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2-Indolinethiones. Tautomerism and Oxidation to the Disulfides[1]

Tohru Hino, Toshikazu Suzuki, and Masako Nakagawa

Faculty of Pharmaceutical Sciences, Chiba University[2]

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The thione-thiol tautomerism and the oxidation of the 2-indolinethione have been studied. The ultraviolet (UV) and nuclear magnetic resonance spectra of 3-aryl-2-indolinethiones disclosed the predominance of their thiol form in various solvents, while the oxo form was the sole species in the 3-phenyloxindole. However, the spectral data of 1-methyl-3-aryl-2-indolinethiones showed the predominance of the thione form in solution.

The oxidation of the 2-indolinethiones with oxygen to the corresponding disulfide in EtOH has been followed by the oxygen uptake and the UV spectral change. The oxidation of 3-(*p*-nitrophenyl)-2-indolinethiones (**5** and **9**) was very rapid, while 3-*tert*-butyl-(**14**), 1-methyl-(**11**), and 2-indolinethione (**10**) resisted the oxidation. Other 2-indolinethiones were oxidized to the disulfide at moderate speed. The prolonged oxidation of **11** gave a small amount of 3-oxo-2-indolinethione (**18**) instead of the disulfide.

In the previous paper[3] we described the preparation of 3-substituted 2-indolinethiones by the reduction of diindolyl disulfides. We now discuss the thione-thiol tautomerism and the airoxidation of these 2-indolinethiones.

The Thione-thiol Tautomerism of 2-Indolinethiones

The oxindole has been known to exist mostly as the oxo form (**1a**) from the spectral data.[4] We reported that the ultraviolet (UV) and the nuclear magnetic resonance (NMR) spectra of methyl substituted 2-indolinethiones showed the thione form (a) was predominant in solution.[5] Furthermore, we found the presence of a small amount of the thiol form in the NMR spectra of 3-methyl-2-indolinethione (**11**).[5] In present paper we examined the tautomerism of 3-aryl-2-indolinethiones whose thiol forms were assumed to be more stable than that of the 3-methyl derivative.

The UV spectra of 3-phenyl-2-indolinethione (**2**) in various solvents are shown in Fig. 1. The methanolic solution of **2** showed a maximum at 292 nm which is similar to that of 2-ethylthio-3-phenylindole, a model compound for the thiol form, and is different from that of typical 2-indolinethione such as 1,3-dimethyl-2-indolinethione[5] which has a maximum at 318 nm in 95% EtOH. In ethanol **2** showed the maximum at 323 nm which is similar to that of the typical 2-indolinethione, but a shoulder at 300 nm indicates the presence of the thiol form. However the spectrum taken in chloroform reverts to a thione type with a maximum at 325 nm. Similar solvent effects were observed in the UV spectra of 3-(*p*-methoxyphenyl)-2-indolinethione (**3**) which are shown in Fig. 2. The spectrum taken in benzene immediately after dissolving **3** is a thione type and changed to a thiol type as shown in the Fig. 2 after 30 min. The gradual UV spectral change of **3** in benzene from the thione to the thiol form during 30 min is shown in Fig. 3. These results may be explained as follows. The

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[1] A part of this paper has been published as a communication: T. Hino, M. Nakagawa, T. Suzuki, S. Takeda, N. Kano, and Y. Ishii, *Chem. Commun.*, **1971**, 836.

[2] Location: *Yayoi-cho, Chiba-shi, 280, Japan.*

[3] T. Hino, T. Suzuki, S. Takeda, N. Kano, Y. Ishii, A. Sasaki, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 2739 (1973).

[4] A.R. Katritzky (ed.), "Advances of Heterocyclic Chemistry," Vol. 2, Academic Press New York, 1963, Chapter 1.

[5] T. Hino, K. Tsuneoka, M. Nakagawa, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **17**, 550 (1969).

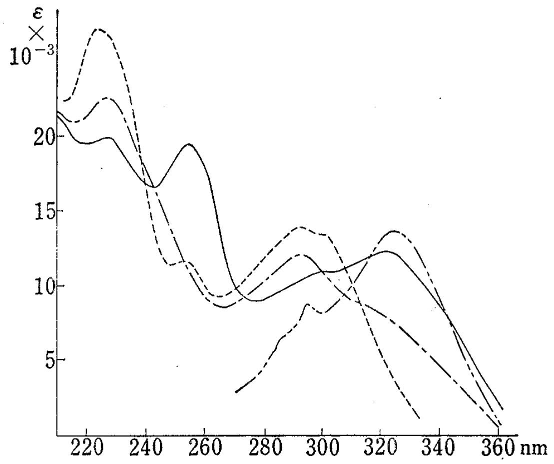

Fig. 1. The UV Spectra of 3-Phenyl-2-indolinethione

———: EtOH
———: MeOH
– – – –: $CHCl_3$
- - - - - -: 2-ethylthio-3-phenylindole in EtOH

