609. *The Chemistry of Carcinogenic Nitrogen-compounds. Part III. Polysubstituted Pyrroles and Indoles as Potential Cocarcinogens.*

By Ng.Ph. Buu-Hoï.

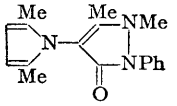
Numerous new pyrroles and indoles have been prepared by known methods for examination as potential cocarcinogens when associated with carcinogenic hydrocarbons or dyestuffs. This has provided an opportunity for a contribution to the chemistry of pyrroles and indoles, and of the Knorr–Paal and Fischer reactions involved in their synthesis; in addition, 9 : 10-phenanthrenoselenodiazole has been prepared.

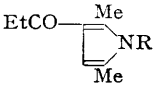
Cook (*Amer. J. Cancer*, 1940, **39**, 386) has reported that some simple heterocyclic nitrogen compounds, *e.g.*, quinaldine and *iso*quinoline, accelerate the carcinogenic action of 3 : 4-benzpyrene; a growth-accelerating effect, on certain plant tissues, by polymethylquinolines such as 2 : 6-dimethylquinoline has also been detected (Buu-Hoï and Guettier, *Rec. Trav. chim.*, 1946, **65**, 502). These observations led us to synthesise diversely polysubstituted derivatives of pyrrole and indole, for examination as potential cocarcinogens, either on the skin in association with carcinogenic hydrocarbons, or on the liver in association with active azo-dyes.

A series of *N*-substituted 2 : 5-dimethylpyrroles was prepared by the well known Knorr–Paal reaction (Knorr, *Ber.*, 1885, **18**, 2254) from acetonylacetone and many primary amines which have not previously been investigated in this respect. In the aliphatic series, allylamine, on admixture with acetonylacetone, underwent a vigorous exothermic reaction to give 2 : 5-*di*-

methyl-1-*allylpyrrole*. The reaction was less easy with saturated amines, and even required heat for a short time, but almost quantitative yields of the following condensation *products* were obtained: 2 : 5-dimethyl-1-*n*-hexyl-, -1-*n*-dodecyl-, and -1-*n*-octadecyl-pyrrole, and 1 : 1′-hexamethylenebis-(2 : 5-dimethylpyrrole). The Knorr–Paal reaction involving aromatic amines appeared not to be sensitive to steric hindrance when it was performed at high temperatures and without a solvent. Thus, acetonylacetone readily condensed with the following aromatic primary amines whose amino-groups are subject to more or less strong steric hindrance: *vic.-o-* and *vic.-m*-xylidine, 6-chloro- and 4-*iso*propyl-*o*-toluidine, and 2 : 4-diaminotoluene. Condensation of 2 : 4-diaminotoluene in acetic acid involved one molecule of ethyl αβ-diacetylsuccinate when the reaction was performed at ordinary pressure, and two molecules when the temperature was raised to 150—160° (Knorr, *Annalen*, 1886, **236**, 313).

In addition, the following hitherto unknown substances were similarly prepared: 1-p-*chlorophenyl*-, 1-o-*xylyl*-, 1-p-tert.-*amylphenyl*- and 1-p-sec.-*amylphenyl*-2 : 5-*dimethylpyrrole*; from *p*-dimethylaminoaniline and *o*-aminoselenoanisole, 1-p-*dimethylaminophenyl*- and 1-o-*methylselenophenyl*-2 : 5-*dimethylpyrrole*, two derivatives expected to have marked toxicity, were also synthesised. In view of the interesting antimalarial activity of some quinolyl derivatives of 2 : 5-dimethylpyrrole (Gilman and Fullhart, *J. Amer. Chem. Soc.*, 1946, **68**, 978), some heterocyclic amines were condensed with acetonylacetone, giving 1-(3- 1-(4-, and 1-(6-*methyl*-2-*pyridyl*)-, and 1-2′-*thiazyl*-2 : 5-*dimethylpyrrole*. The first-mentioned compound had a strong anæsthetising effect on mucous membranes. From 4-aminoantipyrine, 1-*phenyl*-2 : 3-*dimethyl*-4-(2 : 5-*dimethyl*-1-*pyrryl*)*pyrazol*-5-*one* (I) was also easily obtained; compared with pyramidon (*N*-dimethylaminoantipyrine), this has a remarkably low toxicity, and may therefore be of practical interest.

(I.) 

 (II.)

