As mentioned above, our methods are much superior to the conventional ones,[8,13–15] in reaction time, simplicity, purity and yield.

We could increase the reaction size up to 100 mmoles of thiols without any decrease of yields, although variation of the ratio of $ClSO_3H$ or acetic acid to thiol led to reduce yields.

Acknowledgements We would like to thank Analytical Laboratory of this faculty for analysis of carbon, hydrogen and nitrogen, and also Chugai Co. Ltd. for analysis of sulfur. We are grateful to Mr. Yazawa for his assistance in our work.

[Chem. Pharm. Bull.
22(11)2728—2731(1974)]

UDC 547.751.04 : 546.15.04

Reaction of Skatole with Iodine in the Presence of Thiourea

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(Received April 30, 1974)

The reaction of 3-carboethoxy-2,4-dimethylpyrrole (**1**) and other pyrrole derivatives with I_2-KI in the presence of thiourea has been investigated to give S-(α or β-pyrryl)-pseudothiourea hydroiodides such as **2**.[2] The reaction was successfully applied to indole (**3**) and 3-mercaptoindole (**5**) was prepared *via* 3-indolylpseudothiourea hydroiodide (**4**) in excellent yield. The intermediacy of sulfenyl iodide (**6**), which presumably be formed by the reaction of thiourea with iodine, has been postulated to react with pyrrole or indole to form pseudothiourea derivatives.

This results led us to investigate the similar reaction of 3-alkylindoles in the hope that a new synthetic route to 2-indolinethiones[3] *via* **7** might result. We describe here the reaction of skatole with iodine in the presence of thiourea.

When a solution of skatole (**8**) and thiourea in aqueous ethanol was treated with one mole of iodine solution following the Haris procedure, a number of products were obtained unexpectedly. Separation of the products by column chromatography and fractional recrystallizations yielded the expected pseudothiourea (**9**, 12%), mp 204—205°, 3-oxindolylpseudothiourea (**10**, 23%), mp 134—135.5°, a dimeric product (**11**, 13%), 2-indolyl sulfide (**12**, 2%), oxindole (**13**, 3%), and the dioxindole (**14**, 6%). The structure of **9** was elucidated from correct elemental analysis and the following spectral data. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ε): 219 (46700), 284 (12500). IR (KBr) cm^{-1}: 3430—3100 (multiplets, NH), 1654 (C=N). NMR (D_2O): δ 2.33 (s, 3H, CH_3). Further confirmation of structure **9** was obtained by the comparison with an authentic specimen prepared by the reaction of 2-bromoskatole (**15**) with thiourea in the presence of an acid.[4]

The compound (**10**) showed $\lambda_{\text{max}}^{\text{EtOH}}$ at 214 (37600) and 295 (1400) nm, similar to those of 3-bromo-3-methyloxindole.[5] The infrared (IR) spectrum of **10** was consistent with the suggested structure and in particular, the new band at 1700 cm^{-1} and the bands at 1654, 3400—3100 cm^{-1} in its spectrum supported the presence of a carbonyl and a pseudothiourea, res-

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1) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
2) R.L.N. Haris, *Tetrahedron Letters*, **1969**, 4465; *idem*, *Austr. J. Chem.*, 23, 1199 (1970).
3) T. Hino, K. Tsuneoka, M. Nakagawa, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 550 (1969); T. Hino, T. Suzuki, S. Takeda, N. Kano, Y. Ishii, A. Sasaki, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2739 (1973).
4) T. Hino, M. Tonozuka, and M. Nakagawa, *Tetrahedron*, **30**, 2123 (1974).
5) R.L. Hinman and C.P. Bauman, *J. Org. Chem.*, **29**, 2431 (1964).

