423. *Carcinogenic Nitrogen Compounds. Part XXXVI.*[1] *The Use of Dimethyltetralones for the Synthesis of Polymethylated Angular Benzacridines and Benzocarbazoles.**

By N. P. Buu-Hoï, G. Saint-Ruf, P. Jacquignon, and Michèle Marty.

5,7- and 6,7-Dimethyl-1-tetralone, but not the 5,8-isomer, readily underwent Pfitzinger reactions with dimethylisatins, leading to tetramethylbenz[*c*]acridines. All three tetralones, on the other hand, were susceptible to the Fischer reaction, thus giving a new series of polymethyl-11*H*-benzo[*a*]carbazoles.

Almost all the benzacridines tested so far, and found to be carcinogenic, bear a substituent in a *meso*-position,[2] and this activity has been attributed, *inter alia*, to an increase in the π-electron density in the *meso*-phenanthrenic region (*K*-zone) brought about by *meso*-substitution; in theory, an accumulation of electron-donating groups in other positions can also enhance electron density. Were the high electron density of the *K*-zone the only factor significant for carcinogenicity in compounds of this type, then derivatives of benz[*c*]acridine (I) bearing several non-*meso* methyl groups would also be active. To settle this point, we have synthesised several tetramethylbenz[*c*]acridines.

A convenient route was the Pfitzinger reaction of *Bz*-dimethylisatins with the

* In view of the several conflicting methods of numbering benzacridines and benzocarbazoles, the nomenclature used in this and subsequent papers follows that of I.U.P.A.C.

[1] Part XXXV, Buu-Hoï, Roussel, and Petit, *J.*, 1963, 956.

[2] Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

appropriate tetralones, and thus, the behaviour of 5,6-, 4,7-, 5,7-, and 6,7-dimethylisatin towards 5,7-, 6,7-, and 5,8-dimethyl-1-tetralone was investigated. This benzacridine synthesis involves condensation of the isatin with the tetralone to give a 5,6-dihydrobenz[*c*]acridine-7-carboxylic acid, thermal decarboxylation of which yields a 5,6-dihydrobenz[*c*]acridine (Table 1) which is dehydrogenated over palladium–charcoal to a benz[*c*]acridine (Table 2). The first step was successful when 5,6-, 5,7-, and 6,7-di-

TABLE 1.

5,6-Dihydrobenz[*c*]acridines.

			Found (%)			Required (%)		
Compound	M. p.	Formula	C	H	N	C	H	N
2,3,9,10-Tetramethyl- ...	215°	$C_{21}H_{21}N$	87·8	7·3	—	87·8	7·3	—
picrate	266 decomp. >230	$C_{27}H_{24}N_4O_7$	—	—	10·7	—	—	10·8
2,4,9,10-Tetramethyl- ...	135 [a]	$C_{21}H_{21}N$	88·0	7·0	5·0	87·8	7·3	4·9
picrate	312	$C_{27}H_{24}N_4O_7$	—	—	11·1	—	—	10·8
2,3,10,11-Tetramethyl-	131 [b]	$C_{21}H_{21}N$	87·9	7·4	5·0	87·8	7·3	4·9
picrate	195 decomp. >170	$C_{27}H_{24}N_4O_7$	—	—	10·6	—	—	10·8
2,4,10,11-Tetramethyl-	104	$C_{21}H_{21}N$	87·7	7·3	5·2	87·8	7·3	4·9
picrate	202 decomp. >170	$C_{27}H_{24}N_4O_7$	—	—	10·9	—	—	10·8
2,3,9,11-Tetramethyl- ...	134	$C_{21}H_{21}N$	88·1	7·2	5·0	87·8	7·3	4·9
picrate	191	$C_{27}H_{24}N_4O_7$	—	—	10·7	—	—	10·8
2,4,9,11-Tetramethyl- ...	102	$C_{21}H_{21}N$	87·7	7·3	5·0	87·8	7·3	4·9
picrate	203 decomp. >170	$C_{27}H_{24}N_4O_7$	—	—	10·8	—	—	10·8
9-Fluoro- [c]	97	$C_{17}H_{12}FN$	81·6	4·8	5·6	81·9	4·8	5·6
picrate	207	$C_{23}H_{15}FN_4O_7$	—	—	11·9	—	—	11·7
9-Fluoro-2,3-dimethyl-	139	$C_{19}H_{16}FN$	82·0	5·9	5·1	82·3	5·8	5·1
picrate	219	$C_{25}H_{19}FN_4O_7$	—	—	11·0	—	—	11·1

