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Indoles. III.[1] A New Synthesis of 4-Indolecarboxylic Acid

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As a new and convenient method for the synthesis of 4-indolecarboxylic acid (**1**), the synthesis was started with the reduction of 3-nitrophthalimide (**4**) with sodium borohydride, followed by hydrolysis of the product to obtain 3-hydroxy-4-nitrophthalide (**6**). Treatment of **6** with 2 moles of diazomethane gave 2-methoxycarbonyl-6-nitrostyrene oxide (**7**) whose reductive cyclization afforded methyl 4-indolecarboxylate (**2**) and it was saponified to the desired **1**.

A new and convenient method for the synthesis of 4-indolecarboxylic acid (**1**), one of the key intermediates in the synthesis of 4-substituted indoles, and its methyl ester (**2**) is reported.

In general, 4-substituted indoles are fewer than the 2- or 3-substituted indoles, either as a natural product or synthesized.[3] Nevertheless, some of 4-substituted indoles, for instance, lysergic acid diethylamide and psilocybin, are now known to have interesting pharmacological activity. **1** has already been synthesized by Uhle[4] but through a comparatively difficult and multiple steps of derivation of 2-chloro-6-nitrotoluene to 2-chloro-6-nitrophenylpyruvic acid, its reductive cyclization to 4-chloroindole-2-carboxylic acid, and heating this acid with cuprous cyanide to obtain 4-cyanoindole. Saponification of the latter gave **1** and its esterification, **2**.

In the present series of work, 3-nitrophthalic anhydride (**3**) was used as the starting material, and **1** and **2** were synthesized by the route shown in Chart 1.

Horii and others[5] reported the reduction of phthalimide with sodium borohydride and this method was utilized. Reduction of 4-nitrophthalimide (**4**) with 2 moles of sodium borohydride in 90% methanol, at room temperature, was found to effect selective reduction of the carbonyl near the nitro group, and 3-hydroxy-4-nitrophthalimidine (**5**) was obtained. Its hydrolysis afforded 3-hydroxy-4-nitrophthalide (**6**) in 85% yield calculated from 3-nitrophthalic anhydride (**3**). **6** is also obtained by reduction of **3** with sodium borohydride in tetrahydrofuran, but the yield is smaller. **6** has already been obtained by Dúbrav and others[6] as a by-product from the nitration of *o*-formylbenzoic acid but in a poor yield. **6** is considered to be present as an equilibrium mixture with its noncyclized form, 2-formyl-3-nitrobenzoic acid (**6'**), but its infrared (IR) spectrum (in KBr disc) exhibited two carbonyl absorption at 1780 and 1840 cm^{-1}, and one carbonyl band at 1780 cm^{-1} in chloroform, so that **6** would be present in its cyclized form (**6**) in the latter and in noncyclized form (**6'**) or a mixture of **6'** and **6** in the former.

For the nuclear magnetic resonance (NMR) spectrum of phthalaldehydic acid, Kagan[7] assigned the one proton signal at around 7 ppm to the C-3 proton in the cyclized form (**9**) and that around 10 ppm to the aldehyde proton in the noncyclized form (**10**), and discussed

1) Part II: T. Nagasaka and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **19**, 603 (1971).
2) Location: *10-19 Ueno-Sakuragi 1-chome, Daito-ku, Tokyo.*
3) R.C. Elderfield, "Heterocyclic Compounds," Vol. 3, by John Wiley and Sons, Inc., New York.
4) C. Uhle, *J. Am. Chem. Soc.*, **71**, 761 (1949).
5) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).
6) R. Wegscheider, L. Kuśy, and V. Dúbrav, *Monatsh. Chem.*, **24**, 811 (1903).
7) J. Kagan, *J. Org. Chem.*, **32**, 4060 (1967).

