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A NEW METHOD FOR THE PREPARATION OF OXINDOLES FROM PARENT INDOLES

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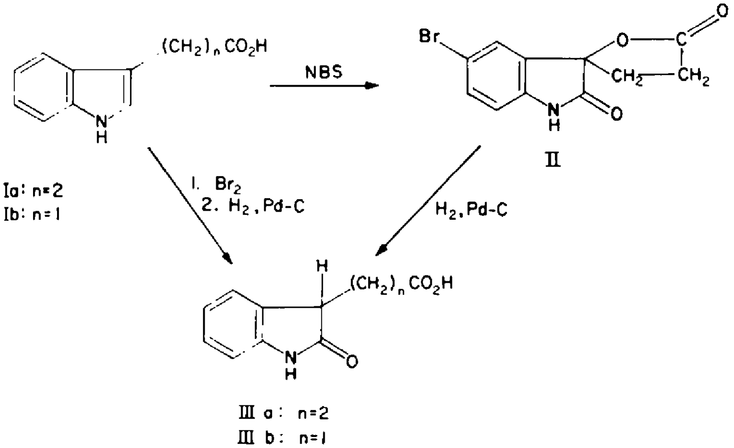
Abstract—3-Substituted oxindoles have been prepared by acid hydrolysis from the pyridinium salts derived from 3-substituted 2-bromoindoles obtained from 3-substituted indoles, N-bromosuccinimide and pyridine. 3-Phenyloxindole, 3-methyloxindole, oxindole-3-propionic acid and oxindole-3-butyric acid have been prepared from the parent indoles by this method. 2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid has been obtained from indole-3-acetic acid by the same reaction.

The following methods are known for the conversion of indoles into oxindoles: (1) the oxidation by peracetic acid,[1] (2) the oxidation by persulfuric acid,[2] (3) the reaction with disulfur dichloride,[3] (4) the treatment with ferric chloride in the presence of diethylamine.[4] The overall yields of these methods are relatively low and they leave much to be desired from a preparative point of view.

In 1961, Lawson and Witkop[5] showed that the lactone (II) obtained by the action of N-bromosuccinimide on indole-3-propionic acid (Ia), gave oxindole-3-propionic acid (IIIa) by the reductive hydrolysis in 49% yield. Oxindole-3-acetic



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[1] B. Witkop, *Liebigs Ann.* **558**, 98 (1947).

[2] C. E. Dalgliesh and W. Kelly, *J. Chem. Soc.* 3726 (1958).

[3] T. Wieland, O. Weiberg, E. Fischer and G. Hörlein, *Liebigs Ann.* **587**, 146 (1954); T. Wieland, O. Weiberg and W. Dilger, *Ibid.* **592**, 69 (1955); K. Freter, J. Axelrod and B. Witkop, *J. Amer. Chem. Soc.* **79**, 3191 (1957); K. Freter, H. Weissbach, B. Redfield, S. Udenfriend and B. Witkop, *Ibid.* **80**, 983 (1958).

[4] H. Dobeneck and W. Lehnerer, *Chem. Ber.* **90**, 161 (1957).

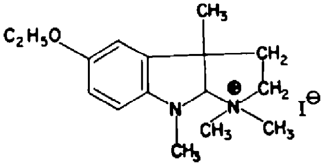
[5] W. B. Lawson and B. Witkop, *J. Org. Chem.* **26**, 263 (1961).

acid (IIIb) was prepared from indole-3-acetic acid (Ib) in the same manner using bromine instead of N-bromosuccinimide in 49% yield.

The present investigation describes a practical method for the conversion of indoles into oxindoles.

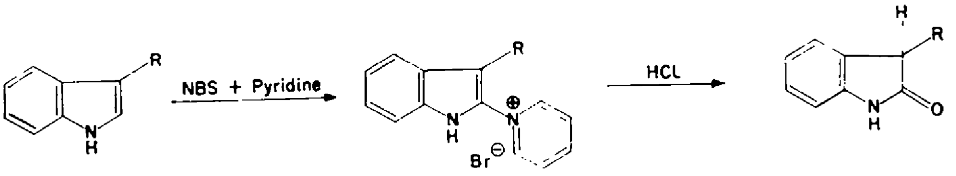
The reaction of 3-phenylindole (Va) with N-bromosuccinimide and pyridine in benzene at room temperature results in a quantitative yield of the pyridinium salt derived from 2-bromo-3-phenylindole (VIa). Similarly, the reaction of Va with β-phenyl- and γ-phenylpyridine yields the β-phenyl- and γ-phenylpyridinium salts respectively. In the case of α-phenylpyridine or quinoline, the corresponding quaternary salts are not obtained and this is presumably due to steric effects and the weak ionization constants of the bases.