[a] B. p. *ca.* 290°/19 mm. [b] B. p. 280°/16 mm. [c] B. p. 255°/22 mm.

TABLE 2.

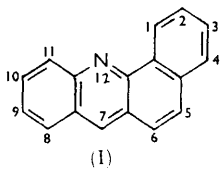
5,6-Benz[*c*]acridines.

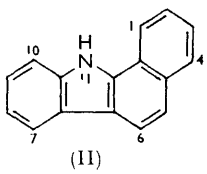
			Found (%)			Required (%)		
Compound	M. p.	Formula	C	H	N	C	H	N
2,3,9,10-Tetramethyl- ...	280° [a]	$C_{21}H_{19}N$	88·3	6·9	5·1	88·4	6·7	4·9
picrate	325 decomp. >285	$C_{27}H_{22}N_4O_7$	—	—	10·5	—	—	10·9
2,4,9,10-Tetramethyl- ...	172	$C_{21}H_{19}N$	88·7	6·5	4·9	88·4	6·7	4·9
picrate	336 decomp. >290	$C_{27}H_{22}N_4O_7$	—	—	11·1	—	—	10·9
2,3,10,11-Tetramethyl- ...	191	$C_{21}H_{19}N$	88·4	6·8	4·9	88·4	6·7	4·9
picrate	198 decomp. >178	$C_{27}H_{22}N_4O_7$	—	—	10·7	—	—	10·9
2,4,10,11-Tetramethyl- ...	134	$C_{21}H_{19}N$	88·2	6·6	5·0	88·4	6·7	4·9
picrate	260 decomp. >180	$C_{27}H_{22}N_4O_7$	—	—	10·6	—	—	10·9
2,3,9,11-Tetramethyl- ...	182	$C_{21}H_{19}N$	88·2	7·1	4·9	88·4	6·7	4·9
picrate	262	$C_{27}H_{22}N_4O_7$	—	—	10·6	—	—	10·9
2,4,9,11-Tetramethyl- ...	137	$C_{21}H_{19}N$	88·2	6·7	5·0	88·4	6·7	4·9
picrate	188	$C_{27}H_{22}N_4O_7$	—	—	11·0	—	—	10·9
9-Fluoro-	142	$C_{17}H_{10}FN$	82·9	4·3	5·8	82·6	4·0	5·7
picrate	232	$C_{23}H_{13}FN_4O_7$	—	—	11·8	—	—	11·8
9-Fluoro-2,3-dimethyl- ...	166	$C_{19}H_{14}FN$	83·2	5·4	5·2	82·9	5·1	5·1
picrate	259	$C_{25}H_{17}FN_4O_7$	—	—	10·9	—	—	11·1

[a] Sublimation >230°.

methylisatin together with 5,7- and 6,7-dimethyl-1-tetralone were used. With 4,7-dimethylisatin, however, the Pfitzinger reaction gave only minimal amounts of impure products, even when heating was continued longer than for the other isatins; and similar

unsatisfactory results were recorded when 5,8-dimethyl-1-tetralone was condensed with each of the dimethylisatins. Steric hindrance could account for these anomalies, as


(I)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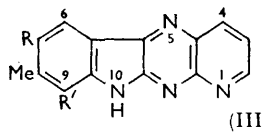
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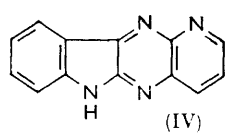
(IV)

observed earlier;[3] in line with this explanation was the failure of 4,7-dimethylisatin to react with 2,3-diaminopyridine[4] in conditions which, with the less hindered 6,7-isomer, readily afforded the compound (III). With *o*-phenylenediamine, which is more reactive than its pyridine analogue, such a radical difference had not been noted[5] [in this reaction, the formulation of the products as (III) is considered more probable than (IV)[6]].