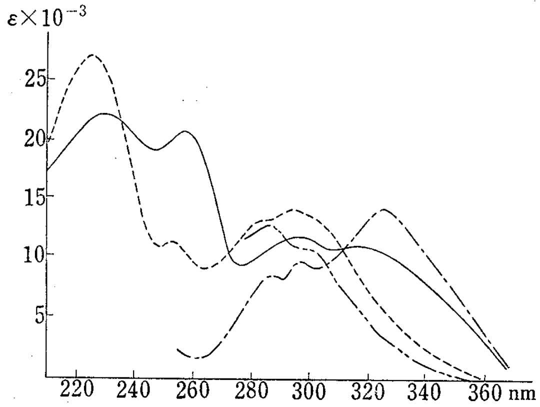

Fig. 2. The UV Spectra of 3-(*p*-Methoxyphenyl)-2-indolinethione

———: EtOH
– – – –: $CHCl_3$
– – – –: benzene
- - - - - -: 2-ethylthio-3-phenylindole in EtOH

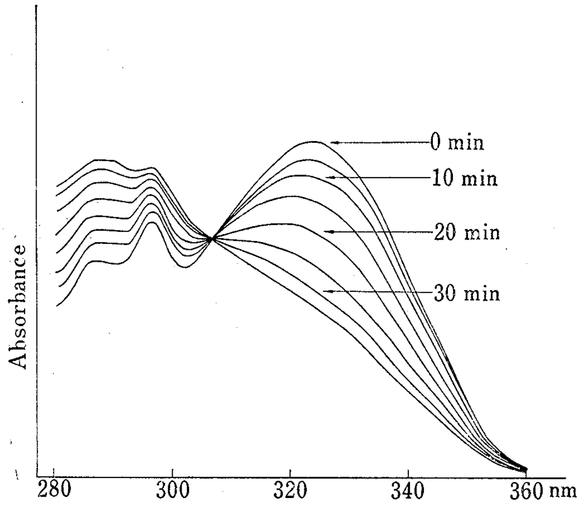

Fig. 3. The UV Spectral Change of 3-(*p*-Methoxyphenyl)-2-indolinethione (3) in Benzene

crystals of **3** possess the thione form which is also predominant in fresh benzene solution, but the solution reaches slowly to the equilibrium where the thiol form is predominant. On the other hand the equilibrium in ethanolic solution of **3** is established rapidly at the middle between the thione and the thiol form.

Presence of the thiol form in these compounds was further demonstrated in the NMR spectra in deuterochloroform and benzene (Table I). The NMR spectrum of 3-phenyl-2-indolinethione (**2**) in deuterochloroform showed two singlets at 3.41 and 4.89 ppm corresponding to that of SH in the thiol form and that of 3-H in the thione form. Other two broad singlets corresponding to NH in the thiol and the thione form were observed at 8.10 and 10.01 ppm. Chemical shifts of 3-H and NH of the thione form were similar to those of methylsubstituted 2-indolinethiones. Intensities of these signals indicate the ratio of the thione and the thiol form in deuterochloroform is roughly 1: 2. In benzene signals for 3-H and SH shifted to higher fields and the ratio is increased to 1: 4. Nearly the same feature was obtained from the NMR spectra of 3-(*p*-methoxyphenyl)-2-indolinethione (**3**) in which the singlet due to the methoxy group made clear to find out the ratio.

The corresponding oxindole, 3-phenyloxindole, is known to have the UV maxima at 249 and 286 nm in dioxane,[6] an oxindolic chromophore. The NMR spectrum of 3-phenyloxindole in deuterochloroform showed a singlet at 4.58 ppm for 3-H, and a broad singlet at 9.10 ppm for NH of the oxindole, and no other signal corresponding to 2-hydroxy-3-phenylindole. This indicated that the 3-phenyl group made possible to detect the presence of the thiol form in

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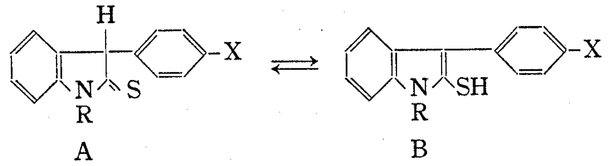
6) J.M. Bruce and F.K. Sutcliffe, *J. Chem. Soc.*, **1957**, 4789; J.M. Bruce, P. Knowles, and L.S. Besford, *ibid.*, **1964**, 4044.

