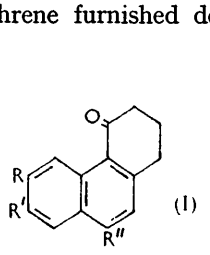
477. *Carcinogenic Nitrogen Compounds. Part XLIV.*[1] *Naphtho- and Phenanthro-carbazoles*

By N. P. Buu-Hoï and G. Saint-Ruf

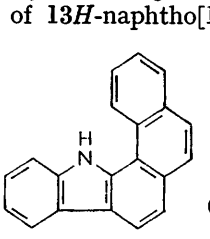
A number of naphthocarbazoles, phenanthrocarbazoles, and benzonaphtho- and benzophenanthro-carbazoles, with or without methyl substituents, have been synthesised from the appropriate polycyclic ketones, for chemical and biological investigation.

Polycyclic derivatives of carbazole have been encountered in coal-tar,[2] in soot from atmospheric pollution, and among the products of pyrolysis of vegetable material including tobacco,[3] and some of them have been found to display carcinogenic activity.[4] It was of interest to investigate this class of compound further, not only for biological study but also as reference materials in the detection and determination of carbazole components of atmospheric pollutants and tars.

Many benzo- and dibenzo-carbazoles had already been prepared,[5] but few naphthocarbazoles,[6] and no phenanthrocarbazole. Several of these have now been synthesised, by indolisation of arylhydrazones of the appropriate cyclanones derived from phenanthrene and from benz[*a*]anthracene, followed by dehydrogenation of the various di- and tetrahydrocarbazoles obtained. Methyl homologues (I) of 1,2,3,4-tetrahydro-4-oxophenanthrene furnished derivatives of 13*H*-naphtho[1,2-*a*]carbazole (II), and from methyl



(I)



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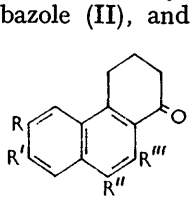

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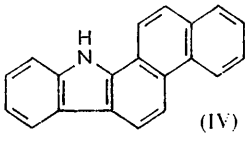

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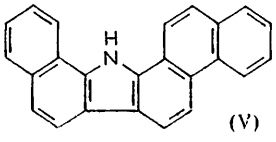

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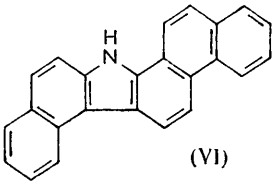


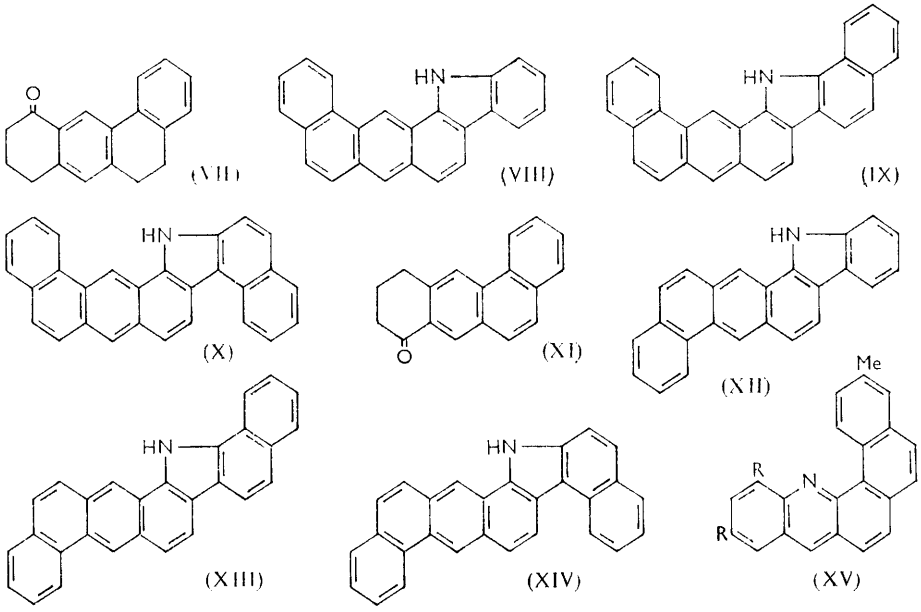
(VI)