In contrast with the poor reactivity of 5,8-dimethyl-1-tetralone in Pfitzinger condensations, in Fischer reactions it was a satisfactory intermediate, as were the 5,7- and the 6,7-isomer. A series of 5,6-dihydrobenzo[*a*]carbazoles thus obtained are listed in Table 3

TABLE 3.

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

			Found (%)			Required (%)		
Compound	M. p.	Formula	C	H	N	C	H	N
8,9-Dimethyl-	241°	$C_{18}H_{17}N$	87·2	7·0	5·7	87·4	6·9	5·7
2-Isopropyl-	161	$C_{19}H_{19}N$	87·2	7·2	5·5	87·3	7·3	5·4
2,3,10-Trimethyl-	190	$C_{19}H_{19}N$	87·1	7·5	5·5	87·3	7·3	5·4
1,4,10-Trimethyl-	93 [a]	$C_{19}H_{19}N$	87·1	7·2	5·4	87·3	7·3	5·4
2,3,9-Trimethyl-	256	$C_{19}H_{19}N$	87·2	7·3	5·5	87·3	7·3	5·4
2,3,8-Trimethyl-	227	$C_{19}H_{19}N$	87·3	7·2	5·4	87·3	7·3	5·4
picrate	206	$C_{25}H_{22}N_4O_7$	—	—	11·6	—	—	11·4
2,4,8-Trimethyl-	222	$C_{19}H_{19}N$	—	—	5·4	—	—	5·4
picrate	213	$C_{25}H_{22}N_4O_7$	—	—	11·5	—	—	11·4
2,7,10-Trimethyl-	155	$C_{19}H_{19}N$	87·2	7·2	5·5	87·3	7·3	5·4
2,9,10-Trimethyl-	143	$C_{19}H_{19}N$	87·0	7·5	5·4	87·3	7·3	5·4
2,8,10-Trimethyl-	138	$C_{19}H_{19}N$	87·2	7·2	5·7	87·3	7·3	5·4
2,8,9-Trimethyl-	223	$C_{19}H_{19}N$	87·2	7·3	5·5	87·3	7·3	5·4
2,3,9,10-Tetramethyl-	236 [b]	$C_{20}H_{21}N$	87·1	7·8	5·4	87·2	7·7	5·1
2,4,9,10-Tetramethyl-	224	$C_{20}H_{21}N$	87·0	7·8	5·3	87·2	7·7	5·1
1,4,9,10-Tetramethyl-	172	$C_{20}H_{21}N$	87·2	8·0	5·3	87·2	7·7	5·1
2,3,8,9-Tetramethyl-	277	$C_{20}H_{21}N$	—	—	5·1	—	—	5·1
1,4,8,9-Tetramethyl- [c]	166	$C_{20}H_{21}N$	86·9	7·9	5·1	87·2	7·7	5·1
1,4,8,10-Tetramethyl- [c]	106	$C_{20}H_{21}N$	87·1	7·9	5·3	87·2	7·7	5·1
picrate	190	$C_{26}H_{24}N_4O_7$			not analysed			
2-Isopropyl-8,10-dimethyl-	183	$C_{21}H_{23}N$	87·0	8·3	5·0	87·2	8·0	4·8

[a] Recrystallised from hexane. [b] 6,7-Dimethyl-1-tetralone 2,3-dimethylphenylhydrazone, orange needles, m. p. 165° (ethanol) (Found: N, 9·3. $C_{20}H_{24}N_2$ requires N, 9·6%). [c] Very poor yield (less than 30%).

(along with homologues prepared from 1-tetralone and 7-methyl- and 7-isopropyl-1-tetralone). Dehydrogenation over palladium–charcoal furnished the corresponding polymethyl derivatives of benzo[*a*]carbazole (II), listed in Table 4.

