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THE REACTIONS OF OXINDOLES AND ISATIN WITH NITROBENZYL CHLORIDES

FORMATION OF 2'-HYDROXY-SPIRO[2H-INDOLE-2,3'-3'H-INDOLE]

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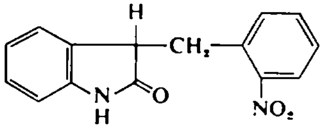
Abstract—Oxindole reacts with *p*-nitrobenzyl chloride to give 3-(4'-nitrobenzyl) oxindole, but with *o*-nitrobenzyl chloride abnormal product, 2'-hydroxy-spiro[2H-indole-2,3'-3'H-indole] (Vb) is produced. The structure of Vb has been elucidated on the basis of the IR, UV and mass spectra, and confirmed by the analogous reactions of 3-methyl-, 4-methyl- and 3,3-dimethyloxindoles with *o*-nitrobenzyl chloride. Isatin reacts with *o*-nitrobenzyl chloride to give *o*-nitrobenzyloxireno[α,3]-oxindole (X).

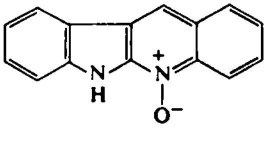
Oxindole reacts with *p*-nitrobenzyl chloride in the presence of sodium ethoxide to give 3-(4'-nitrobenzyl) oxindole, m.p. 228°, $C_{15}H_{12}N_2O_3$, but, with *o*-nitrobenzyl chloride under similar conditions oxindole gives an extremely stable compound (I), m.p. above 350°, $C_{15}H_{10}N_2O$, which sublimes under reduced pressure, possesses no nitro group and is insoluble in most organic solvents.

Sodium *o*-aminophenylacetate, on the other hand, reacts normally with *p*- and *o*-nitrobenzyl chloride to give 1-(4'-nitrobenzyl)-, m.p. 150° and 1-(2'-nitrobenzyl) oxindole, m.p. 155°, $C_{15}H_{12}N_2O_3$. Further treatment of the latter with sodium ethoxide does not lead to the formation of I and it has been found that 3,3-dimethyloxindole is inactive toward nitrobenzyl chlorides under similar conditions. These observations suggest that 3-(2'-nitrophenyl) oxindole (II) is probably intermediate in the formation of the abnormal product (I).

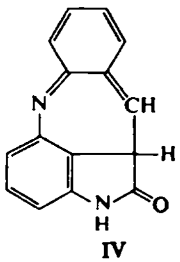


II

Quinindoline-N-oxide (III) which could be derived from II was synthesized by oxidation of quinindoline, but its properties and m.p. 294–296° (dec) do not agree with those of I. Structure IV was also excluded since 4-methyloxindole reacts with *o*-nitrobenzyl chloride to give a product, m.p. above 350°, $C_{16}H_{12}N_2O$, of abnormal type similar to I.

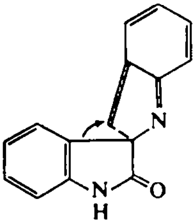


III

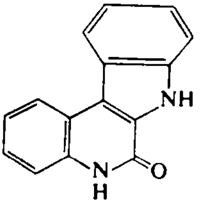


IV

Another possibility could be spiro[2H-indole-2,3′-oxindole] (Va), which can be derived by ring closure between the *o*-nitro-group and the active methylene at *β*-position of oxindole. 3-Keto-3,4-dihydro-5,6-benzo-4-carboline (VI),[1] which might be derived from Va by rearrangement, was also considered but its IR spectra and m.p. 320–321° do not agree with those of I.



