the easy formation [2] of 4,5-dinitrohemimellitene by direct nitration demonstrates the surprising reactivity of position 5. This is now further shown in the Friedel–Crafts succinoylation of hemimellitene, which gives predominantly β-(3,4,5-trimethylbenzoyl)propionic acid, with only a small amount of the expected β-(2,3,4-trimethylbenzoyl)propionic acid. The structure of these acids was determined by sodium hypobromite oxidation to 3,4,5- and 2,3,4-trimethyl-benzoic acid, respectively. Both keto-acids were reduced by the Huang-Minlon method to γ-(3,4,5-trimethylphenyl)- and γ-(2,3,4-trimethylphenyl)-butyric acid; these last acids were cyclised with polyphosphoric acid at 90° to 6,7,8- and 5,6,7-trimethyl-1-tetralone, a procedure which, although giving lower yields, is far more convenient than the Friedel–Crafts aluminium chloride cyclisation of the corresponding acid chlorides.

The tetralones thus obtained are convenient intermediates for the synthesis of polymethylated homo- and hetero-cyclic compounds. Thus, 6,7,8-trimethyl-1-tetralone underwent a Grignard reaction with methylmagnesium iodide to give an alcohol, which

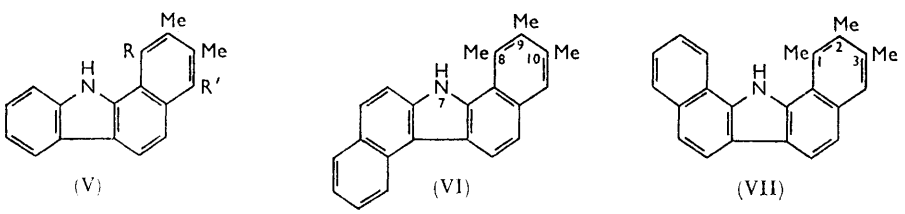
[1] Part XLI, Buu-Hoï, Jacquignon, Roussel, and Hoeffinger, *J.*, 1964, 3924.
[2] Buu-Hoï, Jacquignon, and Roussel, *Compt. rend.*, 1963, **257**, 4193.

was dehydrated to 5,6-dihydro-1,2,3,8-tetramethylnaphthalene, this giving, on dehydrogenation over palladised charcoal, the hitherto unknown, readily oxidisable 1,2,3,8-tetramethylnaphthalene in 80% yield. The alkali-catalysed condensation of 6,7,8-trimethyl-1-tetralone with benzaldehyde furnished the chalcone (I), which with polyphosphoric acid



afforded 1,2,3-trimethyl-7*H*-benzo[*c*]fluorene (II); similarly the chalcone obtained by condensation of 6,7,8-trimethyltetral-1-one with 1-naphthaldehyde underwent cyclodehydration to 7,8,9-trimethyl-13*H*-dibenzo[*a*,*g*]fluorene (III). Both cyclodehydrations gave low yields, probably because of steric hindrance exerted by the *peri*-methyl group, as the cyclisation of the condensation product of 1-naphthaldehyde with 6,7-dimethyl-1-tetralone (in which there is no such *peri*-group) gave excellent yields of 8,9-dimethyl-13*H*-dibenzo[*a*,*g*]fluorene (IV). The hydrocarbons (III) and (IV) are biologically interesting as homologues of the slightly carcinogenic [3] but strongly tumour-growth inhibitory [4] 13*H*-dibenzo[*a*,*g*]fluorene. Benzo[*c*]fluorene, the parent compound of hydrocarbon (II), is non-carcinogenic but exerts a slight inhibitory action on certain grafted tumours.[5]

