[Chem. Pharm. Bull. 14(11)1263~1272(1966)]

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172. Kōichi Nagata and Satoshi Mizukami: Studies on Thiohydroxamic Acids and Their Metal Chelates. III.[*1] Syntheses of Some Thiohydroxamic Acid Derivatives and Their Structures.

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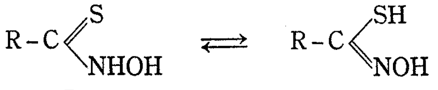
We have elucidated in the preceding paper that thiohydroxamic acids (I) exist in thione-form (Ia) in the soild state, but the both thiol and thione tautomers are present in equilibrium in the liquid state or in the solution. Hence, it is a question of which tautomer react more preferentially in the solution. Although a few monoalkyl or dibenzoyl derivatives of I have been reported,[1~5] their structures have not been confirmed positively, except in the case of some S-alkyl and S,O-dibenzoyl derivatives of benzothiohydroxamic acid.[6] This work deals with systematic syntheses of some thiohydroxamic acid derivatives and examinations of their structures mainly by investigations of the infrared spectra. Consequently, it was found that I react as thiol-form (Ib) in aqueous solution at least. The knowledges obtained in this work are very useful for the study on the structures of metal chelates of I as shown in following papers.[*3]


Ia Ib

A) Alkyl Derivatives

Monoalkyl derivatives (IV) which are most stable and well crystallizable solids among the thiohydroxamic acid derivatives were obtained by the addition of equivalent alkyl halides to sodium thiohydroxamate (II) in ethanol. Dialkyl derivatives (V) could be derived from IV, and V ($R''=CH_3$) were found to be identical in all respects with the compounds prepared from sodium O-methylthiohydroxamate (III) and the alkyl halide.

The structures of IV were confirmed by comparing their infrared spectra with those of their deuterated compounds. Typical spectra are shown in Fig. 1. On deuteration, the bands at about $1600\,cm^{-1}$ shift to the lower wave numbers and the bands at about $1400\,cm^{-1}$ disappear, accompanied with the occurrence of new bands around $1100\,cm^{-1}$. Hence, it is to be pointed out that such spectral changes are closely analogous with those of oximes,[7,8] in which the C=N stretching band at $1610\sim1670\,cm^{-1}$ shifts to the original position at lower wave numbers after deuteration because of the decoupling among the C=N stretching and OH in-plane deformation vibration at $1500\sim1300\,cm^{-1}$ with the shifts of the latter band to the lower wave numbers. From these analogies the above-mentioned bands of IV at 1600 and $1400\,cm^{-1}$ which are both sensitive to deuteration and the new band at $1100\,cm^{-1}$ must be ascribed to the C=N stretching and the OH and OD in-plane deformation vibrations, respectively. In Fig. 1

[*1] Part II: This Bulletin, **14**, 1255 (1966).

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[*3] Part V, VI: This Bulletin, to be published.

1) L. Cambi: Atti. Acad. Lincei, **18**, I 687 (Chem. Abstr., **4**, 1738 (1910)).
2) *Idem*: Gazz. chim. ital., **41**, I 170 (Beilstein, **2**, I 39, **6**, I 228).
3) T. Bacchetti, A. Alemagna: Rend. Ist. Lombardo Sci. Lettere, B. **91**, 574 (1957).
4) *Idem*: Atti. Acad. naz. Lincei, Rend. Classe Sci. fis. mat. nat., **24**, 161 (1958).
5) J. Houben, R. Zivadinovitsch: Chem. Ber., **69**, 2352 (1936).
6) T. Bacchetti, A. Alemagna: Rend. Ist. Lombardo Sci. Lettere, B. **91**, 30 (1957), A **97**, 182 (1963).
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8) Y. Matsui: Nippon Kagaku Zasshi, **83**, 985, 990 (1962).

the bands at about 3200 cm^{-1} which shift to the range 2370 cm^{-1} on deuteration belong to the associated OH stretching vibration, and these bands split off in carbon tetrachloride solution to give the sharp non-associated bands at 3610 cm^{-1} and the broad associated bands at 3300 cm^{-1}. Furthermore, the broad bands at about 740 cm^{-1}, sensitive to deuteration, are probably due to the OH out-of-plane deformation vibration, and the strongest band near 900 cm^{-1} may be mainly due to the N-O stretching vibration. These wave numbers are all in fair agreement with those of oximes,[7~14)] namely the non-associated and associated OH stretching bands, the OH out-of-plane deformation, and the N-O stretching bands have been located within the range 3500~3650, 3000~3400, 630~900 and 900~1000 cm^{-1}, respectively. The assignments for the absorption bands of IV were summarized in Table I. It is to be noted that the aromatic V display medium bands due to the C=N stretching vibration around 1560±10 cm^{-1} and these frequencies resemble those of deuterated IV.