homologues (III) of 1,2,3,4-tetrahydro-1-oxophenanthrene, derivatives of 11*H*-naphtho[2,1-*a*]carbazole (IV), 13*H*-benzo[*i*]naphtho[2,1-*a*]carbazole (V), and 13*H*-benzo[*g*]naphtho[2,1-*a*]carbazole (VI) were obtained. 5,6,8,9,10,11-Hexahydro-11-oxobenz[*a*]anthracene (VII), prepared from 9,10-dihydrophenanthrene by the succinic anhydride method,[7] afforded 15*H*-phenanthro[3,2-*a*]carbazole (VIII) and its homologues, and 17*H*-benzo[*i*]phenanthro[3,2-*a*]carbazole (IX) and the isomeric 17*H*-benzo[*g*]phenanthro[3,2-*a*]carbazole (X). The phenanthrocarbazoles (XII), (XIII), and (XIV), isomeric with compounds (VIII), (IX), and (X), were similarly prepared from 8,9,10,11-tetrahydro-8-oxobenz[*a*]anthracene (XI), which was readily obtained from phenanthrene and succinic anhydride by a modification of Haworth's synthesis[8] which was both more convenient

[1] Part XLIII, Buu-Hoï, Dufour, and Jacquignon, *J.*, 1964, 5622.
[2] Cf. Kikkawa, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, 1951, **54**, 631; Mabille and Buu-Hoï, *J. Org. Chem.*, 1960, **25**, 1937.
[3] Van Duuren, Bilbao, and Joseph, *J. Nat. Cancer Inst.*, 1960, **25**, 53.
[4] Boyland and Brues, *Proc. Roy. Soc.*, 1957, *B*, **122**, 429; Boyland and Mawson, *Biochem. J.*, 1938, **32**, 1460; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.
[5] For latest Papers on the subject, see Buu-Hoï and Saint-Ruf, *J.*, 1962, 2630; Buu-Hoï, Saint-Ruf, Jacquignon, and Marty, *J.*, 1963, 2274.
[6] Cf. Buu-Hoï and Jacquignon, *J.*, 1951, 2965; 1956, 1517.
[7] Cf. Burger and Mosettig, *J. Amer. Chem. Soc.*, 1937, **59**, 1302; Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 456.
[8] Haworth, *J.*, 1933, 1012.

and gave better yields. A characteristic of the carbazoles thus prepared was the strong fluorescence of their benzene solutions; an interesting difference between the hexacyclic carbazoles and the heptacyclic ones was that whereas the great majority of the former gave monopicrates, all the latter formed dipicrates.

1,2,3,4-Tetrahydro-7-methyl-4-oxophenanthrene (I; R = R″ = H, R′ = Me) readily underwent the Pfitzinger reaction to give cinchoninic acids, which were converted through decarboxylation and dehydrogenation into the homologues (XV) of naphth[2,1-*c*]acridine,



which are related to the carcinogenic benz[*c*]acridine series,[9] and to naphthocarbazole (II)

Carcinogenicity, if it does exist in the compounds reported herein, can be only very slight, as no sarcomas have yet appeared after 6 months' subcutaneous injections in rats.