Although quite unresponsive to Pfitzinger reactions with isatins, 6,7,8-trimethyl-1-tetralone and its 5,6,7-trimethyl isomer are convenient intermediates for the preparation of polymethylated benzo[*a*]carbazoles (V), through indolisation of their arylhydrazones followed by dehydrogenation of the dihydrocarbazoles obtained, by heating over palladised charcoal (with almost theoretical yields). A series of tri-, tetra-, and penta-methylbenzo[*a*]carbazoles thus prepared are listed in Tables 1 and 2. 8,9,10-Trimethyl-7*H*-dibenzo[*a*,*g*]- (VI) and 1,2,3-trimethyl-13*H*-dibenzo[*a*,*i*]-carbazole (VII) were similarly prepared. The parent compounds of these various methylated carbazoles are all known carcinogens.[6]



Experimental

Succinoylation of Hemimellitene.—To an ice-cooled solution of pure hemimellitene (60 g.) and succinic anhydride (55 g.) in anhydrous methylene chloride (300 c.c.), finely powdered aluminium chloride (86 g.) was added in small portions, with stirring, and the mixture kept for 12 hr. at room temperature. After decomposition with dilute hydrochloric acid, the solvent was steam-distilled, and the solid (78 g.) obtained on cooling was crystallised from acetic acid, giving a solid, and a filtrate (A). Recrystallisation of the solid from acetic acid afforded β-(3,4,5-*trimethylbenzoyl*)*propionic acid* as prisms (59 g.), m. p. 147° (Found: C, 70·6; H, 7·5.

[3] Bachmann, Cook, Dansi, De Worms, Haslewood, Hewett, and Robinson, *Proc. Roy. Soc.*, 1937, *B*, **123**, 343.
[4] Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1941, *B*, **130**, 255.
[5] Haddow and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 277.
[6] Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79; Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.

$C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). The *oxime* formed needles, m. p. 164° (from benzene) (Found: C, 66·4; H, 7·5; N, 6·1. $C_{13}H_{17}NO_3$ requires C, 66·4; H, 7·3; N, 6·0%). A suspension of this acid (5 g.) in aqueous sodium hypobromite (prepared from 4 c.c. of bromine, 8 g. of sodium hydroxide, and 60 c.c. of water) was shaken for 12 hr. and the excess of oxidant was decomposed with sodium hydrogen sulphite. The precipitate obtained on acidification with hydrochloric acid was crystallised twice from aqueous acetic acid, giving 3,4,5-trimethylbenzoic acid, m. p. 216° (lit.,[7] 215—216°) (Found: C, 72·9; H, 7·4. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·3%).

The filtrate (A) was diluted with water (3 vol.), boiled with charcoal, and filtered. The crystals obtained on cooling were esterified by refluxing for 2 hr. with ethanol (250 c.c.) and sulphuric acid (15 c.c.). After the usual treatment, and fractionation *in vacuo* of the product, *ethyl* β-(2,3,4-*trimethylbenzoyl*)*propionate* (13 g.) was obtained as an oil, b. p. 205°/15 mm., $n_D^{17\cdot4}$ 1·5252 (Found: C, 72·5; H, 8·7. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·7%). Hydrolysis of this ester with boiling 10% aqueous sodium hydroxide (125 c.c.) and acidification with hydrochloric acid afforded β-(2,3,4-*trimethylbenzoyl*)*propionic acid*, prisms (9 g.), m. p. 105° (from cyclohexane) (Found: C, 70·8; H, 7·4%) [*oxime*, needles, m. p. 148° (from cyclohexane) (Found: N, 5·8%)]. Oxidation of this acid with sodium hypobromite furnished 2,3,4-trimethylbenzoic acid, m. p. 166—167° (from aqueous methanol) (lit.,[8] 167°).

γ-(3,4,5-*Trimethylphenyl*)*butyric Acid.*—A solution of β-(3,4,5-trimethylbenzoyl)propionic acid (20 g.) and 95% hydrazine hydrate (10 g.) in diethylene glycol (250 c.c.) was refluxed with potassium hydroxide (17 g.) for 6 hr., with removal of water. After cooling, dilution with water, and acidification with hydrochloric acid, the solid formed was recrystallised from aqueous acetic acid, giving needles (17 g.) of the *acid*, m. p. 98° (Found: C, 75·5; H, 8·9. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%).