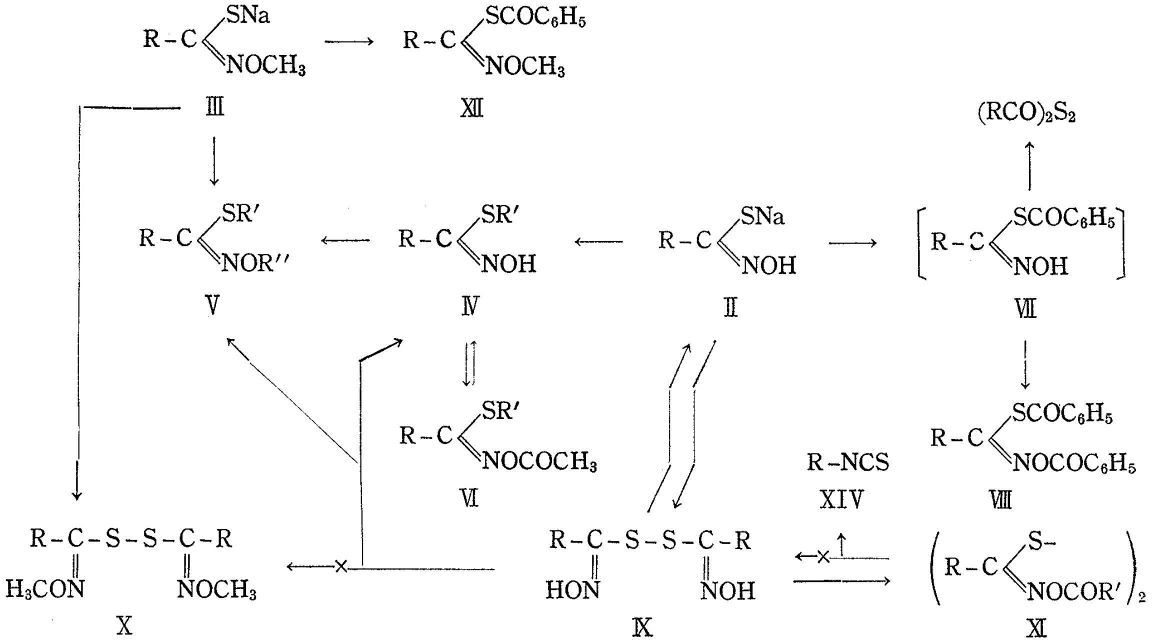

Chart 1.

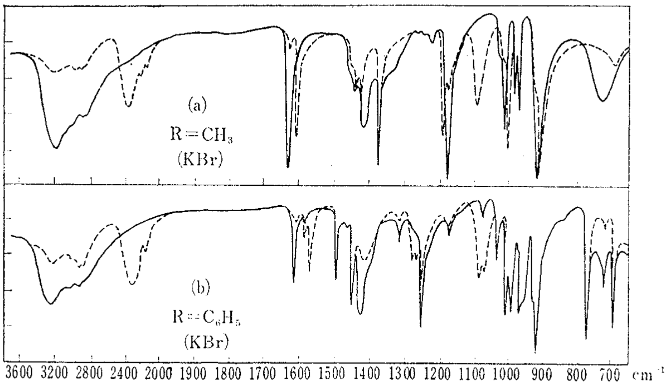

Fig. 1. Infrared Spectra of $R-C\langle^{S-CH_3}_{NOH}$ (IV)

——— simple - - - - - deuterated

From these results there is no doubt that IV are S-alkylated derivatives which include oxime group. If they were N- or O-alkylated derivatives they should show the "N-C=S bands"[15)] which are always found in N,N-disubstituted thioamides.

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9) A. Palm, H. Werbin: Can. J. Chem., **31**, 1004 (1953).
10) *Idem*: *Ibid*., **32**, 858 (1954).
11) M. Kimura, Y. Kuroda, H. Takagi: Bull. Chem. Soc. Japan, **33**, 1086 (1960).
12) J. Fabian, M. Legrand: Bull. soc. chim. France, **1956**, 1461.
13) S. Califano, W. Lüttke: Z. Physik. Chem. (Frankfurt) [N. F.], Bd. **6**, 83 (1956).
14) J. Goubeau, I. Fromme: Z. Anorg. Chem., **258**, 18 (1949).
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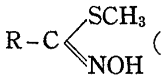

TABLE I. Assigned Bands in $R-C\begin{smallmatrix}SCH_3\\NOH\end{smallmatrix}$ (IV)

R	ν_{OH}	ν_{OD}	ν_{OH}/ν_{OD}	$\nu_{C=N(H)}$	$\nu_{C=N(D)}$	Shift	δ_{OH}	δ_{OD}	δ_{OH}/δ_{OD}	γ_{OH}
CH_3	3225br, m 3081 w	2370	1.36	1630	1605	−25	1420	1095	1.30	738br
n-C_3H_7	3215br, m 3085 w	2383	1.35	1626	1600	−26	1417	1109	1.28	741br
C_6H_5	3235br,[a] m 3160 sh	2367	1.37	1608	1570	−38	1426	1086	1.31	739br
p-$CH_3C_6H_4$	3200 sh 3142br, m	2305	1.36	1604	1575	−29	1440	1090	1.32	774br
p-Cl-C_6H_4	3200 sh 3125br, m	2372	1.32	1596[b]	1583	−13	1447	1087	1.33	762br
p-CH_3O-C_6H_4	3244br, m 3160 sh	2385	1.36	1618[b]	1575	−43	1430	1093	1.31	714br

m: medium w: weak sh: shoulder br: broad
a) ν_{OH} (monomer); 3612 cm^{-1} (CCl_4)
b) These bands are also attributed to $\nu_{C=C}$ of benzene ring.

S-Methylbenzothiohydroxamic acid and acetyl chloride give S-methyl-O-acetylbenzothiohydroxamic acid (VI, $R=C_6H_5$, $R'=CH_3$) which is easily hydrolysed to produce the starting material. Its C=O stretching frequency at 1782 cm^{-1} is identical with those of =N-O-C=O link.[16~18]

B) Acyl Derivatives

Treatment of II with the equivalent benzoyl chloride in various solvents failed to yield S-benzoylthiohydroxamic acid (VII) and gave dibenzoyl disulfide, S,O-dibenzoylthiohydroxamic acid (VIII) and other decomposed products such as the corresponding nitrile and sulfur. The fact that dibenzoyl disulfide was obtained suggests the instability of VII, and analogous observations have been known for II ($R=C_6H_5$)[6] and for the corresponding derivatives of hydroxamic acid.[19] On the one hand, treatment of II with a large excess of benzoyl chloride in sodium hydroxide solution gave VIII as reported by Cambi.[1] In carbon tetrachloride solution VIII show the two C=O stretching bands at $1690\sim1698^{-1}$ and $1766\sim1771$ cm^{-1} which are in fair agreement with the frequencies of -S-C=O[20] and =N-O-C=O[16~18] link, respectively. Attempts to prepare the S,O-diacetyl derivatives by treating II with acetyl chloride in pyridine failed and gave nitrile and sulfur.

C) Oxidation Products

The oxidation of II in aqueous solution by hydrogen peroxide or iodine gave the disulfide (IX) which are apt to be decomposed by heating. Their molecular weights were in agreement with the calculated values by vapor pressure osmometer method, and their structures including =NOH group were confirmed by investigations of the infrared spectra, of which typical examples are shown in Fig. 2. These spectra are interpreted by analogy with those of IV, and then the assignments for the characteristic absorption bands are presented in Table II. By warming with zinc in glacial acetic acid, IX were easily converted to zinc thiohydroxamate.

