after removal of solvent, the product which was distilled *in vacuo* b.p. 146–150°/9 mm.; yield, 26.5 g. (71%).

The *picrate*, after two crystallizations from methanol, melted at 150–151°.

Anal. Calc'd for $C_{18}H_{19}N_5O_7$: C, 51.8; H, 4.6. Found: C, 52.0; H, 4.7.

The methiodide was obtained by mixing equimolar amounts of II and methyliodide in absolute methanol or ethanol solution. The analytical sample was prepared by repeated washing with absolute ethanol and ether, m.p. 210–220° (decomp.).

Anal. Calc'd for $C_{13}H_{19}IN_2$: C, 47.3; H, 5.8. Found: C, 47.4; H, 6.0.

1-Skatylacetamide (VII) and 1-skatylacetic acid (VI). A solution of 8.3 g. (0.025 mole) of III and 5 g. (0.1 mole) of sodium cyanide in 50 ml. of water was refluxed for 2.25 hr. Trimethylamine evolved steadily during this period. The reaction mixture was cooled in an ice-salt mixture and filtered. The semisolid obtained (3.7 g.) was extracted with hot benzene and the benzene extract when cooled deposited crystals of VII (1 g.); m.p. 164–166°. A crystallization from benzene furnished material m.p. 169–170°.

Anal. Calc'd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4. Found: C, 70.4; H, 6.3.

The benzene extract was stripped of solvent and the residue sublimed at 100°/1 mm. The sublimed material (98 mg.) was identified as skatole by mixed melting point with an authentic sample and by preparation of the picrate.

The alkaline filtrate left after filtration of the crude amide when acidified deposited crystals (51 mg.) of VI; m.p. 171°. After two further crystallizations from benzene the m.p. was 174° (lit.[4] m.p. 178°).

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.9. Found: C, 69.8; H, 5.9.

The same acid was obtained in 50% yield by hydrolysis of the amide with ethanolic potassium hydroxide solution.

Decarboxylation of VI to 1,3-dimethylindole. In a microdistillation flask 200 mg. of VI was heated in an atmosphere of nitrogen at 225–230° for 0.5 hr. The brown residual liquid was distilled at 17 mm. with the bath temperature at 170°. The distillate furnished a picrate, which after a crystallization from ethanol had m.p. 140–141°. This melting point was not depressed by admixture with an authentic sample of the picrate of 1,3-dimethylindole prepared as described by Snyder and Eliel.[9]

DL-*α-Amino-β-(1-skatyl) propionic acid (V).* To a solution prepared from 0.86 g. (0.037 g. atom) of sodium and 94 ml. of absolute ethanol were added 12.2 g. (0.037 mole) of III and 6.4 g. (0.038 mole) of ethyl acetamidocyanoacetate and the mixture was refluxed for 43 hr. The reaction mixture was then concentrated *in vacuo* and the residue diluted with water and extracted with ether. The ether extract furnished, after removal of solvent, 9.4 g. of the crude alkylated product IV. This was refluxed with 40 ml. of 15% sodium hydroxide solution for 25 hr. in a copper vessel. The mixture was cooled, filtered, and the filtrate extracted with ether to remove 1.3 g. of some unsaponifiable material. The aqueous solution was treated with animal charcoal and acidified with 9 ml. of glacial acetic acid. The crude amino acid which separated was collected and extracted with five 60-ml. portions of boiling water. The combined aqueous extracts when cooled deposited 2.9 g. of material m.p. 195–196°. The analytical sample (m.p. 217–218°) was obtained after seven recrystallizations from 50% methanol.

Anal. Calc'd for $C_{12}H_{14}N_2O_2 \cdot H_2O$: C, 61.0; H, 6.8. Found: C, 61.0; H, 7.2.

A sample of the amino acid hydrate when dried *in vacuo* for 6 hr. at 178° lost one mole of water of crystallization and had m.p. 214°. The anhydrous sample was analyzed.

Anal. Calc'd for $C_{12}H_{14}N_2O_2$: C, 66.0; H, 6.5. Found: C, 66.0; H, 6.8.

The picrolonate was readily obtained by mixing hot solutions of equal amounts of the amino acid and picrolonic acid in water and was crystallized from water; m.p. 145°.

