Wasser wurde 24 Stunden lang unter Rückfluss gekocht. Die Reaktionsmischung wurde einmal mit aktiver Kohle behandelt und das Filtrat mit 10%iger HCl bis Kongorotsauer neutralisiert. Hierbei schieden sich Nadeln aus. Sie wurden abgesaugt und aus Wasser umkristallisiert. Nadeln vom Schmp. über 280°. Die Ausbeute : 1.65 g. $C_9H_7NO_3S$—Ber. : N, 6.7. Gef. : N, 7.35.

4-Cyanopyridin—1 g Natrium-pyridin-4-sulfonat wurde mit 0.9 g KCN innig gemischt, in ein Destillierkolben versetzt und unter vermindertem Druck (ca. 40 mm Hg-Druck) auf direkter Flamme vorsichtig erhitzt. Das hierbei übergehende Destillat erstarrte sich kristallinisch. Aus Petroläther umkristallisiert bildet es Nadeln vom Schmp. 79°. Eine Mischprobe mit dem 4-Cyanopyridin[4] schmolz bei 79°. Die Ausbeute : 0.31 g. Pikrat : Nadeln vom Schmp. 198~199. $C_6H_4N_2 \cdot C_6H_3O_7N_3$—Ber. : C, 43.3; H, 2.1. Gef. : C, 43.54; H, 2.18.

4-Cyano-α-pikolin—8.7 g Natrium-α-pikolin-4-sulfonat und 7.4 g KCN wurden innig gemischt und in einem Destillierkolben auf direkter Flamme analogerweise erhitzt. Das übergegangene, schwach gelbe ölige Destillat wurde in Äther aufgenommen, mit wasserfreiem Na_2SO_4 getrocknet, der Äther abdestilliert und der Rückstand im Vakuum destilliert. Sdp_{20} 90~94°. Das Destillat erstarrte sich zu Nadeln vom Schmp. 44~46°. Die Ausbeute betrug 3.1 g. Eine Mischprobe mit dem 4-Cyano-α-pikolin[1] zeigte keine Depression. Pikrat : Nadeln vom Schmp. 165~167°. $C_7H_6N_2 \cdot C_6H_3O_7N_3$—Ber. : C, 45.0; H, 2.6; N, 20.2. Gef. : C, 45.26; H, 2.38; N, 20.02.

4-Cyano-2,6-lutidin—Aus 1 g. Natrium-2,6-lutidin-4-sulfonat und 0.9 g. KCN analogerweise wie oben dargestellt. Nadeln vom Schmp. 81~82°. Die Ausbeute : 0.35 g. $C_8H_8N_2$—Ber. : C, 72.7; H, 6.1; N, 21.2. Gef. : C, 72.53; H, 6.05; N, 21.30. Pikrat : Nadeln vom Schmp. 175~177.5°. $C_8H_8N_2 \cdot C_6H_3O_7N_3$—Ber. : C, 46.5; H, 3.1; N, 19.4. Gef. : C, 46.57; H, 3.24; N, 19.92.

4-Cyanochinolin—Aus 0.9 g Natrium-chinolin-4-sulfonat und 0.9 g KCN analogerweise wie oben dargestellt. Nadeln vom Schmp. 100~101.5°. Die Ausbeute : 0.52 g. Pikrat : Nadeln vom Schmp. 175~177°. Eine Mischprobe der freien Base sowie des Pikrates mit dem entsprechenden Präparat des 4-Cyanochinolins[2] zeigte keine Depression.

Zusammenfassung

Das 4-Chlorderivat des Pyridins, α-Pikolins, 2,6-Lutidins bzw. Chinolins gibt beim Erhitzen mit Natriumsulfit im wässerigen Medium das entsprechende Natrium-4-sulfonat mit befriedigender Ausbeute. Jedes Sulfonat wurde durch Erhitzen mit Kaliumcyanid in das entsprechende 4-Cyanoderivat mit befriedigender Ausbeute übergeführt.

(Eingegangen am 3. Juni, 1954)

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56. Shigeru Yoshida : Studies on the Allied Compounds of Vitamin B_1. XVII[1]. Structure of N-Substituted Thiocarbamates.

(*Takamine Research Laboratory, Sankyo Co., Ltd.**)

In the previous papers of this series[2~4], the writers concluded that the substance formed by the condensation of the amine (I), α-haloketone (II), and carbon disulfide does not have the structure of a dithiocarbamate (III) but is an N-substituted 4-hydroxythiazolidine-2-thione (IV), from the infrared and ultraviolet absorption spectra, and the color reactions.