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[16] J.P. Freeman: J. Am. Chem. Soc., **80**, 5954 (1958).
[17] H. Bredreck, A. Wagner, D. Hummel, H. Kreiselmer: Chem. Ber., **89**, 1532 (1956).
[18] T. Kaneko: Yakugaku Zasshi, **79**, 428 (1959).
[19] A. Werner, H. Buss: Chem. Ber., **27**, 2193 (1894); *Ibid.*, **32**, 1654 (1899).
[20] R.A. Nyquist, W.J. Potts: Spectrochim. Acta, **7**, 514 (1959).

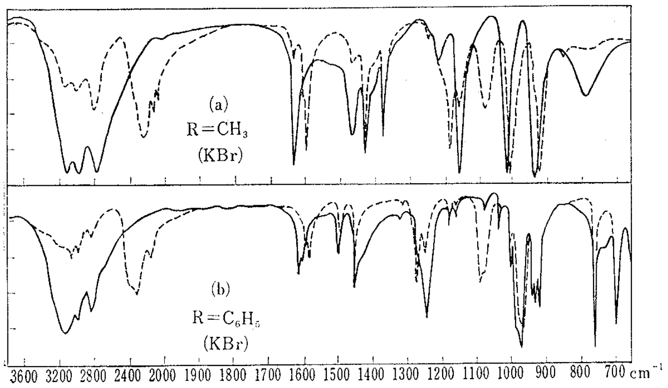

Fig. 2. Infrared Spectra of $\left(\mathrm{R{-}C}\begin{smallmatrix}\diagup \mathrm{S-}\\ \diagdown \mathrm{NOH}\end{smallmatrix}\right)_2$ (IX)

——— simple - - - - - - deuterated

Oxidation of III by iodine yielded the disulfide (X), but the treatment of IX with methyl iodide by warming in alkaline solutlon failed to yield X, and gave IV and V. This result indicates that the S-S linkage of IX is apt to be cleaved by alkali on warming. By cooling with ice, however, IX and benzoyl chloride gave the dibenzoyl derivatives (XI, R' $=C_6H_5$) without the cleavage of the S-S linkage. The diacetyl derivatives (XI, $R'=CH_3$) were also prepared from IX and acetyl chloride in pyridine. Their molecular weights are in agreement with the calculated values and their C=O stretching bands in carbon tetrachloride solution fall within the range 1766~1770 cm^{-1} (for dibenzoyl derivatives) or 1788 cm^{-1} (for diacetyl derivatives), the frequencies of which are in fair agreement with those of =N-O-C=O link.[16~18)]

Table II. Assigned Bands in $\left(\mathrm{R{-}C}\begin{smallmatrix}\diagup \mathrm{S-}\\ \diagdown \mathrm{NOH}\end{smallmatrix}\right)_2$ (IX)

R	ν_{OH}	ν_{OD}	ν_{OH}/ν_{OD}	$\nu_{C=N(H)}$	$\nu_{C=N(D)}$	Shift	δ_{OH}	δ_{OD}	δ_{OH}/δ_{OD}	γ_{OH}
CH_3	3156br, m 3026br, m	2300m 2264w	1.34	1629	1610	−19	1464	1089	1.34	797br, m
n-C_3H_7	3225br, m 3100w	2380br, m 2280sh	1.36	1635	1610	−25	1443	1109	1.30	725br, m
C_6H_5	3140br,[a] m	2375sh 2300m	1.32	1613	1590	−23	1431	1085	1.32	737br, m
p-CH_3-C_6H_4	3233br, m	2403m 2355sh	1.35	1612	1582	−30	1425	1080	1.32	705br, w
p-CH_3O-C_6H_4	3240br, m	2400br, m 2352sh	1.43	1608[b]	1594	−14	1442	1086	1.33	723br, w

m: medium w: weak sh: shoulder br: broad

a) ν_{OH} (monomer); 3612 cm^{-1} (CCl_4).

b) This band is also attributed to $\nu_{C=C}$ of benzene ring.

It was found that XI give very easily the corresponding isothiocyanate (XIV) and 1,3-dialkyl-2-thiourea (XV) by treatment with sodium carbonate solution. This reaction evidently corresponds to the Lossen rearrangement of hydroxamic acids, but it seems to proceed under extremely milder conditions than that of the Lossen rearrangement. Since the S-S linkage are apt to be cleaved in alkaline solution as already mentioned, the mechanism of this rearrangement can be explained satisfactorily by the assumption of the existence of O-acylthiohydroxamate ion (XIII) as intermediate, just as in the Lossen rearrangement.[21,22)] The rate-determining step seems to be the preliminary ionization, the intermediate anion rearranging very rapidly, because, if XIII is accumulated, it must be isolated easily as the orange nickel salts as described in a following paper*3, but such a nickel salt could not be obtained. The rearrangement passing through the course XI→IX→II→XIV is very unlikely, for IX or II gave only a trace of the corresponding aniline under the same condition as XI were rearranged.

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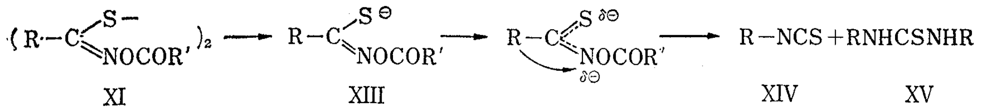
21) H. L. Yale: Chem. Rev., **33**, 209 (1943).

22) F. Mathis: Bull. soc. chim. France, **1953**, D9.

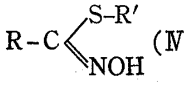


The reduction of Ⅺ by the alkaline reagent, such as Na_2S or $LiAlH_4$, also gave XIV as main product with a small quantity of thiohydroxamic acid. In acetic acid, zinc and Ⅺ did not react under mild conditions, and yielded the decomposed products such as nitrile by the boiling.

Experimental

All melting points were uncorrected. Sodium thiohydroxamate (Ⅱ) and sodium O-methylthiohydroxamate (Ⅲ) were prepared by previously reported methods in Part I.[*4] Infrared spectra were taken with a Nippon Bunkō double-beam spectrophotometer model DS 201-B. Deuteration was performed by addition of heavy water to the solution of the substance in dry dioxane until precipitation occurred, with subsequent drying *in vacuo*. Molecular weights were determined by using a Mechrolab vapor pressure osmometer model 301-A.