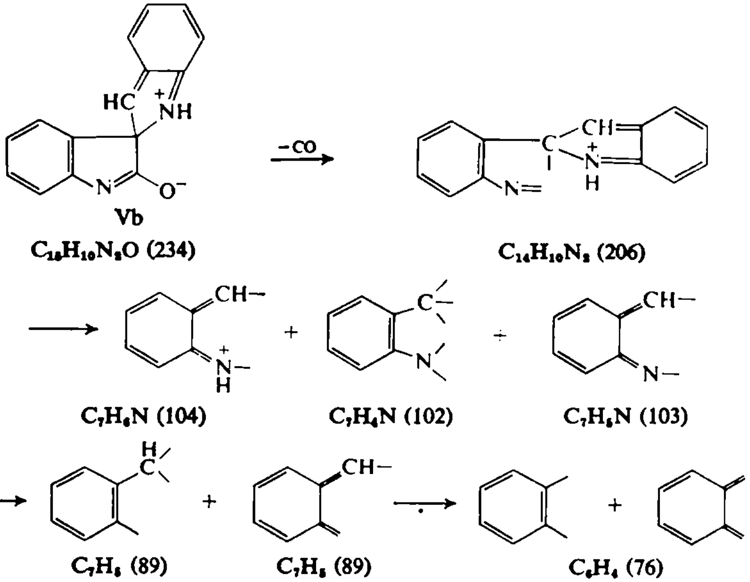
Va



VI

The unusual structure, 2′-hydroxyspiro[2H-indole-2,3′-3′H-indole] (Vb), accommodates all the evidence obtained for I. The high m.p. and the low solubility of I in organic solvents indicate a dipolar ionic structure. The IR spectrum of I shows a broad band at 3360–3140 cm^{-1} (hydrogen bond) and two peaks at 1640, 1610 cm^{-1} (=C=N—). The broad band suggests strong hydrogen bonding and appears to support the 2-hydroxyindolenine formula (Vb) better than the oxindole structure (Va). The indolenine (3H-indole) structure can be attributed to the UV max at 226 and 249 m*μ* and the 2H-indole portions to the max at 323 and 338 m*μ*.

The mass spectrum of I exhibits two intense peaks at *m*/*e* 234 and 233 due to the parent ($M=C_{15}H_{10}N_2O$) and M—H ions. The most revealing aspect is the loss of CO to give the $C_{14}H_{10}N_2$ ion (*m*/*e* 206), indicating the presence of a C—O— group in I. The presence of an abundant ion at *m*/*e* 103 can be explained by the fragmentation of the $C_{14}H_{10}N_2$ ion giving rise to the C_7H_5N ion as shown by the following scheme.



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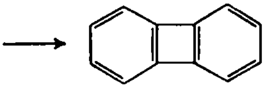
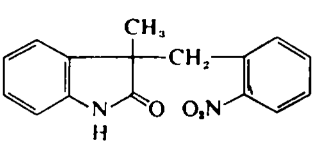
[1] W. O. Kermack and R. H. Slater, *J. Chem. Soc.* 32 (1928).



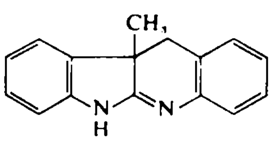
$C_{12}H_8$ (152)

Compounds such as spiro[cyclopentane-3′-oxindole][2] and spiro[oxindole-3.3′-pyrrolidine],[3] have been reported.

Further support for the structure Vb was obtained by the following analogous reactions. Unlike oxindole, 3-methyloxindole yields the normal product, 3-methyl-3-(2′-nitrobenzyl) oxindole (VII) on treatment with *o*-nitrobenzyl chloride in the presence of sodium ethoxide. The reduction of VII with stannous chloride gives 10b,11-dihydro-10b-methyl-6H-quinindoline (VIII) and zinc dust distillation of VIII affords quinindoline by aromatization accompanied by loss of the angular methyl group.