γ-(2,3,4-*Trimethylphenyl*)*butyric Acid.*—Similarly prepared from β-(2,3,4-trimethylbenzoyl)-propionic acid (17 g.), this *acid* formed needles (13 g.), m. p. 85° (from aqueous acetic acid) (Found: C, 75·8; H, 8·8%).

6,7,8-*Trimethyl*-1-*tetralone.*—(*a*) A solution of γ-(3,4,5-trimethylphenyl)butyric acid (17 g.) and thionyl chloride (20 g.) in anhydrous ether (100 c.c.) was refluxed for 1 hr. with 2 drops of pyridine, and the solvent and the excess of thionyl chloride were distilled off. The residue was dissolved in methylene chloride (100 c.c.), and aluminium chloride (15 g.) was added in small portions, with stirring, at 0°. After 12 hr. at room temperature, the mixture was decomposed with dilute hydrochloric acid, and the organic layer was washed with aqueous sodium hydroxide and water, dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The *tetralone*, b. p. 181°/20 mm., formed needles (8 g.), m. p. 52° (from aqueous methanol) (Found: C, 82·3; H, 8·7. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%) [*semicarbazone*, prisms, m. p. 208—209° (from cyclohexane) (Found: N, 17·1. $C_{14}H_{19}N_3O$ requires N, 17·1%); *oxime*, needles, m. p. 218° (from ethanol–benzene) (Found: N, 6·9. $C_{13}H_{17}NO$ requires N, 6·9%)].

(*b*) A mixture of γ-(3,4,5-trimethylphenyl)butyric acid (28 g.) and polyphosphoric acid (180 g.) was heated at 90° for 25 min. with stirring. After cooling, water was added, and the precipitate formed was washed with water and recrystallised from aqueous methanol (yield, 8 g.).

5,6,7-*Trimethyl*-1-*tetralone.*—Obtained from γ-(2,3,4-trimethylphenyl)butyric acid (12 g.) and polyphosphoric acid (70 g.) as above, this *tetralone* was an oil (8 g.), b. p. 187—188°/20 mm., $n_D^{20\cdot1}$ 1·5749 (Found: C, 82·6; H, 8·5%) [*oxime*, prisms, m. p. 185°) (from ethanol–benzene) (Found: N, 6·9%); *semicarbazone*, needles, m. p. 245° (from ethanol–benzene) (Found: N, 17·1%)].

5,6-*Dihydro*-1,2,3,8-*tetramethylnaphthalene.*—To an ethereal solution of methylmagnesium iodide (prepared from 8 g. of methyl iodide and 0·8 g. of magnesium), 6,7,8-trimethyl-1-tetralone (6 g.) was added in small portions, and the mixture refluxed for 30 min. and, on cooling, decomposed with aqueous ammonium chloride. The organic layer was dried (Na_2SO_4), the solvent removed, and the residue treated with boiling formic acid. After dilution with water, the dehydration *product* was taken up in benzene and purified by fractionation *in vacuo*, giving an oil (4 g.), b. p. 165°/20 mm., n_D^{22} 1·5682 (Found: C, 90·0; H, 9·5. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%).

1,2,3,8-*Tetramethylnaphthalene.*—Obtained by heating the above compound at 210° with

[7] Jannasch and Weiler, *Ber.*, 1894, **27**, 3444.
[8] Jacobson, *Ber.*, 1886, **19**, 1214.

5% palladised charcoal for 3 hr., fractionation *in vacuo*, and purification of the product by conversion into its *picrate* [vermilion-red needles, m. p. 146° (from ethanol) (Found: C, 58·0; H, 4·6; N, 10·3. $C_{20}H_{19}N_3O_7$ requires C, 58·1; H, 4·6; N, 10·2%)], this *hydrocarbon* was an oil, darkening rapidly in air and light, b. p. 182—183°/20 mm., $n_D^{21.9}$ 1·5771 (Found: C, 90·8; H, 9·0. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%).

