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78. Isoo Ito : Synthesis of Antibiotics. I. Synthesis of N-Substituted Compounds of Monochloroacylamide and Their Antitrichophyton Effect.

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The purpose of the work reported here is the synthesis of some N-substituted compounds of monoacylamide which are chloramphenicol analogs, and examination of their antitricophyton effect.

Aromatic primary amines or halogenated aromatic primary amines were condensed with monochloroacyl derivatives in good yield, and their general synthesis is shown in a following chart.

(R_1, R_2 : Refer to Table Ⅱ. Compounds (Ⅰ~Ⅵ) are known substance.)

Chart 1.

The compound (Ⅶ) (in Table Ⅱ), one of seven new compounds (Ⅶ~XⅢ), was obtained as a following procedure, that is *O*-hydroxybenzoic acid and chloroacetyl chloride were reacted in benzene, solvent was removed under reduced pressure, and a small amount of toluene was added into the residue to obtain crystals, which dissolved again in benzene to remove insoluble material. By distillation of benzene compound (Ⅶ) (m.p. 153°) was obtained.

2-Chlorocrotonoyl chloride,[1] the starting material of *trans*-2,4′-dichlorocrotonanilide (Ⅷ), was synthesized as a following procedure, that is, *trans*-crotonic acid (a) (m.p. 71° colorless prisms) was prepared first by the method of Michael.[2] In this case the presence of a small amount of piperidine improved the yield to 85%. Then, according to the method of Pfeiffer,[3] *trans* compound (a) was converted to 2,3-dichlorobutyric acid (b) ($b.p_{20}$ 124~126,° colorless prisms,m.p.63° (from ether)) by introducing Cl_2 under sunlight. Dehalogenation of (b) by heating in pyridine gave *trans*-2-chlorocrotonic acid (c) in 28.5% yield. Colorless needles, m.p. 99~99.5° from hexane. This reaction is due to easy release of halogen atom in 3-position by hyperconjugation[4] effect of CH_3-group in 4-position. 2-Chloro compound (c) was reacted with $SOCl_2$ to give acid chloride (d)

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1) H. Scheibler, J. Magsanik : Ber., **48**, 1814 (1915).
2) A. Michael, O.D.E. Bunge : *Ibid.*, **41**, 2910 (1908).
3) P. Pfeiffer : *Ibid.*, **43**, 3039 (1910).
4) J.M. Robertson : J. Chem. Soc., **1945**, 249.

(colorless oil b.p.142°), and by the reaction of (d) and *p*-chloroaniline (g) in benzene at room temp. *trans*-2-chloro-amide compound (Ⅷ) was obtained. Colorless leaves, m.p. 93.5°, *cis*-2-chlorocrotonoyl chloride (f), starting material of *cis*-2,4′-dichlorocrotonanilide (Ⅸ)

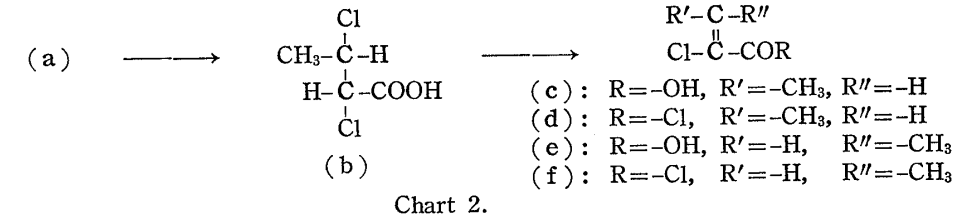


Chart 2.

was prepared as a following method, *i.e.*, according to Wislicenus,[5] 2,3-dichloro compound (b) was heated in 10% NaOH for 6 hr., the reaction mixture was made acid with sulfuric acid and the resulting oil was converted to potassium-salt with potassium hydroxide. This potassium-salt was dissolved in abs. ethanol and insoluble *trans* potassium-salt was filtered off, and the solvent of filtrate was distilled. The residue was dissolved again in water and made acid with sulfuric acid to liberate oily substance, which was extracted with ether. By the evaporation of ether resulting oily residue was recrystallized from hot water to afford *cis*-2-chloro compound (e) (colorless needles m.p. 63~65°). Acid chloride (f) was obtained by the reaction of *cis*-2-chloro compound (e) and thionyl chloride. Acid chloride (f) and amine (g) by the method of Schotten-Baumann gave crude amide (Ⅸ). Since this crude amide contained *trans* compound (Ⅷ), it was refined as a following procedure, *i.e.*, crude (Ⅸ) was dissolved in hexane, insoluble *trans* compound (Ⅷ) was removed and filtrate was condensed to obtain *cis* compound (Ⅸ) (colorless needles m.p. 58°) in 38% yield. As shown in Table I, infrared spectrum of this compound supports its structure, and elemental analytical data agreed well.