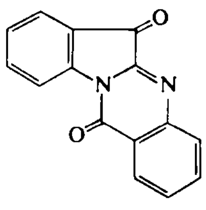


VII

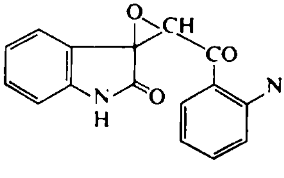


VIII

The reaction of N-sodioisatin with *o*-nitrobenzoyl chloride gives 1-(2′-nitrobenzoyl) isatin and its reduction affords 12,2′-dioxoindolo[2,1-b] quinazoline (IX), $C_{15}H_8N_2O_2$, m.p. 260°, which has been known as anhydroisatin-α-anthranilide,[4] m.p. 261°, and obtained as an oxidation product[4] of indigo. Gopinath *et al.*[5] recently obtained 1-(2′-nitrophenylacetyl) isatin by the reaction of 1-sodioisatin and phenylacetyl chloride. As a rule, 1-sodioisatin condenses with acyl chloride at 1-position of isatin, but the reaction of 1-sodioisatin with *o*-nitrophenacyl bromide yields 2′-nitrophenacyl-oxireno[α,3] oxindole[6] (X) which can be converted to an α,β-diketone on treatment with alkali.



IX



X

The reactions of 1-sodioisatin with *o*- and *p*-nitrobenzyl chloride yield 2′- and 4′-nitrobenzyl-oxireno[α,3] oxindole, $C_{15}H_{10}N_2O_4$, which forms neither the corresponding hydrazones nor oximes. The reduction of the *o*-nitro compound (XI) with stannous chloride in hydrochloric acid gives 5,11-dihydro-11-oxoquinindoline (XII), $C_{15}H_{10}N_2O$, as a result of the isomerization of ethylene oxide and the cyclization

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[2] J. B. Patrick and B. Witkopf, *J. Amer. Chem. Soc.* **72**, 633 (1950).

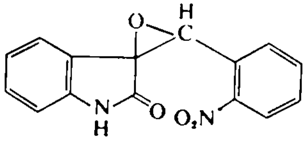
[3] A. B. A. Jansen and G. G. Richards, *Tetrahedron* **21**, 1327 (1965).

[4] P. Friedlander and N. Roschdestwensky, *Ber. Dtsch. Chem. Ges.* **48**, 1841 (1915).

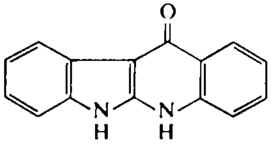
[5] K. W. Gopinath, T. R. Govindachari and S. Rajappa, *Tetrahedron* **8**, 291 (1960).

[6] A. D. Ainley and R. Robinson, *J. Chem. Soc.* 1508 (1934); Reaction of benzaldehyde and phenacyl bromide, S. Bodforss, *Ber. Dtsch. Chem. Ges.* **51**, 192 (1918).

between the 2-oxo and o-amino groups. The IR spectrum of XII indicates a carbonyl band at 1700, and two N—H bands at 3320, 3245 cm^{-1}. The Clemmensen reduction of XII yields quinindoline.



XI



XII

EXPERIMENTAL

3-(4'-*Nitrobenzyl*) *oxindole*

A soln of oxindole (2·7 g) and p-nitrobenzyl chloride (3·4 g) in abs EtOH (20 ml) was mixed with NaOEt soln (Na, 0·8 g in abs EtOH, 50 ml) and allowed to stand at room temp for 2 days. After acidifying with dil HCl, the mixture was evaporated on a water bath, and water added. The dark yellow precipitate was washed, dried and recrystallized twice from EtOH (charcoal), needles, 1·5 g (30%), m.p. 228–229° (colour changes at 215°). (Found: C, 67·75; H, 4·57; N, 10·59. $C_{15}H_{12}N_2O_3$ requires: C, 67·15; H, 4·51; N, 10·44%.) IR spectrum (KBr): band at 3120 cm^{-1} (NH).

3-(4'-*Aminobenzyl*) *oxindole*, m.p. 205°, plates (EtOH), was obtained by the catalytic reduction with Raney-Ni. (Found: C, 75·48; H, 6·05; N, 11·62. $C_{15}H_{14}N_2O$ requires: C, 75·60; H, 5·92; N, 11·72%.)

3-(4'-*Acetylaminobenzyl*) *oxindole*, m.p. 280–281°, prisms (EtOH), was obtained by treatment of the amino compound with AcOH–Ac_2O.