Experimental (with M. Dufour)

1,2,3,4-*Tetrahydro*-7-*methyl*-4-*oxophenanthrene* (I; R = R″ = H, R′ = Me).—This ketone, b. p. 223°/20 mm., m. p. 68° (lit.,[10] m. p. 63°), was prepared from 2-methylnaphthalene and succinic anhydride by a modification of Haworth, Letsky, and Mavin's procedure [10] involving reduction of the keto-acid m. p. 164° (from methanol) (lit.,[10] 162°) obtained, by use of hydrazine hydrate and potassium hydroxide in 1,2-ethanediol, followed by cyclisation of the chloride of the resulting acid with aluminium chloride in methylene chloride solution. It was characterised by its condensation products with aromatic aldehydes (the reaction was effected in a 4% solution of potassium hydroxide in ethanol): 3-*benzylidene*-1,2,3,4-*tetrahydro*-7-*methyl*-4-*oxophenanthrene* formed pale yellow prisms, m. p. 134° (from ethanol), the solutions of which in sulphuric acid were cherry red (Found: C, 88·5; H, 6·3. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%); 1,2,3,4-*tetrahydro*-7-*methyl*-3-(1-*naphthylmethylene*)-4-*oxophenanthrene*, pale yellow needles, m. p. 145° (from ethanol–benzene), the solutions of which in sulphuric acid were violet (Found: C, 89·3; H, 5·8. $C_{26}H_{20}O$ requires C, 89·6; H, 5·8%).

1,2,3,4-*Tetrahydro*-6,7-*dimethyl*-4-*oxophenanthrene* (I; R = R′ = Me, R″ = H).—This compound, b. p. 234°/20 mm., m. p. 115°, was prepared by a similar modification of Haworth and Bolan's method.[11] 6,9- (III; R = R″ = Me, R′ = R‴ = H), 7,9- (III; R = R‴ = H,

[9] Cf. Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.
[10] Haworth, Letsky, and Mavin, *J.*, 1932, 1784.
[11] Haworth and Bolan, *J.*, 1932, 2248.

TABLE 1

13*H* Naphtho[1,2-*a*]carbazoles

Derivative	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
7,8-Dihydro-3-methyl-	152°	$C_{21}H_{17}N$	88·7	6·2	4·8	89·0	6·1	4·9
3-Methyl-	197	$C_{21}H_{15}N$	89·5	5·6	5·0	89·7	5·4	5·0
picrate	202	$C_{27}H_{18}N_4O_7$	—	—	11·5	—	—	11·0
7,8-Dihydro-2,3-dimethyl-	179	$C_{22}H_{19}N$	88·8	6·3	—	88·9	6·4	—
2,3-Dimethyl-	222	$C_{22}H_{17}N$	89·3	6·0	4·7	89·5	5·8	4·7
picrate	188	$C_{28}H_{20}N_4O_7$	—	—	10·5	—	—	10·7