Based on the assumption that the thiocarbamate, obtained by Todd and others[5,6] and

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[1] Part XVI : Unpublished

[2] Yoshida, Ishizuka : *Ibid.*, **74**, 331 (1954).

[3] *Ibid.*, **74**, 335 (1954).

[4] *Ibid.*, **74**, 604 (1954).

[5] P. Sykes, A. R. Todd : J. Chem. Soc., **1951**, 535.

[6] *Ibid.*, **1951**, 2507.

by Matsukawa and others⁷⁾, as an intermediate in the synthesis of thiamine-thiazolone, might also be an N-substituted 4-hydroxythiazolidin-2-one formed by cyclization as in the case of dithiocarbamate, examination of the structure of the thiocarbamate was carried out.

Following the method of Todd and others, S-phenacyl N-benzylthiocarbamate (VIII) was obtained from benzylamine (V), carbonyl sulfide (VI), and ω-bromoacetophenone (VII). (VIII) failed to react with carbonyl reagents and lacked the absorption of a carbonyl in its infrared absorption spectrum (Fig. 1), showing a strong absorption at 6.09 μ.

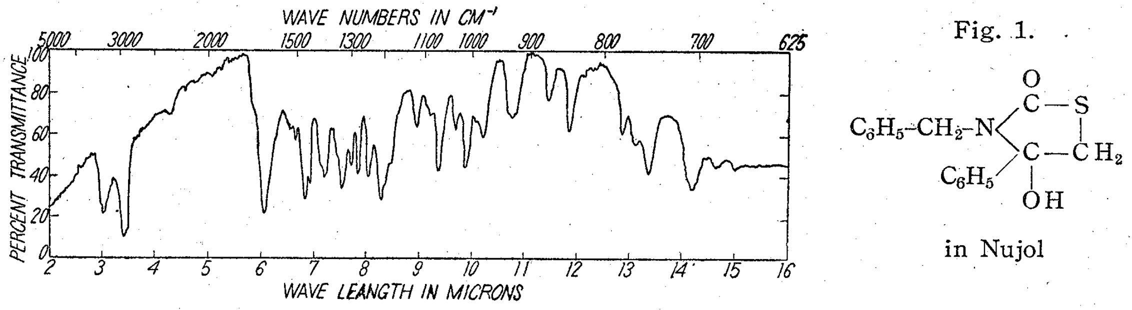

Fig. 1.

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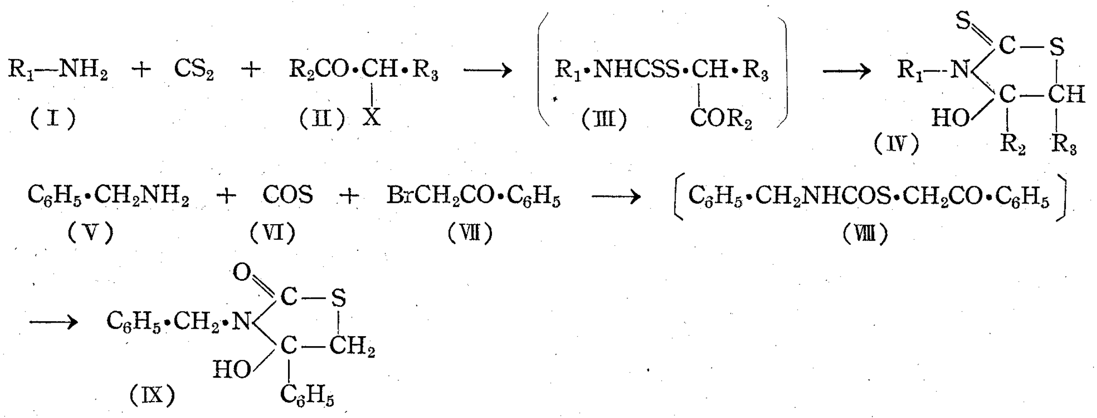
Therefore, the substance should not be represented by formula (VIII) but should be assumed as N-benzyl-4-hydroxy-4-phenylthiazolidin-2-one (IX). The absorption at 6.09 μ is assumed to be that of a disubstituted amide, >N-C=O.⁸⁾



Further, the thiocarbamates (XII) obtained from 2-methyl-4-amino-5-aminomethylpyrimidine (X), (VI), and γ-aceto-γ-chloropropyl alcohol (XI, R=OH) or γ-aceto-α,γ-dichloropropane (XI, R=Cl), lack the carbonyl absorption and each shows a strong absorption of a disubstituted amide that the structure should not be (XII) and (XIII) is more appropriate (Figs. 2 and 3).