Anal. Calc'd for: $C_{22}H_{22}N_6O_7 \cdot H_2O$: C, 52.8; H, 4.8. Found: C, 53.1; H, 4.6.

Acknowledgments. We are grateful to Mr. Selvavinayakam for the analyses reported herein. One of the authors (S. R.) is indebted to the government of India for the award of a scholarship.

MADRAS 25, INDIA

(9) Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 1703 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Some 2,3-Polymethylene-indoles and -quinolines. An Attempt to Synthesize Large-Ring Nitrogen Heterocycles

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Several new 2,3-polymethylene-indoles and -quinolines have been prepared from various macrocyclic ketones by Fischer and Pfitzinger reactions. An attempt to use some of these compounds for the preparation of fully conjugated large-ring nitrogen-containing heterocycles was unsuccessful.

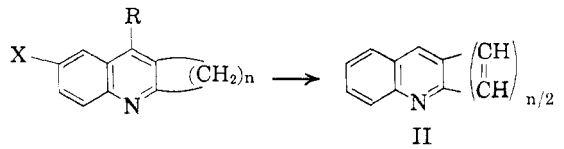
A possibility, at least theoretical, exists for the dehydrogenation of 2,3-polymethylenequinolines (I; R = H) with an even number (n) of methylene groups, to fully conjugated large-ring acridine analogs (II). Similarly, it is theoretically feasible to convert 2,3-polymethyleneindoles (III) bearing an odd number ($n + 1$) of methylene groups to fully conjugated macrocyclic analogs (IV) of 1-aza-2,3-benzazulene (VII). Treibs, Steinert and Kirchhof[1] did, in fact, succeed in preparing the latter substance by treating [(1′,2′-2,3)cyclohept-1′,2′-eno]indole (IIIb) with three moles of chloranil, a reagent frequently used for the aromatization of hydrogenated carbazoles[2] and acridines.[3]

(1) Treibs, Steinert, and Kirchhof, *Ann.*, **581**, 54 (1953).

(2) Barclay and Campbell, *J. Chem. Soc.*, 530 (1945); Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, **14**, 492 (1949); **15**, 511, 957 (1950); **16**, 315 (1951).

(3) Buu-Hoï, Hoán, and Xuong, *J. Chem. Soc.*, 279 (1952)

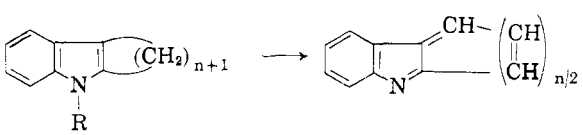
In the framework of a research program on carcinogenesis induced by polycyclic conjugated molecules,[4] an attempt was made to synthesize large-ring nitrogen heterocycles represented by



II

Ia; X = H, R = CO_2H, n = 6
b; X = R = H, n = 6
c; X = Cl, R = CO_2H, n = 6
d; X = Br, R = CO_2H, n = 6
e; X = Cl, R = H, n = 6
f; X = Br, R = H, n = 6
g; X = Br, R = H, n = 13
h; X = R = H, n = 13

the general formulas II and IV. The Pfitzinger condensation of cycloöctanone with isatin gave in excellent yields [(1′,2′-2,3)cycloöct-1′,2′-eno]cinchoninic acid (Ia), which readily underwent thermal decarboxylation to [(1′,2′-2,3)cycloöct-1′,2′-eno]-quinoline (Ib). This latter compound, previously obtained as a noncrystallized mass by Ruzicka, Goldberg, and Hürbin[5] through a Friedländer condensation of *o*-aminobenzaldehyde and cycloöctanone, was now prepared in the crystalline state. Condensation of cycloöctanone with 5-chloro- and 5-bromo-isatin similarly yielded 6-chloro- (Ic) and 6-bromo-[(1′,2′-2,3)cycloöct-1′,2′-eno]cinchoninic acid (Id), and the halogenated quinolines (Ie) and (If) obtained therefrom by thermal decarboxylation were likewise well crystallized substances. An attempt to dehydrogenate with chloranil either these cinchoninic acids or the corresponding quinolines failed, some of the starting material being recovered, and some undergoing resinification.