As some fluorobenz[*c*]acridines bearing a *meso* methyl group have been found carcinogenic,[7] and as other fluorobenzacridines and fluoro-derivatives of various carcinogenic

[3] Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1946, **13**, 123, 134; Buu-Hoï, *J.*, 1946, 785; Buu-Hoï, Sy, and Riché, *Bull. Soc. chim. France*, 1960, 1492.

[4] Buu-Hoï and Saint-Ruf, *Bull. Soc. chim. France*, 1960, 1920.

[5] Buu-Hoï and Guettier, *Bull. Soc. chim. France*, 1946, **13**, 586.

[6] Cf. Ziegler, *J. Amer. Chem. Soc.*, 1949, **71**, 1891.

[7] Buu-Hoï and Jacquignon, *J.*, 1952, 4173; Buu-Hoï, Royer, Hubert-Habart, and Mabille, *J.*, 1953, 3584; Zajdela and Buu-Hoï, *Acta Unio Intern. contra Cancrum*, 1955, **11**, 736; Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, 1956, **4**, 315.

hydrocarbons have recently been reported,[8] we prepared various quinolines and benz[*c*]-acridines by applying the Pfitzinger reaction to 5-fluoroisatin. 5-Fluoroisatin and 1-tetralone gave 9-fluoro-5,6-dihydrobenz[*c*]acridine-7-carboxylic acid which, like the unfluorinated compound, shows a pronounced strychnine-like activity; thermal decarboxylation, followed by dehydrogenation of the product, afforded 9-fluorobenz[*c*]acridine. 9-Fluoro-2,3-dimethylbenz[*c*]acridine was similarly prepared. Both acridines were non-carcinogenic. 6-Fluorocinchoninic acids were also obtained in excellent yields by Pfitzinger reactions with cyclopropyl methyl ketone and various cyclanones.

TABLE 4.

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

Compound	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
8,9-Dimethyl-	295°	$C_{18}H_{15}N$	88·0	6·5	5·8	88·1	6·2	5·7
picrate	213	$C_{24}H_{18}N_4O_7$	—	—	11·5	—	—	11·8
2-Isopropyl-	150	$C_{19}H_{17}N$	87·7	6·8	5·4	88·0	6·6	5·4
picrate	216	$C_{25}H_{20}N_4O_7$	—	—	11·6	—	—	11·5
2,3,10-Trimethyl-	223	$C_{19}H_{17}N$	87·7	6·6	5·4	88·0	6·6	5·4
1,4,10-Trimethyl-	182 *	$C_{19}H_{17}N$	88·1	6·6	5·4	88·0	6·6	5·4
2,3,9-Trimethyl-	302	$C_{19}H_{17}N$	88·0	6·8	5·5	88·0	6·6	5·4
2,3,8-Trimethyl-	276	$C_{19}H_{17}N$	87·9	6·8	5·4	88·0	6·6	5·4
picrate	218	$C_{25}H_{20}N_4O_7$	—	—	11·7	—	—	11·5
2,4,8-Trimethyl-	257	$C_{19}H_{17}N$	88·2	6·6	5·4	88·0	6·6	5·4
picrate	226 decomp. >200	$C_{25}H_{20}N_4O_7$	—	—	11·6	—	—	11·5
2,7,10-Trimethyl-	178	$C_{19}H_{17}N$	87·9	6·6	5·3	88·0	6·6	5·4
picrate	198	$C_{25}H_{20}N_4O_7$	—	—	11·7	—	—	11·5
2,9,10-Trimethyl-	184	$C_{19}H_{17}N$	87·8	6·8	5·5	88·0	6·6	5·4
2,8,10-Trimethyl-	161	$C_{19}H_{17}N$	87·8	6·5	5·5	88·0	6·6	5·4
picrate	221	$C_{25}H_{20}N_4O_7$	—	—	11·7	—	—	11·5
2,8,9-Trimethyl-	279	$C_{19}H_{17}N$	88·1	6·5	5·6	88·0	6·6	5·4
picrate	232	$C_{25}H_{20}N_4O_7$	—	—	11·2	—	—	11·5
2,3,9,10-Tetramethyl-	241	$C_{20}H_{19}N$	87·6	7·3	5·3	87·9	7·0	5·1
picrate	234	$C_{26}H_{22}N_4O_7$	—	—	10·9	—	—	11·2
2,4,9,10-Tetramethyl-	258	$C_{20}H_{19}N$	87·7	7·1	5·2	87·9	7·0	5·1
picrate	219	$C_{26}H_{22}N_4O_7$	—	—	11·3	—	—	11·2
1,4,9,10-Tetramethyl-	239	$C_{20}H_{19}N$	87·6	7·1	5·2	87·9	7·0	5·1
2,3,8,9-Tetramethyl-	307	$C_{20}H_{19}N$	87·8	7·1	5·1	87·9	7·0	5·1
picrate	226	$C_{26}H_{22}N_4O_7$	—	—	10·9	—	—	11·2
1,4,8,9-Tetramethyl-	198	$C_{20}H_{19}N$	87·8	7·3	5·0	87·9	7·0	5·1
1,4,8,10-Tetramethyl-	222	$C_{20}H_{19}N$	—	—	5·2	—	—	5·1
picrate	194	$C_{26}H_{22}N_4O_7$	—	—	11·0	—	—	11·2
2-Isopropyl-8,10-dimethyl-	144	$C_{21}H_{21}N$	—	—	5·0	—	—	4·9
picrate	203	$C_{27}H_{24}N_4O_7$	—	—	10·8	—	—	10·9