S-Alkylthiohydroxamic Acid (IV)——For S-methyl derivatives, a small excess of CH_3I was added to the solution of Ⅱ in EtOH and the mixture was allowed to stand overnight at room temperature. For S-benzyl derivatives, the mixture of Ⅱ and an equivalent of benzyl bromide was allowed to react at 60~70° for few hours. Removal of the solvent and recrystallization from petroleum benzin gave Ⅳ as colorless crystals as summarized in Table Ⅲ.

Table Ⅲ.  $R-C(=NOH)-S-R'$ (Ⅳ)

No.	R	R′	Appearance	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	S	Found C	H	S
Ⅳa	CH_3	CH_3	plate	92~ 93	C_3H_7ONS	34.26	6.71	30.49	34.20	6.74	30.35
Ⅳb	〃	$C_6H_5CH_2$	needle	136~137$^{a)}$	$C_9H_{11}ONS$	59.64	6.12	17.69	59.71	6.33	17.76
Ⅳc	n-C_3H_7	CH_3	〃	71~ 72	$C_5H_{11}ONS$	45.08	8.32	24.07	45.66	8.42	24.16
Ⅳd	C_6H_5	〃	prism	83	C_8H_9ONS	57.46	5.42	19.17	57.36	5.44	19.38
Ⅳe	〃	$C_6H_5CH_2$	needle	120~121$^{b)}$	$C_{14}H_{13}ONS$	69.10	5.39	13.18	69.08	5.65	13.26
Ⅳf	p-CH_3-C_6H_4	CH_3	〃	77~ 78	$C_9H_{11}ONS$	59.64	6.12	17.69	59.64	6.13	17.50
Ⅳg	〃	$C_6H_5CH_2$	〃	143~144	$C_{15}H_{15}ONS$	70.01	5.88	12.46	70.04	5.94	12.40
Ⅳh	p-Cl-C_6H_4	CH_3	amorph.	71~ 72	C_8H_8ONSCl	47.64	4.00	15.90	47.60	4.27	15.35
Ⅳi	m-Cl-C_6H_4	$C_6H_5CH_2$	prism	89~ 90	$C_{14}H_{12}ONSCl$	60.53	4.35	11.54	60.64	4.62	11.71
Ⅳj	p-CH_3O-C_6H_4	CH_3	amorph.	88	$C_9H_{11}O_2NS$	54.80	5.62	16.25	54.93	5.75	16.17
Ⅳk	β-$C_{10}H_7$-	$C_6H_5CH_2$	needle	107~108	$C_{18}H_{15}ONS$	73.69	5.15	10.93	73.93	5.32	10.76
Ⅳl	α-C_4H_3O	CH_3	〃	45~ 46	$C_6H_7O_2NS$	45.84	4.49	20.40	46.25	4.53	20.57
Ⅳm	〃	$C_6H_5CH_2$	〃	111~112	$C_{12}H_{11}O_2NS$	61.78	4.75	13.74	61.85	4.77	13.69

Ref. m.p.: *a*) 145~147°,[4] *b*) 120~122°[1]

S,O-Dialkylthiohydroxamic Acid (V)——a) From Ⅳ: To a solution of Ⅳ in 50% NaOH was added a small excess of dimethyl sulfate, and the mixture was first stirred for 2 hr. at room temperature and then warmed for 0.5 hr. at 40~50°. Benzylation was carried out by addition of an equivalent of benzyl bromide and heating for 1 hr. on a steam bath. After addition of a large quantity of water, the separated oil was extracted with ether. The ether layer was washed with 5% NaOH and water, and dried. After evaporation of ether, the solid residue was recrystallized from dil. MeOH. If the oily residue was obtained, it was purified by chromatography over alumina, using 8:2 petroleum ether-ether as eluent.

b) From Ⅲ: S,O-Dialkylthiohydroxamic acids were also prepared by allowing to stand overnight at room temperature after addition of an equivalent of methyl sulfate to the solution of Ⅲ in EtOH, or by warming at 60~70° for few hours after addition of an equivalent of benzyl bromide. The sample which was refined

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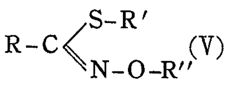
[*4] Part I: This Bulletin, **14**, 1249 (1966).

by the same manner as method (a) was identical in all respects with the corresponding compound by method (a).

The obtained V were all summarized in Table Ⅳ.

TABLE Ⅳ.

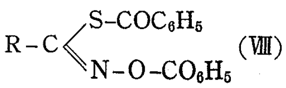


$$R-C\begin{cases}S-R'\\N-O-R''\end{cases}\quad(\text{V})$$

No.	R	R′	R″	Appearance	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	S	Found C	H	S
Va	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	amorph.a)	61	$C_{16}H_{17}ONS$	70.81	6.31	11.82	70.89	6.38	11.76
Vb	C_6H_5	CH_3	CH_3	prismb)	41～42	$C_9H_{11}ONS$	59.64	6.12	17.69	59.39	6.15	17.81
Vc	〃	$C_6H_5CH_2$	〃	〃 a,b)	27～28*	$C_{15}H_{15}ONS$	70.01	5.88	12.46	70.22	5.94	12.73
Vd	〃	〃	$C_6H_5CH_2$	needlea)	76	$C_{21}H_{19}ONS$	75.64	5.74	9.62	75.71	5.76	9.32
Ve	*p*-CH_3-C_6H_4	CH_3	CH_3	〃 a,b)	34～35	$C_{10}H_{13}ONS$	61.50	6.71	16.42	61.07	6.70	16.28
Vf	〃	〃	$C_6H_5CH_2$	〃 a)	42*	$C_{16}H_{17}ONS$	70.81	6.31	11.82	70.62	6.37	12.03
Vg	〃	$C_6H_5CH_2$	CH_3	〃 a,b)	89～90	〃	70.81	6.31	11.82	71.05	6.29	11.88
Vh	*p*-Cl-C_6H_4	CH_3	〃	prisma,b)	32～33	$C_9H_{10}ONSCl$	50.11	4.67	14.87	50.44	4.70	14.64
Vi	〃	〃	$C_6H_5CH_2$	needlea)	82	$C_{15}H_{14}ONSCl$	61.74	4.84	10.99	62.00	4.88	11.10
Vj	*m*-Cl-C_6H_4	$C_6H_5CH_2$	CH_3	oila)	*	〃	61.74	4.84	10.99	61.95	5.03	11.30
Vk	*p*-CH_3O-C_6H_4	CH_3	〃	needleb)	35～36*	$C_{10}H_{13}O_2NS$	56.85	6.20	15.18	57.32	6.23	15.07
Vl	β-$C_{10}H_7$	$C_6H_5CH_2$	〃	oila)	*	$C_{19}H_{17}ONS$	74.24	5.57	10.43	74.53	5.67	10.48
Vm	α-C_4H_3O	CH_3	$C_6H_5CH_2$	〃 a)	*	$C_{13}H_{13}O_2NS$	63.13	5.30	12.96	63.48	5.44	13.01