These *N*-substituted 2 : 5-dimethylpyrroles readily underwent smooth Friedel–Crafts reactions with aluminium chloride and acid chlorides, to give ketones (II). For instance, from 2 : 5-dimethyl-1-*n*-dodecylpyrrole and propionyl chloride in carbon disulphide, 3-*propionyl*-2 : 5-*dimethyl*-1-n-*dodecylpyrrole* was readily obtained; in the aromatic series, 1-vic.-o-*xylyl*- and 3-*propionyl*-1-vic.-o-*xylyl*-2 : 5-*dimethylpyrrole* were similarly prepared. Ketones bearing their carbonyl group attached to the aromatic substituent on the nitrogen atom were synthesised by condensing acetonylacetone with aromatic ketones having a nuclear amino-group; thus, *m*-aminoacetophenone and *p*-aminopropiophenone gave 1-*m*-acetylphenyl- (III; R = Ac, R′ = H) and 1-p-*propionylphenyl*-2 : 5-*dimethylpyrrole* (III; R = H, R′ = COEt) respectively. It may be recalled in that respect that Hazlewood *et al.* (*Proc. Roy. Soc. New South Wales*, 1937, **71**, 92) could not condense 6-aminoacetoveratrone with acetonylacetone. Both ketones (III) underwent Pfitzinger reactions with isatin giving 2-[m-(2 : 5-*dimethyl*-1-*pyrryl*)*phenyl*]- (IV; R′ = A, R = R″ = H) and 2-[p-(2 : 5-*dimethyl*-1-*pyrryl*)*phenyl*]-3-*methyl-cinchoninic acid*

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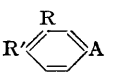

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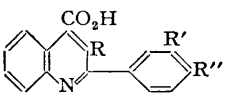
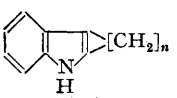


(IV.)

(IV; R = Me, R′ = H, R″ = A); these substances are of interest because of their structural connection both with the liver-poison " Atophan " and with *p*-(2 : 5-dimethyl-1-pyrryl)phenylarsinic acid, a powerful icterogenic substance (cf. Fischer and Orth, " Die Chemie des Pyrrols," Vol. 1, p. 70, Leipzig, 1934). Decarboxylation by heat produced 2-[m-(2 : 5-*dimethyl*-1-*pyrryl*)-*phenyl*]*quinoline*. Use of 5-bromoisatin led to 6-*bromo*-2-[p-(2 : 5-*dimethyl*-1-*pyrryl*)*phenyl*]-3-*methylcinchoninic acid*.

In view of the biological significance of the indole nucleus on the one hand, and of the occurrence of macrocyclic ketones in certain animal glands on the other, a number of 2 : 3-*cyclo*polymethyleneindoles (V) have been prepared by means of a modified Fischer synthesis. *cyclo*Tridecanone, *cyclo*pentadecanone, and *cyclo*hexadecanone gave 2 : 3-*undecamethylene*- (V; *n* = 11), 2 : 3-*tridecamethylene*- (V; *n* = 13), and 2 : 3-*tetradecamethylene-indole* (V; *n* = 14), respectively. The phenylhydrazone of α-civetone could also be cyclised to cyclo*pentadec*-9-*eno*(1′ : 2′-2 : 3)*indole* (VI) (for indolisation of ethylenic ketones, see Buu-Hoï

and Royer, *Rec. Trav. chim.*, 1947, **66**, 308). Unlike the corresponding ketones, these macrocyclic indoles are devoid of marked odour. A Pfitzinger reaction with *cyclo*tridecanone and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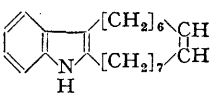
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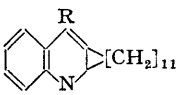
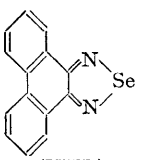

(VII.)

isatin yielded 2 : 3-*undecamethylenecinchoninic acid* (VII; R = CO_2H) which was readily decarboxylated to 2 : 3-*undecamethylenequinoline* (VII; R = H) (for analogous macrocyclic compounds, see Buu-Hoï and Royer, *Rec. Trav. chim.*, 1947, **66**, 300).