2'-*Hydroxyspiro*[2H-*indole*-2,3'-3'H-*indole*] (I)

A soln of oxindole (1·33 g) in abs EtOH (15 ml) was mixed with NaOEt (Na, 0·45 g in abs EtOH, 10 ml) and added dropwise to a soln of o-nitrobenzyl chloride (1·60 g) in abs EtOH at room temp under magnetic stirring, while the yellow colour changed to brown. After allowing to stand for 2 days, dil AcOH and AcONaaq were added and the soln evaporated on a water bath. After cooling, the precipitate was washed with water, dried and treated with EtOH. The EtOH-insoluble part (0·54 g, 24%) was heated *in vacuo* (3 mm) and the sublimate recrystallized from AcOH as plates, 0·33 g, m.p. above 350°. (Found: C, 76·96, 76·98; H, 4·68, 4·61; N, 11·98, 12·18. $C_{15}H_{10}N_2O$ requires: C, 76·91; H, 4·31; N, 11·96%.) IR spectrum (KBr): broad band at 3360–3140 (=NH$^+$—) and two bands at 1640, 1610 cm^{-1} (=C=N—). UV spectrum (95% EtOH): 226, 249, 323 and 338 mμ (ε, 3·9, 4·8, 1·6 and 2·2 × 10^4).

1-(4'-*Nitrobenzyl*) *oxindole*

o-Aminophenylacetate trihydrate was prepared by the reduction[7] of o-nitrophenylacetic acid and also by the hydrolysis[8] of oxindole by $Ba(OH)_2$.

To a stirred soln of Na o-aminophenylacetate (0·23 g) in water (2·5 ml) was added a soln of p-nitrobenzyl chloride (0·17 g) in EtOH (3 ml), and after standing for 2 hr, the mixture was refluxed on a water bath for 1 hr and then concentrated. On cooling pale yellow crystals separated, which were washed with Na_2CO_3aq and recrystallized from EtOH, pale yellow needles, 0·18 g (66%), m.p. 149–151°. (Found: C, 67·33; H, 4·60; N, 10·23. $C_{15}H_{12}N_2O_3$ requires: C, 67·15; H, 4·51; N, 10·44%.) IR spectrum showed lack of NH band.

1-(2'-*Nitrobenzyl*) *oxindole*

A soln of Na o-aminophenylacetate (4·6 g in 20 ml water) was added to a soln of o-nitrobenzyl chloride (3·4 g) in EtOH (25 ml) under magnetic stirring (20 min). After heating for 1 hr, the solvent was evaporated and the separated crystals were washed with Na_2CO_3aq and water, dried and recrystallized from EtOH, pale yellow plates, 4·0 g (75·4%), m.p. 155–157°. (Found: C, 67·25; H, 4·78; N, 10·41. $C_{15}H_{12}N_2O_3$ requires: C, 67·15; H, 4·51; N, 10·44%.) IR spectrum showed lack of NH band.

[7] P. N. Weber, *Ber. Dtsch. Chem. Ges.* **55**, 826 (1922).

[8] C. Marschalk, *Ber. Dtsch. Chem. Ges.* **45**, 585 (1912).

4-*Methyloxindole*

Pulverized Na (2 g) in dry toluene (15 ml) was dissolved in abs EtOH (15 ml), excess EtOH was expelled under red. press. (20 mm). Diethyl oxalate (12 g) was added to the residue; the mixture was stirred and then 3-nitro-*o*-xylene[9] (12 g) in dry C_6H_6 (15 ml) was added. On allowing to stand for 2 days at 35°, a reddish brown insoluble Na salt separated and NaOHaq was added. After 30 min, the brown soln was acidified with dil HCl. The resulting reddish mass was collected by filtration, dissolved in 2N NaOH, and 5% H_2O_2 was added until the colour changed to pale red accompanied by CO_2 evolution. The soln was filtered with the aid of charcoal, and the filtrate acidified with dil HCl. The pale yellow precipitate (crude 2-nitro-6-methylphenylacetic acid, 4·7 g) was taken up in EtOH (60 ml) and hydrogenated over Pd–C in an autoclave.