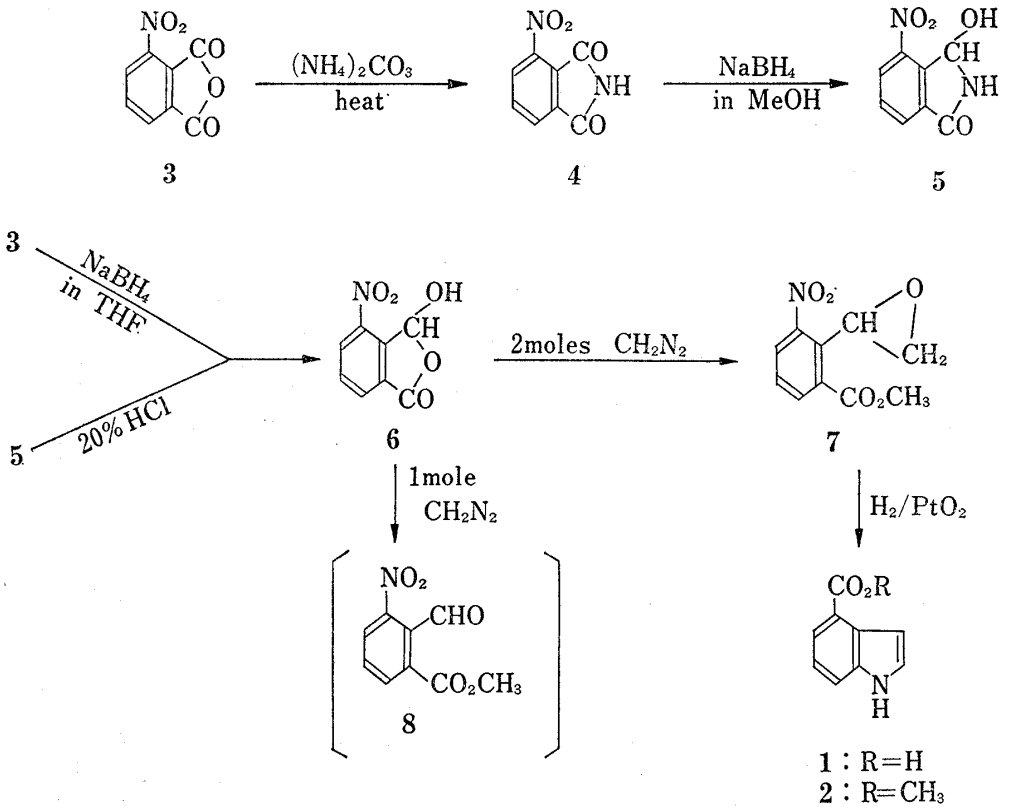


Chart 1

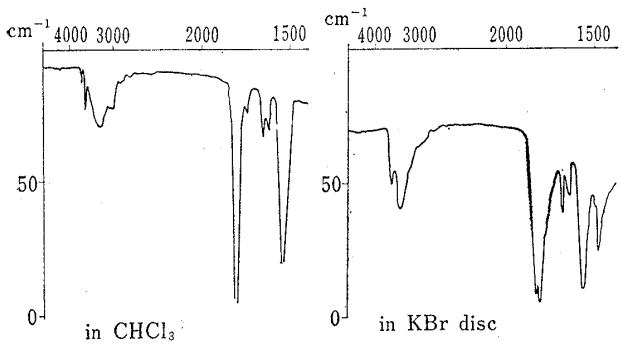


Fig. 1. IR Spectrum of **6**

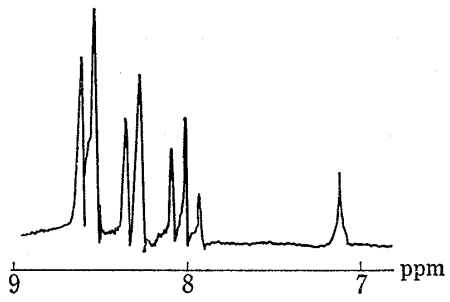


Fig. 2. NMR Spectrum of **6** in Me_2SO-d_6

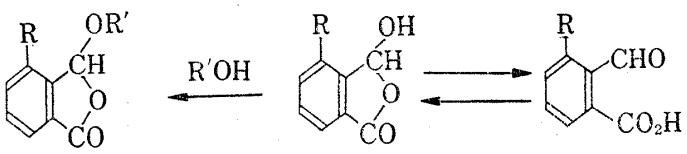
the equilibrium of **9** and **10** in solution. He stated that this acid took the cyclized form (**9**) in general, except in strong acid or in basic media.

The NMR spectrum of **6** in dimethyl ($^2H_6$) sulfoxide shows one proton signal at 7.03 ppm and **6** is therefore considered to be in cyclized form. Taken together with the result of IR spectrum, **6** seems to be the useal form in a solution.