In the same line of research, and in view of the normal occurrence of scatole among the products of animal excreta, an extensive study has been made of the synthesis of 3-alkyl-indoles bearing various aromatic or heterocyclic substituents in the 2-position. Such substances were found to be readily accessible by cyclisation of the phenylhydrazones of aryl alkyl ketones by dry hydrochloric acid in pure acetic acid; it should be mentioned in this respect that the phenylhydrazones of aryl methyl ketones could not be indolised to any significant extent by this reagent. 2-p-*Ethylphenyl*-, 2-p-iso*propylphenyl*-, 2-p-tert.-*butylphenyl*-, 2-3′-*pyrenyl*-, and 2-2′-*tetralyl*-3-*methylindole*, and 2-2′-*tetralyl*-3-*ethylindole* were thus easily obtained. Alkoxy-groups are present in various positions in 2-(4-*methoxy*-3-*methylphenyl*)-, 2-(4-*methoxy*-2-*methylphenyl*)-, 2-(2-*methoxy*-5-*methylphenyl*)-, 2-(2-*methoxy*-3 : 4-*dimethylphenyl*)-, 2-(4-n-*propoxy*-2 : 5-*dimethylphenyl*)-, and 2-(4-*ethoxy*-5-iso*propyl*-2-*methylphenyl*)-3-*methylindole*. The hydrogen chloride–acetic acid method of indolisation proved particularly convenient for fragile ketones derived from polyphenols, such as 1-propionyl-3 : 4- and -2 : 4-dimethoxybenzene [which readily gave 2-(3 : 4- and 2-(2 : 4-*dimethoxyphenyl*)-3-*methylindole*], and 1-*n*-butyryl-3.: 4- and -2 : 4-dimethoxybenzene [which formed 2-(3 : 4- and 2-(2 : 4-*dimethoxyphenyl*)-3-*ethylindole*]. The presence of a nitro-group in the molecule of the ketone presents no obstacle to the reaction, since *m*-nitropropiophenone readily gave 2-m-*nitrophenylscatole*. Some indoles bearing a heterocyclic radical were also prepared by the same method, *viz.*, 3-*phenyl*-2-3′-*thionaphthenyl*-, 2-3′-*dibenzfuryl*-3-n-*propyl*-, and 2-3′-*dibenzfuryl*-3-n-*butyl*-, 2-(9-*ethyl*-3-*carbazyl*)-3-n-*amyl*-, and 2-(6-*nitro*-9-*ethyl*-3-*carbazyl*)-3-n-*amyl*-*indole*. A remarkable feature in the substitution of indole molecules by nitro-groups is the unusual shift in light-absorption, resulting in orange-coloured substances, even when the substituent is not directly attached to the indole nucleus itself. This peculiarity is being spectographically investigated.

Following an early suggestion made by E. Fischer that derivatives of piazselenole should be tested for potential anticarcinogenic properties (see Duisberg, E. Fischer's obituary notice in *Ber.*, 1919, **52**, *A*, 161), and in view of the biological significance of the phenanthren enucleus, *phenanthreno*(9′ : 10′)-2 : 1 : 3-*selenadiazole* (VIII) was prepared by condensation of selenium dioxide with 9 : 10-diaminophenanthrene. However, this compound, tested against spontaneous adenocarcinoma of the breast in mice proved to be highly toxic and showed no therapeutic effect, at least in the late stage of the disease (private communication from Professor Lacassagne).


(VIII.)

Most of the new substances mentioned above have been, or are now, under biological investigation by Professor Lacassagne.

Experimental.

2 : 5-*Dimethyl*-1-*allylpyrrole*.—Allylamine (10 g., a great excess) was added cautiously to ice-cooled acetonylacetone (10 g.); heat was evolved, and after a few minutes the mixture became turbid and deposited almost the theoretical amount of water. The mixture was fractionated by distillation, giving 10 g. of 2 : 5-*dimethyl*-1-*allylpyrrole* as a colourless liquid, b. p. 184°, with a pleasant camphoraceous odour, which became yellow on exposure to air (Found: C, 79·7; H, 9·8; N, 10·2. $C_9H_{13}N$ requires C, 80·0; H, 9·6; N, 10·4%).

2 : 5-*Dimethyl*-1-n-*hexylpyrrole*.—A mixture of hexylamine (10 g.) and acetonylacetone (15 g.) was heated under reflux for ½ hour, and the reaction product fractionated in a vacuum; the *N*-substituted *pyrrole* (15 g.) formed a mobile colourless liquid, b. p. 124—125°/14 mm., with an unpleasant aromatic odour (Found: N, 7·6. $C_{12}H_{21}N$ requires N, 7·8%).

2 : 5-*Dimethyl*-1-n-*dodecylpyrrole* (60 g.) was similarly obtained from acetonylacetone (35 g.) and *n*-dodecylamine (45 g.), as a colourless faint-smelling oil, b. p. 194—195°/15 mm. (Found: N, 5·2. $C_{18}H_{33}N$ requires N, 5·3%).

2 : 5-*Dimethyl*-1-n-*octadecylpyrrole* (15 g.), obtained from acetonylacetone (10 g.) and *n*-octadecylamine (10 g.), crystallised from light petroleum in long, colourless, almost odourless prisms, m.p. 44—45°,

b. p. 253—255°/15 mm., very soluble in the ordinary solvents (Found: N, 4·2. $C_{24}H_{45}N$ requires N, 4·3%).

3-*Propionyl*-2 : 5-*dimethyl*-1-n-*dodecylpyrrole*.—25 G. of 2 : 5-dimethyl-1-*n*-dodecylpyrrole and 10 g. of propionyl chloride were dissolved in dry carbon disulphide (100 c.c.); to the well-shaken, ice-cooled mixture, 25 g. of finely powdered aluminium chloride were gradually added; no evolution of hydrogen chloride was noted, but a dark red halochromic colour appeared. After a further 3 hours at 0°, the mixture was poured on ice, the carbon disulphide layer separated and washed with water and then with dilute aqueous sodium hydroxide, the solvent removed, and the residue fractionated in a vacuum. The *ketone* (15 g.) was thus obtained as a viscous yellowish oil, b. p. 288—290°/22 mm., which darkened very rapidly in the open (Found: N, 4·2. $C_{21}H_{37}ON$ requires N, 4·4%).