* These compounds were purified by chromatography over alumina.
a) and b) indicate the synthetic method (a) and (b), respectively.

TABLE V.



$$R-C\begin{cases}S-COC_6H_5\\N-O-CO_6H_5\end{cases}\quad(\text{Ⅷ})$$

No.	R	Appearance	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S	IR (CCl_4) $\nu_{C=O}$
Ⅷa	CH_3	amorph.	78	$C_{16}H_{13}O_3NS$	64.19	4.38	4.68	10.71	64.15	4.56	4.95	10.79	1767 1692
Ⅷb	*n*-C_3H_7	prism	69～70	$C_{18}H_{17}O_3NS$	66.03	5.23	4.28	9.79	65.78	5.38	4.50	9.90	1766 1690
Ⅷc	C_6H_5	〃	98～99*a*)	$C_{21}H_{15}O_3NS$	69.79	4.18	3.88	8.87	69.91	4.42	3.86	8.80	1770 1694
Ⅷd	*p*-$CH_3C_6H_4$	needle	110	$C_{22}H_{17}O_3NS$	70.38	4.56	3.73	8.54	70.03	4.67	3.68	8.78	1769 1695
Ⅷe	*m*-CH_3-C_6H_4	〃	131	〃	70.38	4.56	3.73	8.54	70.24	4.59	3.80	8.46	1769 1696
Ⅷf	*p*-Cl-C_6H_4	〃	117	$C_{21}H_{14}O_3NSCl$	63.71	3.56	3.54	8.10	63.73	3.65	3.42	8.14	1769 1694
Ⅷg	*m*-Cl-C_6H_4	〃	82～83	〃	63.71	3.56	3.54	8.10	63.57	3.70	3.41	8.15	1772 1696
Ⅷh	*p*-$C_6H_5CO_2$-C_6H_4	〃	158	$C_{28}H_{19}O_5NS$	69.84	3.98	2.91	6.66	69.69	4.10	2.90	6.49	1770 1746 1696
Ⅷi	*m*-$C_6H_5CO_2$-C_6H_4	〃	122	〃	69.84	3.98	2.91	6.66	69.62	3.97	2.85	6.85	1771 1746 1698
Ⅷj	β-$C_{10}H_7$	plate	161～162	$C_{25}H_{17}O_3NS$	72.93	4.16	3.40	7.79	72.59	4.24	3.49	8.10	1769 1695
Ⅷk	α-C_4H_3O	〃	97～98	$C_{19}H_{13}O_4NS$	64.95	3.73	3.99	9.13	64.58	3.88	3.93	9.35	1771 1699
Ⅷl	α-C_4H_3S	prism	116～117	$C_{19}H_{13}O_3NS_2$	62.11	3.57	3.81	17.45	61.82	3.58	4.00	17.43	1770 1698

a) Ref. m.p.: 135°[1]

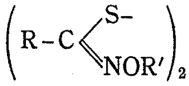
S-Methyl-O-acetylbenzothiohydroxamic Acid (VI; R=C_6H_5, R'=CH_3)——S-Methylbenzothiohydroxamic acid (Ⅳd) (0.8 g.) was dissolved in pyridine (4 ml.), and cooled with dry ice-acetone. After addition of acetyl chloride (0.3 ml.), the mixture was kept first in an ice bath and allowed to raise to room temperature slowly during a period of about one hour. Water was added, and the precipitated solid was filtered and recrystallized from 10 ml. of 70% EtOH to give 0.98 g. (95%) of Ⅵ (R=C_6H_5, R'=CH_3) as colorless needles, m.p. 71°. IR $\nu_{C=O}$ cm^{-1}: 1782 (CCl_4). *Anal.* Calcd. for $C_{10}H_{11}O_2NS$: C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.61; H, 5.38; N, 6.80; S, 15.23.

The suspension of the crystals obtained above in 5% Na_2CO_3 was stirred at 60° for 1 hr., and neutralized with dil. HCl. Extraction with ether and subsequent removal of the solvent yielded again Ⅳd almost quantitatively.

Acylation of Sodium Thiohydroxamate——a) S,O-Dibenzoylthiohydroxamic acid (Ⅷ): To a solution of Ⅱ (about 0.2 g.) in ice-cold 10% NaOH (2 ml.) was added two equivalent of benzoyl chloride a little at a time. The mixture was shaken vigorously in a stopped flask whenever benzoyl chloride was added. The resulting colorless precipitate was filtered, washed with dil. NaOH and water, and recrystallized from acetone-H_2O. The analytical data are presented in Table V with the frequencies of the C=O stretching band.

b) Sodium *p*-methoxybenzothiohydroxamate (0.5 g.) was dissolved in pyridine (12 ml.) and cooled in dry ice-acetone. After addition of acetyl chloride (0.25 ml.), the solution was kept first in an ice bath and allowed to raise to room temperature. After another one hour, a small quantity of water was added, and the separated

TABLE Ⅵ.



$$\left(R-C\begin{matrix}S-\\NOR'\end{matrix}\right)_2$$

; R'=H (Ⅸ), R'=CH_3 (Ⅹ)