Treatment of **6** with methanol, in the presence of an acid, afforded colorless needles, mp 145°, which agreed with the substance obtained by Dúbrav[6] by the same treatment of **6**. He assigned methyl 2-formyl-3-nitrobenzoate (**8**) to this crystalline substance but, since its NMR spectrum (in $CDCl_3$) one proton signal as a singlet at 6.74 ppm and its IR spectrum (in KBr) has one carbonyl absorption at 1790 cm^{-1}, this substance should be 3-methoxy-4-nitrophthalide (**11**). This methylation progresses in a high yield by merely warming **6** with methanol, and the use of ethanol in this case give the 3-ethoxy compound (**12**) of mp 134°.

A substance considered to be **8** was obtained as liquide by treatment of **6** with an equimolar amount of diazomethane, while the use of an excess of diazomethane result in consumption of 2 moles to give 2-methoxycarbonyl-6-nitrostyrene oxide (**7**) in a good yield. The

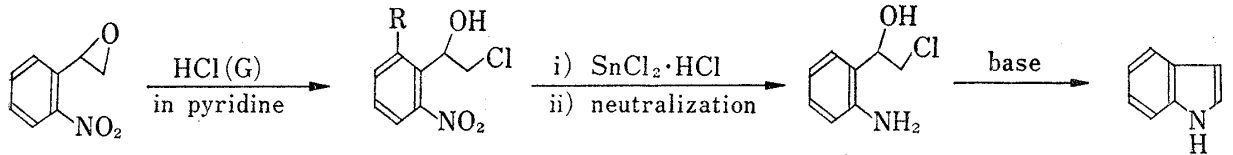
NMR spectrum ($CDCl_3$) of **8** shows one proton signal for the aldehyde at 10.65 ppm and its IR spectrum ($CHCl_3$) has two carbonyl absorption at 1770 and 1740 cm^{-1}. The NMR spectrum ($CDCl_3$) of **7** exhibits ABM-type signals for an oxirane ring at 2.53 ppm (1H, dd, J=2.5 and 3.0 Hz), 3.16 ppm (1H, t, J=2.5 and 3.0 Hz), and 4.52 ppm (1H, t, J=2.5 and 3.0 Hz), and a signal for methyl carboxylate at 3.93 ppm (3H, s). Its IR spectrum (KBr) has absorption at 1720 ($\nu_{C=O}$), 1530 and 1360 cm^{-1} (ν_{NO_2}).



11 : R=NO_2, R'=CH_3
12 : R=NO_2, R'=C_2H_5
6 : R=NO_2
9 : R=H
6' : R=NO_2
10 : R=H

Chart 2

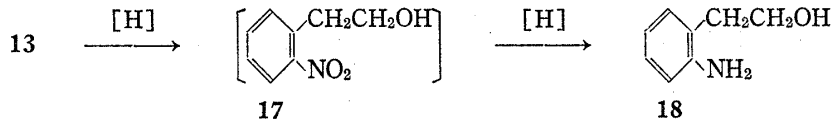
As a model experiment for the derivation of **2** from **7**, condition were examined for the derivation of 2-nitrostyrene oxide (**13**) to indole (**16**).



13
14 : R=H
19 : R=CO_2CH_3
15
16

Chart 3

13 would be let to chlorohydrin (**14**) which would be reduce to the amine (**15**) but, according to Arndt and Eistert,[8] cyclization of **15** to **16** with alkali give a very poor yield. In the present work, however, treatment of **15** with sodium ethoxide afforded **16** in 75% yield. Preparation of **16** by the reductive cyclization of **13** was also attempted. Catalytic reduction of **13** over platinium oxide or Raney nickel gave *o*-aminophenethyl alcohol (**18**) and a resinous substance, while the use of 10% palladium carbon resulted in the recovere of majority of **13**, with a small amount of **18** and *o*-nitrophenethyl alcohol (**17**). These experimental evidences indicate that the reductive cleavage of the oxirane ring precedes reduction of the nitro group and, for that reason, it would be difficult to obtain **16** in one step.



17
18

Chart 4

Based on these result, application of the former method was considered and an attempt was made to synthesize β-chloro-α-(2-methoxycarbonyl-6-nitrophenyl)ethanol (**19**), corresponding to the formation of **14** from **13** but only a small amount of a substance considered to be **19** was obtained. Consequentry, preparation of **2** by the reductive cyclization of **7** was attempted. Catalytic reduction of **7** over platinium oxide afforded crystals of mp 64—65° in 65% yield. Although the oxirane ring of **13** was preferentially cleaved by reduction rather than reduction of the nitro group, the oxirane ring in **7** was comparatively difficult to be cleaved by reduction due to steric hindrance and reduction of the nitro group preceded, producing **2** in one step.