1 : 1′-*Hexamethylenebis*-(2 : 5-*dimethylpyrrole*).—A mixture of freshly redistilled 1 : 6-diaminohexane (10 g.) and acetonylacetone (25 g.) was heated under reflux for 15 minutes, water being abundantly evolved; the reaction product solidified on cooling, and yielded after vacuum-distillation an almost quantitative yield of the *bispyrrole*, which crystallised from ethanol in elongated colourless prisms, m. p. 106°, b. p. 222—225°/17 mm. (Found: N, 10·2. $C_{18}H_{28}N_2$ requires N, 10·2%).

1-vic.-o-*Xylyl*-2 : 5-*dimethylpyrrole*.—vic.-*o*-Xylidine (10 g.) was heated for 2 hours with acetonylacetone (10 g.) and some drops of acetic acid; the *pyrrole* obtained (12 g.) was a mobile, pale yellow oil, b. p. 160—161°/20 mm., with a strong odour of turpentine (Found: N, 7·0. $C_{14}H_{17}N$ requires N, 7·0%).

3-*Propionyl*-1-vic.-o-*xylyl*-2 : 5-*dimethylpyrrole*.—7 G. of the foregoing compound and 5 g. of propionyl chloride were dissolved in ice-cooled carbon disulphide (100 c.c.), and the mixture was treated with aluminium chloride (10 g.) as above; the *ketone* (4 g.), after vacuum-distillation (b. p. *ca.* 250—255°/25 mm.) and crystallisation from methanol, formed colourless prisms, m. p. 121°, easily soluble in alcohol (Found: N, 5·5. $C_{17}H_{21}ON$ requires N, 5·5%).

1-vic.-m-*Xylyl*-2 : 5-*dimethylpyrrole*.—This *compound*, obtained from *vic.*-*m*-xylidine (5 g.) and acetonylacetone (5 g.), formed a colourless oil, b. p. 155—157°/18 mm. (Found: N, 6·8. $C_{14}H_{17}N$ requires N, 7·0%).

1-4′-o-*Xylyl*-2 : 5-*dimethylpyrrole*.—Similarly obtained from 3 : 4-dimethylaniline (5 g.) and acetonylacetone (5 g.) as a fluid colourless oil, b. p. 154—156°/15 mm., this *pyrrole* crystallised from ligroin in elongated transparent prisms, m. p. 40—41°, very soluble in alcohol (Found: N, 6·8. $C_{14}H_{17}N$ requires N, 7·0%).

3-*Propionyl*-1-4′-o-*xylyl*-2 : 5-*dimethylpyrrole*.—Prepared in the usual way with propionyl chloride (5 g.), 1-4′-*o*-xylyl-2 : 5-dimethylpyrrole (5 g.), and aluminium chloride (8 g.) in carbon disulphide (50 c.c.) (dark red halochromic coloration), this *ketone* (4 g.) was purified by distillation (b. p. *ca.* 255—260°/24 mm.), and crystallised from aqueous methanol in colourless prisms, m. p. 113° (Found: N, 5·3. $C_{17}H_{21}ON$ requires N, 5·5%).

1-(6-*Chloro*-o-*tolyl*)-2 : 5-*dimethylpyrrole*.—This *product*, obtained from 6-chloro-*o*-toluidine (5 g.) and acetonylacetone (5 g.), formed a pale yellow mobile oil, b. p. 146—148°/15 mm. (Found: N, 6·4. $C_{13}H_{14}NCl$ requires N, 6·4%).

1-p-*Chlorophenyl*-2 : 5-*dimethylpyrrole* crystallised from ligroin in hard colourless prisms, m. p. 56°, with a pleasant aromatic odour (Found: N, 6·8. $C_{12}H_{12}NCl$ requires N, 6·8%).

1-(2-*Methyl*-5-iso*propylphenyl*)-2 : 5-*dimethylpyrrole* was a pale yellow oil, b. p. 272—274° (Found: N, 6·0. $C_{16}H_{21}N$ requires N, 6·1%).

1-p-tert.-*Amylphenyl*-2 : 5-*dimethylpyrrole*, obtained from *p*-*tert.*-amylaniline (6 g.) and acetonylacetone (5 g.), formed, from ligroin, large shiny prisms, m. p. 96°, b. p. 302—303°, with a pleasant camphoraceous odour (Found: N, 5·7. $C_{17}H_{23}N$ requires N, 5·8%).

1-p-sec.-*Amylphenyl*-2 : 5-*dimethylpyrrole*, similarly prepared, formed, from light petroleum–ether, large, transparent, quadrangular plates, b. p. 301—303°, m. p. 83—85° (Found: N, 5·6. $C_{17}H_{23}N$ requires N, 5·8%).

as-m-*Toluylene*-1 : 1′-*bis*-(2 : 5-*dimethylpyrrole*) (10 g.), prepared from 2 : 4-diaminotoluene (5·5 g.) and acetonylacetone (10 g.), crystallised from aqueous ethanol in large colourless prisms, m. p. 97° (Found: N, 10·0. $C_{19}H_{22}N_2$ requires N, 10·1%).