TABLE 2

11*H*-Naphtho[2,1-*a*]carbazoles

Derivative	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
5,6-Dihydro-12,13-dimethyl-	215°	$C_{22}H_{19}N$	—	—	4·6	—	—	4·7
picrate	155	$C_{28}H_{22}N_4O_7$	—	—	10·7	—	—	10·6
12,13-Dimethyl-	260	$C_{22}H_{17}N$	89·3	6·0	4·8	89·5	5·8	4·9
5,6-Dihydro-2,13-dimethyl-	249	$C_{22}H_{19}N$	89·0	6·4	—	88·9	6·4	—
2,13-Dimethyl-	226	$C_{22}H_{17}N$	89·8	5·6	4·9	89·5	5·8	4·7
dipicrate	191	$C_{34}H_{23}N_7O_{14}$	—	—	12·8	—	—	13·0
5,6-Dihydro-3,13-dimethyl-	195	$C_{22}H_{19}N$	88·9	6·3	4·9	88·9	6·4	4·7
3,13-Dimethyl-	247	$C_{22}H_{17}N$	89·5	5·7	4·9	89·5	5·8	4·7
picrate	210	$C_{28}H_{20}N_4O_7$	—	—	10·9	—	—	10·7
5,6-Dihydro-2,8,13-trimethyl-	188	$C_{23}H_{21}N$	89·0	6·8	—	88·7	6·8	—
2,8,13-Trimethyl	332	$C_{23}H_{19}N$	89·0	6·5	4·6	89·3	6·2	4·5
picrate	213	$C_{29}H_{22}N_4O_7$	—	—	10·2	—	—	10·4
5,6-Dihydro-3,8,13-trimethyl-	252	$C_{23}H_{21}N$	88·8	6·8	4·5	88·7	6·8	4·5
3,8,13-Trimethyl-	288	$C_{23}H_{19}N$	89·1	6·2	4·5	89·3	6·2	4·5
picrate	244[a]	$C_{29}H_{22}N_4O_7$	—	—	10·6	—	—	10·4
5,6-Dihydro-3,10,13-trimethyl-	224	$C_{23}H_{21}N$	88·4	6·5	4·5	88·7	6·8	4·5
3,10,13-Trimethyl-	235	$C_{23}H_{19}N$	89·1	6·3	4·5	89·3	6·2	4·5
picrate	216	$C_{29}H_{22}N_4O_7$	—	—	10·3	—	—	10·4
5,6-Dihydro-2,9,10,13-tetramethyl-	153	$C_{24}H_{23}N$	88·5	7·3	4·3	88·6	7·1	4·3
2,9,10,13-Tetramethyl-	209	$C_{24}H_{21}N$	89·0	6·8	—	89·1	6·6	—
picrate	177	$C_{30}H_{24}N_4O_7$	—	—	10·0	—	—	10·1
5,6-Dihydro-3,9,10,13-tetramethyl-	275	$C_{24}H_{23}N$	88·5	7·0	4·5	88·6	7·1	4·3
3,9,10,13-Tetramethyl-	293	$C_{24}H_{21}N$	88·8	6·7	4·3	89·1	6·6	4·3
picrate	Dissoc. >195	$C_{30}H_{24}N_4O_7$	—	—	10·3	—	—	10·1
5,6-Dihydro-3,8,9,13-tetramethyl-	253	$C_{24}H_{23}N$	88·6	7·1	4·2	88·6	7·1	4·3
3,8,9,13-Tetramethyl-	283	$C_{24}H_{21}N$	89·1	6·5	4·5	89·1	6·6	4·3
picrate	244	$C_{30}H_{24}N_4O_7$	—	—	9·9	—	—	10·1
5,6-Dihydro-3,7,10,13-tetramethyl-	228	$C_{24}H_{23}N$	88·5	7·3	4·3	88·6	7·1	4·3
3,7,10,13-Tetramethyl-	237	$C_{24}H_{21}N$	89·1	6·6	4·4	89·1	6·6	4·3
picrate	246	$C_{30}H_{24}N_4O_7$	—	—	10·3	—	—	10·1

[a] Dissoc. >200°.

