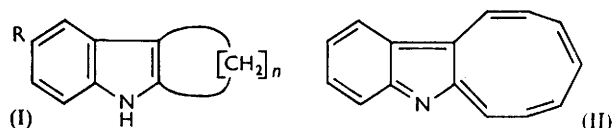


### 143. Carcinogenic Nitrogen Compounds. Part XXIV.\* The Synthesis of Indole and Quinoline Compounds from Cyclic Ketones.

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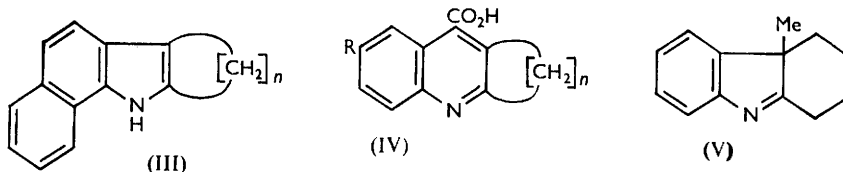
Indole, benzindole, and quinoline compounds fused to an 8-, 9-, or 10-membered *cycloalkene* ring have been synthesised by the Fischer and the Pfitzinger reaction from *cyclooctanone*, *cyclononanone*, and *cyclodecanone*; the compounds are not dehydrogenated by chloranil. Fischer cyclisation of phenylhydrazones of  $\alpha$ -substituted *cyclohexanones* to carbazolenines is discussed, and the properties of some of these bases are reported.

TREIBS, STEINERT, and KIRCHHOF<sup>1</sup> recently reported the dehydrogenation of 2:3-*cycloheptenoindole* to 1-aza-2:3-benzazulene by means of chloranil; the possibility therefore exists, at least in theory, of preparing the next higher, fully conjugated analogous heterocycle (II), by dehydrogenation of 2:3-*cyclononenindole* (I; R = H,  $n = 7$ ). Since highly conjugated molecules such as (II) would be of interest as potential carcinogens, an attempt was made to prepare them in this way. 2:3-*cyclononenindole* and its 5-methyl



homologue (I; R = Me,  $n = 7$ ) were obtained by Fischer cyclisation<sup>2</sup> of the phenylhydrazone and *p*-tolylhydrazone of *cyclononanone*; from the  $\alpha$ -naphthylhydrazone of the same ketone, compound (III;  $n = 7$ ) was similarly prepared. *cycloDecanone* underwent similar cyclisations to give compounds (I; R = H and Me,  $n = 8$ ), and its 6:7-benzanalogue (III;  $n = 8$ ). These *cycloalkenoindoles* gave violet picrates and red molecular complexes with tetrachlorophthalic anhydride,<sup>3</sup> but all attempts to dehydrogenate the 2:3-*cyclononenindoles* with chloranil in boiling xylene or with selenium failed.

Pfitzinger condensation<sup>4</sup> of *cyclooctanone*, *cyclodecanone*, and *cyclononanone* with isatin and 5-substituted isatins afforded, in excellent yields, the 2:3-*cycloalkenocinchonic* acids (IV). Thermal decomposition of these acids furnished the 2:3-*cycloalkenoquinolines*; here, again, attempts at dehydrogenation of the acids and of the bases were unsuccessful.



1:2:3:4-Tetrahydro-11-methylcarbazolenine (V), a by-product of the Fischer cyclisation of 2-methyl*cyclohexanone* phenylhydrazone and described as its yellow picrate,<sup>5</sup> was now prepared crystalline; so was the *cyclohexyl* analogue, obtained as a by-product in the preparation of 1-*cyclohexyl*-1:2:3:4-tetrahydrocarbazole.<sup>6</sup> Similar cyclisation of the phenylhydrazones of 2-ethyl-, 2-propyl-, 2-butyl-, 2-hexyl-, and 2-octyl-*cyclohexanone* afforded the corresponding oily 11-alkyl-1:2:3:4-tetrahydrocarbazolenines, which gave yellow picrates. An attempt to prepare 3-ethyl-2:3-*cyclopentenoindolenine* from the phenylhydrazone of 2-ethyl*cyclopentanone* gave only impure resins.