8) F. Arndt and B. Eistert, *Chem. Ber.*, **61**, 1107 (1928).

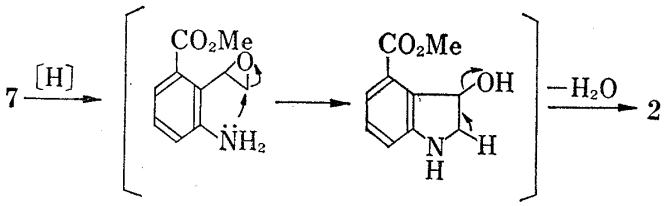


Chart 5

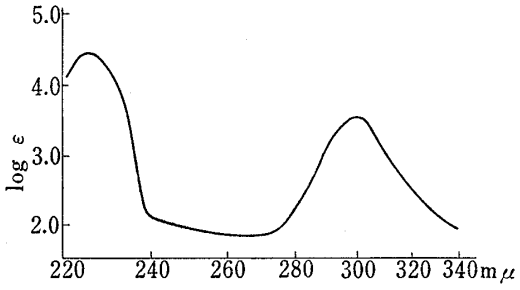


Fig. 3 UV Spectrum of **2** in Ethanol

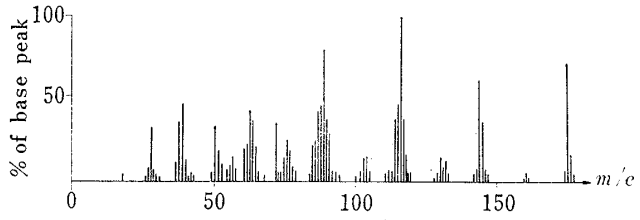


Fig. 4 Mass Spectrum of **2**

Saponification of **2** with potassium hydroxide gives **1** which is obtained as labil crystals of mp 212—213°, agreeing with the data reported by Uhle,[4] but the melting point of **2** does not agree with mp 146—147° reported by him. The substance obtained in the present work must be **2** from its ultraviolet (UV) (Fig. 3) and mass (Fig. 4 and Chart 6) spectra.

The foregoing experiments indicate that 2-nitrostyrene oxides with an oxirane ring whose activity is suppressed to a certain degree can be derives easily to indoles by reductive cyclization, and this is especially advantageous for the synthesis of 4-substituted indoles.

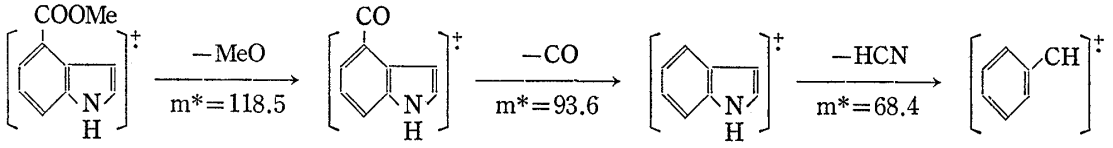


Chart 6

Experimental

Synthesis of 3-Hydroxy-4-nitrophthalide (6)——To a solution of 4.3 g of 3-nitrophthalimide (4) dissolved in 50 ml of 90% MeOH, 1.9 g $NaBH_4$ was added over 30 min, while stirring the solution vigorously at room temperature, and the mixture was stirred for 2 hr. The solution was acidified with 20% HCl, MeOH was evaporated under a reduced pressure, and the dried residue was treated with acetone. Evaporation of acetone left 3.9 g (88%) of crude 3-hydroxy-4-nitrophthalimidine (5), which was recrystallized from acetone to pale yellow plates, mp 214—215°. This crude product can be used *per se* for the next reaction.

Hydrolysis: A solution of 3.9 g of 5 in 40 ml of 20% HCl was stirred for 10 hr on a water bath of 80—90°. HCl was distilled off, the residue was stirred with acetone, and the mixture was filtered. Acetone was evaporated from the filtrate and purification of the residue by column chromatography afford 3.4 g (77%) of 3-hydroxy-4-nitrophthalide (6), mp 100—120°. Recrystallization from $CHCl_3$ gave colorless needles, mp 155—156°. *Anal.* Calcd. for $C_8H_5O_5N$: C, 49.24; H, 2.58; N, 7.18. Found: C, 49.38; H, 2.64; N, 7.21.