1-p-*Dimethylaminophenyl*-2 : 5-*dimethylpyrrole*.—This *compound*, obtained from *p*-dimethylaminoaniline (10 g.) and acetonylacetone (10 g.) (rapid reaction), formed, from aqueous ethanol, colourless lustrous needles, m. p. 95° (Found: N, 13·2. $C_{14}H_{18}N_2$ requires N, 13·0%).

1-o-*Methylselenophenyl*-2 : 5-*dimethylpyrrole*.—*o*-Aminoselenoanisole (7 g.) was prepared from the zinc salt of *o*-aminoselenophenol (10 g.) and methyl sulphate in the presence of aqueous sodium hydroxide, and was a pale yellow liquid, b. p. 137—138°/23 mm., with a strong nauseating smell of oysters (Found: N, 7·2. Calc. for C_7H_9NSe: N, 7·5%). 7 G. of this amine were heated under reflux for 18 hours with acetonylacetone (10 g.) and a drop of acetic acid, giving 1-o-*methylselenophenyl*-2 : 5-*dimethylpyrrole* (7 g.) which was purified by distillation (b. p. *ca.* 172—175°/20 mm.) and crystallised from ligroin in colourless plates, m. p. 95°, with the customary odour of 2 : 5-substituted pyrroles (Found: N, 5·5. $C_{13}H_{15}NSe$ requires N, 5·3%).

1-(3-*Methyl*-2-*pyridyl*)-2 : 5-*dimethylpyrrole*.—A mixture of 2-amino-3-methylpyridine (10 g.), acetonylacetone (10 g.), and 2 drops of acetic acid was heated under reflux for 48 hours, and the residue fractionated (b. p. 140—142°/13 mm.); the *pyrrole* (15 g.) crystallised from light petroleum–ether in very long, fibrous, colourless prisms, m. p. 58° extremely soluble in ethanol, and with an anæsthetising effect on the skin and the nasal mucous membrane similar to that of menthol (Found: N, 14·8. $C_{12}H_{14}N_2$ requires N, 15·0%). The additive compound with picric acid formed, from methanol, small yellow prisms, m. p. 127° (decomp.).

1-(4-*Methyl*-2-*pyridyl*)-2 : 5-*dimethylpyrrole*, similarly prepared from 2-amino-4-methylpyridine, crystallised from methanol or ligroin in hard transparent elongated prisms, m. p. 75°, b. p. 154—156°/14 mm., extremely soluble in alcohol (Found: N, 15·1%). Its additive compound with picric acid formed, from aqueous methanol, silky deep-yellow needles, m. p. 108—109° (decomp.).

1-(6-*Methyl*-2-*pyridyl*)-2 : 5-*dimethylpyrrole*, obtained from 2-amino-6-methylpyridine, was a pale

yellow oil, b. p. 148—150°/13 mm., or 268—272°/760 mm. (Found : N, 15·3%), giving a picrate which crystallised from methanol in deep yellow prisms, m. p. 156—158° (decomp.).

1-2′-*Thiazyl*-2 : 5-*dimethylpyrrole*.—Obtained in poor yield from 2-aminothiazole (10 g.), acetonylacetone (10 g.), and a few drops of acetic acid in the usual way, this *pyrrole* was a pale yellow, mobile oil, b. p. 130—132°/13 mm., with a faint smell of tobacco, rapidly becoming brown in the air (Found : N, 15·5. $C_9H_{10}N_2S$ requires N, 15·7%).

1-*Phenyl*-4-(2 : 5-*dimethyl*-1-*pyrryl*)-2 : 3-*dimethylpyrazol*-5-*one* ("Pyrromidon").—This compound was obtained in quantitative yield by heating, under reflux for an hour, a mixture of 4-amino-1-phenyl-2 : 3-dimethylpyrazol-5-one (10 g.), acetonylacetone (10 g.), 2 drops of acetic acid, and 25 c.c. of ethanol; the reaction *product*, which solidified on cooling, crystallised from methanol in hard colourless prisms, m. p. 177° (Found : N, 15·1. $C_{17}H_{19}ON_3$ requires N, 14·9%).

1-m-*Acetylphenyl*-2 : 5-*dimethylpyrrole* (III; R = Ac, R′ = H).—A mixture of *m*-aminoacetophenone (10 g.), acetonylacetone (12 g.), and two drops of acetic acid was heated under reflux for 24 hours; the reaction product (90%) gave, on vacuum-distillation (b. p. *ca.* 190°/15 mm.) and crystallisation from methanol, hard colourless prisms, m. p. 71° (Found : N, 6·4. $C_{14}H_{15}ON$ requires N, 6·6%); the *semicarbazone* formed, from ethanol, glistening, colourless, sparingly soluble leaflets, m. p. *ca.* 217—219° (decomp.) (Found : N, 20·6. $C_{15}H_{18}ON_4$ requires N, 20·7%).

