

Notes

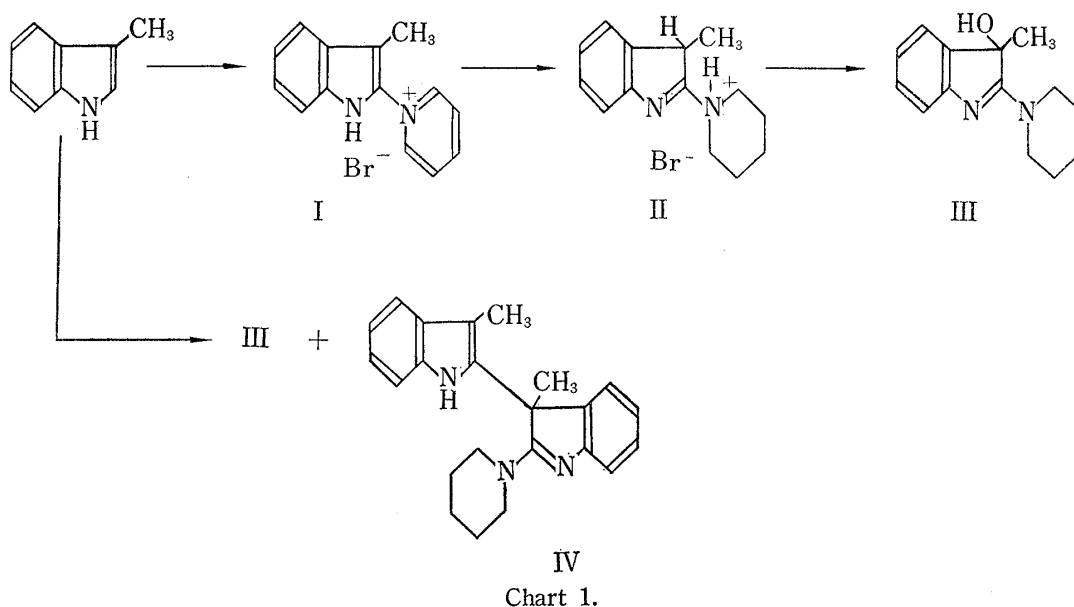
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Tohru Hino, Masako Nakagawa, and Sanya Akaboshi*¹ :
Bromination of Skatole. A Simple Preparation of
3-Methyloxindole and 2-Bromo-3-methylindole.*(Department of Pharmaceutical Sciences, National
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In the preceding paper¹⁾ we described that 1-(3-methyl-2-indolyl)pyridinium bromide (I) was obtained in excellent yield by the bromination of skatole with dioxane-dibromide in the presence of pyridine, and the pyridinium bromide was reduced catalytically to 2-piperidino-3-methyl-3*H*-indole hydrobromide (II) which was easily autoxidized to 3-hydroxy-3-methyl-2-piperidino-3*H*-indole (III) upon basification.



To extend the reaction skatole was treated with dioxane-dibromide in the presence of piperidine instead of pyridine. Any piperidino derivative (II or III) could not be isolated from the reaction mixture and piperidine hydrobromide was only isolable product. After several trials to modify the reaction condition, 3-hydroxy-2-piperidino derivative (III) was obtained in low yield by the simultaneous addition of dioxane-dibromide and piperidine into the ethereal solution of skatole in the presence of triethylamine.*²

The slight modification of the reaction condition did not improve the yield of III, but gave distinct nature of by products. In one experiment a crystalline by-product, m.p. 267~268°, was obtained and its structure was tentatively assigned as IV from the following facts: Its ultraviolet spectrum, λ_{\max} 282 m μ (ϵ 22700), showed the presence of skatole and 2-piperidino-3*H*-indole moieties, and its infrared spectrum showed the presence of C=N

*¹ Anagawa, Chiba-shi (日野 亨, 中川昌子, 赤星三弥).*² In the same reaction condition I was obtained in good yield when pyridine was used instead of piperidine (See experimental).1) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, S. Yamada: *Tetrahedron*, **23**, 1441 (1967).

double bond at 1545 cm^{-1} . The nuclear magnetic resonance (NMR) spectrum revealed the presence of piperidine ring (1.39 p.p.m. (broad singlet, 6H) and 3.31 p.p.m. (broad, 4H)), two methyl signals (1.99 p.p.m. (singlet, aliphatic Me) and 2.31 p.p.m. (singlet, aromatic Me)), and indolic NH (9.73 p.p.m. (broad)). And its molecular weight (343) was confirmed by the molecular ion peak of its mass spectrum.