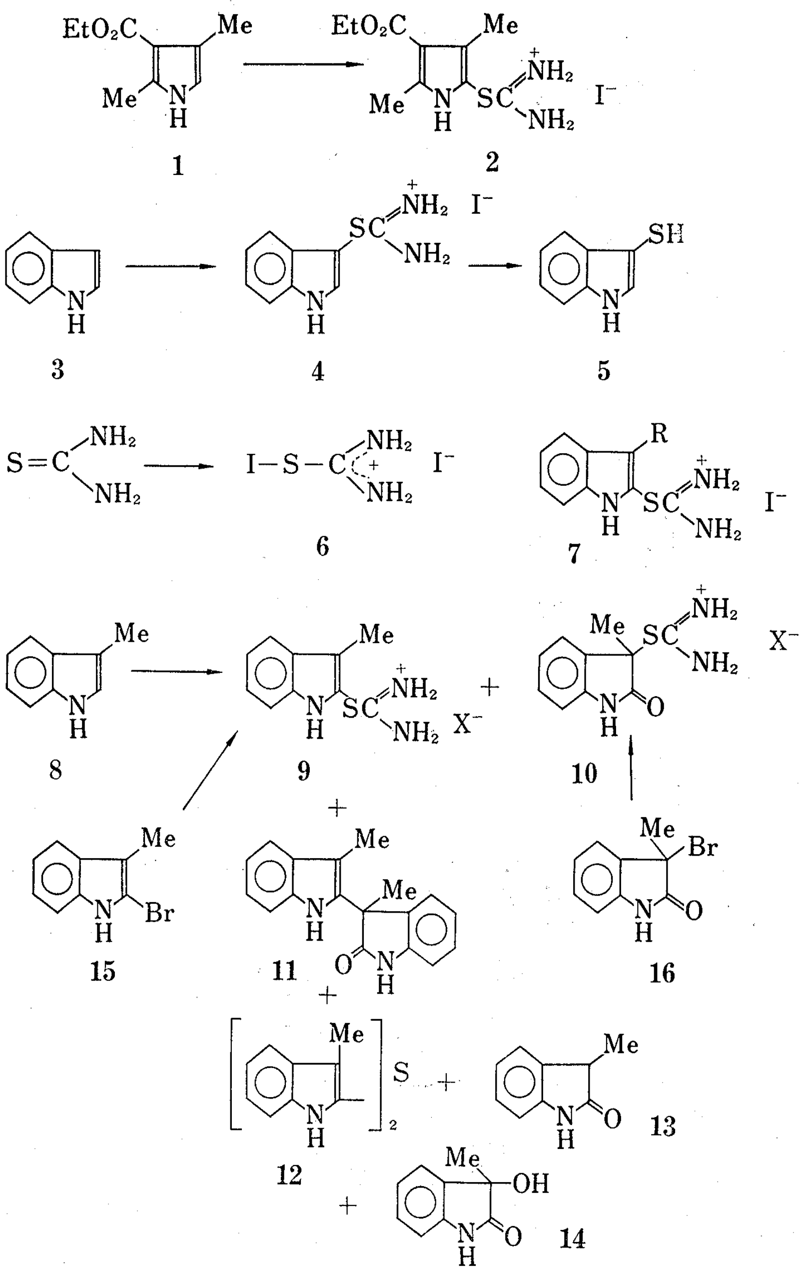

Chart 1

pectively. The nuclear magnetic resonance (NMR) spectrum (D_2O) of **10** showed a singlet due to C_3–CH_3 at 1.93 ppm. The structure of **10** was confirmed by comparisons of spectral data and by its undepressed mixed melting point with an authentic specimen prepared by the reaction of 3-bromo-3-methyloxindole (**16**) with thiourea. The structures of the other compounds, **11**, **12**, **13**, and **14** were identified by the comparison with standard samples. In spite of the wide variation in the reaction conditions, the yield of **9** was not increased.

In our previous report, we described the oxidation of 2-ethanesulfonyl-3-methylindoles (**17**) with hydrogen peroxide in acetic acid to give the oxindole (**18**) accompanying migration of the substituent at 2-position.[6] However, when **9** was treated with iodine in aqueous ethanol, **10** was not formed. This explains **10** has not been obtained by the similar oxidative rearrangement of **9**. Moreover, sluggishness of the reaction of **8** with iodine in absence of thiourea excludes initial formation of oxindole (**13**) which then converts to **10** *via* 3-iodo deriva-

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[6] T. Hino, H. Yamaguchi, and M. Nakagawa, *Chem. Commun.*, **1972**, 473.