2-[m-(2 : 5-*Dimethyl*-1-*pyrryl*)*phenyl*]*cinchoninic Acid* (IV; R′ = A, R = R″ = H).—A solution of the foregoing ketone (5 g.), isatin (3·5 g.) and potassium hydroxide (4 g., in 2 c.c. of water) in ethanol (25 c.c.) was heated under reflux for 24 hours; the reaction mixture was diluted with water, the neutral impurities were removed by ether, and the *cinchoninic acid* precipitated by the addition of acetic acid (yield, 98%); it crystallised from methanol in cream-yellow fluffy needles, m. p. 243—244° (decomp.) (Found : N, 8·1. $C_{22}H_{18}O_2N_2$ requires N, 8·2%). 2-[m-(2 : 5-*Dimethyl*-1-*pyrryl*)*phenyl*]*quinoline*, obtained by heating the acid above its m. p., formed, from methanol, fine yellow prisms, m. p. 107—108° (Found : N, 9·4. $C_{21}H_{18}N_2$ requires N, 9·4%), giving a picrate crystallising from chlorobenzene in fine deep-yellow needles.

1-p-*Propionylphenyl*-2 : 5-*dimethylpyrrole* (III; R = H, R′ = COEt).—Obtained in 90% yield from *p*-aminopropiophenone (10 g.) and acetonylacetone (10 g.) as in the above instance, it formed, from methanol, elongated colourless prisms, m. p. 65°, b. p. *ca.* 196—197°/18 mm., very soluble in ethanol (Found : N, 5·8. $C_{15}H_{17}ON$ requires N, 6·1%).

2-[p-(2 : 5-*Dimethyl*-1-*pyrryl*)*phenyl*]-3-*methylcinchoninic Acid* (IV; R = Me, R′ = H, R″ = A).—Obtained in the usual way from the foregoing ketone (17 g.), isatin (4·5 g.) and potassium hydroxide (5·1 g.), this *acid* (90%) formed, from ethanol (sparingly soluble), colourless prisms, m. p. *ca.* 313—315° (decomp.) (Found : N, 8·0. $C_{23}H_{20}O_2N_2$ requires N, 7·9%). Its decarboxylation yielded 2-[p-(2 : 5-*Dimethyl*-1-*pyrryl*)*phenyl*]-3-*methylquinoline*, crystallising from ethanol in pale yellowish plates, m. p. 152° (Found : N, 8·6. $C_{22}H_{20}N_2$ requires N, 8·9%).

6-*Bromo*-2-[p-(2 : 5-*dimethyl*-1-*pyrryl*)*phenyl*]-3-*methylcinchoninic acid*, prepared in the usual way by substituting 5-bromoisatin for isatin in the foregoing synthesis, crystallised from acetic acid in silky yellowish needles, m. p. >310°, almost insoluble in ethanol (Found : N, 6·2. $C_{23}H_{19}O_2N_2Br$ requires N, 6·4%).

2 : 3-cyclo*Undecamethyleneindole* (V; *n* = 11).—A mixture of *cyclo*tridecanone (2 g.) and phenylhydrazine (3 g.) was heated above 100° until steam ceased to be evolved; after the mixture had cooled, 15 c.c. of glacial acetic acid saturated with dry hydrogen chloride were cautiously added to the crude phenylhydrazone, and the mixture was boiled for 5 minutes and poured into water. The sticky jelly obtained was dissolved in benzene, the organic layer washed with water, the solvent removed, and the residue distilled in a vacuum (b. p. *ca.* 290—295°/50 mm.); after crystallisation from methanol, long, colourless, almost odourless, glistening needles, m. p. 116°, were obtained in almost quantitative yield (Found : N, 5·2. $C_{19}H_{27}N$ requires N, 5·2%); this *indole* gave a picrate forming, from ethanol, long silky violet needles, m. p. 139—140°.

2 : 3-cyclo*Tridecamethyleneindole* (V; *n* = 13).—Obtained as above in almost quantitative yield from exaltone (2 g.) and phenylhydrazine (3 g.), this *indole* was purified by vacuum-distillation (b. p. *ca.* 300—305°/40 mm.) and then crystallised from methanol in silky, colourless, odourless prisms, m. p. 68—69° (Found : N, 4·6. $C_{21}H_{31}N$ requires N, 4·7%). The picrate formed, from methanol, long brownish-violet needles, m. p. 132°.