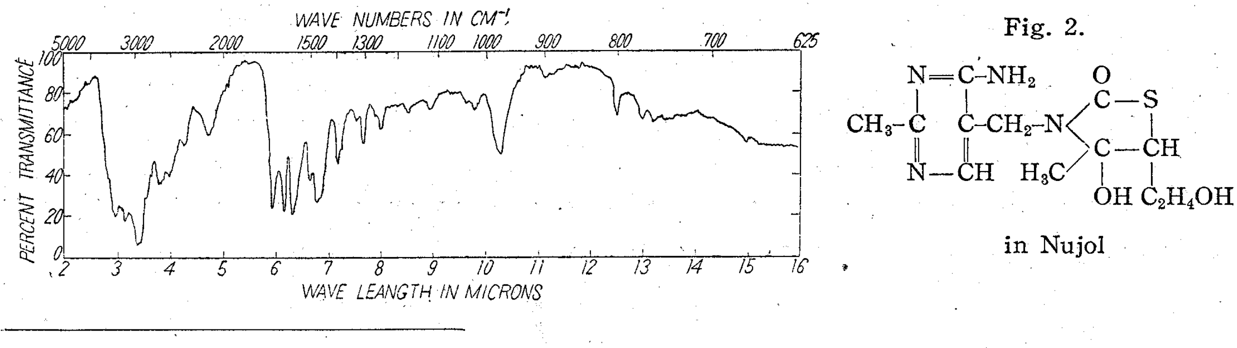


Fig. 2.

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7) T. Matsukawa, T. Iwatsu: Science, **115**, 215 (1952).
8) a) R. E. Richards, H. W. Thompson: J. Chem. Soc., **1947**, 1248.
b) N. G. Ettlinger: J. Am. Chem. Soc., **72**, 4699 (1950).

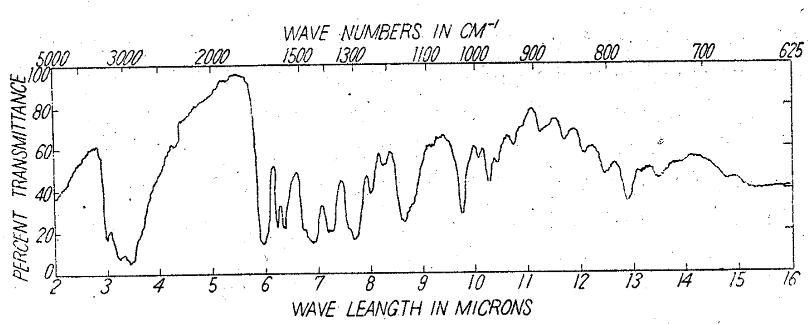
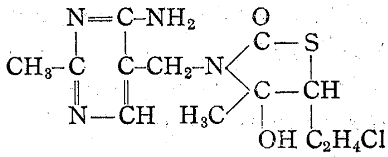


Fig. 3.



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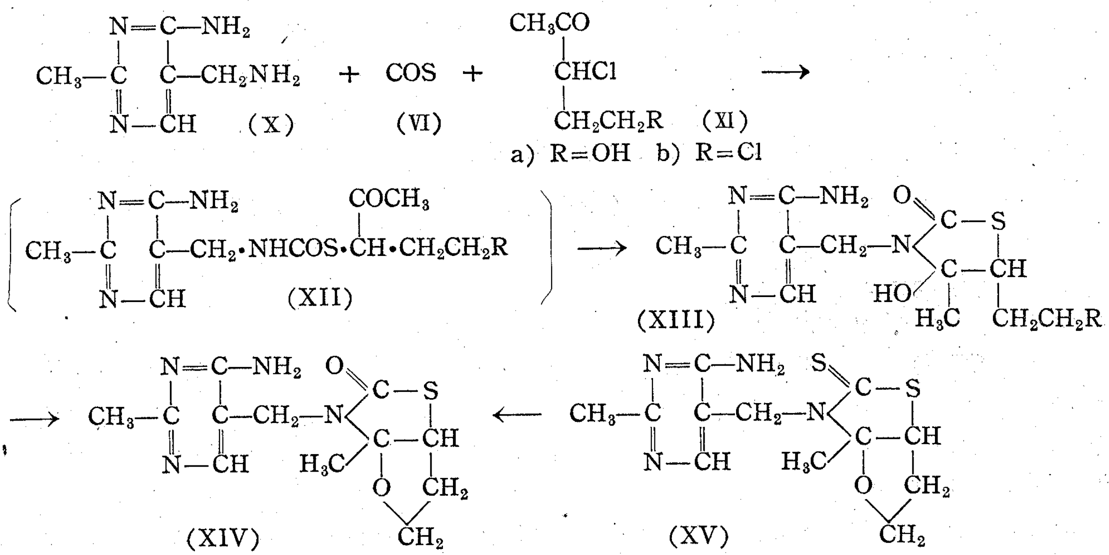