Synthesis of *trans*-4-bromo-4′-chlorocrotonanilide (Ⅺ) followed two methods: method (A) starting with *trans*-4-bromo compound (i) and method (B) starting with *trans*-4′-chlorocrotonanilide (Ⅹ). The compound obtained by two methods was assigned to be amide compound (Ⅺ) by the mixed melting point determination and the comparison of the infrared spectrum.

Method A. *trans* compound (a) was reacted in tetrachlorocarbon with N.B.S. under the presence of benzoylperoxide. The end of reaction was tested by iodostarch paper, and treated by usual method to obtain *trans*-4-bromocrotonic acid (i) (m.p. 75° needles from hexane) in 60% yield, which was identical with a sample obtained by Wohl[6] from *trans* compound (a) and N.B.A.

The reaction of 4-bromo compound (i) and thionyl chloride gave acid chloride (j) as colorless oil (b.p_{20} 80°), which was reacted with amine (g) to obtain 4-bromo-amide (Ⅺ).

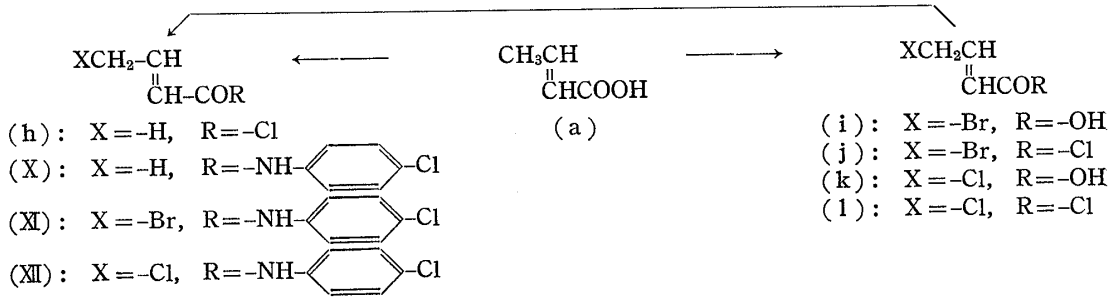


Chart 3.

5) J. Wislicenus : Ber., **20**, 1008 (1887).
6) A. Wohl, K. Jaschinowski : *Ibid.*, **54**, 476 (1921); G. Broun : J. Am. Chem. Soc., **52**, 3173 (1930).

Being brown grutinous substance and difficult to crystallize, it was converted to hexamine salt. Colorless prisms. m.p. 199° (decomp.) from hydrated acetone.

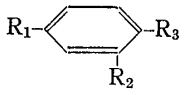
Method B. Acid chloride (h) was obtained quantitatively by the reaction of (a) and thionyl chloride as colorless oil (b.p_{12} 66~67°[7]), which was reacted with amine (g) to give amide (X). This was reacted with N.B.S. in solvents of tetrachlorocarbon and

Table I. Infrared Spectra of R_1-NHCOCR_2=CHCH_2R_3 (in KBr)

No.	Compound R_1	R_2	R_3	ν_{NH} cm^{-1} *trans*	*cis*	$\nu_{C=C}$ cm^{-1} *trans*	*cis*	$\nu_{C=O}$ cm^{-1} *trans*	*cis*	δ_{-CH} cm^{-1} *trans*	*cis*
X	Cl	H	H	3320 s	—	1670 m	—	1640 m	—	956 s	—
Ⅷ, Ⅸ	〃	Cl	〃	3320 〃	3320 s	1660 m	1680 s	1630 m	1635 m	956 m	936 m
Ⅻ	〃	H	Cl	3200 〃	—	1660 broad (m)	—	—	—	960 s	—

s: strong m: medium

Table Ⅱ. Fungical Effect of N-Substituted Compounds of Monoalkyl Amide Derivatives