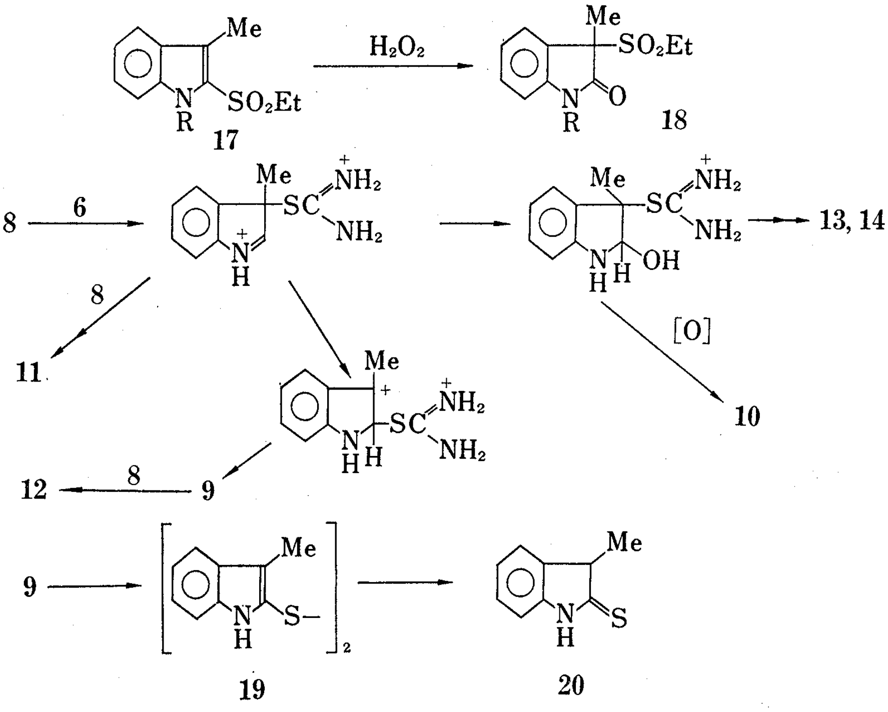

Chart 2

tive. Thus mechanistic pathways for the formation of the products may be depicted as in chart.

Although the reaction of **8** with iodine in the presence of thiourea did not give a satisfactory yield, an alternative route to obtain **9** *via* **15** may serve as a possible way to 3-methyl-2-indolinethione (**20**). This was carried out by alkaline hydrolysis of **9** to give the corresponding disulfide (**19**) which is known to be easily reduced to **20** with $NaBH_4$.[3]

Experimental[7]

Reaction of Skatole (8) with I_2-KI in the Presence of Thiourea——To a stirred solution of **8** (1.31 g, 0.01 mole) and thiourea (0.76 g, 0.01 mole) in EtOH (35 ml) and H_2O (5 ml) was added I_2 solution (20 ml) (prepared from I_2 (12.7 g) and KI (25 g) in H_2O (100 ml)) at 25—30° during 20 min under cooling. The color of the iodine solution faded immediately after the addition. The mixture was stirred at room temperature for 2 hr and the ethanol was evaporated. The aqueous solution was extracted with benzene (benzene extracts). The aqueous solution was condensed to give **10** (X=I, 652 mg), mp 135—136°, and the mother liquor was condensed *in vacuo* to precipitate **9** (X=I, 246 mg), mp 203—204°. The mother liquor was extracted with CH_2Cl_2 and the aqueous layer was condensed again to give a mixture of **9** and **10** (354 mg) as colorless crystals, mp 123—126°. The ratio of intensities of two methyl signals in the NMR spectrum of the mixture indicated that it was consisted of **9** (136 mg) and **10** (218 mg). Total yield of **9**: 380 mg (11.6%); **10**: 870 mg (23%). The crude **9** (X=I) was recrystallized from H_2O to give an analytical specimen, mp 204.5—205° (decomp), as colorless crystals. *Anal.* Calcd. for $C_{10}H_{12}N_3SI$: C, 36,05; H, 3.60; N, 12.62. Found: C, 36.19; H, 3.66; N, 12.57. UV λ_{max}^{EtOH} nm (ε): 219 (46700), 284 (12500); λ_{min} 252 (3200) nm. IR (KBr) cm^{-1}: 3430, 3250, 3220, 3180, 3130 (NH), 1654, 1613 (C=N). NMR (D_2O, TMS as an external standard); δ 2.23 (s, 3H, CH_3), 7.0—8.0 (m, 4H, arom. H). Mass Spectrum: *m/e* (relative abundance), 254 (**9**, I_2), 205 (8, M-HI), 163 (41), 130 (100, M-(thiourea+I)), 128 (65), 127 (46), 103 (25), 78 (44). The crude **10** (X=I) was recrystallized from H_2O to give an analytical specimen, mp 134—135.5° (decomp), as colorless crystals. *Anal.* Calcd. for $C_{10}H_{12}ON_3SI \cdot H_2O$: C, 32.71; H, 3.84; N, 11.44. Found: C, 32.81; H, 3.72; N, 11.60. UV λ_{max}^{EtOH} nm (ε): 214 (37600), 295 (1400); UV λ_{min} 279 (700). IR (KBr) cm^{-1}; 3020, 3180, 3400, 3500 (NH), 1624, 1654 (C=N), 1700 (C=O). NMR (D_2O, TMS as an external standard); δ 1.93 (s, 3H, CH_3), 7.0—7.6 (m, 4H, arom. H). Mass Spectrum;