2 : 3-cyclo*Tetradecamethyleneindole* (V; *n* = 14).—Similarly obtained from *cyclo*hexadecanone, this *compound* formed fine colourless prisms, m. p. 72—73°, from methanol (Found : N, 4·5. $C_{22}H_{33}N$ requires N, 4·5%); the corresponding picrate crystallised from methanol (very soluble) in long violet needles, m. p. 115—116°.

cyclo*Pentadec*-9-*eno*(1′ : 2′-2 : 3)*indole* (VI).—α-Civetone (1 g.) was treated with phenylhydrazine (1·5 g.), and the phenylhydrazone (which was formed at room temperature) was cyclised in the usual way; the *indole* (VI) was an almost odourless, yellowish oil, b. p. 302—304°/13 mm., sparingly soluble in ethanol (Found : N, 4·0. $C_{24}H_{35}N$ requires N, 4·1%); its picrate crystallised from methanol in long brownish-violet needles, m. p. 101°.

2 : 3-*Undecamethylenecinchoninic Acid*.—A solution of *cyclo*tridecanone (2 g.), isatin (1·5 g.), and potassium hydroxide (1·7 g. in 2 c.c. of water) in 20 c.c. of ethanol was heated under reflux for 24 hours and then poured into water; after ether-extraction and acidification of the aqueous layer with acetic acid, a *cinchoninic acid* was obtained in quantitative yield, this formed, from acetic acid, long, silky, glistening, colourless needles m. p. >320° (sublimation), very sparingly soluble in ethanol (Found : N, 4·0. $C_{21}H_{27}O_2N$ requires N, 4·3%). Decarboxylation of this product by heat yielded 2 : 3-*undecamethylenequinoline* (VII; R = H), crystallising from methanol in long silky colourless prisms, m. p. 80° (Found : N, 5·2. $C_{20}H_{27}N$ requires N, 5·0%), the picrate of which formed long silky yellow prisms, m. p. 175°, from ethanol.

2-p-*Ethylphenylscatole*.—A mixture of *p*-ethylpropiophenone (2 g.) and phenylhydrazine (3 g.) was heated at about 180° until steam ceased to be evolved; after cooling, the crude phenylhydrazone was boiled with 20 c.c. of acetic acid, saturated with dry hydrogen chloride, for 2 minutes; the reaction mixture

was poured into water, the sticky mass dissolved in benzene, the organic layer washed with water and dried, the solvent removed, and the residual *product* distilled (b. p. 238—240°/12 mm.); after crystallisation from light petroleum, long glistening colourless prisms (2 g.), m. p. 68°, very soluble in methanol, were obtained (Found : N, 6·1. $C_{17}H_{17}N$ requires N, 5·9%).

The compounds shown in the Table were prepared similarly.

Indoles.	Crystn. solvents and form.	B. p.	M. p.	Formula.	Found, N, %.	Reqd., N, %.
2-p-iso*Propylphenyl*-3-*methyl* [1]		262—265°/ 20 mm.		$C_{18}H_{19}N$	5·6	5·6
2-(2 : 4 : 5-*Trimethylphenyl*)-3-*methyl*		280—285°/ 38 mm.		,,	5·8	5·6
2-p-tert.-*Butylphenyl*-3-*methyl*	A, prisms	285—290°/ 35 mm.	109°	$C_{19}H_{21}N$	5·1	5·3
2-2′-*Tetralyl*-3-*methyl* [2]	,,	282—285°/ 15 mm.	93	$C_{19}H_{19}N$	5·2	5·3
2-2′-*Tetralyl*-3-*ethyl*	,,	274—276°/ 13 mm.	95	$C_{20}H_{21}N$	5·1	5·0
2-(4-*Methoxy*-3-*methylphenyl*)-3-*methyl*	,,		133	$C_{17}H_{17}ON$	5·5	5·5
2-(4-*Methoxy*-2-*methylphenyl*)-3-*methyl*	,,	*ca.* 250°/ 15 mm.	117	,,	5·2	5·5
2-(2-*Methoxy*-5-*methylphenyl*)-3-*methyl*	B, needles	238—240°/ 12 mm.	83	,,	5·5	5·5
2-(2-*Methoxy*-3 : 4-*dimethylphenyl*)-3-*methyl*	,,	280—284°/ 38 mm.	66	$C_{18}H_{19}ON$	5·0	5·0
2-(4-n-*Propoxy*-2 : 5-*dimethylphenyl*)-3-*methyl* [3]	A, plates	268—270°/ 14 mm.	114—115	$C_{20}H_{23}OH$	4·8	4·7
2-(4-*Ethoxy*-2-*methyl*-5-iso*propyl*-*phenyl*)-3-*methyl* [4]	,,	275—276°/ 30 mm.	128	$C_{21}H_{25}ON$	4·8	4·5
2-(3 : 4-*Dimethoxyphenyl*)-3-*methyl* [5]	C, needles		198	$C_{17}H_{17}O_2N$	5·0	5·2
2(-2 : 4-*Dimethoxyphenyl*)-3-*methyl*	A, plates		87—88	,,	5·2	5·2
2-(3 : 4-*Dimethoxyphenyl*)-3-*ethyl*	C, needles		211	$C_{18}H_{19}O_2N$	5·1	4·9
2-(2 : 4-*Dimethoxyphenyl*)-3-*ethyl*	needles		94	,,	5·0	4·9
2-m-*Nitrophenyl*-3-*methyl* [6]	C, needles		157	$C_{15}H_{12}O_2N_2$	11·2	11·1
3-*Phenyl*-2-3′-*thionaphthenyl* [7]	B, needles		166	$C_{22}H_{15}NS$	3·8	4·0
2-3′-*Dibenzfuryl*-3-n-*propyl* [8]	A, needles	325—328°/ 16 mm.	90—92	$C_{23}H_{19}ON$	4·5	4·3
2-3′-*Dibenzfuryl*-3-n-*butyl* [9]	needles		122	$C_{24}H_{21}ON$	4·2	4·1
2-(9-*Ethyl*-3-*carbazolyl*)-3-n-*amyl* [10]	D, needles		146	$C_{27}H_{28}N_2$	7·2	7·4
2-(6-*Nitro*-9-*ethyl*-3-*carbazolyl*)-3-n-*amyl* [11]	,,		177	$C_{27}H_{27}O_2N_3$	10·0	9·9