Synthesis of 2-Methoxycarbonyl-6-nitrostyrene Oxide (7)——An ether solution of CH_2N_2, prepared by the useal method,[9] was added to 1.93 g of 6 in a 100-ml flask until the reaction was no longer evident. Excess CH_2N_2 was decomposed with AcOH and ether was evaporated. The residue was purified by column chromatography and 1.92 g (86%) of 7, mp 62—64°, was obtained. *Anal.* Calcd. for $C_{10}H_9O_5N$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.93; H, 4.13; N, 6.25. Mass Spectrum *m/e*: 223 (M^+).

Methyl 4-Indolecarboxylate (2)——A solution of 560 mg of 7 dissolved in 50 ml of abs. MeOH, added with 50 mg PtO_2, was submitted to catalytic reduction. The reaction mixture was then filtered, MeOH

9) T.J. de Boer and H.J. Backer, *Org. Synthesis Coll. Vol.*, **IV**, 250 (1963).

was evaporated from the filtrate under a reduced pressure, and the residue was recrystallized from benzene to 270 mg (62%) of **2**. mp 64—65°. *Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.15; N, 8.00. Found: C, 68.55; H, 5.25; N, 8.00. Mass Spectrum *m/e*: 175 (M^+). IR (KBr) cm^{-1}: 3320 (ν_{NH}), 1690 ($\nu_{C=O}$). UV λ_{max}^{EtOH} mμ(log ε): 226 (4.23), 303 (3.82).

Hydrolysis of Methyl 4-Indolecarboxylate (2)——A mixture of 250 mg of **2** in 2 ml of 0.05M KOH solution was stirred at room temperature for 6 hr. The solution was cautiously neutralized with 10% HCl, avoiding excessive evolution of heat, and the colorless crystals that precipitated out were collected by filtration. The dried product amounted to 126 mg of **1** as colorless cubic crystals, mp 212—213° (lit.[4] mp 213—214°). This substance is labile to heat and turns resinous with coloration.

Indole (16) from β-Chloro-α-(O-aminophenyl)ethanol (15)——To EtOH solution of NaOEt, prepared from 32 mg of metallic Na and 30 ml of abs. EtOH, 218 mg of **15** was added and the mixture was stirred at room temperature until the solution no longer colored red to phenolphthalein. EtOH was evaporated under a reduced pressure, a small amount of water added to residue and extracted with ether, extract was dried over $CaCl_2$ and ether evaporated. Recrystallization of the residue from benzene afforded 102 mg (75%) of **16**, mp 52—53°.

Preparation of 11 and 12 from 6——A mixture of 195 mg of **6** in 2 ml of MeOH was warmed until the crystals dissolved, the solution was allowed to cool, and the crystals that precipitated out were collected and dried to 197 mg of **11** as colorless needles, mp 144—145°. *Anal.* Calcd. for $C_9H_7O_5N$: C, 51.68; H, 3.37; N, 6.70. Found: C, 51.72; H, 3.35; N, 6.72.

Similarly, 195 mg of **6** and 2 ml of EtOH afforded 3-ethoxy-4-nitrophthalide (**12**) as colorless needles, mp 134°, in 197 mg (95%) yield. *Anal.* Calcd. for $C_{10}H_9O_5N$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.85; H, 4.23; N, 6.30.

Catalytic Reduction of O-Nitrostyrene Oxide (13)——A solution of 165 mg of **13** dissolved in 20 ml of EtOH, added with 10 mg of PtO_2 or 20 mg of 10% Pd-C, was submitted to catalytic reduction. After completion of the reaction, the catalyst was filtered off, EtOH was evaporated from the filtrate at room temperature under a reduced pressure, and the residue was purified by column chromatography. When PtO_2 was used as catalyst, 113 mg (74%) of **18** and a small amount of resinous substance were obtained. In the case of 10% Pd-C, 136 mg of the starting **13** was recovered besides 18 mg of **17** and 13 mg of **18**. When Raney Ni (W2) was used, its 200 mg was added and the mixture was reacted in an autoclave at 80°, 22 atm for 12 hr, and 43 mg (31%) of **18** and 116 mg of unidentified resinous substance were obtained.

Acknowledgement The authors are indebted to the staff of the Central Analysis room and elemental analysis room of this College for the NMR and mass spectral measurements and for elemental analysis.