* Recrystallised from hexane.

EXPERIMENTAL

Isatins and Related Tetracyclic Compounds.—The dimethylisatins and 6-fluoroisatin were prepared, by the Sandmeyer reaction, from the various xylidines or *p*-fluoroaniline, chloral hydrate, and hydroxylamine. A solution of 6,7-dimethylisatin (1·75 g.) and 2,3-diaminopyridine (1·1 g.) in ethanol (15 c.c.) was refluxed for 10 hr.; the precipitate of 8,9-*dimethyl*-10H-*pyrido*[3′,2′-5,6]*pyrazino*[2,3-b]*indole* (III; R = H, R′ = Me), obtained after concentration and cooling, formed yellow needles (1·7 g.) (from xylene), sublimable above 315°, m. p. >350° (Found: N, 22·7. $C_{15}H_{12}N_4$ requires N, 22·6%). The 7,8-*dimethyl compound* (III; R = Me, R′ = H), similarly prepared from 5,6-dimethylisatin, was yellow, sublimable needles (xylene) (Found: N, 22·3%). An attempt to condense in a similar way 2,3-diaminopyridine with 4,7-dimethylisatin and 4,5,7-trimethylisatin failed, even when refluxing was continued for 30 hr. Condensation of 5,6-dimethylisatin with *o*-phenylenediamine yielded 8,9-*dimethyl*-6H-*indolo*[2,3-b]*quinoxaline*, yellow needles, m. p. 329° (from xylene) (Found: N, 17·3.

[8] Bergmann, Blum, Butanaro, and Heller, *Tetrahedron Letters*, 1959, No. 1, 15; Newman, MacDowell, and Swaminathan, *J. Org. Chem.*, 1959, **24**, 509; Newman and Naiki, *J. Org. Chem.*, 1962, **27**, 863.

$C_{16}H_{13}N_3$ requires N, 17·0%); a similar condensation with 4-nitro-*o*-phenylenediamine afforded the 8,9-*dimethyl*-2-*nitro-compound*, yellow needles, m. p. 363° (from nitrobenzene) (Found: N, 19·3. $C_{16}H_{12}N_4O_2$ requires N, 19·2%). 7-*Fluoro*-10H-*pyrido*[3′,2′-5,6]*pyrazino*[2,3-b]-*indole* formed yellow leaflets (from xylene), sublimable >250°, m. p. >340° (Found: N, 23·2. $C_{13}H_{17}FN_4$ requires N, 23·5%).