Treatment of (XIII, R=Cl) with alkali results in dehydrochlorination and forms 3-[2′-methyl-4′-aminopyrimidyl-(5′)]-methyl-3a-methyltetrahydrofuro[2, 3-d]thiazolidin-2-one (XIV), which is identical with the substance obtained by the writers[9] by the oxidation of 3-[2′-methyl-4′-aminopyrimidyl-5′)]-methyl-3a-methyltetrahydrofuro[2,3-d]thiazolidine-2-thione (XV) with hydrogen peroxide in alkaline or acid medium.

S-Phenacyl N-dimethylthiocarbamate (XVII), prepared from dimethylamine (XVI), (VI), and (VII), gives a phenylhydrazone of m.p. 147° and its infrared absorption spectrum shows the absorption of C=O of acetophenone at 5.91 μ and a strong absorption of >N-C=O at 6.06 μ (Fig. 4). Since (XVII) cannot undergo cyclization, it reacts with carbonyl reagents and shows the absorption of C=O in its infrared spectrum. This fact is assumed to give further support to the structures of (IX) and (XIII).

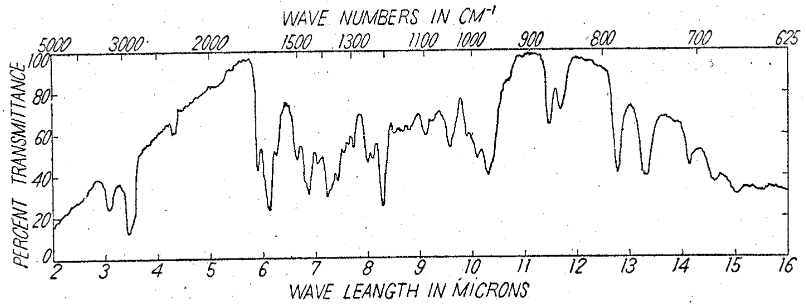
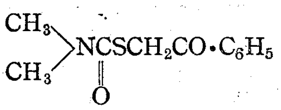


Fig. 4.



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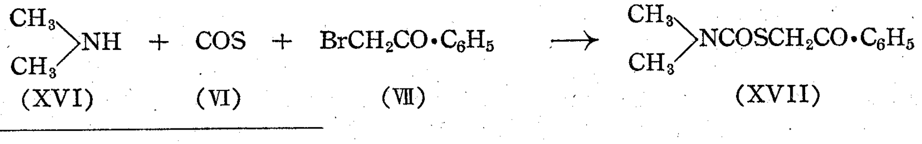