The alcoholic filtrate from the above mixture was evaporated, and the residue distilled *in vavuo*. The distillate was treated with 2N HCl, and the insoluble part distilled again *in vacuo*. Recrystallization from EtOH gave needles, 2 g (17·1% overall), m.p. 207–210°. (Found: C, 73·39; H, 6·26; N, 9·36. C_9H_9NO requires: C, 73·45; H, 6·16; N, 9·52%.) Its IR spectrum showed almost the same bands as those of oxindole.

2′-*Hydroxy*-4′-*methylspiro*[2H-*indole*-2,3′-3′H-*indole*]

4-Methyloxindole (1·19 g) and *o*-nitrobenzyl chloride (1·30 g) were treated with NaOEt (Na, 0·36 g) as described. The EtOH-insoluble part (0·42 g) was obtained, and its vacuum distillation (3 mm) afforded the crystalline sublimate, which was recrystallized from AcOH, plates, m.p. above 350°, 0·30 g. (Found: C, 77·28; H, 5·00; N, 11·40. $C_{16}H_{12}N_2O$ requires: C, 77·40; H, 4·87; N, 11·28%.) Its IR spectrum showed nearly the same bands as those of I.

Quinindoline-N-*oxide* (III)

Quinindoline was prepared by hydrolysis of α-isoindigo,[10] and purified by recrystallization of its hydrochloride (yellow needles) from dil HCl. To a hot acidic soln of the hydrochloride NaOHaq was added and the free base washed, dried, and sublimed *in vacuo* (20 mm), yellowish needles, m.p. 340°, lit. m.p. 342–343°.

To the yellowish soln of quinindoline (0·5 g) in AcOH (20 ml) excess peracetic acid (40–46%, 2·3 g) was added, and the soln allowed to stand for 5·5 hr at 50–60°, The colour of the mixture turned green. The mixture was made alkaline by addition of NaOHaq and the precipitate washed and dried, 0·5 g. Recrystallization from EtOH (charcoal) gave greenish yellow prisms, m.p. 294–296° (dec). (Found: C, 76·79; H, 4·49; N, 11·79. $C_{15}H_{10}N_2O$ requires: C, 76·96; H, 4·30; N, 11·96%.) It was sublimed unchanged at 180–200° *in vacuo* (2 mm) and was more soluble in EtOH than quinindoline. IR spectrum of quinindoline showed bands at 3350–2860 (b) (hydrogen bond of -NH–), 1615 (—C=N—), 1408, 740 and that of III at 3250–2570 (b) (hydrogen bond), 1604 (—C=N—), 1324, 1292 (N-oxide), 1227, 1079, 749, 724 cm^{-1}.

Reduction of III. The greenish soln of III (50 mg) in AcOH (20 ml) was stirred magnetically and Zn dust (100 mg) was added at 50–60° and stirring continued for 4 hr. To the resulting pale yellow solution NaOHaq was added and the precipitate was collected on asbestos together with Zn dust, washed, dried and sublimed *in vacuo* (20 mm). The sublimate, m.p. 324°, was obtained in quantitative yield and was identical with quinindoline.

By prolonged treatment of quinindoline with peracetic acid its colour faded to almost colourless after 15–20 hr. The resulting mixture gave only a slight precipitate by addition of NaOHaq. Treatment with dil peracetic acid (4–6%) gave a poor yield of III. Introduction of oxygen on nitrogen of azaheterocycles, such as pyridine, quinoline, isoquinoline,[11] pyrazine,[12] acridine,[13] phenazine,[14] benzophenazine[15] and quinindoline shows a considerable hyperchromic effect.

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[9] O. H. Emerson and L. I. Smith, *J. Amer. Chem. Soc.* **62**, 141 (1940).

[10] P. Friedlander and L. Sander, *Ber. Dtsch. Chem. Ges.* **57**, 651 (1924).

[11] H. H. Jaffe, *J. Amer. Chem. Soc.* **76**, 3527 (1954); T. Kubota, *Yakugaku Zasshi* (*Bull. Pharm. Soc. Japan*) **77**, 785 (1959).