No.	R	R'	Appearance	m.p. (°C) (decomp.)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
Ⅸa	CH_3[b)]	H	amorph.	129	$C_4H_8O_2N_2S_2$	26.65	4.47	15.54	35.58	26.77	4.71	15.73	35.36
Ⅸb	C_2H_5[a)]	〃	needle	132	$C_6H_{12}O_2N_2S_2$	34.60	5.81	13.45	30.79	34.82	5.87	13.32	30.60
Ⅸc	*n*-C_3H_7[a)]	〃	scale	124～125	$C_8H_{16}O_2N_2S_2$	40.65	6.82	11.85	27.13	40.87	6.88	12.20	26.89
Ⅸd	C_6H_5[c)]	〃	prism	123～124	$C_{14}H_{12}O_2N_2S_2$	55.24	3.97	9.20	21.07	55.22	4.11	8.92	21.07
Ⅸe	*p*-CH_3-C_6H_4	〃	〃	137～138	$C_{16}H_{16}O_2N_2S_2$	57.81	4.85	8.43	19.29	57.69	4.82	8.24	19.37
Ⅸf	*m*-CH_3-C_6H_4	〃	〃	121～122	〃	57.81	4.85	8.43	19.29	58.21	4.88	8.00	19.11
Ⅸg	*p*-Cl-C_6H_4	〃	needle	129～130	$C_{14}H_{10}O_2N_2S_2Cl_2$	45.05	2.70	7.51	17.18	44.99	2.82	7.77	17.01
Ⅸh	*m*-Cl-C_6H_4	〃	〃	137～138	〃	45.05	2.70	7.51	17.18	44.91	2.74	7.63	17.35
Ⅸi	*p*-CH_3O-C_6H_4	〃	amorph.	122	$C_{16}H_{16}O_4N_2S_2$	52.73	4.43	7.69	17.60	52.91	4.54	7.62	17.58
Ⅸj	*o*-CH_3O-C_6H_4	〃	prism	174	〃	52.73	4.43	7.69	17.60	52.88	4.54	7.60	17.67
Ⅸk	*m*-NO_2-C_6H_4	〃	amorph.	134	$C_{14}H_{10}O_6N_4S_2$	42.64	2.56	14.21	16.26	42.93	2.65	14.44	16.37
Ⅸl	*p*-HO_2C-C_6H_4-	〃	〃	226～227	$C_{16}H_{12}O_6N_2S_2$	48.97	3.08	7.14	16.34	49.12	3.18	7.25	16.13
Ⅸm	β-$C_{10}H_7$	〃	plate	139～140	$C_{22}H_{16}O_2N_2S_2$	65.32	3.99	6.93	15.85	65.46	4.17	6.85	15.59
Ⅸn	α-C_4H_3O	〃	needle	128	$C_{10}H_8O_4N_2S_4$	42.24	2.84	9.85	22.56	42.43	3.03	9.93	22.63
Ⅸo	α-C_4H_3S	〃	〃	123～124	$C_{10}H_8O_2N_2S_4$	37.95	2.55	8.85	40.53	37.83	2.63	8.54	40.20
Ⅹa	C_6H_5[d)]	CH_3	〃	61～62	$C_{16}H_{16}O_2N_2S_2$	57.80	4.85	8.43	19.29	57.84	4.93	8.27	19.33
Ⅹb	*p*-CH_3-C_6H_4[e)]	〃	prism	88～89	$C_{18}H_{20}O_2N_2S_2$	59.97	5.59	7.77	17.79	59.92	5.65	7.71	17.93
Ⅹc	*p*-CH_3O-C_6H_4	〃	〃	115～116	$C_{18}H_{20}O_4N_2S_2$	55.08	5.14	7.14	16.34	55.66	5.21	7.16	16.12
Ⅹd	*m*-NO_2-C_6H_4	〃	amorph.	131	$C_{16}H_{14}O_6N_4S_2$	45.49	3.34	13.26	15.18	45.37	3.37	13.20	15.16

a) These compounds were unstable and decomposed on standing in desiccator.
b) mol. wt.: Calcd. 180. Found (in acetone) 188
c) mol. wt.: Calcd. 304. Found (in acetone) 317
d) mol. wt.: Calcd. 332. Found (in CCl_4) 345
e) mol. wt.: Calcd. 361. Found (in CCl_4) 376

oily material was extracted with ether, and the ether layer was washed with dil. HCl and water, and dried. Evaporation of the solvent left yellow powder (0.4 g.) which was taken up in EtOH, and filtered to give sulfur (70 mg.) as residue. From the filtrate, 0.3 g. (93%) of *p*-methoxybenzonitrile was obtained.

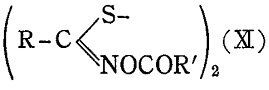
c) To a stirred suspension of sodium benzothiohydroxamate in anhydrous ether was added an equivalent of benzoyl chloride in ether during a period of about 1 hr., and the stirring was continued for another 1 hr. After addition of water, the separated ether layer was dried and evaporated. The residue was recrystallized from MeOH to yield dibenzoyl disulfide, m.p. 127~128°, identical in all respects with the authentic sample. The analogous procedure with a solution in acetone gave S,O-dibenzoylbenzothiohydroxamic acid (VIIIc) in 20% yield.

Oxidation of Thiohydroxamic Acid and O-Methylthiohydroxamic Acid——To aqueous solution of II was added 0.1*N* I_2 with stirring until the supernatant liquor turned a pale yellow. The precipitate was collected by filtration, washed with water, and dissolved in a minimal amount of EtOH. (Warming should be avoided for the dissolution.) The recrystallization was performed by addition of water until the solution became turbid, thereafter by allowing to stand at 0°. If necessary, the obtained crystals were recrystallized additionally from ether-petroleum ether. Diluted hydrogen peroxide solution could be used in place of 0.1*N* I_2. The disulfides (IX) which were obtained in 80~90% yields as colorless crystals were presented in Table VI. The disulfides of O-methylthiohydroxamic acid (X) as shown in Table VI were prepared by the analogous procedure. They were recrystallized from hot petroleum ether as colorless crystals.

To a solution of bis(N-hydroxybenzimidoyl) disulfide (IXd) (0.3 g.) was added zinc powder (0.1 g.), and the mixture was stirred at 50~60° until the zinc powder was almost consumed. After filtration, the residue was washed with water, EtOH and ether. Recrystallization from acetone gave white crystalline powder, the infrared spectrum of which was identical with that of bis(benzothiohydroxamato)Zn (II) which was directly prepared from sodium benzothiohydroxamate and zinc acetate.