IV

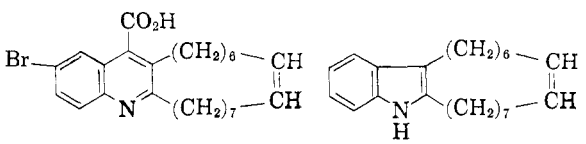
IIIa; R = H
b; R = H, n = 5
c; R = CH_3, n = 5
d; R = CH_3, n = 12

The Pfitzinger reaction was also applied with success to the synthesis of the solid 6-bromo-[(1′,2′-2,3)cyclopentadec-1′,2′-eno]quinoline (Ig) from 5-bromoisatin and cyclopentadecanone (exaltone) *via* the corresponding cinchoninic acid; the nonhalogenated base (Ih) which Ruzicka, Goldberg, and Hürbin[5] obtained through a Friedländer reaction, and Buu-Hoï[6] through a Pfitzinger reaction, was in both instances described as a tallowy mass.

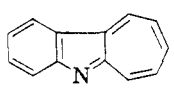
On the other hand, 6-bromo-[(1′,2′-2,3)cycloheptadeca-1′,2′,9′,10′-dieno]cinchoninic acid (V), prepared from 5-bromoisatin and civettone, failed, as did the nonhalogenated substance,[7] to give a crystalline decarboxylation product.

[(1′,2′-2,3)Cycloheptadeca-1′,2′,9′,10′-dieno]-indole (VI), prepared by Fischer cyclization of the phenylhydrazone of civettone,[7] could not be dehydrogenated by means of chloranil to a well defined product.

Other new macrocyclic indoles prepared in the ccurse of this work included [(1′,2′-2,3)cycloöct-1′,2′-eno]indole (IIIb) and its 1-methyl derivative (IIIc), prepared from cycloöctanone phenylhydrazone and N-methyl-N-phenylhydrazone, and 1-



V VI



VII

methyl-[(1′,2′-2,3)cycloöct-1′,2′-eno]indole (IIId), obtained from exaltone N-methyl-N-phenylhydrazone. The theoretical possibility of dehydrogenating compound IIIb to 2′,3′-indolocycloöctatetraene did not materialize in this research. The failure encountered in our dehydrogenation experiments could be accounted for by modern valency studies,[8] the explanation being that beyond a certain critical size (apparently IIIb), the polymethylene chain exists in a sufficiently staggered arrangement that stable conjugated systems are not possible (as, for example, with cycloöctatetraene). Thus, not only does a considerable bond strain resist the dehydrogenation of our macrocycles, but the conjugated systems if formed would have the same reactivity as cycloöctatetraene—in other words, there could be no stabilization by virtue of an aromatic-type conjugation which requires a planar, or near planar, arrangement.

The macrocyclic indoles described in this work gave with tetrachlorophthalic anhydride[9] well crystallized, strongly colored molecular addition compounds, and are best characterized in that way.

In biological tests for carcinogenic properties, 1-aza-2,3-benzazulene proved inactive when painted on the skin of mice.

EXPERIMENTAL

Pfitzinger reaction of cycloöctanone with isatin. A mixture of 13 g. of redistilled cycloöctanone, 15 g. of isatin, and 16

(4) cf. Buu-Hoï, *Arzneimittel-Forsch.*, **6**, 251 (1956).
(5) Ruzicka, Goldberg, and Hürbin, *Helv. Chim. Acta*, **16**, 1335 (1933).
(6) Buu-Hoï, *J. Chem. Soc.*, 2882 (1949).
(7) Buu-Hoï, *J. Chem. Soc.*, 795 (1946).
(8) See Prelog, *J. Chem. Soc.*, 420 (1950).
(9) Pfeiffer, *Ber.*, **55**, 413 (1922); Buu-Hoï and Jacquignon, *Compt. rend.*, **234**, 1056 (1952).

g. of potassium hydroxide dissolved in 100 ml. of ethanol was refluxed for 15 hr. on the water bath, and most of the solvent was distilled off. The aqueous layer formed on addition of water was extracted with ether to remove the neutral impurities, acidified with acetic acid, and the precipitate which formed was recrystallized from a mixture of ethanol and benzene. Yield: 80–85% of [(1',2'-2,3)cycloöct-1',2'-eno]cinchoninic acid (Ia), in the form of fine, colorless, sublimable prisms, m.p. 342–343° (decomposition above 290° on prolonged heating).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.1; H, 6.6.