Table I. The NMR Spectra of 3-Aryl-2-indolinethiones (ppm from TMS)



Compd. No.	R	X	Solv.	B NH	B SH	B NMe (OMe)	A NH	A 3-H	A NMe (OMe)	B/A
2	H	H	c($CDCl_3$)	8.10	3.41	—	10.01	4.89	—	2
			b(C_6H_6)	—	2.84	—	—	4.50	—	4
6	Me	H	c	—	3.28	3.85	—	4.90	3.65	1/10
			b	—	2.72	3.14	—	4.60	3.08	1/4
3	H	OMe	c	8.05	3.38	3.83	9.97	4.83	3.75	2
				—	2.90	3.41	—	—	3.30	4
7	Me	OMe	c	—	—	3.83(O)	—	4.87	3.66(N) 3.77(O)	1/5
			b	—	—	3.20(N) 3.43(O)	—	4.65	3.11(N) 3.29(O)	1/6
4	H	Br	c	8.15	3.39	—	—	4.85	—	3
			b	—	2.79	—	—	4.35	—	5
8	Me	Br	c	—	3.25	3.89	—	4.90	3.68	1/7
			b	—	2.63	3.20	—	4.49	3.11	1/4
9	Me	NO_2	c	—	3.27	3.89	—	5.01	3.61	1/4

the 2-indolinethione, but not in the oxindole.

The UV spectra of 3-(*p*-nitrophenyl)-2-indolinethione (**5**) in various solvents are shown in Fig. 4. The spectra taken in benzene, chloroform and ethanol–hydrochloric acid are corresponded to that of 2-ethylthio derivative,[3] indicating the thiol form predominates in these solvents. However, maxima at 320 and 510 nm are observed in 95% ethanol. The similar spectrum was obtained in chloroform–triethylamine solution. These maxima may be attributed to contributions of the structures, **c**, **d** and **g** shown in Chart 2. Therefore information on the thiol and thione tautomerism in ethanol is not clear from the UV spectra. The NMR spectra of **5** in deuterochloroform gave a poor spectrum due to the low solubility, but two singlets at 3.49 and 2.85 ppm corresponding to 3-H of the thione form and SH of the thiol form were observed. The oxindole analog, 3-(*p*-nitrophenyl) oxindole (**17**), was prepared from 3-(*p*-nitropheny)indole (**15**) *via* 2-bromo derivative (**16**). This compound showed an oxindolic chromophore with the maxima at 260 (ε 13900), and 275^{sh} (11700) nm in ethanol.[7]

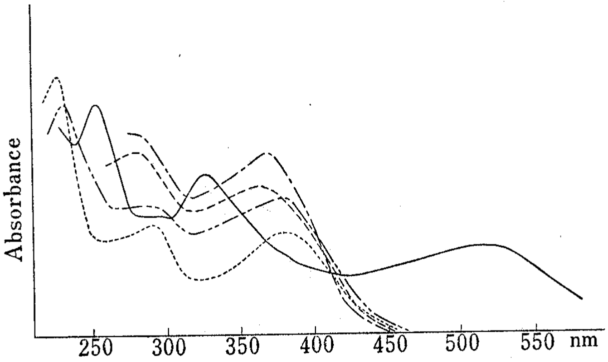


Fig. 4. The UV Spectra of 3-(*p*-Nitrophenyl)-2-indolinethione

——— : EtOH
- - - - - : $CHCl_3$
—·—·— : benzene
—··—··— : EtOH-HCl
············ : 2-ethylthio-1-methyl-3-(*p*-nitrophenyl)indole in EtOH