Pfitzinger Reactions.—5,7-, 6,7-, and 5,8-Dimethyl-1-tetralone were prepared according to the literature.[9] A solution of 5,6-dimethylisatin (6 g.), 6,7-dimethyl-1-tetralone (7 g.), and potassium hydroxide (7 g.) in ethanol (70 c.c.) was refluxed on a water-bath for 70 hr., and the solvent then distilled. The solid obtained was washed with cyclohexane to remove the excess of ketone, the residue was dissolved in water, and the aqueous solution acidified with acetic acid. The yellow precipitate (10 g.) was crystallised from ethanol–benzene or xylene. The other Pfitzinger reactions were performed in the same way, and the products are tabulated below.

5,6-Dihydrobenz[*c*]acridine-7-carboxylic acids.[a]

			Found (%)			Required (%)		
Substituent	M. p.	Formula	C	H	N	C	H	N
2,3,9,10-Tetramethyl-	308°	$C_{22}H_{21}NO_2$	79·4	6·4	—	79·7	6·4	—
2,4,9,10-Tetramethyl-	312	$C_{22}H_{21}NO_2$	79·6	6·6	—	79·7	6·4	—
2,3,10,11-Tetramethyl-	248	$C_{22}H_{21}NO_2$	79·4	6·5	4·4	79·7	6·4	4·2
2,4,10,11-Tetramethyl-	240	$C_{22}H_{21}NO_2$	79·4	6·4	4·2	79·7	6·4	4·2
2,3,9,11-Tetramethyl-	248	$C_{22}H_{21}NO_2$	—	—	4·1	—	—	4·2
2,4,9,11-Tetramethyl-[b]	226	$C_{22}H_{21}NO_2$	—	—	4·2	—	—	4·2
9-Fluoro-	297	$C_{18}H_{12}FNO_2$	73·4	4·2	4·9	73·7	4·1	4·8
9-Fluoro-2,3-dimethyl-	243	$C_{20}H_{16}FNO_2$	74·7	5·1	4·5	74·8	5·0	4·4

[a] All the acids formed yellowish prisms. [b] Recrystallised from aqueous methanol.

Preparation of Dihydrobenz[c]*acridines.*—This was achieved by thermal decarboxylation of the foregoing cinchoninic acids, distillation of the reaction-products *in vacuo*, and recrystallisation from methanol for the lower-melting substances or ethanol for the others; yields were 70—90%. All the dihydroacridines crystallised as pale yellow needles; the picrates, prepared in ethanol, were recrystallised from benzene or ethanol for the easily soluble ones, *i.e.*, those with a methyl group in a *peri*-position to the heterocyclic nitrogen atom, or from xylene or nitrobenzene for the rest. Decarboxylation of 5,6-dihydro-2,4,9,11-tetramethylbenz[*c*]-acridine-7-carboxylic acid was accompanied by partial dehydrogenation.

Dehydrogenation of Dihydrobenz[c]*acridines.*—The dihydro-compounds (2 parts) were heated, and then distilled over 5% palladium–charcoal (1 part), and the distillate recrystallised from methanol or ethanol, except for the almost insoluble 2,3,9,10-tetramethylbenz[*c*]acridine, which was recrystallised from toluene. Yields exceeded 70%.

Preparation of 11H-*Benzo*[a]*carbazoles.*—The arylhydrazones of the various tetralones used were prepared by refluxing a solution of the ketone, the arylhydrazine hydrochloride, and sodium acetate in ethanol for 30 min.; indolisation was effected by refluxing for a few seconds a solution of the hydrazone in acetic acid saturated with hydrogen chloride. The precipitate obtained on dilution with water was recrystallised from cyclohexane or ethanol, to give shiny, colourless leaflets. Dehydrogenation was effected by heating with 5% palladium–charcoal as for the acridines, and the dehydrogenation-product was purified by crystallisation from cyclohexane or ethanol; with the high-melting carbazoles, purification was by sublimation. All the carbazoles formed shiny, colourless leaflets. The dihydro-compounds gave dark brown picrates which were recrystallised from ethanol. The dehydrogenation-products gave brick-red to brown-red picrates in ethanol. Dehydrogenation yields were almost quantitative; in some cases, dehydrogenation was effected with chloranil in xylene, but here the yields were considerably lower and the products more difficult to purify. Some isomeric polymethylbenzocarbazoles had already been prepared.[10]