Although quaternary salts are generally stable to alkali, those with a nitrogen–carbon–nitrogen bond such as in eserethole methyliodide (IV), are easily decomposed by cold alkaline solution.[6] The pyridinium salt VIa has a similar bond and hydrolysis with alkali, ammonia, sodium hydrogen carbonate, sodium hydrogen sulfite, sodium acetate and acetate buffer failed and only resinous materials were obtained.



IV

Pyridinium salt VIa on treatment with hydrochloric acid yields 3-phenyloxindole (VIIa; 67%); which was identified by comparison with an authentic sample prepared by the method of Brunner.[7]



V a: R=C_6H_5
V b: R=CH_3

VI a: R=C_6H_5
VI b: R=CH_3

VII a: R=C_6H_5
VII b: R=CH_3

This method has been applied to the synthesis of 3-methyloxindole (VIIb). The pyridinium salt (VIb) obtained in 79·5% yield gives on acid hydrolysis 3-methyloxindole (VIIb) in 81·5% yield. Similarly, methyl indole-3-propionate (VIIIa) and -3-butyrate (VIIIb) give pyridinium salts (IXa and IXb) in 83% and 86% yield respectively, and on acid hydrolysis oxindole-3-propionic acid (Xa) and -butyric acid (Xb) are obtained in 88% and 89% yield respectively.

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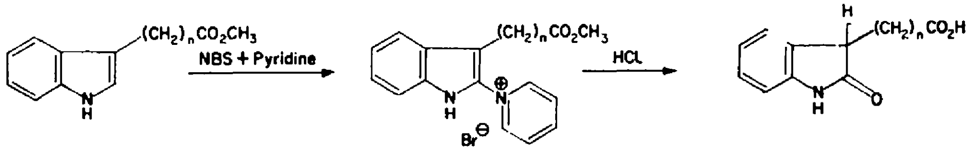
[6] T. Kobayashi, *Liebigs Ann.* **536**, 148 (1938).

[7] K. Brunner, *Monatsh.* **18**, 547 (1897).

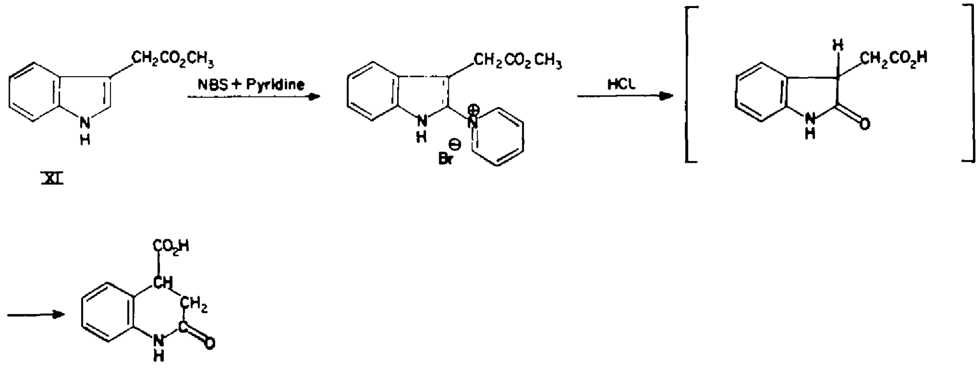


VIII a : n=2
VIII b : n=3

IX a : n=2
IX b : n=3

X a : n=2
X b : n=3

In the case of methyl indole-3-acetate (XI), 2-oxo-1,2,3,4-terahydroquinoline-4-carboxylic acid (XII) is formed in 50% yield by hydrolytic rupture of the oxindole ring and ring closure.[8]



XI

XII

EXPERIMENTAL

Microanalyses were carried out by Y. Fujiyoshi. All m.ps are uncorrected.