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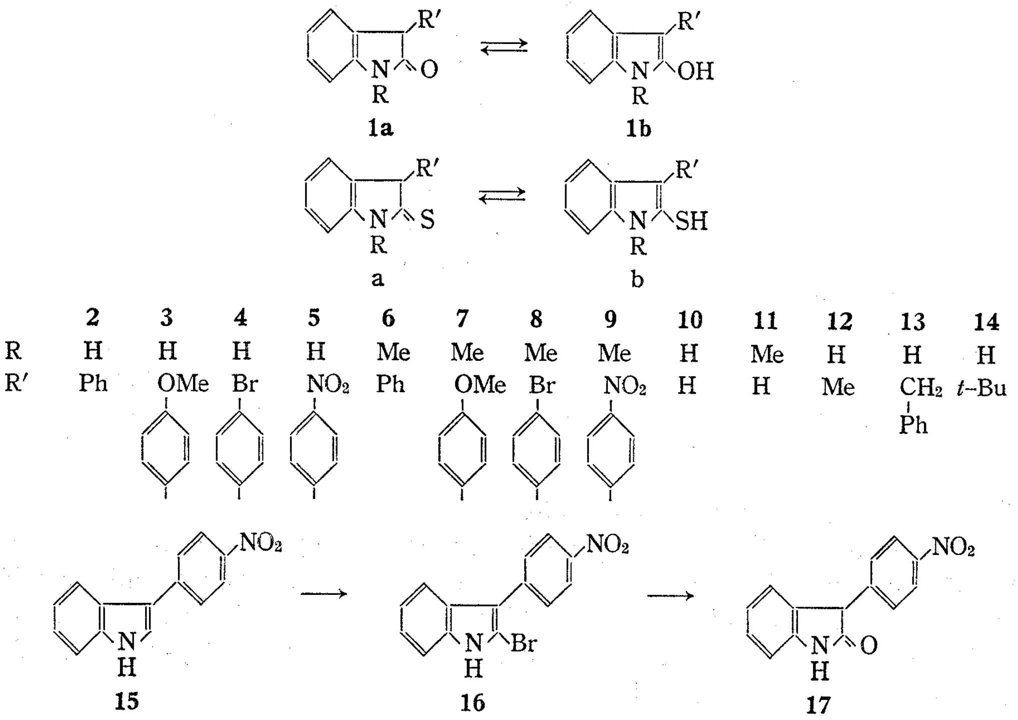
[7] The oxindole (**17**) has a small maximum at 578 nm (ε 300). Since the maximum increased its intensity by the addition of alkali, the maximum probably due to the structures of oxo analog of **c**, **d**, and **g** in Chart 2.

The NMR spectrum of the compound in deuterochloroform showed a singlet at 4.71 ppm for 3-H and a broad singlet at 8.95 ppm for NH of the oxindole, and no other signal corresponding to the enol form was observed. This indicated that the oxindole exists solely as the oxo form in the solution.

The predominance of the thiol form in solution is thus demonstrated in these 2-indolinethiones having NH group as expected. However, N-methylation of these compounds cause a striking effect on the thione-thiol tautomerism. The UV spectra of these compounds in ethanol are shown in Fig. 5. No solvent effect was observed in N-methylated compounds in contrast to the NH compounds, and the UV spectra showed the predominance of the thione form. The NMR spectra of these compounds also showed the predominance of the thione



	2	3	4	5	6	7	8	9	10	11	12	13	14
R	H	H	H	H	Me	Me	Me	Me	H	Me	H	H	H
R′	Ph	OMe	Br	NO_2	Ph	OMe	Br	NO_2	H	H	Me	CH_2 Ph	*t*-Bu