8,9,10-*Trimethyl*-7H-*dibenzo*[a,g]*carbazole* (VI).—A solution of 6,7,8-trimethyl-1-tetralone (1·9 g.), β-naphthylhydrazine hydrochloride (2·2 g.), and sodium acetate (1 g.) in ethanol (22 c.c.) was refluxed for 1 hr., and the crude hydrazone formed on cooling and dilution with water was treated with a boiling solution of hydrogen chloride in acetic acid. After cooling and dilution with water, the precipitate was recrystallised from cyclohexane, giving 12,13-*dihydro*-8,9,10-*trimethyl*-7H-*dibenzo*[a,g]*carbazole*, needles (2 g.), m. p. 223° (Found: N, 4·5. $C_{23}H_{21}N$ requires N, 4·5%). Sublimation over 5% palladised charcoal afforded the dehydrogenation *product*, prisms, m. p. 283° (from cyclohexane–benzene) (Found: C, 89·3; H, 6·2. $C_{23}H_{19}N$ requires C, 89·3; H, 6·2%) [*picrate*, brown needles, m. p. 254° (from ethanol) (Found: N, 10·3. $C_{29}H_{22}N_4O_7$ requires N, 10·4%)].

1,2,3-*Trimethyl*-13H-*dibenzo*[a,i]*carbazole* (VII).—Prepared as above, with α-naphthylhydrazine hydrochloride, 5,6-*dihydro*-1,2,3-*trimethyl*-13H-*dibenzo*[a,i]*carbazole* formed needles, m. p. 138° (from hexane) (Found: C, 88·7; H, 6·8. $C_{23}H_{21}N$ requires C, 88·7; H, 6·8%). Dehydrogenation gave the *carbazole*, as colourless prisms, m. p. 276° (from ethanol) (Found: C, 89·2; H, 6·2%).

The monobenzocarbazoles listed in Tables 1 and 2 were prepared in the same way.

TABLE 1.

5,6-Dihydro-11*H*-benzo[*a*]carbazoles.

Compound	M. p.*	Found (%) C	H	N	Formula	Required (%) C	H	N
1,2,3-Trimethyl-	164°	87·3	7·2	5·5	$C_{19}H_{19}N$	87·3	7·3	5·4
2,3,4-Trimethyl- †	173	87·3	7·3	5·3	$C_{19}H_{19}N$	,,	,,	,,
1,2,3,10-Tetramethyl- ...	121	—	—	5·1	$C_{20}H_{21}N$	—	—	5·1
1,2,3,8-Tetramethyl-	157	—	—	5·1	$C_{20}H_{21}N$	—	—	,,
1,2,3,7,10-Pentamethyl-	170	87·1	7·8	5·1	$C_{21}H_{23}N$	87·2	8·0	4·8
1,2,3,8,9-Pentamethyl- ...	222	87·1	8·1	5·0	$C_{21}H_{23}N$	,,	,,	,,
1,2,3,9,10-Pentamethyl-	148	—	—	5·0	$C_{21}H_{23}N$	—	—	,,

* From hexane, cyclohexane, or ethanol; all gave brown-violet picrates. † 5,6,7-Trimethyl-1-tetralone phenylhydrazone, cream-coloured needles, m. p. 117° (from ethanol).

TABLE 2.

11*H*-Benzo[*a*]carbazoles.