[(1',2'-2,3)Cycloöct-1',2'-eno]quinoline (Ib). The foregoing acid was dried, heated above its melting point, and the residue vacuum-fractionated. Yield: 90% of a thick yellow base, which solidified on scratching with a glass rod, and crystallized from petroleum ether in fine colorless prisms, m.p. 59°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.1. Found: C, 85.2; H, 8.3.

The corresponding picrate crystallized from ethanol in bright yellow needles, m.p. 206–207° (decomp. above 180°).

6-Chloro-[(1',2'-2,3)cycloöct-1',2'-eno]cinchoninic acid (Ic). 5-Chloroisatin was most conveniently prepared by halogenation of isatin with N-chlorosuccinimide in carbon tetrachloride medium[10]; a mixture of 2 g. of 5-chloroisatin, 1.5 g. of cycloöctanone, and 1.7 g. of potassium hydroxide in 10 ml. of ethanol was treated as above. Yield: 85–90% of an acid, crystallizing from a mixture of ethanol and benzene in fine, colorless, sublimable needles, m.p. 348–349° (decomp. above 296° on prolonged heating).

Anal. Calc'd for $C_{16}H_{16}ClNO_2$: C, 66.3; H, 5.5. Found: C, 66.0; H, 5.4.

Thermal decomposition gave an 80% yield of *6-chloro-[(1',2'-2,3)cycloöct-1',2'-eno]quinoline* (Ie), crystallizing from methanol in colorless prisms, m.p. 120–121°.

Anal. Calc'd for $C_{15}H_{16}ClN$: C, 73.3; H, 6.5. Found: C, 73.3; H, 6.6.

Its picrate crystallized from ethanol in fine, deep yellow prisms, m.p. 239° (decomp. above 200°).

Anal. Calc'd for $C_{21}H_{19}ClN_4O_7$: N, 11.8. Found: N, 11.5.

6-Bromo-[(1',2'-2,3)cycloöct-1',2'-eno]cinchoninic acid (Id). Prepared in 90% yield from 5 g. of cycloöctanone, 9.5 g. of 5-bromoisatin, and 8 g. of potassium hydroxide in ethanol (24 hours' refluxing), this compound crystallized from a mixture of ethanol and benzene in fine, straw-colored prisms, m.p. 350–351° (sublimation and decomposition on prolonged heating above 305°).

Anal. Calc'd for $C_{16}H_{16}BrNO_2$: C, 57.5; H, 4.8. Found: C, 57.6; H, 5.0.

6-Bromo-[(1',2'-2,3)cycloöct-1',2'-eno]quinoline (If) crystallized from ethanol in fine, shiny, colorless needles, m.p. 129–130°.

Anal. Calc'd for $C_{15}H_{16}BrN$: C, 62.1; H, 5.5. Found: C, 61.8; H, 5.5.

Its picrate crystallized from ethanol in deep yellow prisms, m.p. 238–239° (decomp. above 210°).

Anal. Calc'd for $C_{21}H_{19}BrN_4O_7$: N, 10.8. Found: N, 11.0.

Attempted dehydrogenation of quinolines Ia, Ic, and Id. These quinolines (1 mole) were heated in xylene medium with 3 moles of chloranil for 6 hr., most of the solvent was distilled off in a vacuum, and the dark violet residue then treated with an ethanolic solution of picric acid; in each instance, only the picrate of the starting material could be isolated.

[(1',2'-2,3)Cycloöct-1',2'-eno]indole (IIIb). A mixture of 4 g. of cycloöctanone and 3 g. of phenylhydrazine was heated for 20 min. at 120–130° with removal of water. To the crude phenylhydrazone thus obtained a solution of hydrogen chloride in acetic acid was added and the mixture was refluxed for a few seconds, then poured into water. The cyclization-product was taken up in benzene and purified by vacuum-distillation. Yield: 90% of a product, b.p. 215–216°,18 mm., crystallizing from petroleum ether (b.p. 35–65°) in fine colorless needles, m.p. 71°, turning yellow on exposure to the light and air. This compound was recovered in part unchanged, and in part resinified on treatment with 3 moles of chloranil in boiling xylene.