Ph=phenyl

Chart 1

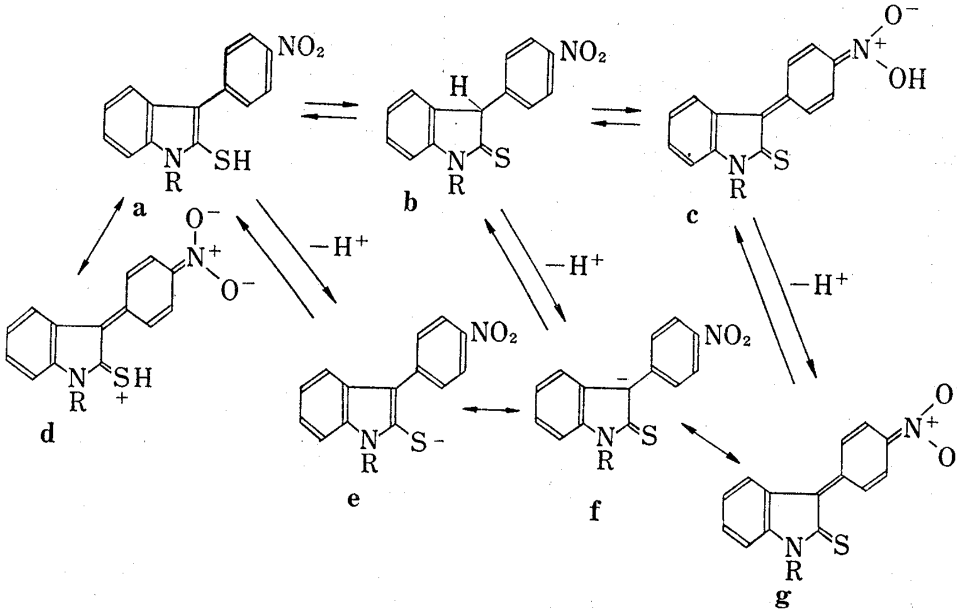


Chart 2

form (Table I). The UV spectra of 1-methyl-3-(*p*-nitrophenyl)-2-indolinethione (**9**) are shown in Fig. 6. In benzene, chloroform, and ethanol–hydrochloric acid **9** gave the similar UV spectra which were different from that of 2-ethylthio-1-methyl-3-(*p*-nitrophenyl)indole, indicating the thione form was predominant. The spectrum in 95% ethanol, however, showed a maximum at 513 nm due to chromophores such as **c**, **d**, and **g** in Chart 2.

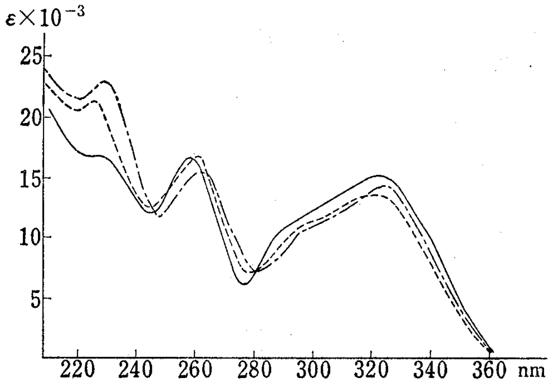


Fig. 5. The UV Spectra of 1-Methyl-3-aryl-2-indolinethiones in EtOH

———: 3-phenyl
--------: 3-(*p*-methoxyphenyl)
– – – – –: 3-(*p*-bromophenyl)

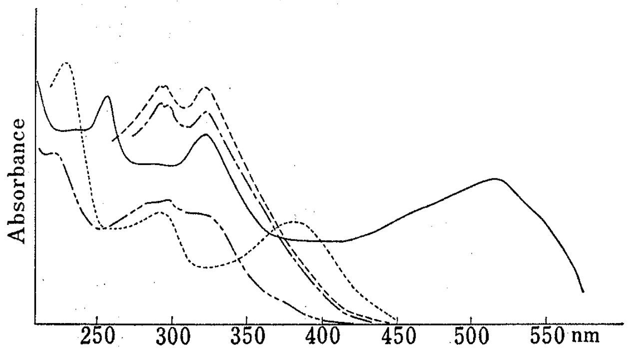


Fig. 6. The UV Spectra of 1-Methyl-3-(*p*-nitrophenyl)-2-indolinethione

———: EtOH
– – – –: EtOH–HCl
--------: $CHCl_3$
—-—: benzene
...........: 2-ethylthio-1-methyl-3-(*p*-nitrophenyl)-indole in EtOH

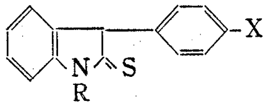
The relative stability of the thiol form in 3-aryl-2-indolinethiones in comparison with the corresponding oxindoles may be attributed to the following factors. The 3-aryl group should stabilize both the thiol and the enol form. However, the thione form is less stable than the oxo form due to involving the C=S double bond formed by the 2p—3p overlap instead of 2p—2p overlap in the C=O double bond. The effect of N-methyl group is not clear but N-methylation might destabilize the thiol form due to the steric hindrance caused by 1 and 3-substituents which is relieved in the thione form.

The UV and NMR data are summarized in Table I and II.

Air Oxidation of 2-Indolinethiones

During the purification of the 2-indolinethiones some 2-indolinethiones were found to be oxidized easily to the corresponding disulfides. 2-Indolinethione derived from tryptophan

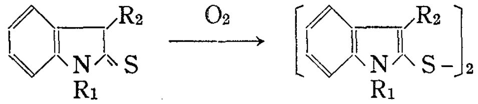
TABLE II. The UV Spectra of 3-Aryl-2-indolinethiones