Compound	M. p.*	Found (%) C	H	N	Formula	Required (%) C	H	N
1,2,3-Trimethyl-	205°	88·0	6·5	5·5	$C_{19}H_{17}N$	88·0	6·6	5·4
picrate	199	—	—	11·6	$C_{25}H_{20}N_4O_7$	—	—	11·5
2,3,4-Trimethyl-	196	88·0	6·6	5·5	$C_{19}H_{17}N$	88·0	6·6	5·4
picrate	213	—	—	11·6	$C_{25}H_{20}N_4O_7$	—	—	11·5
1,2,3,10-Tetramethyl-	215	87·9	7·1	5·3	$C_{20}H_{19}N$	87·9	7·0	5·1
picrate	159	—	—	11·4	$C_{26}H_{22}N_4O_7$	—	—	11·2
1,2,3,8-Tetramethyl-	187	88·3	7·0	5·1	$C_{20}H_{19}N$	87·9	7·0	5·1
1,2,3,7,10-Pentamethyl-	224	88·0	7·2	5·0	$C_{21}H_{21}N$	87·8	7·3	4·9
picrate	196	—	—	10·8	$C_{27}H_{24}N_4O_7$	—	—	10·9
1,2,3,8,9-Pentamethyl-	254	87·9	7·3	5·0	$C_{21}H_{21}N$	87·8	7·3	4·9
picrate	217	—	—	10·8	$C_{27}H_{24}N_4O_7$	—	—	10·9
1,2,3,9,10-Pentamethyl-	228	87·8	7·4	5·0	$C_{21}H_{21}N$	87·8	7·3	4·9
picrate	178	—	—	10·9	$C_{27}H_{24}N_4O_7$	—	—	10·9

* From cyclohexane or ethanol.

1,2,3-*Trimethyl*-7H-*benzo*[c]*fluorene* (II).—A solution of 6,7,8-trimethyl-1-tetralone (1·8 g.) and benzaldehyde (1 g.) in a 4% solution of potassium hydroxide in ethanol (50 c.c.) was shaken vigorously for 15 min. then kept at 0° for 72 hr. The solid that was formed was collected, washed with water, and recrystallised from ethanol, giving 2-*benzylidene*-6,7,8-*trimethyl*-1-*tetralone* (I), as needles (1·5 g.), m. p. 122°, whose solution in sulphuric acid was orange-red (Found: C, 87·1; H, 7·1. $C_{20}H_{20}O$ requires C, 87·0; H, 7·3%). A solution of this chalcone

(1 g.) in polyphosphoric acid (10 g.; 60% P_2O_5) was heated for 20 min. at *ca.* 135°. After cooling and addition of water, the product was taken up in toluene, the organic layer washed with aqueous sodium hydroxide and water, the solvent removed, and the residue fractionated *in vacuo*. The portion, b. p. 255—260°/12 mm., was recrystallised several times from ethanol to furnish the *benzofluorene* (II), needles (0·1 g.), m. p. 117°, giving no halochromy in sulphuric acid (Found: C, 92·0; H, 7·5. $C_{20}H_{18}$ requires C, 92·3; H, 7·7%), $\lambda_{max.}$ (EtOH) 204, 244, and 312 mμ, analogous to those recorded for benzo[*c*]fluorene.[9]

7,8,9-*Trimethyl*-13H-*dibenzo*[a,g]*fluorene* (III).—2-(1-*Naphthylmethylene*)-6,7,8-*trimethyl*-1-*tetralone*, prepared as above with 1-naphthaldehyde, formed prisms, m. p. 86° (from ethanol) giving a violet-red halochromy in sulphuric acid (Found: C, 88·6; H, 6·5. $C_{24}H_{22}O$ requires C, 88·3; H, 6·8%). Cyclodehydration afforded the *hydrocarbon* (III), needles (15%), m. p. 151° (from ethanol) (Found: C, 93·2; H, 6·3. $C_{24}H_{20}$ requires C, 93·5; H, 6·5%).

8,9-*Dimethyl*-13H-*dibenzo*[a,g]*fluorene* (IV).—2-(1-*Naphthylmethylene*)-6,7-*dimethyl*-1-*tetralone*, prepared from 6,7-dimethyl-1-tetralone [10] and 1-naphthaldehyde, formed prisms (90%), m. p. 140° (from ethanol) (Found: C, 88·1; H, 6·6. $C_{23}H_{20}O$ requires C, 88·5; H, 6·4%). Cyclodehydration gave the *hydrocarbon* (IV), needles (70%), m. p. 205° (from ethanol) (Found: C, 93·7; H, 6·3. $C_{23}H_{18}$ requires C, 93·8; H, 6·2%).

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[9] Mayneord and Roe, *Proc. Roy. Soc.*, 1937, *A*, **158**, 634.
[10] de Barry Barnett and Sanders, *J.*, 1933, 434.