Solvents : A, methanol; B, ligroin; C, ethanol; D, ethanol–benzene.

[1] Faint odour of indole. [2] Mauve fluorescence in alcohol. [3] From 4-*n*-propoxy-2 : 5-dimethylpropiophenone (cf. De Clerq and Buu-Hoï, *Compt. rend.*, 1948, **227**, 1377). [4] From 4-ethoxy-2-methyl-5-*iso*propylpropiophenone (*idem, ibid.*). [5] Brownish-yellow colour in sulphuric acid. [6] Orange-yellow; not distilled. [7] From 3-phenylacetylthionaphthen (Buu-Hoï and Cagniant, *Rec. Trav. chim.*, 1948, **67**, 70); yellow; gives a brownish-violet picrate. [8] From 3-*n*-valeryldibenzfuran (cf. Buu-Hoï and Royer, *ibid.*, p. 175). [9] From 3-*n*-hexoyldibenzfuran (*idem, ibid.*); intense violet fluorescence in benzene; picrate, long violet-red needles, m. p. 141°. [10] Orange-yellow in sulphuric acid. [11] From the preceding compound by concentrated nitric acid; decomposes when distilled in vacuum; orange needles.

3-n-*Heptoyl*-9-*ethylcarbazole*.—Finely powdered aluminium chloride (18 g.) was stirred in small portions into an ice-cooled solution of 9-ethylcarbazole (20 g.) and heptoyl chloride (19 g.) in carbon disulphide (150 c.c.) or in dry benzene. After 24 hours at room temperature, the dark reaction product was poured on ice; the organic layer was washed with dilute aqueous sodium hydroxide and then with water and dried (Na_2SO_4), the solvent evaporated, and the residue distilled in a vacuum. The ketone (12 g.) had b. p. 295—300°/13 mm., and crystallised from methanol in colourless needles, m. p. 67° (Found : C, 82·1; H, 8·3; N, 4·4. $C_{21}H_{25}ON$ requires C, 82·0; H, 8·1; N, 4·5%). Treatment of a cold solution of this ketone in acetic acid with nitric acid (*d* 1·49) readily yielded 6-*nitro*-3-n-*heptoyl*-9-*ethylcarbazole* as silky, pale yellow needles, m. p. 117°, sparingly soluble in ethanol (Found : C, 71·3; H, 7·1; N, 7·6. $C_{21}H_{24}O_3N_2$ requires C, 71·5; H, 6·8; N, 7·9%).

2-3′-*Pyrenylscatole*.—This compound, obtained from 3-propionylpyrene (readily prepared from pyrene, propionyl chloride, and aluminium chloride in benzene), had b. p. >350°/12 mm., and crystallised from ethanol (very sparingly soluble) in fine yellow needles, m. p. 172°, the benzene solutions of which showed a strong green fluorescence; sulphuric acid produced a deep brownish-red halochromic colour (Found: N, 4·0. $C_{25}H_{17}N$ requires N, 4·2%).

Phenanthreno(9′ : 10′)-2 : 1 : 3-*selenodiazole* (VIII).—9 : 10-Diaminophenanthrene dihydrochloride (7 g.), finely powdered selenium dioxide (2 g.), and sodium acetate (excess) in ethanol were heated under reflux for a few minutes; the precipitate, collected after cooling, was washed with water and recrystallised from ethanol–benzene, giving shiny yellow needles, m. p. 209—210° (sublimation and decomp.) (Found: N, 10·0. $C_{14}H_8N_2Se$ requires N, 9·9%); sulphuric acid produced a deep brownish-yellow colour.

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Department of Organic Chemistry,
The Radium Institute, University of Paris. [*Received, July 11th*, 1949.]