Pyridinium salt derived from 2-*bromo*-3-*phenylindole* (VIa). To a stirred solution of 3-phenylindole (0·300 g) and pyridine (0·160 g) in dry benzene (8 ml) at room temp, N-bromosuccinimide (NBS; 0·270 g) was added during 15 min with the formation of a yellow precipitate. The mixture was stirred for an additional 1½ hr and refluxed on a water bath for 1 hr. Benzene (4 ml) was added and the precipitate filtered while hot, washed with a little benzene, and dried; yield 0·545 g (100%), m.p. 224–226° (dec). Recrystallization from 4N HBr and from ethanol gave yellow needles, m.p. 225° (dec). The IR spectrum (KBr) exhibited a band at 3400 cm^{-1} (>NH). (Found: C, 65·21; H, 4·36; N, 8·06. $C_{19}H_{15}N_2Br$ requires: C, 64·96; H, 4·30; N, 7·98%).

β-Phenylpyridinium salt derived from 2-*bromo*-3-*phenylindole*. The reaction of 3-phenylindole (0·570 g) with β-phenylpyridine (0·515 g) and NBS (0·525 g) was similarly performed yielding 0·755 g (59·9%) of the product, m.p. 278–281° (dec). After recrystallization orange needles, m.p. 284–285° (dec) were obtained. (Found: C, 70·34; H, 4·48; N, 6·52. $C_{25}H_{19}N_2Br$ requires: C, 70·28; H, 4·48; N, 6·56%).

γ-Phenylpyridinium salt derived from 2-*bromo*-3-*phenylindole*. The reaction of 3-phenylindole (0·565 g) with γ-phenylpyridine (0·500 g) and NBS (0·525 g) yielded 0·841 g (67·3%) of the product, m.p. 284–286° (dec) which recrystallized in reddish orange plates, m.p. 293–295 dec. (Found: C, 70·32; H, 4·72; N, 6·66. $C_{25}H_{19}N_2Br$ requires: C, 70·28; H, 4·48; N, 6·56%).

Attempted hydrolysis of pyridinium salt VIa. The attempts to hydrolyse VIa with NaOH aq, NH_4OH, $NaHCO_3$ aq, $NaHSO_3$ aq, sodium acetate and acetate buffer failed and resulted in dark brown resinous materials.

3-*Phenyloxindole* (VIIa). Pyridinium salt VIa (0·300 g) and 6 N HCl aq (3 ml) were placed in a sealed tube and heated at 140° for 2 hr. After cooling, the solid was filtered off, washed with water

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[8] P. L. Julian, H. C. Printy, R. Ketcham and R. Doone, *J. Amer. Chem. Soc.* **75**, 5305 (1953).

and dried; yield 0·120 g (67·2%), m.p. 181–184°, undepressed by admixture with an authentic sample prepared by the method of Brunner.[7] The yield of VIIa by the Brunner's method was less than 5%.*

Pyridinium salt derived from 2-bromo-3-methylindole (VIb). A solution of 3-methylindole (0·395 g) and pyridine (0·317 g) in dioxan (8 ml) was stirred at 12 to 15° while NBS (0·538 g) was added during 5 min with formation of a yellow precipitate. After stirring for an additional 30 min, the precipitate was filtered off, washed with a little dioxan, and dried; yield 0·692 g (79·5%), m.p. 226–228° dec. Recrystallization from ethanol–ether gave yellow needles, m.p. 231–233° dec. (Found: C, 58·30; H, 4·61; N, 9·89. $C_{14}H_{13}N_2Br$ requires: C, 58·15; H, 4·53; N, 9·69%).

3-Methyloxindole (VIIb). Pyridinium salt VIb (0·200 g) was heated with 3N HCl aq (2·5 ml) at 160° for 2 hr in a sealed tube. The reaction mixture was extracted with ether, the ethereal solution washed with NaCl aq and dried over Na_2SO_4. After evaporation of ether, the product was distilled under red. press. (3 mm). The distillate, a colourless syrup, solidified rapidly; yield 0·083 g (81·5%), m.p. 123–124° (lit.,[8] 122–123°). (Found: C, 73·48; H, 6·16; N, 9·37. Calc. for C_9H_9NO: C, 73·45; H, 6·16; N, 9·52%).