To a solution of IXd in an equivalent of 20% NaOH was added an equivalent of dimethyl sulfate. The mixture was stirred for 2 hr. at 40°, and extracted with ether. After washing with dil. NaOH and wetar, the ether layer was dried, evaporated, and the resulting oil was purified by chromatography over alumina. Elution with 8:2 petroleum ether-ether gave Vb. On the one hand, the aqueous layer was acidified with dil. HCl, and the separated oil was isolated by extraction with ether. Evaporation of the solvent and recrystallization of the resulting residue from petroleum benzin gave IVd. An attempt of treating a suspension of IXd in ice cold 5% Na_2CO_3 with dimethyl sulfate did not show any reaction.

Acylation of IX——a) Benzoylation: To a solution of IX in ice-cold 7% NaOH was added a small excess of benzoyl chloride a little at a time, and the mixture was shaken vigorously whenever benzoyl chloride was added. The precipitated solid was filtered, washed with 7% NaOH and water. Recrystallization from AcOEt-EtOH gave the dibenzoyl derivatives (XI; $R'=C_6H_5$) in 50~80% yields as colorless crystals as shown in Table VII. Since the above mentioned procedure yielded the S,O-dibenzoyl derivative (VIIIk) for bis(N-hydroxy-2-furancarboimidoyl) disulfide (IXn), 5% Na_2CO_3 was used in place of 7% NaOH. For bis-(N-hydroxy-*m*-methylbenzimidoyl) disulfide (IXf), the both procedures gave VIIIe.

TABLE VII.

$$\left(R-C\begin{matrix}\diagup S- \\ \diagdown NOCOR'\end{matrix}\right)_2 \quad (XI)$$

No.	R	R'	Appearance	m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S	IR (CCl_4) $\nu_{C=O}$
XIa	CH_3	C_6H_5[a]	needle	165~166	$C_{18}H_{16}O_4N_2S_2$	55.65	4.15	7.21	16.51	55.98	4.46	6.89	16.69	1769
XIb	*n*-C_3H_7	〃	prism	95~96	$C_{22}H_{24}O_4N_2S_2$	59.44	5.44	6.30	14.43	59.52	5.21	6.18	14.14	1766
XIc	C_6H_5	CH_3	〃	112~113	$C_{18}H_{10}O_4N_2S_2$	55.65	4.15	7.21	16.51	55.74	4.17	7.33	16.10	1788
XId	〃	C_6H_5[b]	〃	173~174	$C_{28}H_{20}O_4N_2S_2$	65.60	3.93	5.47	12.51	65.80	4.21	5.65	12.27	1768
XIe	*p*-CH_3-C_6H_4	〃	scale	194~195	$C_{30}H_{24}O_4N_2S_2$	66.65	4.47	5.81	11.86	66.73	4.51	5.36	11.86	1767
XIf	*p*-Cl-C_6H_4	〃	〃	175	$C_{28}H_{18}O_4N_2S_2Cl_2$	57.87	3.12	4.82	11.03	57.95	3.14	4.91	11.31	1769
XIg	α-C_4H_3O	〃	prism	137~139	$C_{24}H_{16}O_6N_2S_2$	58.53	3.27	5.69	13.02	58.41	3.35	5.38	13.29	1770

[a] mol. wt.: Calcd. 389. Found (in acetone) 393

[b] mol. wt.: Calcd. 513. Found (in $CHCl_3$) 495

b) Acetylation: A solution of Ⅸd (0.3 g.) in pyridine (2 ml.) was cooled in dry ice-acetone, and an equivalent of acetyl chloride was added. The mixture was allowed to raise to room temperature slowly during a period of about one hour. After addition of 50 ml. of water, the separated oil was extracted with ether, washed with dil. HCl and water, and dried. Evaporation of the solvent left an oil (0.3 g.) which solidified on standing. The solid was taken up in ether, treated with charcoal, and filtered. Concentration of the solution and allowing to stand at 0° afforded 0.16 g. (50%) of bis(N-acetoxybenzimidoyl) disulfide (Ⅺc).

Rearrangement of XI with Alkali——a) A suspension of Ⅺc (0.48 g.) in 5% Na_2CO_3 (20 ml.) was stirred for 1 hr. at 80°. After cooling, the reaction mixture was extracted with ether, and the ether layer was washed with dil. NaOH and water, dried, and evaporated to dryness. The residue was taken up in a small amount of CCl_4, and filtered. An oil obtained from the filtrate was chromatographed on alumina. Elution with 8:2 petroleum ether-ether yielded the mixture (130 mg.) of benzisothiocyanate and benzonitrile in which the content of benzisothiocyanate was determined to be 120 mg. by ultraviolet spectrophotometric method in cyclohexane at 282 mμ. On the one hand, the insoluble material in CCl_4 was also chromatographed. With petroleum ether was eluted colorless crystals, m.p. 150°, and then with ether colorless crystals, m.p. 235~240°. Their infrared spectra were identical with those of authentic thiocarbanilide (m.p. 151°) and carbanilide (m.p. 234°), respectively. Furthermore, the above remaining aqueous solution after extraction with ether was acidified and extracted with ether again. From the extract was obtained yellow oil (25 mg.). The oil was taken up with a minimal amount of CCl_4 to give 5 mg. of thiocarbanilide as insoluble material, and benzothiohydroxamic acid was identified as nickel salt from the soluble material.

b) A suspension of Ⅺd (0.25 g.) in 10% Na_2CO_3 (5 ml.) was stirred at 60° for 1 hr. A portion of the mixture which was taken out occasionally onto a spot plate was added a solution of nickel acetate, but the orange precipitate of bis(O-benzoylbenzothiohydroxamato)Ni (Ⅱ)*3 did not occur. Then, after addition of a small amount of the solution of nickel acetate to the remaining reaction mixture, the solution was allowed to stir for another one hour, and extracted with $CHCl_3$. From the chloroform layer was obtained 95 mg. of Ⅺd and 70 mg. of the mixture of benzisothiocyanate and benzonitrile. Acidification of the aqueous layer yielded a small amount of bis(benzothiohydroxamato)Ni (Ⅱ) and benzoic acid.