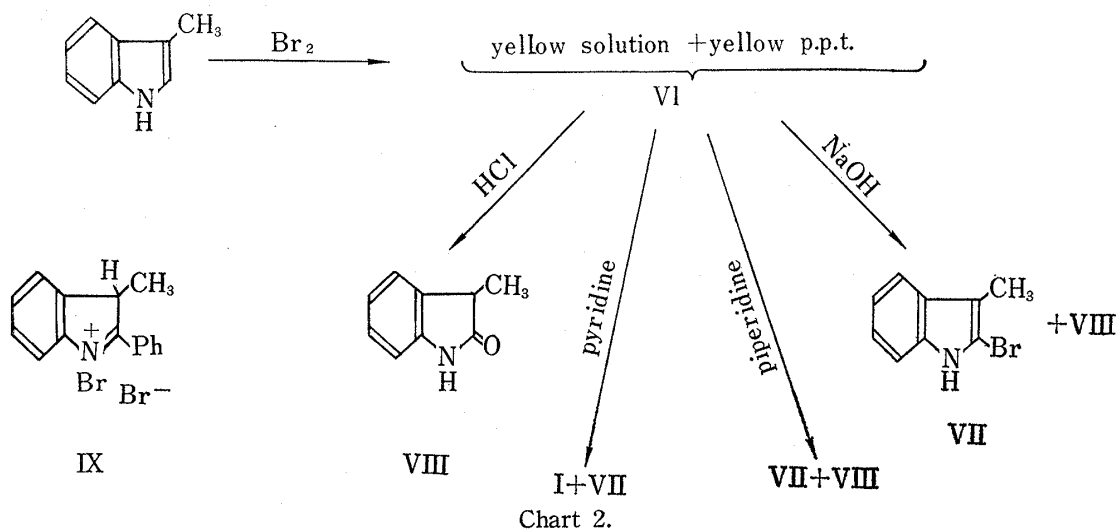
As a constant result was not obtained by this reaction, we examined a simple bromination of skatole with bromine in ether under low temperature. The bromination of skatole with NBS was investigated by Witkop,²⁾ Hinman,³⁾ and Kobayashi,⁴⁾ and reported to afford 2-bromoindole in anhydrous condition or 3-methyloxindole in wet conditions.

When one mole of bromine was added to an ethereal solution of skatole at -60° , a yellow solution with yellow precipitates (VI) was obtained. This yellow precipitates were highly unstable at room temperature and became resinous colored materials. This yellow intermediate gave I in low yield by treatment with an excess of pyridine at room temperature. By the addition of piperidine, however, the yellow intermediate gave 2-bromoskatole and 3-methyloxindole in 60% and 5% yield respectively, and piperidino derivative (II or III) could not be isolated.

The yield of 2-bromoskatole increased up to 70% when the intermediate was treated with 10% sodium hydroxide at room temperature, accompanying with 7% of 3-methyloxindole. As the separation of 2-bromoskatole from 3-methyloxindole and skatole was accomplished easily by column chromatography, this procedure might be another simple method of preparation of 2-bromoskatole.

On the other hand, 3-methyloxindole was obtained in 20% yield beside 2-bromoskatole (35%) when the intermediate was treated with 10% hydrochloric acid at room temperature. 3-Methyloxindole was isolated in 78% yield when the intermediate was treated with 10% hydrochloric acid and refluxed for 3 hours. The yield was better than that obtained by the bromination of skatole with NBS in *tert.* butanol. This procedure might be an alternative method for the preparation of 3-methyloxindole from skatole.

A similar yellow precipitates was isolated by Witkop²⁾ in the bromination of 3-methyl-2-phenylindole with bromine in acetic acid as an intermediate to 6-bromo-3-methyl-2-phenylindole and its structure was assigned to N-bromoindolenium bromide (IX). However, the structure of the yellow intermediate in this paper was ambiguous due to its highly unstable nature.



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3) R. L. Hinman, C. P. Bauman: *J. Org. Chem.*, **29**, 1206 (1964).

4) T. Kobayashi, N. Inokuchi: *Tetrahedron*, **20**, 2055 (1964).