Pyridinium salt derived from methyl 2-bromoindole-3-propionate (IXa). Methyl indole-3-propionate (1·023 g), obtained in quantitative yield by the action of diazomethane on indole-3-propionic acid in ether–methanol, was stirred at 12 to 15° in pyridine (0·589 g) and dioxan (15 ml) while NBS (0·900 g) was added during 5 min with formation of a yellow precipitate. The mixture was stirred for an additional 30 min. The precipitate filtered off, washed with a little dioxan, and dried; yield 1·513 g (83·2%), m.p. 218–220° dec. Recrystallization from ethanol–ether gave yellow needles, m.p. 225–226° dec. (Found: C, 56·41; H, 4·80; N, 7·90. $C_{17}H_{17}N_2O_2Br$ requires: C, 56·52; H, 4·75; N, 7·76%).

Oxindole-3-propionic acid (Xa). A solution of pyridinium salt IXa (1·012 g) in 3 N HCl aq (10 ml) was placed in a sealed tube and kept at 125° for 2 hr. The resulting mixture was evaporated to dryness leaving a colourless syrup. Upon the addition of water (1 ml), the product solidified and was collected by filtration, washed with a little water, and dried; yield 0·506 g (88·1%), m.p. 165–168°. Recrystallization from water gave colourless crystals, m.p. 168–170° (lit., 165–167°[5] or 169–170°[8]). (Found: C, 64·19; H, 5·31; N, 6·66. Calc. for $C_{11}H_{11}NO_3$: C, 64·38; H, 5·40; N, 6·83%).

Pyridinium salt derived from methyl 2-bromoindole-3-butyrate (IXb). To a stirred solution of methyl indole-3-butyrate (1·106 g) and pyridine (0·637 g) in dioxan (14 ml) at 12 to 15°, NBS (0·905 g) was added over a period of 10 min. The resulting solution deposited a yellow precipitate and was stirred for an additional 30 min. The precipitate filtered off, was washed with a little dioxan, and dried; yield 1·630 g (85·7%), m.p. 165–168° dec. Recrystallization from ethanol–ether gave yellow needles, m.p. 169–170° dec. (Found: C, 57·58; H, 5·39; N, 7·60. $C_{18}H_{19}N_2O_2Br$ requires: C, 57·61; H, 5·10; N, 7·47%).

Oxindole-3-butyric acid (Xb). Pyridinium salt IXb (1·005 g) and 3N HCl aq (10 ml) were heated at 150° for 1½ hr in a sealed tube. The resulting mixture was worked up as described above for Xa; yield 0·523 g (89·0%), m.p. 168–170°. Recrystallization from water gave colourless needles, m.p. 169–170°. (Found: C, 65·91; H, 6·20; N, 6·41. $C_{12}H_{13}NO_3$ requires: C, 65·74; H, 5·98; N, 6·39%).

2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (XII). Methyl indole-3-acetate (XI) was prepared in almost quantitative yield by the action of diazomethane on indole-3-acetic acid in ether–methanol. To a stirred solution of XI (1·011 g) and pyridine (0·618 g) in dioxan (15 ml) at 12 to 15°, NBS (0·955 g) was added during 5 min and the solution stirred for an additional 2 hr and allowed to stand overnight in an ice box. The reddish orange oil which separated, was washed with a little dioxan and the solvent evaporated *in vacuo*. To the residue 3N HCl aq (15 ml) was added and the mixture heated under reflux on an oil bath (130°) for 3½ hr. After treatment with charcoal while hot, colourless needles crystallized on cooling; yield 0·514 g (50·4%), m.p. 212–213°. Recrystallization from water gave colourless needles, m.p. 214–215° (lit., 210–214°[5] or 218°[8]). (Found: C, 63·01; H, 4·92; N, 7·07. Calc. for $C_{10}H_9NO_3$: C, 62·82; H, 4·75; N, 7·33%).

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* G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.* **83**, 211 (1953), reported that the attempts to prepare 3-phenyloxindole by the method of Brunner[7] were fruitless and that the method of J. Meisenheimer and H. Meis, *Ber. Dtsch. Chem. Ges.* **57**, 289 (1924) gives a much lower yield than that reported by them.

[8] P. J. Lulian and H. C. Printy, *J. Amer. Chem. Soc.* **75**, 5301 (1953).