No.	R_1	R_2	R_3	m.p. (°C)	Formula	Grade of stimulation on skin	Minimum stopping growth concentration bouillon	γ/ml.
Ⅰ	H	H	-NHCOCH_2Cl	135	C_8H_8ONCl	##	10, 000	100
Ⅱ	CH_3CH_2O	〃	〃	145	$C_{10}H_{12}O_2NCl$	##	10, 000	100
Ⅲ	H	〃	-CH_2NHCOCH_2Cl	97	$C_9H_{10}ONCl$	##	9, 000	110
Ⅳ	Cl	〃	-NHCOCH_2Cl	170	$C_8H_7ONCl_2$	##	300, 000	3
Ⅴ	H	Cl	〃	73	〃	##	10, 000	100
Ⅵ	Br	H	〃	183	$C_8H_7ONClBr$	+	9, 000	110
Ⅶ	H	COOH	-OCOCH_2Cl	135. 5	$C_9H_7O_4Cl$	—	5, 000	200
Ⅷ	Cl	H	-NHCOC(Cl)=CHCH_3	93. 5	$C_{10}H_9ONCl_2$	+	5, 000	200
Ⅸ	〃	〃	-NHCOCCl(CH_3-CH)	58	〃	+	5, 000	200
X	〃	〃	-NHCOCH(CHCH_3)	172	$C_{10}H_{10}ONCl$	+	1, 000	100
Ⅺ	〃	〃	-NHCOCH(CHCH_2Br)	199 (decomp.) (hexamin salt)	$C_{10}H_9ONClBr$	+	5, 000	200
Ⅻ	〃	〃	-NHCOCH=CHCH_2Cl	204 (decomp.) (hexamin salt)	$C_{10}H_9ONCl_2$	+	10, 000	100
XIII	〃	〃	-NHCOC(Cl)=CH_2	109	$C_9H_7ONCl_2$	+	3, 000	333

Trichophyton interditale obtained from patient was used as test fungy. Sabouroud glucose agar was used as cultured medium (27, 10 hr.).

1% EtOH solution of test drugs was made as original solution and diluted gradually from 1000 times bouillon.

The following marks mean the grades of stimulation on skin (man's hand). ##: very strong, +: strong, −: no effect.

Ⅰ) 2-Chloroacetanilide. Ⅱ) 2-Chloro-*p*-acetophenetidide. Ⅲ) N-benzyl-2-Chloroacetamide.
Ⅳ) 2,4′-Dichloroacetanilide. Ⅴ) 2,2′-Dichloroacetanilide. Ⅵ) 2-Chloro-2′-bromoacetanilide.
Ⅶ) *o*-Chloroacetoxybenzoic acid. Ⅷ) *trans*-2,4′-Dichlorocrotonanilide. Ⅸ) *cis*-2,4′-Dichlorocrotonanilide.
X) *trans*-*p*-Chlorocrotonanilide. Ⅺ) *trans*-4-Bromo-4′-chlorocrotonanilide.
Ⅻ) *trans*-4,4′-Dichlorocrotonanilide. XIII) 2,4′-Dichloroacrylanilide.

7) N. H. Cromwell, F. Pelltier: J. Org. Chem., **15**, 877 (1950).

chloroform, then treated by usual procedure to 4-bromo-amide (XI) (hexamine salt m.p. 199° (decomp.)). Mixed melting point of hexamine salt obtained by the method A and the method B did not show any depression and infrared spectra of the two substances were identical and characteristic peaks were exhibited in Table I.

Synthesis of *trans*-4,4′-dichlorocrotonanilide (XII) was carried out by the method (C) to start with chloro compound (k) and the method (D) to use 4-bromo-amide (XI), and confirmed to be identical by the mixed melting point determination.

Method (C). In order to convert bromo compound (i) to chloro compound (k), following procedure was carried out: Bromo compound was reacted with stirring in a dark place at room temp. under the presence of silver chloride and acetone. Solvent was distilled and the residue was recrystallized from hexane to obtain colorless leaves 4-chloro compound (k) (m.p. 83° from hexane) in 90% yield. Melting point of this compound was identical with that of a sample obtained by other method.[6] By the reaction of chloro compound (k) and thionyl chloride acid chloride (l) ($b.p_{16}$ 74° colorless oil) was obtained, and from acid chloride (l) and amine (g) *trans*-4,4′-dichlorocrotonanilide (XII) was prepared. Being oil, it was induced to hexamine salt (colorless prisms m.p. 204° (decomp.)) and its elemental analysis was satisfactory.