[12] K. Lehmstedt, *Ber. Dtsch. Chem. Ges.* **68**, 1455 (1935).

[13] B. Klein and J. Berkowitz, *J. Amer. Chem. Soc.* **81**, 5160 (1959).

[14] H. McIlwain, *J. Chem. Soc.* 322 (1943).

[15] I. J. Pachter and M. C. Kloetzel, *J. Amer. Chem. Soc.* **73**, 4958 (1951).

3-*Keto-3,4-dihydro-5,6-benzo-4-carboline* *(VI)

Compound VI was prepared by the method of Kermack and Slator.[1] Recrystallization from pyridine gave prismatic needles, m.p. 320–321,° lit. m.p. above 316°. IR spectrum: 3450–3350 (b) (hydrogen bond of —NH—), 3060 (—NHCO—) and 1660 cm^{-1} (=CO).

3-*Methyloxindole*

3-Methyloxindole[16] was prepared from β-propionylphenylhydrazine by treatment of CaH_2 (41–44%) or CaO (20–30%). 3-Methyloxindole was prepared in better yield by the following procedure using CaO.

A mixture of β-propionylphenylhydrazine (33 g) and freshly ground CaO (33 g) in kerosine (b.p. 180–190° fraction, 80 ml) was heated on an oilbath at 200–205° under stirring for 2 hr. The yellow viscous mixture was cooled and added to 6N HCl (240 ml) and ice. After addition of C_6H_6 (90 ml) the contents of the flask were boiled gently for 1 hr. The hot mixture was filtered with the aid of charcoal, and allowed to stand overnight. The separated crystals were collected by filtering under suction, washed with C_6H_6 and water, and dried, yellow crystals, 10·7 g, m.p. 120–123°. The C_6H_6–kerosine layer separated from the above filtrate was evaporated to remove the solvants (20 mm). The vacuum distillation (20 mm) of the residue gave crystals (2·4 g); m.p. 121–123° (recrystallized from C_6H_6), yield, 13·1 g (44·6%).

3-*Methyl-3-(2′-nitrobenzyl) oxindole* (VII)

To a stirred soln of NaOEt (Na, 0·45 g) in abs EtOH (10 ml) was added a soln of 3-methyloxindole (1·5 g) in abs EtOH (12 ml), and then mixed well with a soln of *o*-nitrobenzyl chloride (1·7 g) in abs EtOH (8 ml) at room temp. Meanwhile the colour of the mixture did not change unlike the abnormal reactions. After standing for 2 days, the mixture was acidified with AcOH, and concentrated to 15 ml. The colourless crystals, which separated on cooling, were washed, dried and recrystallized from C_6H_6, needles, 1·8 g, m.p. 171–172°. (Found: C, 68·18; H, 4·91; N, 9·91. $C_{16}H_{14}N_2O_3$ requires: C, 68·07; H, 5·00; N, 9·92%.) IR spectra: 3200 cm^{-1} (—NH—).

10b,11-*Dihydro*-10b-*methyl*-6H-*quinindoline* (VIII)

A suspension of VII (1·4 g) in EtOH (3 ml) was added to a soln of $SnCl_2$ (3·8 g) in conc HCl (5 ml) under stirring, and the reaction mixture heated on a water bath for 15 min. The solution was diluted with water, and added into NaOHaq. The colourless precipitate was collected, washed and dried. Its distillate *in vacuo* (2 mm) was recrystallized from EtOH, needles, 1·05 g (90%), m.p. 200·5–202·5°. (Found: C, 82·16; H, 5·92; N, 11·96. $C_{16}H_{14}N_2$ requires: C, 82·02; H, 6·02; N, 11·96%.)

The Zn dust distillation of VIII under H_2 gave a pale yellow sublimate, needles m.p. 332°, which were identical with quinindoline, m.p. 334°, by comparison of their IR spectra and m.p.