Experimental*3

Bromination of Skatole with Dioxane-dibromide in the Presence of Piperidine: Formation of III and IV—To a stirred solution of 1.3 g. (0.01 mole) of skatole and 1.0 g. (0.01 mole) of Et_3N in 60 ml. of anhyd. ether, cooled to $-15\sim 16^\circ$, was added a solution of 0.52 ml. of bromine in 30 ml. of dioxane and 860 mg. (0.01 mole) of piperidine by the following way; About 2/3 volume of dioxane- Br_2 solution was added to the above solution within 1 min., immediately followed by about 1/3 volume of piperidine, and then the rest of dioxane- Br_2 solution, and the rest of piperidine, in turn, was added. The ethereal solution was washed with NaCl aq. solution, diluted with 30 ml. of CH_2Cl_2 and extracted with 10% HCl . The aqueous layer was basified with NaHCO_3 and extracted with CH_2Cl_2 . The CH_2Cl_2 extracts were washed, dried, and evaporated. Crystallization of the resulting solid, 170 mg. (7.4%), from acetone yielded colorless needles of III, m.p. $205\sim 206^\circ$, identical in all respects with a sample¹⁾ prepared previously. The ether- CH_2Cl_2 layer was neutralized with aq. NaHCO_3 , washed, dried, and evaporated to leave 1.35 g. of residue, which was crystallized to give 340 mg. (19%) of colorless crystals, m.p. $258\sim 259^\circ$. Recrystallization from MeOH gave colorless needles (IV), m.p. $267\sim 268^\circ$. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_3$: C, 80.43; H, 7.34; N, 12.23. Found: C, 80.49; H, 7.29; N, 11.68. UV $\lambda_{\text{max}}^{\text{95\% EtOH}}$ m μ (ϵ): 230 (46800), 282 (22700), 292 (19900). IR $\nu_{\text{max}}^{\text{KBr}}$ 1545 cm^{-1} (C=N). NMR (in CDCl_3 , p.p.m. from TMS): 1.39 (6H, β , and γ protons of piperidine ring), 1.99 (singlet, 3H, Me on indolenine), 2.31 (singlet, 3H, Me on indole ring), 3.31 (broad doublet, 4H, α protons in piperidine ring), 7.04~7.46 (multiplet, 8H, aromatic protons), 9.73 (broad singlet, 1H, NH). Mass spectrum: M^+ 343.

1-(3-Methyl-2-indolyl)pyridinium Bromide (I)—To a stirred solution of 1.3 g. (0.01 mole) of skatole and 1.0 g. (0.01 mole) of Et_3N in 30 ml. of anhyd. ether, cooled to -10° , was added a solution of 0.52 ml. of Br_2 in 30 ml. of dioxane and 800 mg. (0.01 mole) of pyridine in the same manner as described for III, except that the reaction mixture was stirred for 1.5 hr. at room temperature. The resulting yellow precipitate was collected and recrystallized from EtOH to give 1.33 g. (46%) of yellow needles (I), m.p. $250\sim 252^\circ$ (decomp.), which was shown to be identical with an authentic sample¹⁾ of I by comparison of spectra as well as a mixed melting point test.

Preparation of 2-Bromo-3-methylindole (VII)—To a solution of 6.5 g. (0.05 mole) of skatole in 70 ml. of anhyd. ether, cooled to -60° with dry-ice: acetone, was added with shaking 2.6 ml. (0.05 mole) of Br_2 within 3 min. to afford yellow precipitates. The reaction mixture was kept at -60° with occasional shaking for 10 min., at which time 20 ml. of 10% NaOH was added and warmed up to room temperature. The ethereal solution was neutralized with dil. HCl , washed, dried, and evaporated to dryness to leave 9.35 g. of a solid which was taken up in hexane-benzene (4:1) and chromatographed on 200 g. of alumina. Elution with hexane-benzene (4:1) furnished 7.3 g. (70%) of colorless crystals, which was recrystallized from aq. AcOH to give 6.5 g. of colorless needles of VII, m.p. $88\sim 90^\circ$, which were identified by spectral data (IR, UV and NMR) and TLC as well as gas chromatography with an authentic specimen prepared by Hinman's method.³⁾