Compd. No.	R	X	λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$)
2	H	H	226(20.2), 255(19.9), 297(11.0), 320(12.5)
6	Me	H	228(17.0), 260(16.5), 295^{sh}(10.5), 323(15.0)
3	H	MeO	229(22.0), 256(21.0), 296(11.8), 315(11.6)
7	Me	MeO	230(23.0), 261(15.4), 296(10.9), 321(13.7)
4	H	Br	225(21.2), 257(17.5), 297(11.1), 321(12.7)
8	Me	Br	227(21.6), 261(16.7), 296^{sh}(10.2), 325(14.8)
5	H	NO_2	228, 253, 293^{sh}, 323, 510
9	Me	NO_2	233, 257, 290^{sh}, 323, 520

was reported[8] to be oxidized to the disulfide even in the solid phase. We examined the air oxidation of 2-indolinethiones in ethanol to find out the effect of the substituents upon the oxidation. The oxidation of these 2-indolinethiones were monitored by oxygen absorption using a hydrogenation apparatus, or by the UV spectral change at room temperature. Table III showed the amount of oxygen absorbed during 24 hr in ethanol under oxygen atmosphere using $1/2 \times 10^{-3}$ mole of the thiones.

Table III. The Oxygen Uptake of 2-Indolinethiones in EtOH ($1/2 \times 10^{-3}$ mole in EtOH (30 ml))



Compd. No.	R_1	R_2	O_2uptake ml/24 hr	Products
2	H	Ph[a]	5.0	disulfide
6	Me	Ph[a]	3.0	disulfide+SM
3	H	*p*-MeOPh[a]	6.7	disulfide
7	Me	*p*-MeOPh[a]	5.6	disulfide
4	H	*p*-BrPh[a]	4.3	disulfide+SM
8	Me	*p*-BrPh[a]	2.5	disulfide+SM
12	H	Me	6.0	disulfide
14	H	*t*-Bu	0	SM
10	H	H	2.0	SM+others
11	Me	H	1.0	SM+others

a) Ph=phenyl

3-*tert*-Butyl-2-indolinethione (**14**) was very stable to oxygen, and the most of the thione was recovered. 2-Indolinethione (**10**) and 1-methyl derivative (**11**) resisted to the oxidation and were mostly recovered with some unidentified oxidation products. Other thiones were oxidized to the disulfides after 24 hr, except **4**, **6**, and **8**, which survived in a small amount after 24 hr oxidation.

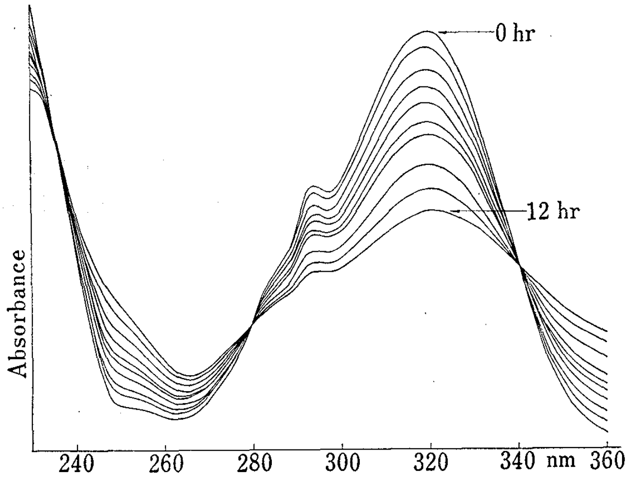


Fig. 7. The UV Spectral Change of 3-Methyl-2-indolinethione (12) in EtOH at Room Temperature

The UV spectral change of these 2-indolinethiones in ethanol was followed at room temperature. In the case of 3-methyl-2-indolinethione (**12**) maximum at 320 nm gradually decreased as increasing the intensity at 360 nm (Fig. 7). The UV spectral change from the thione to the disulfide showed the isosbestic points at 280 and 340 nm. After 24 hr the spectrum became nearly identical with that of the disulfide. 1-Methyl-3-aryl-2-indolinethiones in ethanol showed the similar spectral change, but more complex change was observed in the NH compounds due to the thione-thiol tautomerism. 3-(*p*-Nitrophenyl)-2-indolinethione (**5**) in ethanol was oxidized rapidly, and the UV spectrum changed to that of the disulfide within 4 hr. The oxidation of its N-methyl derivative (**9**) is slightly slower, and the spectrum in ethanol

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[8] T. Wieland, O. Weiberg, and W. Dilger, *Ann.*, **592**, 69 (1955).

changed to that of the disulfide after 7 hr. The accerelation of the autoxidation of the carbanion in the presence of nitrobenzene has been discussed by Russel and his coworkers.[9] The similar effect might be operated in the oxidation of 3-(*p*-nitrophenyl)-2-indolinethiones.