\* Part XXIII, Buu-Hoï, Jacquignon, and Long, *J.*, 1957, 4994.

<sup>1</sup> Treibs, Steinert, and Kirchlhof, *Annalen*, 1953, 581, 54.

<sup>2</sup> Cf. Buu-Hoï, *J.*, 1949, 2882.

<sup>3</sup> Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, 234, 1056; *Bull. Soc. chim. France*, 1957, 4, 488.

<sup>4</sup> Pfitzinger, *J. prakt. Chem.*, 1897, 56, 283; Buu-Hoï and Royer, *Rec. Trav. chim.*, 1947, 66, 300.

<sup>5</sup> Plancher, *Atti R. Acad. Lincei*, 1900, 9, 221; Pausacker and Schubert, *J.*, 1949, 1384.

<sup>6</sup> Buu-Hoï, Binh, Loc, Xuong, and Jacquignon, *J.*, 1957, 3126.

## EXPERIMENTAL

**2 : 3-cycloNonenoindole.**—A mixture of *cyclononanone* (3 g.) and redistilled phenylhydrazine (3.5 g.) was heated at 120—130°, until steam had ceased to be evolved; the cooled crude phenylhydrazone was treated with a solution of hydrogen chloride in glacial acetic acid (25 c.c.), and the mixture brought to the b. p. After dilution with water, the product was taken up in benzene, the benzene solution washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated, and the residue fractionated. The portion (1.9 g.), b. p. 231—232°/22 mm.,  $n_D^{20}$  1.6060, crystallised as colourless prisms, m. p. 65°, from light petroleum (b. p. 35—60°) (Found: C, 84.2; H, 9.1; N, 6.3.  $\text{C}_{15}\text{H}_{19}\text{N}$  requires C, 84.5; H, 9.0; N, 6.6%). This *indole* gave a *picrate*, as brown-violet needles, m. p. 110°, from ethanol (Found: N, 12.4.  $\text{C}_{21}\text{H}_{22}\text{O}_7\text{N}_4$  requires N, 12.7%); the complex with tetrachlorophthalic anhydride formed red needles, m. p. 110°, from acetic acid.

**5-Methyl-2 : 3-cyclononenoindole.**—Prepared from *cyclononanone* (1.5 g.) and *p*-tolylhydrazine (3 g.), this *indole* (0.6 g.), b. p. 224—225°/15 mm., formed colourless prisms, m. p. 110°, from light petroleum (Found: C, 84.3; H, 9.1.  $\text{C}_{16}\text{H}_{21}\text{N}$  requires C, 84.5; H, 9.3%); the *picrate* crystallised as brown-violet needles, m. p. 112°, from ethanol, and the complex with tetrachlorophthalic anhydride as dark red needles, m. p. 147°, from acetic acid.

**2 : 3-cycloNoneno-6 : 7-benzindole.**—Prepared from *cyclononanone* (1.5 g.) and  $\alpha$ -naphthylhydrazine (4 g.), this *indole* (0.7 g.), b. p. 270—275°/15 mm., formed colourless prisms, m. p. 104°, from cyclohexane (Found: N, 5.2.  $\text{C}_{18}\text{H}_{21}\text{N}$  requires N, 5.3%); its *picrate* crystallised from ethanol as brown-red prisms, m. p. 174° (decomp. >165°).

Attempts were made to dehydrogenate this indole and the two foregoing ones, (a) by refluxing for 12 hr. their solution in xylene with chloranil (4 mol.), but gave indole and resins; (b) by heating them with selenium at 350°, which resulted in complete decomposition.