5,6-*Dihydro*-8,10-*dimethyl*-7H-*benzo*[c]*carbazole.*—This was prepared from 2-tetralone and *m*-xylylhydrazine, m. p. 182° (from cyclohexane) (Found: N, 5·6. $C_{18}H_{17}N$ requires N, 5·7%); 8,10-*dimethyl*-7H-*benzo*[c]*carbazole* formed colourless prisms, m. p. 145° (from ethanol) (Found:

[9] de Barry Barnett and Sanders, *J.*, 1933, 434.

[10] Buu-Hoï, Hoán, and Khôi, *Rec. Trav. chim.*, 1950, **69**, 1053; Buu-Hoï, Cagniant, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 950.

N, 5·7. $C_{18}H_{15}N$ requires N, 5·7%); *picrate*, brown-red needles, m. p. 229° (decomp. >220°) (from ethanol) (Found: N, 11·8. $C_{24}H_{18}N_4O_7$ requires N, 11·8%).

2-*Cyclopropyl*-6-*fluorocinchoninic Acid*.—Prepared from cyclopropyl methyl ketone, this *acid* formed colourless needles (87%), m. p. 195° (from ethanol) (Found: C, 67·2; H, 4·4; N, 6·1. $C_{13}H_{10}FNO_2$ requires C, 67·5; H, 4·3; N, 6·1%). 2-*Chloro*-6-*cyclopropylcinchoninic acid*, obtained from 5-chloroisatin, formed colourless needles, m. p. 237° (decomp. >215°) (from ethanol) (Found: Cl, 14·0; N, 5·5. $C_{13}H_{10}ClNO_2$ requires Cl, 14·3; N, 5·7%); the quinoline was a yellow oil, b. p. 162—163°/12 mm.; *picrate*, pale yellow prisms, m. p. 203° (from toluene) (Found: N, 12·7. $C_{18}H_{13}ClN_4O_7$ requires N, 13·0%).

Condensation of 5-*Fluoroisatin with Alicyclic Ketones*.—(*a*) *With cycloheptanone*. 6-*Fluoro*-2,3-*pentamethylenecinchoninic acid* formed colourless prisms, m. p. 300° (sublimation >255°) (from aqueous acetic acid) (Found: C, 69·2; H, 5·5. $C_{15}H_{14}FNO_2$ requires C, 69·5; H, 5·4%); derived *quinoline*, needles, m. p. 97° (from ethanol) (Found: C, 77·8; H, 6·5; N, 6·4. $C_{14}H_{14}FN$ requires C, 78·1; H, 6·5; N, 6·5%); *picrate*, yellow leaflets, m. p. 194° (Found: N. 12·3. $C_{20}H_{17}FN_4O_7$ requires N, 12·6%).

(*b*) *With cyclo-octanone*. 6-*Fluoro*-2,3-*hexamethylenecinchoninic acid* had m. p. >330° (sublimation >320°) (Found: C, 70·1; H, 6·1. $C_{16}H_{16}FNO_2$ requires C, 70·3; H, 5·9%); *picrate* of the corresponding quinoline, leaflets, m. p. 201° (Found: N, 12·5. $C_{21}H_{19}FN_4O_7$ requires N, 12·2%).

(*c*) *With cyclopentadecanone*. 6-*Fluoro*-2,3-*tridecamethylenecinchoninic acid* formed colourless leaflets, m. p. 317° (decomp. >260°) (from ethanol–benzene) (Found: C, 74·5; H, 8·2; N, 4·1. $C_{23}H_{30}FNO_2$ requires C, 74·4; H, 8·1; N, 3·8%).

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