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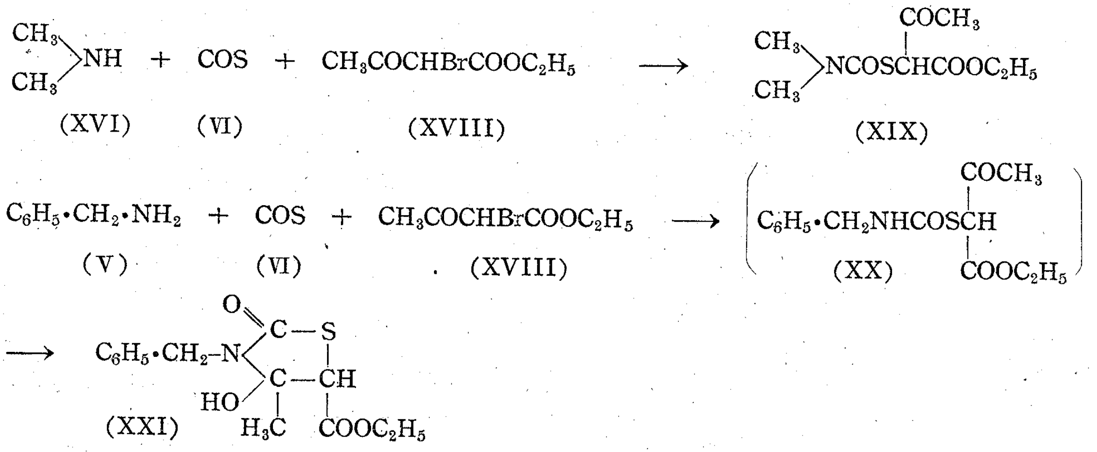
9) Yoshida, Asai, Kataoka: J. Pharm. Soc. Japan, **74**, 856 (1954)

S-α-Carbethoxyacetonyl N-dimethylthiocarbamate (XIX) and S-α-carbethoxyacetonyl N-benzylthiocarbamate (XX) were respectively prepared from (XVI) or (V), (VI), and ethyl α-bromoacetoacetate (XVIII). The ferric chloride color reaction of these two thiocarbamates in alcoholic solution[10] are different, (XIX) giving a reddish purple coloration while (XX) remains colorless. In other words, the latter substance does not possess the structure as shown in (XX) but is N-benzyl-4-methyl-4-hydroxy-5-carbethoxythiazolidin-2-one (XXI).



Ultraviolet absorption spectra of (IX), (XIII), and (XXI) were measured but the intensity of absorption was so low and distinct absorption bands, such as were seen in (IV)[3], could not be observed.

The writer expresses his gratitude to Dr. Fukuchi, the Director of the Laboratory, and to Mr. Matsui, Director of Research, for their unfailing encouragement during the course of this work. The writer is indebted to Mr. Wataru Ishizuka for his cooperation in carrying out these experiments, to Mr. Masao Maruyama for infrared spectral measurements, and to Messrs. Furukawa and Ono for elemental analyses.

Experimental

N-Benzyl-4-hydroxy-4-phenylthiazolidin-2-one (IX)—The method of Todd[5] was followed. Application of heat during the reaction resulted in the formation of a dibenzylurea of m.p. 169° in part. *Anal.* Calcd. for $C_{16}H_{15}O_2NS$: N, 4.9. Found : N, 4.7.

N-[2′-Methyl-4′-aminopyrimidyl-(5′)]-methyl-4-hydroxy-4-methyl-5-β-chloroethylthiazolidin-2-one (XIII, R=Cl)—To a solution of 1.6 g. NaOH dissolved in 30 cc. MeOH, 4.2 g. of 2-methyl-4-amino-5-aminomethylpyrimidine hydrochloride was added and the crystals that separated out were removed by filtration. COS was bubbled through the filtrate by which the thiocarbamate, m.p. 154° (decomp.), began to separate out after 20 mins. To this was added 2 g. of γ-aceto-α,γ-dichloropropane and thoroughly mixed by which the whole mixture became a clear solution with generation of heat and gradually separated crystals. The crystals were collected by filtration and washed with EtOH to m.p. 158~161° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}O_2N_4ClS$: N, 17.7. Found : N, 18.8.

During the formation of this substance, a part transited to 1,2,3,4-tetrahydro-7-methyl-2-oxo-1,3,6,8-tetrazonaphthalene.

N-[2′-Methyl-4′-aminopyrimidyl-(5′)]-methyl-3a-methyltetrahydrofuro[2,3-d]thiazolidin-2-one (XIV)—A mixture of 1 g. of (XIII, R=Cl), 0.12 g. NaOH, and 20 cc. EtOH was warmed on a water bath at 40° by which the whole dissolved and crystals separated out on being cooled. Recrystallized from EtOH, m.p. 180°. *Anal.* Calcd. for $C_{12}H_{15}O_2N_4S$: N, 20.0. Found : N, 19.8.

Hydrochloride : A mixture of 0.1 g. of (XIV) and 5 cc. abs. EtOH was warmed to effect complete solution, 0.2 g. of 22% ethanolic HCl was added, and the mixture was allowed to stand in an ice chest for 2 days by which the hydrochloride, m.p. 253~254° (decomp.), separated out.