**2 : 3-cycloDecenoindole.**—Prepared from *cyclodecanone* (2 g.) and phenylhydrazine (3 g.), this *indole* (0.8 g.), b. p. 240—245°/26 mm.,  $n_D^{20}$  1.6020, crystallised as colourless needles, m. p. 89°, from light petroleum (Found: C, 84.5; H, 9.2; N, 5.9.  $\text{C}_{16}\text{H}_{21}\text{N}$  requires C, 84.5; H, 9.3; N, 6.2%). The *picrate* formed brown-violet needles, m. p. 112°, from ethanol.

**5-Methyl-2 : 3-cyclodecenoindole** (1 g.), prepared from *cyclodecanone* (1.5 g.) and *p*-tolylhydrazine (3.5 g.), crystallised as colourless prisms, m. p. 100°, from light petroleum (Found: C, 84.5; H, 9.4; N, 5.5.  $\text{C}_{17}\text{H}_{23}\text{N}$  requires C, 84.6; H, 9.5; N, 5.8%); the *picrate* formed violet-black needles, m. p. 136° (decomp. >128°) from ethanol, and the complex with tetrachlorophthalic anhydride formed red needles (from acetic acid), m. p. 178° (decomp. >170°).

**2 : 3-cycloDeceno-6 : 7-benzindole.**—Prepared from *cyclodecanone* (1.5 g.) and  $\alpha$ -naphthylhydrazine (3 g.), this *indole*, b. p. 272—275°/15 mm., formed colourless prisms, m. p. 119°, from cyclohexane (Found: C, 86.8; H, 8.3.  $\text{C}_{20}\text{H}_{23}\text{N}$  requires C, 86.6; H, 8.4%) (*picrate*, brown-violet needles, m. p. 189°, from ethanol; complex with tetrachlorophthalic anhydride, deep red leaflets, m. p. 187°, from acetic acid).

**6-Methyl-2 : 3-cyclooctocinchoninic Acid** (IV; R = Me,  $n = 6$ ).—A mixture of *cyclooctanone* (4 g.), 5-methylisatin (5 g.), and 25% ethanolic potassium hydroxide (20 c.c.) was gently refluxed for 24 hr.; after cooling, water was added, the neutral impurities were removed by ether-extraction, the aqueous layer was acidified with acetic acid, and the precipitate (95%) washed with water, dried, and recrystallised from benzene. The *cinchoninic acid* formed colourless needles, m. p. 354—355° (Found: C, 75.2; H, 6.6; N, 5.2.  $\text{C}_{17}\text{H}_{19}\text{O}_2\text{N}$  requires C, 75.8; H, 7.1; N, 5.2%). **6-Methyl-2 : 3-cyclooctenoquinoline** (V; R = Me,  $n = 6$ ), obtained by heating the foregoing acid above its m. p., and distilling the residue *in vacuo*, crystallised as colourless prisms, m. p. 102°, from ethanol (Found: C, 85.0; H, 8.3.  $\text{C}_{16}\text{H}_{19}\text{N}$  requires C, 85.3; H, 8.5%); its *picrate* crystallised as yellow prisms, m. p. 185—186°, from ethanol (Found: N, 12.1.  $\text{C}_{22}\text{H}_{22}\text{O}_7\text{N}_4$  requires N, 12.3%).