Method (D). 4-chloro-amide (XII) was obtained by heating 4-bromo-amide (XI) and silver chloride in anhydrous acetone, and hexamine salt of XII was identical with that of the sample obtained by the reaction of acid chloride (l) and amine (g).

On the infrared spectrum, the C=C stretching is strong in *cis* form and weak in *trans*, because of symmetry of molecule. The CH deformation in *trans* is sifted to higher frequency.

Experimental*2

General Procedure for Synthesis of Substance (Table II, No. I [8], II[9])——To a solution of $ClCH_2COCl$ (1 mole) dissolved in benzene, a solution of 2 moles of corresponding amine dissolved in benzene was added with stirring and treated by usual method. stimulant to skin.

General Procedure for Synthesis of Substance (Table II, No. III,[10] IV,[11] V,[12] VI[13])——Corresponding amine (1 mole) was acylated in benzene with monochloroacetylchloride (1 mole). 10% NaOH was used as dehydrochloric acid agent. Strong stimulant to skin.

***O*-Chloroacetoxybenzoic Acid (VII)**——To 30 ml. of benzene solution containing 6.9 g. (1 mole) of salicylic acid, a solution of 8.4 g. (1.5 moles) of monochloroacetyl chloride in 10 ml. of benzene was added and heated on an oil bath and refluxed for 5 hr. After evolution of HCl ceased, solvent and excess acid halide were distilled under reduced pressure. By the addition of a small amount of toluene into the residue and by cooling, the resulting crystals were extracted with benzene. Insoluble substance (m.p. 185~189°) in benzene was filtered off, benzene was distilled to get crystals which were recrystallized from benzene. Colorless needles. m.p. 135°, yield 4 g. *Anal.* Calcd. for $C_9H_7O_4Cl$: C, 50.46; H, 3.27; Cl, 16.57. Found: C, 50.26; H, 3.41; Cl, 17.09.

***trans*-2,4′-Dichlorocrotonanilide (VIII)**——To a cooled benzene solution of 11 g. of *p*-chloroaniline, a solution of 0.6 g. of 2-chlorocrotonoyl chloride in benzene was added under stirring and cooling with ice water, and stirring was continued for 24 hr. at room temp. Solvent was distilled and the residue was extracted with petroleum ether, which was evaporated to get crystals. Colorless leaves m.p. 93~93.5° (from petr. ether). *Anal.* Calcd. for $C_{10}H_9ONCl_2$: C, 52.17; H, 3.91; N, 5.08; Cl, 30.86. Found: C, 51.90; H, 4.44; N, 5.34; Cl, 30.43.

***cis*-2,4′-Dichlorocrotonanilide (IX)**——To a benzene solution of 0.5 g. of *cis*-2-chlorocrotonoyl chloride, a solution of 0.92 g. (2 moles) of *p*-chloroanilide dissolved in benzene was added under stirring and cooling

*2 All melting points are uncorrected.

8) E. Votocek, J. Burda: Ber., **48**, 1003 (1915).
9) A. Bistrzycki, F. Ulffers: *Ibid.*, **31**, 2789 (1898).
10) C. A. Buchler: J. Am. Chem. Soc., **59**, 421 (1937).
11) J. Hill, B. Kelsey: *Ibid.*, **44**, 2359 (1922).
12) C. G. Schwalbe, W. Schulz: Ber., **41**, 3791 (1908).
13) W. A. Jacobs: J. Biol. Chem., **21**, 110 (1915).

with ice water. The resulting crystals were collected by filtration, washed with 10% HCl, 3% $NaHCO_3$, and then with water. By recrystallization from petr. ether 0.2 g. of m.p. 93°(*trans*) was obtained. From the mother liquor colorless needles (m.p. 58° from petr. ether) were obtained. *Anal.* Calcd. for $C_{10}H_9ONCl_2$: N, 5.08; Cl, 30.86. Found: N, 4.89; Cl, 31.24.

***trans*-*p*-Chlorocrotonanilide (X)**——To a benzene solution of 2.5 g. of *p*-chloroaniline and 2.0 g. of *trans*-crotonoyl chloride (b.p. 124~125°), 10 ml. of 10% NaOH was added with stirring to obtain crystals which were collected by filtration, and washed with dil. HCl and then water. Needles, m.p. 172°(from EtOH), yield 2.7 g.(71%). *Anal.* Calcd. for $C_{10}H_{10}ONCl$: C, 61.38; H, 5.11; N, 7.16. Found: C, 61.03; H, 5.32; N, 6.92.