Preparation of 3-Methyloxindole (VIII)—To a solution of 13.0 g. (0.1 mole) of skatole in 150 ml. of anhyd. ether, cooled to -60° , was added with shaking 5.2 ml. (0.1 mole) of Br_2 within 5 min. and the reaction mixture was kept at -60° for 10 min., at which time 40 ml. of 10% HCl was added and the ether was evaporated under reduced pressure. Small amount of EtOH was added to the mixture to dissolve the separated oil in H_2O and the solution was refluxed for 3 hr. and the solvent was concentrated. The residue was taken up in CH_2Cl_2 , neutralized, washed, and dried. The solvent was removed and the residue was crystallized from EtOH to give 7.3 g. of pale yellow crystals, m.p. $101\sim 105^\circ$, and 2.61 g., m.p. $105\sim 110^\circ$, of second crops on concentration of the mother liquor. Recrystallization from EtOH gave colorless needles of VIII, m.p. $123\sim 124^\circ$ (reported m.p. $123.8\sim 124.6^\circ$ ⁵⁾). *Anal.* Calcd. for $\text{C}_9\text{H}_9\text{ON}$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.63; H, 5.77; N, 9.96. Its IR, UV and NMR spectral data were identical with those of an authentic specimen.⁵⁾

The residue (3.55 g.) obtained on evaporation of the mother liquor was dissolved in benzene and chromatographed on 20 g. of silica gel prepared in benzene. Elution with CH_2Cl_2 furnished 1.54 g. of VIII, totaling 11.45 g. of VIII in 78% yield.

When a brominated intermediate was treated with 10% HCl at room temperature, VII and VIII were obtained in 35% and 20% yields respectively.

Reaction of Yellow Intermediate with Piperidine: Formation of VII and VIII—To a brominated solution of 6.5 g. (0.05 mole) of skatole in ether prepared by the previous method, was added 5 ml. of piperidine. The reaction mixture was brought to room temperature and washed with 10% HCl and neutralized with NaHCO_3 , washed, dried, and evaporated to dryness to give 9.18 g. of a solid, which was chromatographed on 60 g. of silica gel prepared in hexane-benzene (4:1). Elution with hexane-benzene (4:1) gave 6.3 g. (60%) of

*3 All melting points are uncorrected. The IR spectra were taken with a JASCO DS-301 spectrophotometer, and the UV spectra were measured with a Perkin-Elmer 202 or Cary Model 14, and the NMR spectra were measured with a Varian Associate HR-100 spectrometer.

5) A. S. Endler, E. I. Becker: *Org. Syntheses Col. Vol. IV* 657 (1963).

VII and 2.25 g. (35%) of skatole. Further elution of the column by CH_2Cl_2 -AcOEt (1:1) provided 433 mg. (5.9%) of VIII.

When pyridine was added to a brominated solution, small amount of I was obtained besides VI.

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Tadahiro Iwashige and Hiromichi Saeki*¹: Benzylolation of Carbohydrate Derivatives in Dimethyl Sulfoxide.*²

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Alkylation which is an essential procedure in the carbohydrate chemistry mainly consisting of methylation and benzylolation; the former is worth structural determination and the latter is useful as an important synthetic procedure.

Various reaction conditions of benzylolation have been described in the literature.^{1,2)} Some attempts were carried out under milder conditions recently, where silver oxide³⁾ or sodium hydride⁴⁾ in dimethylformamide, sodium hydride in the absence of solvent^{5,6)} have been employed. Further, the elegant benzylolation⁷⁾ of acetyl carbohydrate derivatives has been reported. As inferred from these results obtained so far, relatively excessive basic reagents and benzyl halogenides are employed, and longer reaction periods, sometimes higher temperature, are required, and satisfactory yields are not obtained constantly depending greatly on the carbohydrate derivatives and the reaction conditions. Therefore, it is desirable for benzylolation to be done with less basic reagent and benzyl halogenide, at mild temperature for a short reaction period to get good yields.

Now, it is known that the dimethyl sulfoxide promotes the rate of substitution reaction. Although several reports⁸⁾ on the more effective and competitive methylation of some monosaccharides and polysaccharides in aprotic solvents such as dimethylformamide or dimethyl sulfoxide with some basic reagents, comparing with the classical methods of Haworth⁹⁾ and Purdie,¹⁰⁾ have been already published, studies on the benzylolation of carbohydrate derivative in dimethyl sulfoxide have not been made.

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