Similar reactions gave: **2 : 3-cyclononenocinchoninic acid** (IV; R = H,  $n = 7$ ) (95% yield), prisms, m. p. 313—314° (Found: C, 75.5; H, 6.8; N, 5.5%); **2 : 3-cyclononenocinquinoline** (V; R = H,  $n = 7$ ), purified *via* its *picrate*, yellow needles, m. p. 179—180° (from ethanol), formed prisms, m. p. 55° (Found: N, 5.9%); **6-methyl-2 : 3-cyclononenocinchoninic acid** (IV; R = Me,  $n = 7$ ), needles, m. p. 338—339°, from benzene (Found: C, 76.0; H, 7.2.  $\text{C}_{18}\text{H}_{21}\text{O}_2\text{N}$  requires C, 76.3; H, 7.5%); **6-methyl-2 : 3-cyclononenocinquinoline**, prisms, m. p. 79°, from light petroleum (Found: C, 85.1; H, 9.0.  $\text{C}_{17}\text{H}_{21}\text{N}$  requires C, 85.3; H, 8.8%) (*picrate*, yellow prisms, m. p. 183—184°, from ethanol); **2 : 3-cyclodecencinchoninic acid** (IV; R = H,  $n = 8$ ) (yield ~100%), needles, m. p. 299°, from ethanol-benzene (Found: C, 75.9; H, 7.4%). **2 : 3-cycloDecenoquinoline**, prisms, m. p. 92°, from light petroleum (Found: N, 6.0.  $\text{C}_{17}\text{H}_{21}\text{N}$  requires N,

5.9%); 6-methyl-2 : 3-cyclodecenocinchoninic acid (IV; R = Me,  $n = 8$ ) (yield ~100%), needles, m. p. 321—322°, from ethanol-benzene (Found: C, 76.4; H, 7.9; N, 4.7.  $C_{19}H_{23}O_2N$  requires C, 76.7; H, 7.8; N, 4.7%); 6-methyl-2 : 3-cyclodecenoquinoline, prisms, m. p. 93° (light petroleum) (Found: C, 85.3; H, 9.3.  $C_{18}H_{23}N$  requires C, 85.3; H, 9.2%) (picrate, yellow needles, m. p. 202°, from ethanol).

1 : 2 : 3 : 4-Tetrahydro-11-methylcarbazolenine (V; R = Me).—A mixture of 2-methylcyclohexanone (10 g.) and phenylhydrazine (10 g.) was heated at 120° with removal of steam, and the crude phenylhydrazone cyclised with a solution of hydrogen chloride in glacial acetic acid in the usual way; the product was then diluted with water, and the oil obtained on basification was taken up in benzene and purified by distillation *in vacuo*. The carbazolenine, purified *via* its yellow picrate, m. p. 174° (lit., 169—171°), had b. p. 158°/20 mm.,  $n_D^{21}$  1.5672, which crystallised as prisms, m. p. 69°, from light petroleum (Found: N, 7.3. Calc. for  $C_{13}H_{15}N$ : N, 7.5%). 11-cyclohexyl-1 : 2 : 3 : 4-tetrahydrocarbazolenine, prepared in the same way from phenylhydrazine and 2-cyclohexylcyclohexanone, and purified *via* its picrate, yellow prisms, m. p. 185° (Found: N, 11.3.  $C_{24}H_{26}O_7N_4$  requires N, 11.6%), formed colourless prisms, m. p. 82°, from light petroleum (Found: C, 85.1; H, 9.0.  $C_{18}H_{23}N$  requires C, 85.3; H, 9.2%). The other carbazolenines (see Table) were similarly prepared, in 30—40% yield.

#### 11-Alkyl-1 : 2 : 3 : 4-tetrahydrocarbazolenines (V).

Alkyl	B. p./mm. (m. p.)	Formula	N (%), Found	N (%), Req'd.
Et .....	161°/18	$C_{14}H_{17}N$	6.9	7.0
Picrate .....	M. p. 146°	$C_{20}H_{20}O_7N_4$	12.8	13.1
Pr .....	178°/28	$C_{15}H_{19}N$	6.8	6.6
Picrate .....	M. p. 139°	$C_{21}H_{22}O_7N_4$	12.5	12.7
Bu .....	189°/22 mm.	$C_{16}H_{21}N$	6.2	6.2
Picrate .....	M. p. 130°	$C_{22}H_{24}O_7N_4$	12.0	12.3
Hexyl picrate .....	M. p. 135°	$C_{24}H_{26}O_7N_4$	11.3	11.6
Octyl picrate .....	M. p. 124°	$C_{26}H_{32}O_7N_4$	10.7	10.9

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