***trans*-4-Bromo-4′-chlorocrotonanilide (XI). Method A**——To a solution of 1 g. of *p*-chloroaniline in 5 ml. of benzene, a solution of 0.73 g. of *trans*-4-bromocrotonoyl chloride ($b.p_{20}$ 84°) in benzene was added under stirring and ice water cooling. One hour later, the resulting crystals were collected by filtration and washed with hot benzene, which was combined with filtrate and condensed under reduced pressure to give a brown syrupy substance, to which a small amount of CCl_4 was added and warmed and filtered. The filtrate was condensed to yield 0.7 g.(63.6%) of brown glutinous substance, a part of which was added to a solution of hexamine dissolved in $CHCl_3$ and warmed, and resulting crystals were collected by filtration and recrystallized from hydrated acetone to obtain colorless prisms. m.p. 199°(decomp.). *Anal.* Calcd. for $C_{10}H_9ONClBr\cdot(C_6H_{12}N_4)$: C, 46.32; H, 5.06; N, 16.88; halogen (Cl, Br), 27.86. Found: C, 46.73; H, 5.41; N, 16.56; halogen (Cl, Br), 27.56.

Method B——To a mixture of CCl_4(5 ml.) and $CHCl_3$(15 ml.), 0.98 g. of compound (X) was dissolved and 1.8 g. of N. B. S. and 0.2 g. of benzoyl peroxide was added with mechanical stirring at 40° under radiation of ultraviolet rays, until potassium iodide starch paper did not show a reaction, and the resulting succinimide was filtered and the filtrate was distilled under diminished pressure to get oily residue, which was dissolved in ether and treated with active carbon to give brown oil. Yield 0.9 g.(65.7%). Mixed melting point of this compound and a sample obtained by the method A did not show any depression.

***trans*-4,4′-Dichlorocrotonanilide (XII). Method A**——A mixture of 1.2 g. of XI dissolved in 5 ml. of dried acetone and 1.25 g. of AgCl (or 1.2 g. of LiCl) was stood over in a dark place at 40~50° for 6 hr. with mechanical stirring. AgBr was filtered off and the filtrate was condensed to give light brown oil, which was dissolved in ether and treated with active carbon to yield 0.6 g.(60%) of brown syrupy substance, 0.3 g. of which and 0.3 g. of hexamine were dissolved in $CHCl_3$ and heated to obtain crystals. Colorless prisms, m.p. 204°(from acetone). *Anal.* Calcd. for $C_{10}H_9ONCl_2(C_6H_{12}N_4)$: C, 51.89; H, 5.67; N, 18.91; Cl, 19.18. Found: C, 51.54; H, 5.79; N, 19.21; Cl, 19.56.

Method B——To a solution of 1.81 g. of *p*-chloroaniline in 10 ml. of ether, 1 g. of *trans*-4-chlorocrotonoyl chloride ($b.p_{24}$ 78°) was added unde stirring and ice water cooling. After 3 hr. resulting crystals were collected by filtration and washed with ether, which was combined with filtrate and distilled under diminished pressure to yield 1.8 g.(72%) of brown oil. Hexamine salt (colorless prisms, m.p. 204°(decomp.)) and a sample prepared by the method A were comfirmed to be identical by the mixed melting point determination.

2,4′-Dichloroacrylanilide (XIII)——To a solution of 2.9 g. of *p*-chloroaniline in 50 ml. of benzene, a solution of 1.4 g. of 2-chloroacryloyl chloride[14] ($b.p_{80}$ 55°) in 10 ml. of benzene was added dropwise under stirring and cooling with ice water for 6 hr. The resulting crystals were filtered and washed with hot benzene, which was combined with filtrate and distilled to crystals which was washed with 10% HCl, and water, dissolved in CCl_4, dried over anhydrous Na_2SO_4. By condensing CCl_4 solution, and recrystallizing from benzene, colorless needles were obtained. m.p. 109°. *Anal.* Calcd. for $C_9H_7ONCl_2$: C, 50.00; H, 3.26; N, 5.54; Cl, 32.86. Found: C, 50.31; H, 3.43; N, 5.43; Cl, 32.99.