Anal. Calc'd for $C_{14}H_{17}N$: C, 84.4; H, 8.6. Found: C, 84.5; H, 8.8.

The corresponding picrate crystallized from ethanol in silky, brown-violet needles, m.p. 97°. The addition compound with tetrachlorophthalic anhydride, prepared by dissolving equimolar amounts of the indole and the anhydride in hot acetic acid, crystallized from that solvent in shiny, dark red needles, m.p. 132°.

Anal. Calc'd for $C_{22}H_{17}Cl_4NO_3$: Cl, 29.3. Found: Cl, 28.8.

1-Methyl-[(1',2'-2,3)cycloöct-1',2'-eno]indole (IIIc). Similarly prepared in 70% yield from 3 g. of N-methyl-N-phenylhydrazine and 4 g. of cycloöctanone, this indole was a pale yellow oil, b.p. 212–213°/17 mm., n_D^{23} 1.6005.

Anal. Calc'd for $C_{15}H_{19}N$: C, 84.5; H, 9.0. Found: C, 84.4; H, 9.0.

The picrate crystallized from petroleum ether in silky, dark violet needles, m.p. 77°. The addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in shiny bright red needles, m.p. 112°.

Anal. Calc'd for $C_{23}H_{19}Cl_4NO_3$: Cl, 28.4. Found: Cl, 28.1.

1-Methyl-[(1',2'-2,3)cyclopentadec-1',2'-eno]indole (IIId). Prepared in 70–75% yield from 2.5 g. of cyclopentadecanone and 1.7 g. of N-methyl-N-phenylhydrazine, this indole was a pale yellow oil, b.p. 300–302°/40 mm., $n_D^{23.5}$ 1.5151, with an unpleasant, burnt horn odor.

Anal. Calc'd for $C_{22}H_{33}N$: C, 84.8; H, 10.7. Found: C, 8.50; H, 10.5.

The picrate crystallized from ethanol in silky violet needles; the addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in orange prisms, m.p. 147°.

[(1',2'-2,3)Cycloheptadeca-1',2',9',10'-dieno]indole (VI). This compound, prepared from 1 g. of civettone and 0.5 g. of phenylhydrazine, was resinified on heating with 8 moles of chloranil in xylene; its addition-compound with tetrachlorophthalic anhydride crystallized from acetic acid in bright red prisms, m.p. 113°.

Anal. Calc'd for $C_{31}H_{33}Cl_4NO_3$: Cl, 23.3. Found: Cl, 23.5.

6-Bromo-[(1',2'-2,3)cyclopentadec-1',2'-eno]cinchoninic acid. Prepared in 90% yield from 2.2 g. of cyclopentadecanone, 2.2 g. of 5-bromoisatin, and 1.6 g. of potassium hydroxide in 10 ml. of ethanol, this acid crystallized from acetic acid in fine colorless prisms, m.p. 312° (decomp. above 290°).

Anal. Calc'd for $C_{23}H_{30}BrNO_2$: C, 63.9; H, 6.9. Found: C, 64.0; H, 6.8.

6-Bromo-[(1',2'-2,3)cyclopentadec-1',2'-eno]quinoline (Ig) purified *via* its picrate (bright yellow needles, m.p. 194–195°, from ethanol), crystallized from petroleum ether in fine colorless prisms, m.p. 55°.

Anal. Calc'd for $C_{22}H_{30}BrN$: C, 67.0; H, 7.7. Found: C, 67.7; H, 8.0.

6-Bromo-[(1',2'-2,3)cycloheptadeca-1',2',9',10'-dieno]cinchoninic acid (V). Prepared from 1 g. of civettone, 0.9 g. of isatin, and 0.7 g. of potassium hydroxide in 10 ml. of ethanol, this acid crystallized from ethanol in yellowish needles, m.p. 270° (decomp. above 260°).

Anal. Calc'd for $C_{25}H_{32}BrNO_2$: C, 65.5; H, 7.0. Found: C, 65.2; H, 6.9.

(10) Buu-Hoï, *Rec. trav. chim.*, **73**, 197 (1954).

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