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[7] All melting points are uncorrected. The IR spectra were taken with a Hitachi-G-3 spectrophotometer, the ultraviolet (UV) spectra were measured with a Hitachi EPS-3T spectrophotometer, the NMR spectra were recorded on a JEOL-4H-100 spectrometer, and the mass spectra were taken with a Hitachi RMU-6 spectrometer.

m/e (relative abundance); 254 (14, I_2), 147 (36, M-(thiourea+I)), 128 (86), 119 (100, 147-CO), 91 (33). The CH_2Cl_2 extracts gave an oil (152 mg) on evaporation, which was separated by preparative thin-layer chromatography (TLC) (silica gel/CH_2Cl_2–acetone (10: 1)). 3-Methyloxindole (**13**) (58 mg, 3.4%), mp 121—122°, was obtained from the less polar zone, and 3-methyldioxindole (**14**) (21 mg) was isolated from the polar zone. The both samples were identical with standard samples (IR). The above benzene extracts were evaporated in vacuo to leave a brown oil (543 mg) which was chromatographed on silica gel (10 g). The first elution with benzene–hexane (1: 1) gave a mixture (230 mg) which was further separated by preparative TLC (silica gel/benzene–hexane (1: 1)). From the less polar zone skatole (150 mg) was recovered, and bis(3-methyl-2-indolyl)sulfide (**12**) (32 mg, 2.2%), mp 125—127°, was obtained from the polar zone. The latter was confirmed by comparison with a standard sample[8] (mmp and IR). The second elution with benzene–hexane (1: 1) gave a dimeric product (**11**) (200 mg, 13%), mp 196—216°. Recrystallizations from EtOH–H_2O gave pure **11**, mp 215—218° (reported[9] mp 224—225°), whose IR and UV spectra were in agreement with those reported in the literature. The third elution gave **14** (68 mg, total 89 mg, 5.5%).