***p*-Chloroacrylanilide (XIV)**——To a solution of 2.5 g. of *p*-chloroaniline in 30 ml. of benzene, a solution of 0.9 g. of acryloyl chloride[15] (b.p. 75°) prepared from sodium acrylate and $SOCl_2$, in 10 ml. of benzene was added dropwise at room temp. under stirring for 1.5 hr. The resulting crystals were collected by filtration and washed with 10% HCl, and then with water, recrystallized from benzene to afford colorless needles m.p. 177~178°. *Anal.* Calcd. for C_9H_8ONCl: C, 59.55; H, 4.44; N, 7.77; Cl, 19.55. Found: C, 59.32; H, 4.64; N, 7.54; Cl, 19.50.

The author is very grateful to Emeritus Professor S. Sugasawa of the University of Tokyo for his kind guidance throughout the course of this investigation, and also to Professor S. Yamada of the University of Tokyo for his kind advice.

The author is also indebted to Professor H. Ozawa of the University of Tohoku for the evaluation of fungical effect, and Mrs. M. Hasegawa of this Faculty for carrying out the elemental analyses.

14) C. S. Marvel, H. G. Cooke: J. Am. Chem. Soc., **62**, 3495 (1940).
15) G. D. Jones, J. Zomlefer: J. Org. Chem., **9**, 506 (1944).

Summary

Thirteen kinds of monohalogenoacyl substituted aromatic derivatives were synthesized and tested their antitrichophyton effect.

On anilide, Cl substitution of *p*-position is 30 times as strong as that of *o*-position, and Cl substitution is 33 times as strong as Br substitution. The double bond of acyl group of monohalogenoacyl substituted aromatic amide derivatives did not show strong fungical effect, and there was no difference of fungical effect between *cis* and *trans*.

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79. Tetsuji Kametani and Kazuo Kigasawa : Azabenzomorphane and Related Compounds. Ⅸ.*1 A Synthesis of 3-Benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine. (Studies on the Synthesis of Heterocyclic Compounds. CXLI.*2)

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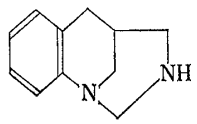
In the previous papers*1,1~5) several kinds of azabenzomorphane derivatives were synthesized. The purpose of the present investigation was to synthesize 3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (I), which appeared to have some analgesic activity.



I

Since the skeleton of compound (I) mentioned above has not yet been synthesized, methods for its synthesis were examined, using 3-cyanoquinoline (Ⅱ) as a starting material according to the procedures reported in the syntheses of imidazolidine and hexahydropyrimidine derivatives6~8) and 1,3-diazoadamantane derivatives9). Thus synthetic methods of 3-(N-benzylaminomethyl)-1,2,3,4-tetrahydroquinoline (Ⅵ), which was thought to be a key compound for synthesis of 3-benzyl-3,4,5,6-tetrahydro-2*H*-1,5-methanobenzo[*d*][1,3]diazocine (Ⅸa) and its 2-phenyl derivative (Ⅸb), were investigated according to the two methods as follows.

Hydrolysis of 3-cyanoquinoline (Ⅱ)10) which was obtained by the Rosenmund-von Braun reaction of 3-bromoquinoline10) gave quinoline-3-carboxylic acid (Ⅲ).11) Catalytic

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*1 Part Ⅷ : T. Kametani, K. Kigasawa, T. Hayasaka : This Bulletin, **13**, 1225 (1965).
*2 Part CXL : T. Kametani, *et al.* : Yakugaku Kenkyu, **37**, No. 2, 1 (1966).
*3 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄).

1) T. Kametani, *et al.* : Yakugaku Zasshi, **84**, 405 (1964).
2) T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru : This Bulletin, **13**, 295 (1965).
3) T. Kametani, K. Kigasawa, T. Hayasaka : *Ibid.*, **13**, 300 (1965).
4) T. Kametani, K. Kigasawa, M. Hiiragi : *Ibid.*, **13**, 1225 (1965).
5) *Idem* : Yakugaku Zasshi, **85**, 871 (1965).
6) R. C. Elderfield : "Heterocyclic Compound," **6**, 314 (1957).
7) H. W. Wanzlick, W. Löckel : Chem. Ber., **86**, 1463 (1953).
8) J. H. Billmann, L. C. Dormann : J. Org. Chem., **27**, 2417 (1962).
9) H. Stetter, H. Hennig : Chem. Ber., **88**, 789 (1955).
10) E. Ochiai, S. Fujise : "Jikken Kagaku Koza," **21**, Ⅲ, 343 (Maruzen Co., Ltd.).
11) H. Gilman, S. M. Spatz : J. Am. Chem. Soc., **63**, 1553 (1941).