TABLE 3

13*H*-Benzo[*i*]naphtho[2,1-*a*]carbazoles

Derivative	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
2,15-Dimethyl-	231°	$C_{26}H_{19}N$	90·0	5·4	4·2	90·4	5·5	4·1
picrate	236	$C_{32}H_{22}N_4O_7$	—	—	9·9	—	—	9·8
3,15-Dimethyl-	251	$C_{26}H_{19}N$	90·6	5·4	4·2	90·4	5·5	4·1
picrate	239	$C_{32}H_{22}N_4O_7$	—	—	9·9	—	—	9·8
5,6-Dihydro-14,15-dimethyl-	225	$C_{26}H_{21}N$	90·0	6·3	4·4	89·9	6·1	4·0
14,15-Dimethyl-	276	$C_{26}H_{19}N$	89·9	5·6	4·3	90·4	5·5	4·1
picrate	179	$C_{32}H_{22}N_4O_7$	—	—	9·4	—	—	9·8
13*H*-Benzo[*g*]naphtho[2,1-*a*]carbazoles								
5,6-Dihydro-2,15-dimethyl-	220	$C_{26}H_{21}N$	90·2	6·2	—	89·9	6·1	—
2,15-Dimethyl-	251	$C_{26}H_{19}N$	90·0	5·6	—	90·4	5·5	—
picrate	216	$C_{32}H_{22}N_4O_7$	—	—	10·1	—	—	9·8
5,6-Dihydro-3,15-dimethyl-	198	$C_{26}H_{21}N$	90·0	6·2	—	89·9	6·1	—
3,15-Dimethyl-	245	$C_{26}H_{19}N$	90·0	5·6	—	90·4	5·5	—
picrate	252	$C_{32}H_{22}N_4O_7$	—	—	9·8	—	—	9·8
5,6-Dihydro-14,15-dimethyl-	229	$C_{26}H_{21}N$	89·6	6·4	4·2	89·9	6·1	4·0
14,15-Dimethyl-	266	$C_{26}H_{19}N$	89·9	5·8	4·2	90·4	5·5	4·1

TABLE 4

15*H*-Phenanthro[3,2-*a*]carbazoles

Derivative	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
5,6,8,9-Tetrahydro-	151°	$C_{24}H_{19}N$	89·8	5·8	—	89·7	6·0	—
Compound (VIII)	276	$C_{24}H_{15}N$	90·9	4·9	4·4	90·8	4·8	4·4
picrate	241	$C_{30}H_{18}N_4O_7$	—	—	10·5	—	—	10·3
1-Methyl-5,6,8,9-tetrahydro-	143	$C_{25}H_{21}N$	89·4	6·2	—	89·5	6·3	—
1-Methyl-	252	$C_{25}H_{17}N$	90·8	5·2	—	90·6	5·2	—
dipicrate	206	$C_{37}H_{23}N_7O_{14}$	—	—	12·6	—	—	12·4
2-Methyl-5,6,8,9-tetrahydro-	167	$C_{25}H_{21}N$	—	—	4·0	—	—	4·2
2-Methyl-	260	$C_{25}H_{17}N$	90·2	5·6	4·1	90·6	5·2	4·2
3-Methyl-5,6,8,9-tetrahydro-	176	$C_{25}H_{21}N$	89·4	6·1	4·3	89·5	6·3	4·2
3-Methyl-	266	$C_{25}H_{17}N$	90·5	5·3	4·4	90·6	5·2	4·2
picrate	225	$C_{31}H_{20}N_4O_7$	—	—	10·4	—	—	10·0
2,3-Dimethyl-5,6,8,9-tetrahydro-	213	$C_{26}H_{23}N$	89·5	6·7	4·1	89·4	6·6	4·0
2,3-Dimethyl-	270	$C_{26}H_{19}N$	90·3	5·4	—	90·4	5·5	—
picrate	228	$C_{32}H_{22}N_4O_7$	—	—	9·8	—	—	9·8