An Alternative Synthesis of 3-Methyl-2-indolylpseudothiourea HI (9)——To a mixture of 2-bromoskatole (**15**)[10] (1.69 g, 8 mmoles) and thiourea (6 g. 80 mmoles) in EtOH (60 ml) was added 47% HBr (3 ml) at room temperature. The mixture was stirred at room temperature for 2 hr and the resulted precipitates (thiourea, 1.04 g) was collected. The combined filtrate and washings were evaporated *in vacuo* to leave a residue which was chromatographed on silica gel (80 g). The first elution with CH_2Cl_2–MeOH (10: 1) gave colorless crystals (300 mg) which showed two spots on TLC. Recrystallization from H_2O gave the bromide (**9**, X=Br, 200 mg), mp 176—181° which showed a single spot on TLC. The second elution with the same solvent gave the bromide (**9**, X=Br, 1.66 g), mp 178—180°. The third elution gave further **9** (X=Br, 200 mg, total 2.06 g, 90%). The crude **9** (X=Br) was recrystallized from EtOH–ether gave an analytical sample, mp 204—207° (decomp). *Anal.* Calcd. for $C_{10}H_{12}N_3SBr$: C, 41.95; H, 4.26; N, 14.63; Br, 27.92. Found: C, 42.02; H, 4.21; N, 14.97; Br, 28.05. UV λ_{max}^{EtOH} nm (ε): 220 (32900), 284 (13800), 295^{sh} (11000); UV λ_{min} 251 (3400). IR (KBr) cm^{-1}; 3452, 3300, 3210, 3160, 3130 (NH), 1660, 1620 (C=N). NMR (D_2O, TMS as an external standard); δ 2.30 (s, 3H, CH_3), 7.25—7.70 (m, 4H, arom. H). Mass Spectrum; *m/e* (relative abundance); 205 (10, M-HBr), 163 (95, M-(HN=C=NH+HBr), 162 (69), 130 (100, M-(thiourea+Br)). An excess of KI was added to an aqueous solution of **9** (X=Br) to give **9** (X=I), mp 203—204° (decomp.), which was identical with the sample obtained above (IR and mmp).

An Alternative Synthesis of S-(3-Methyl-3-oxindolyl)pseudothiourea HI (10)——To a solution of 3-bromio-3-methyloxindole (**16**)[5] (550 mg, 2.4 mmoles) in anhyd *t*-BuOH (30 ml) was added thiourea (185 mg, 2.4 mmoles) in *t*-BuOH (50 ml) at room temperature during 10 min. The mixture was stirred at room temperature for 16 hr, and evaporated in vacuo to leave a residue. Recrystallizations from MeOH–benzene gave the bromide (**10**, X=Br, 493 mg, 62%), mp 183—185°. An excess of KI was added to an aqueous solution of **10** (X=Br, 100 mg) to give precipitates. The precipitates were collected and recrystallized from H_2O to give **10** (X=I, 110 mg, 96%), mp 138—140°, as yellow needles. Further recrystallizations from H_2O gave **10** (X=I), mp 134—135° (decomp.), which was identical with the sample obtained above (IR and mmp).

Reaction of 9 with I_2——To a stirred solution of **9** (X=I, 670 mg, 2 mmoles) in EtOH (8 ml) and H_2O (4 ml) was added I_2 solution (4 ml, 2 mmoles) (prepared from I_2 (12.7 g) and KI (25 g) in H_2O (100 ml)). The mixture was stirred at room temperature for 4 hr and evaporated in vacuo. The black oily residue was chromatographed on silica gel (10 g). Elution with benzene gave recovered I_2. Elution with CH_2Cl_2–MeOH (10: 1) gave crude **9** (640 mg) which was recrystallized from H_2O to give brown crystals (590 mg, 88%). Further recrystallization from EtOH–ether gave colorless **9**, mp 204.5—207° (decomp.) which was identical with the starting material (IR).

Alkaline Hydrolysis of 9——To a solution of **9** (X=I, 283 mg) in EtOH (10 ml) was added 10% NaOH (0.6 ml) and the mixture was refluxed for 5 min under N_2. The solvent was evaporated and the residue was extracted with benzene and H_2O. The benzene solution was washed with H_2O, dried and evaporated to leave a residue which was separated by preparative TLC (silica gel/benzene–hexane (1: 1)). The least polar zone afforded 2-indolyl disulfide (**19**) (63 mg) which was recrystallized from iso-PrOH to give **19**, mp 121—123°. This was identical with a standard sample[8] (IR and mmp.)

Acknowledgements We are indebted to the Ministry of Education for a Grand-in-Aid for Scientific Research (847088) which support this investigation. We also thank to Misses H. Ohida, N. Kikuchi, F. Ishida, and Mrs. S. Yamaguchi in our University for elemental analysis and mass and NMR measurements.

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8) T. Wieland, O. Weiberg, E. Fischer, and G. Horlein, *Ann.*, **587**, 146 (1954).
9) J.C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).
10) R.L. Hinman and C.P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).