S-Phenacyl N-Dimethylthiocarbamate (XVII)—To a solution of 4 g. NaOH dissolved in 50 cc. MeOH, 8.05 g. of dimethylamine hydrochloride was added and NaCl that separated out was removed by filtration. COS was bubbled through the filtrate for 30 mins., 3 g. of ω-bromoacetophenone was added to it, and the reaction occurred with generation of heat. Addition of water separated sparingly

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[10] Hans Henecka : Ber., **81**, 179 (1948).

soluble crystals which were recrystallized from a mixture of ether and petroleum ether, m.p. 98~99°. *Anal.* Calcd. for $C_{11}H_{13}O_2NS$: N, 6.3. Found : N, 6.1.

Phenylhydrazone; m.p. 147°. *Anal.* Calcd. for $C_{17}H_{19}ON_3S$: N, 13.4. Found : N, 13.2.

S-α-Carbethoxyacetonyl N-Dimethylthiocarbamate (XIX)—Sodium chloride formed by mixing 8.05 g. of dimethylamine hydrochloride, 50 cc. MeOH, and 4 g. NaOH was removed by filtration and COS was bubbled through the filtrate for 30 mins. To this was added 5 g. of freshly prepared ethyl α-bromoacetoacetate and mixed thoroughly. After the completion of the reaction, water was added to the mixture and the syrupy substance thereby formed was taken up in ether. After washing with water, the ether extract was concentrated, petroleum ether added, and allowed to stand in an ice chest by which the crystals began to separate out gradually. The crystals were collected by filtration and washed thoroughly with petroleum ether. The methanolic solution of this substance gives a reddish purple coloration with ferric chloride. *Anal.* Calcd. for $C_9H_{15}O_4NS$: N, 6.0. Found : N, 6.1.

N-Benzyl-4-methyl-4-hydroxy-5-carbethoxythiazolidin-2-one (XXI)—Carbonyl sulfide was bubbled through the solution of 5 g. of benzylamine dissolved in 50 cc. MeOH and to this mixture of the amine salt, 7 g. of ethyl α-bromoacetoacetate was added. By thorough mixing, the mixture became a clear solution and this was treated as in the case for (XVII). m.p. 82~83°. The methanolic solution of this substance failed to give any coloration with ferric chloride. *Anal.* Calcd. for $C_{14}H_{17}O_4NS$: N, 4.7. Found : N, 4.4.

Summary

N-Substituted thiocarbamates (VIII and XII) do not show any absorption for carbonyl in their infrared absorption spectra but show absorption of disubstituted amide that they were assumed to have the structure (IX and XIII) of an N-substituted thiazolidin-2-one. (XVII) which cannot undergo cyclization showed absorption for carbonyl. Although (XIX) gives coloration with ferric chloride, (XX) does not give any coloration due probably to the structure of (XXI) assumed for it.

(Received June 18, 1954)

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57. Takashi Isshiki, Toshio Kajima, and Shunsaku Noguchi : On the Polarography of *p*-Aminomethylphenyl Isopentyl Ketone.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

Nowadays literatures on the polarography of ketones are voluminous[1]. It is well known that the reduction potentials of ketones at the dropping mercury electrode are more or less influenced by such factors as solvent, pH, supporting electrolytes, and others. The present study was undertaken to determine the polarographic constants of *p*-aminomethylphenyl isopentyl ketone, which had been prepared by Ishidate and Nambara[2] in order to test its antibacterial activities.

Results

In a basic solution, under the condition which only aqueous buffer solution was used as a solvent, multiple wave was observed for the ketone. However, it was found that the tendency toward producing a single wave increased as the ratios of both isopropanol and tylose to buffer increased. Finally it became clear that the mixture of buffer and isopropanol in equal volume containing 0.05% of tylose as a whole, was the suitable solvent for the polarographic determination in basic medium. In neutral or acidic media, however, the wave is not so complicated as that in basic one. It is unnecessary for the neutral or acidic solvent composed of equal volumes of aqueous buffer and isopropanol

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* Hongo, Tokyo (一色　孝, 梶間俊男, 野口俊作).

[1] cf. Kolthoff, Lingane : "Polarography," Interscience Publishers, Inc., New York, 652(1952).

[2] M. Ishidate, T. Nambara : This Bulletin, **1**, 290 (1953).