TABLE 5

Benzophenanthrocarbazoles

Carbazole	M. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
7,8,10,11-Tetrahydro-17*H*-benzo[*i*]phenanthro[3,2-*a*]-	198°	$C_{28}H_{21}N$	90·2	5·9	3·7	90·5	5·7	3·8
17*H*-Benzo[*i*]phenanthro[3,2-*a*]- (IX)	307	$C_{28}H_{17}N$	91·3	4·8	3·9	91·5	4·7	3·8
dipicrate	239	$C_{40}H_{23}N_7O_{14}$	—	—	11·6	—	—	11·8
5,6,8,9-Tetrahydro-15*H*-benzo[*g*]phenanthro[3,2-*a*]-	181	$C_{28}H_{21}N$	90·8	6·0	3·9	90·5	5·7	3·8
15*H*-Benzo[*g*]phenanthro[3,2-*a*]- (X)	286	$C_{28}H_{17}N$	91·3	4·8	3·9	91·5	4·7	3·8
dipicrate	251 [a]	$C_{40}H_{23}N_7O_{14}$	—	—	11·2	—	—	11·8
7,8-Dihydro-17*H*-benzo[*i*]phenanthro[2,3-*a*]-	286	$C_{28}H_{19}N$	90·7	5·4	3·7	91·0	5·2	3·8
17*H*-Benzo[*i*]phenanthro[2,3-*a*]- (XIII)	347	$C_{28}H_{17}N$	91·3	4·7	3·9	91·5	4·7	3·8
dipicrate	253 [b]	$C_{40}H_{23}N_7O_{14}$	—	—	12·0	—	—	11·8
5,6-Dihydro-15*H*-benzo[*g*]phenanthro[2,3-*a*]-	333	$C_{28}H_{19}N$	90·7	5·1	—	91·0	5·2	—
15*H*-Benzo[*g*]phenanthro[2,3-*a*]- (XIV)	407	$C_{28}H_{17}N$	91·4	4·7	3·7	91·5	4·7	3·8
dipicrate	291 [c]	$C_{40}H_{23}N_7O_{14}$	—	—	11·7	—	—	11·8

[a] Dissoc. >210°; recrystallised from ethanol. [b] Dissoc. >185°; recrystallised from chlorobenzene. [c] Dissoc. >200°; recrystallised from dioxan.

R′ = R″ = Me), and 9,10-dimethyl-1-oxo-1,2,3,4-tetrahydrophenanthrene (III; R = R′ = H, R″ = R‴ = Me) were prepared as reported by the present authors.[12,13]

5,6,8,9,10,11-*Hexahydro*-11-*oxobenz*[a]*anthracene*.—The reaction of succinic anhydride (37 g.) with 9,10-dihydrophenanthrene (90 g.) in the presence of aluminium chloride (60 g.) at 0° (18 hr.) in methylene chloride (400 c.c.) gave a 68% yield of β-(9,10-dihydrophenanthroyl)-propionic acid, m. p. 157°; reduction of this acid (46 g.), effected with hydrazine hydrate (22 g.) and potassium hydroxide (40 g.) in 1,2-ethanediol (400 c.c.), furnished γ-(9,10-dihydrophenanthryl)butyric acid, b. p. 229—230°/0·6 mm., m. p. 93° (40 g.). Cyclisation of the acid chloride afforded ketone (VII), m. p. 96° (lit.,[7] 97°). This ketone was characterised by its condensation-products with benzaldehyde and 1-naphthaldehyde: 10-*benzylidene*-5,6,8,9,10,11-*hexahydro*-11-*oxobenz*[a]*anthracene* formed prisms, m. p. 161° (from ethanol), the solution of which in sulphuric acid was red (Found: C, 89·2; H, 5·9. $C_{25}H_{20}O$ requires C, 89·3; H, 6·0%); 5,6,8,9,10,11-*hexahydro*-10-(1-*naphthylmethylene*)-11-*oxobenz*[a]*anthracene*, pale yellow needles, m. p. 171° (ethanol), giving a violet coloration in sulphuric acid (Found: C, 89·9; H, 5·6. $C_{29}H_{22}O$ requires C, 90·1; H, 5·7%).

7,8-*Dihydro*-3-*methylnaphth*[2,1-c]*acridine*-9-*carboxylic Acid*.—A solution of ketone (I; R = R″ = H, R′ = Me) (3 g.), isatin (2·5 g.), and potassium hydroxide (7 g.) in ethanol (50 c.c.) was refluxed for 20 hr., the solvent was distilled, and the solid residue washed with ether and acidified with dilute acetic acid. The *cinchoninic acid* (3·5 g.) formed yellowish prisms, m. p. 326°,

[12] Buu-Hoï and Saint-Ruf, *Compt. rend.*, 1962, **254**, 2366.
[13] Buu-Hoï and Saint-Ruf, *Bull. Soc. chim. France*, 1963, 2307.