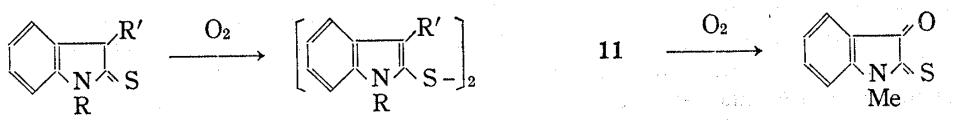
The results from the oxygen absorption and the UV spectral change indicated that easiness of the oxidation of 2-indolinethiones is the following order:

$$\mathbf{5, 9} > \mathbf{2, 3, 7, 12, 13} > \mathbf{4, 6, 8} \gg \mathbf{10, 11, 14}$$

This order is not parallel to the stability of the thiol form.

The oxidation of 3-(*p*-methoxyphenyl)-2-indolinethione (**3**) under some modified conditions was further examined. In ethanol containing NaOH or NaOMe, oxygen uptake proceeded rapidly but the products were not only the disulfide but the other by-products on thin-layer chromatography (TLC). In addition, no oxygen absorption was observed when **3** was stirred in dichloroethane, and the thione was recovered unchanged after 50 hr.

The exhaustive oxidation of 1-methyl-2-indolinethione (**11**) in ethanol was carried out under oxygen atmosphere for 2 weeks in order to examine the oxidation products. However, the most of **11** was recovered and a small amounts of the oxidation products were isolated. One of the products was assigned as 1-methyl-3-oxo-2-indolinethione (**18**) from the spectral data (see Experimental). In this case the oxidation to the disulfide was deeply suppressed and the prolonged oxidation gave 3-oxo derivative. The similar type of oxidation was reported in the 2-aminoindoles[10] and 2-methylindole.[11]



2—14 **18**

Chart 3

These results can be summarized as follows: 3-Substituted 2-indolinethiones are easily oxidized to the corresponding disulfide with oxygen, unless the 3-substituent is bulky. The substituted oxindoles, however, were reported to be oxidized to the 3-hydroxy derivatives when the oxindole was treated with a base under oxygen atmosphere.[12]

Although the mechanism of the air oxidation of the 2-indolinethione was not clear, one quarter of molecular oxygen has been known to require to oxidize one mole of the thiol to the disulfide as shown below.[13]

$$4\,\mathrm{RSH} + \mathrm{O_2} \cdots\cdots 2\,\mathrm{R{-}S{-}S{-}R} + 2\,\mathrm{H_2O}$$

The observed oxygen uptake was corresponded to one half mole of the 2-indolinethione, and this suggested the presence of hydrogen peroxide or an equivalent in the reaction mixture. Investigations along this line is now in progress.

Experimental[14]

Preparation of 3-(*p*-Nitrophenyl)-2-indolinone from 3-(*p*-Nitrophenyl)indole (15) *via* 2-Bromo Derivative (16)——To a solution of **15** (600 mg) in AcOH (15 ml) and CH_2Cl_2 (15 ml) was added dropwise N-

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[9] G.A. Russel and G. Kaupp, *J. Am. Chem. Soc.*, **91**, 3851 (1969) and references cited therein.

[10] T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, Y. Miwa, K. Tsuneoka, and S. Akaboshi, *Tetrahedron*, 27, 775 (1971).

[11] B. Witkop and J.B. Patrick, *J. Am. Chem. Soc.*, **73**, 713 (1951).

[12] P.L. Julian and J. Pikl, *J. Am. Chem. Soc.*, **57**, 539 (1935); R.B. Longmore and B. Robinson, *Coll. Czech. Chem. Comm.*, **32**, 2184, (1967); P. Aeberli and W.J. Houlihan, *J. Org. Chem.*, **33**, 1640 (1968).

[13] J.D. Hopton, C.J. Swan, and D.L. Trimm, "Oxidation of Organic Compounds," Vol. 1, American Chemical Society (Advances in Chemistry Series No. 75), Washington, 1968, p. 216.

[14] All melting points are uncorrected. The UV spectra were taken with a Hitachi EPS-3T spectrophotometer. Spectral grade solvents were used as the solvent except ethanol for which Pharmacopeia grade was used. The NMR spectra were taken with a JOEL 4H-100 spectrometer, and the chemical shifts were expressed with ppm from TMS as an internal standard.

bromosuccinimide (NBS) (450 mg) in AcOH (30 ml) during 20 min at room temperature. The mixture was stirred at room temperature for 1 hr and neutralized with 30% NaOH under cooling. The mixture was extracted with CH_2Cl_2 and the extracts were washed with H_2O and dried. The CH_2Cl_2 solution was evaporated to leave a brown solid (690 mg) which was chromatographed over silica gel. The fractions eluted with benzene–hexane (2: 3) gave crude 2-bromo derivative (**16**), mp 174—179°, as pale brown crystals. UV λ_{max}^{EtOH}: 223, 265, 283^{sh}, 376 nm. Mass Spectrum *m/e* (relative abundance): 318 (M+2,97), 316 (M^+, 100), 191 (59), 190 (30), 164 (28), 163 (22).