Reaction of Sodium Benzothiohydroxamate and Bis(N-hydroxybenzimidoyl) Disulfide (IXd) with Alkali——a) A suspension of Ⅸd (0.7 g.) in 5% Na_2CO_3 (10 ml.) was heated on a steam bath for 2 hr. during which time a pale yellow liquid was obtained. After cooling, the solution was extracted with ether. Evaporation of the ether layer gave yellow oil (190 mg.) which was followed by chromatographic separation on alumina. Elution with petroleum ether and 8:2 petroleum ether-AcOEt gave benzonitrile (160 mg.) and a trace of aniline respectively, which were identified by comparing their infrared spectra with the authentic materials. Furthermore, 440 mg. of benzothiohydroxamic acid was obtained as nickel salt from the remaining aqueous layer.

b) A solution of sodium benzothiohydroxamate (0.9 g.) in 5% Na_2CO_3 (10 ml.) was heated on a steam bath for 8 hr. After cooling, the mixture was treated in the same manner as described in (a). Benzonitrile (0.2 g.), a trace of aniline, and benzothiohydroxamic acid (0.54 g.) were obtained.

Reaction of Bis(N-benzoyloxybenzimidoyl) Disulfide (XId) with Reducing Agents——a) A solution of Ⅺd (0.4 g.) in acetic acid (10 ml.) was heated with zinc powder (0.1 g.) for 0.5 hr. on a steam bath. Addition of water recovered Ⅺd (0.38 g.). Then heating was continued for another 3 hr., and the reaction mixture was extracted with ether after addition of water. The ether layer was washed with 5% $NaHCO_3$ and water, and dried. Concentration of the solution and filtration afforded 0.25 g. of Ⅺd as residue and 0.03 g. of benzonitrile from the filtrate. Zinc salt of O-benzoylthiohydroxamic acid was not obtained from any portion of the reaction mixture.

b) To a suspension of 0.4 g. of Ⅺd in EtOH (30 ml.) was added K_2S (0.5 g.) in a minimal water, and the mixture was stirred for 0.5 hr. as 40~50°, during which time a homogeneous orange solution was obtained. After concentration of the solvent to dryness at reduced pressure, the residue was taken up with ether and filtered. The filtrate was evaporated, and the resulting oil was chromatographed on alumina. The first elution with petroleum ether gave 150 mg. of benzisothiocyanate and the following elution gave a small amount of ethyl benzoate. The above residue which was insoluble in ether was taken up with acetone and filtered. From the filtrate, 80 mg. of potassium benzothiohydroxamate was obtained which was identified as nickel salt. From the residue, sulfur and sodium benzoate were afforded.

The same reaction by using $NaBH_4$ and $LiAlH_4$ in place of K_2S yielded the analogous reaction products.

S-Benzoyl-O-methylthiohydroxamic Acid (XII)——To a suspension of sodium O-methyl-*m*-nitrobenzothiohydroxamate (0.15 g.) in anhydrous benzene (10 ml.) was added a small excess of benzoyl chloride. The mixture was stirred for 1 hr. at 60° and filtered. Removal of the solvent *in vacuo* and recrystallization from petroleum benzine and additionally from MeOH afforded 0.12 g. (65%) of S-benzoyl-O-methyl-*m*-nitrobenzothiohydroxamic acid (Ⅻ; R=*m*-NO_2-C_6H_4) as colorless amorphous crystals, m.p. 61°. IR $\nu_{C=O}$ cm^{-1}: 1691 (CCl_4). *Anal.* Calcd. for $C_{15}H_{12}O_4N_2S$: C, 56.95; H, 3.82; N, 8.86; S, 10.14. Found: C, 56.95; H, 3.85; N, 8.94; S, 10.17.

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Summary

Thiohydroxamic acids react as thiol-form in aqueous solution, and gave S-alkyl and S,O-dialkyl derivatives, dibenzoyl derivatives, and the disulfides (I). Monobenzoyl derivatives were not obtained because of their instability. The structures of these derivatives were confirmed by the investigations of the infrared spectra. It was found that the S-S linkage of I are apt to cleave by alkali so that diacyl derivatives of I are easily rearranged to the corresponding isothiocyanate and 1,3-dialkyl-2-thiourea. The mechanism of the rearrangement seemed to be analogous to that of the Lossen rearrangement.

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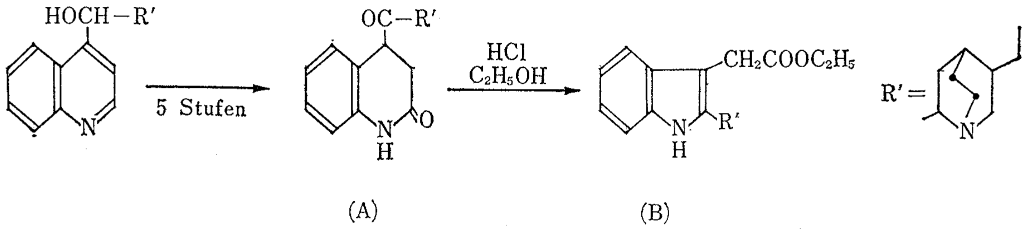
UDC 547.753.07

173. Eiji Ochiai und Makoto Takahashi: Nachtrag zur Synthese von Indolderivaten aus entsprechenden Hydrocarbostyril-Derivaten.[*1]

(*ITSUU Laboratory*[*2])

Seit Entdeckung der Tatsache1), daß 2-Oxohexahydrocinchoninon (A) beim Erhitzen in äthanolischer Chlorwasserstoff-Lösung in 2′-[3-Äthyl-8-chinuclidyl)-3′-indolessigsäureäthylester (B) mit guter Ausbeute übergeht, wurde diese Reaktion zu einer neuen synthetischen Methode von 3-Indolessigsäureester-Derivaten aus Hydrocarbostyrilen entwickelt, die auf ihrer 4-Stellung eine Carbonylgruppe tragen.2-8)



Schema 1.

[*1] Gleichzeitig VIII. Mitteilung über Synthese von Indolderivaten. VII. Mitteilung: M. Takahashi: Dieses Bulletin, **14**, 1144 (1966).

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6) M. Takahashi: *Ibid.*, **13**, 25 (1963).

7) *Idem*: *Ibid.*, **14**, 23 (1965).

8) E. Ochiai, T. Dodo: *Ibid.*, **14**, 33 (1965).