1-(2′-*Nitrobenzoyl*) *isatin*

The 1-sodioisatine[17] (1·7 g) and *o*-nitrobenzoyl chloride obtained from *o*-nitrobenzoic acid (1·7 g) and thionyl chloride (3 ml) were refluxed in dry C_6H_6 for 2 hr. The yellow crystals which separated were washed with hot EtOH and water. Recrystallization from EtOH gave needles, 2·5 g (85%), m.p. 209–210°.

12,2′-*Dioxoindolo*-2,1-b-*quinazoline* (IX) (*Anhydroisatin-α-anthranilide*)[4]

1-(2′-Nitrobenzoyl)isatin (1 g) was suspended in EtOH (20 ml), mixed with $SnCl_2$ (5 g) in conc HCl (7 ml), and refluxed for 1 hr. After cooling, the mixture containing yellow needles was poured into NaOHaq (alkaline). The greenish yellow precipitate was washed with water and recrystallized from xylene as yellow needles, 0·55 g (67%), m.p. 260° (lit.[8] m.p. 261°). (Found: C, 72·87; H, 3·50; N, 11·10. $C_{15}H_8N_2O_2$ requires: C, 72·57; H, 3·25; N, 11·29%.)

The hydrazone of IX was prepared by refluxing with hydrazine hydrate in EtOH, yellow needles, m.p. 250° (dec). (Found: N, 21·21. $C_{15}H_{10}N_4O$ requires: N, 21·37%.)

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* 5,6-Dihydro-6-oxo-7H-indolo[2,3-c]quinoline

[16] Organic Syntheses vol. 37 p. 60.

[17] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).

2′-*Nitrobenzyl-oxireno*[α,3]*oxindole* (XI)

An abs EtOH suspension of isatine (4·5 g in 80 ml) was added to NaOEt (Na, 1·4 g in abs EtOH, 50 ml), and *o*-nitrobenzyl chloride (5·1 g) in abs EtOH (50 ml) was added into the above mixture on cooling. The mixture was stirred for 2 hr at room temp and then acidified with dil AcOH. After adding water, the precipitate was washed, dried and recrystallized from EtOH (charcoal) as pale yellow needles, 5·3 g (63%), m.p. 174–176·5°. (Found: C, 64·04; H, 3·89; N, 9·82. $C_{15}H_{10}N_2O_4$ requires: C, 63·83; H, 3·57; N, 9·93%.) IR spectra (KBr): 1355, 1530, (NO_2) 1740, 1705 (NHCO) and 3350 cm^{-1} (NH).

4′-*Nitrobenyzl-oxireno*[α,3]*oxindole*

The reaction of isatin (4·5 g) and *p*-nitrobenzyl chloride (5·1 g) afforded the *p*-nitro derivative, which crystallized from EtOH as needles, 5·6 g, m.p. 228–234° (dec). (Found: C, 63·74; H, 4·24; N, 10·10. $C_{15}H_{10}N_2O_4$ requires: C, 63·83; H, 3·57; N, 9·93%.)

5,11-*Dihydro*-11-*oxoquinindoline* (XII)

An EtOH suspension of XI (2·8 g in 4 ml) was treated with $SnCl_2$ (8 g) in conc HCl (7·5 ml). The mixture was heated for 1 hr on a water bath. After cooling, the mixture containing yellow crystals was poured into NaOHaq. The precipitate was recrystallized from xylene as yellow needles, 1·2 g (50%), m.p. 234°. (Found: C, 76·93; H, 4·65; N, 11·79. $C_{15}H_{10}N_2O$ requires: C, 76·91; H, 4·30; N, 11·96%.) IR spectra (KBr): 1700 (CO) and 3320 and 3245 cm^{-1} (2NH).

Quinindoline

Compound XII (0·5 g) was reduced in AcOH by the Clemmensen method. Heating was continued for 4 hr and then the mixture was made alkaline. Distillation (20 mm) of the dry precipitate gave a sublimate, 0·26 g, which recrystallized from $C_6H_5NO_2$, m.p. 340°.

Quinindoline was obtained also by Zn dust distillation of VIII, as described above.

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