The crude 2-bromo derivative (240 mg) was dissolved in dioxane (10 ml) and conc. HCl (10 ml). The mixture was refluxed for 6 hr during which period further conc. HCl (3 ml) was added to the mixture. The mixture was evaporated and the residue was extracted with CH_2Cl_2 and H_2O. The CH_2Cl_2 solution was washed with H_2O, dried, and evaporated. The brown solid (290 mg) was purified through silica gel column. Fractions eluted with CH_2Cl_2 gave the oxindole (**17**) (174 mg), mp 142—145°. Recrystallizations from benzene–hexane gave pure **17**, mp 165—167°. *Anal.* Calcd. for $C_{14}H_{10}O_3N_2$: C, 66.14; H, 3.94; N, 11.02. Found: C, 65.97; H, 3.99; N, 10.65. UV: λ_{max}^{EtOH} nm (ε): 260 (13900), 275^{sh} (11700), 578 (300). NMR($CDCl_3$); 4.71 (s, 3-H), 8.95 (br. s, NH). Mass Spectrum *m/e* (relative abundance): 254 (M^+, 100), 225 (17), 180 (19), 152 (16).

Air Oxidation of 2-Indolinethiones——1) Oxygen Uptake: In an Ishii's catalytic hydrogenation apparatus equipped with 25 ml cylinder, 2-indolinethione ($1/2 \times 10^{-3}$ mole) was dissolved in ethanol (30 ml). The solution was stirred under O_2 atmosphere at room temperature, and volume of O_2 absorbed was measured occasionally. After 24 hr the solution was evaporated *in vacuo* and the residue was examined by TLC and infrared (IR) spectra. The results are summarized in Table III.

2) The UV Spectral Change: An ethanolic solution of the 2-indolinethione at UV concentration (*ca.* 10^{-4} molar solution) was kept at room temperature. The UV spectra of the solution was taken time to time during 24 hr. The typical example to the spectral change is shown in Fig. 7. The UV change of 3-*tert*-butyl-(**14**), 1-methyl-(**11**) and 2-indolinethione (**10**) was not practically observed after 24 hr. The UV spectra of **5** and **9** in ethanol changed to those of the disulfides in 4 hr and 7 hr. The oxidation of **3** to the disulfide was completed in 20 hr. The oxidation of **12**, **13**, **2** and **7** in ethanol were completed in *ca.* 24 hr. The UV spectrum of **6** in ethanol after 24 hr showed that the oxidation was not complete. The oxidation of **4** and **8** was not completed within 24 hr, but the spectra were changed to those of the disulfide after 40 hr.

The UV spectra of **3** and **7** in benzene or chloroform after 24 hr showed the oxidation was slower than that in ethanol.

The Exhaustive Oxidation of 1-Methyl-2-indolinethione (11)——A solution of **11** (5.0 g) in EtOH (300 ml) was stirred at room temperature in an atmosphere of O_2 for 16 days. The reaction mixture was evaporated *in vacuo* to leave a residue. The residue was chromatographed over silica gel column. The thione (**11**) (3.3 g) was recovered. The fractions eluted with benzene–hexane (1: 2) gave a yellow products (580 mg). Recrystallization from acetone gave yellow crystals, mp 200—212°, but further purification was failed due to the decomposition. The fractions eluted with benzene gave crude 1-methyl-2-thio-3-indolinone (**18**) (590 mg). Recrystallizations from benzene–hexane gave **18**, mp 168—171°, as purple plates. *Anal.* Calcd. for C_9H_7ONS: C, 61.01; H, 3.98; N, 7.91; S, 18.06. Found: C, 61.17; H, 4.06; N, 7.65; S, 17.96. UV λ_{max}^{EtOH}: 264, 271, 293^{sh}, and 475 nm. IRν_{max}^{KBr}: 1730 cm^{-1} (C=O). Mass Spectrum *m/e* (relative abundance): 177 (M^+, 100), 162 (6), 148 (9), 132 (10), 117 (11), 104 (8), 90 (6), 76 (10).

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