from acetic acid (Found: C, 81·1; H, 5·3; N, 4·1. $C_{23}H_{17}NO_2$ requires C, 81·4; H, 5·1; N, 4·1%). Heating this acid above its m. p., and distillation of the residue *in vacuo*, gave 7,8-*dihydro*-3-*methylnaphth*[2,1-c]*acridine*, pale yellow needles, m. p. 137° (from isopropanol) (Found: N, 4·6. $C_{22}H_{17}N$ requires N, 4·7%); picrate, orange prisms, m. p. 189° (from ethanol). Dehydrogenation of the foregoing base was effected in 80% yield, by distillation over 5% palladised charcoal, giving 3-*methylnaphth*[2,1-c]*acridine* (XV; R = H), cream-coloured needles, m. p. 143° (from ethanol) (Found: C, 89·8; H, 5·1; N, 4·8. $C_{22}H_{15}N$ requires C, 90·1; H, 5·2; N, 4·8%); *picrate*, orange-yellow prisms, m. p. 194° (from ethanol) (Found: N, 10·7. $C_{28}H_{18}N_4O_7$ requires N, 10·7%).

7,8-*Dihydro*-3,11,13-*trimethylnaphth*[2,1-c]*acridine*.—Prepared from 5,7-dimethylisatin (2 g.) as above, this *acid* formed cream-coloured needles (2 g.), m. p. 283° (from ethanol) (Found: C, 81·9; H, 5·5; N, 3·8. $C_{25}H_{21}NO_2$ requires C, 81·7; H, 5·7; N, 3·8%). Thermal decarboxylation was accompanied by dehydrogenation, to give 3,11,13-*trimethylnaphth*[2,1-c]*acridine* (XV; R = Me), pale yellow needles, m. p. 203° (from ethanol) (Found: C, 88·9; H, 6·5; N, 4·4. $C_{24}H_{21}N$ requires C, 89·1; H, 6·6; N, 4·3%); *picrate*, orange needles, m. p. 151° (from ethanol) (Found: N, 9·9. $C_{30}H_{24}N_4O_7$ requires N, 10·2%).

15H-*Phenanthro*[2,3-a]*carbazole* (XII).—A solution of ketone (XI) (2 g.) and phenylhydrazine (1 g.) in ethanol (10 c.c.) was refluxed for 15 min. with one drop of acetic acid, and the crude hydrazone obtained on cooling and dilution with water was collected and treated with a boiling saturated solution of hydrogen chloride in acetic acid (25 c.c.); after cooling and dilution with water, the precipitate was crystallised from ethanol–benzene, giving 5,6-*dihydro*-15H-*phenanthro*[2,3-a]*carbazole* as cream-coloured needles (1·8 g.), m. p. 294° (Found: C, 90·3; H, 5·3; N, 4·5. $C_{24}H_{17}N$ requires C, 90·3; H, 5·4; N, 4·4%). Sublimation of this compound (1 part) over 5% palladised charcoal (5 parts) furnished *compound* (XII) in 90% yield, as faintly yellow prisms, m. p. 364°, from ethanol–benzene (Found: C, 90·7; H, 4·8; N, 4·5. $C_{24}H_{15}N$ requires C, 90·8; H, 4·8; N, 4·4%); *dipicrate*, pale brown prisms (from chlorobenzene), m. p. 256° (dissoc. >180°) (Found: N, 12·5. $C_{36}H_{21}N_7O_{14}$ requires N, 12·6%).

The other carbazoles were all prepared in the same way and with similar yields, and were purified by recrystallisation from ethanol or ethanol–benzene; many of the hydrogenated carbazoles were very soluble, in which case they were recrystallised from hexane or cyclohexane. The picrates and dipicrates were recrystallised from ethanol–benzene and varied in colour from red to brown.

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