[Chem. Pharm. Bull. 11 (10) 1229 ~ 1235]

UDC 547.97 : 582.29

197. **Kōtarō Takahashi, Yoshie Honda** (née Ueda), **and Shūichi Miyashita :** Usnic Acid. V.[*1] Some Decomposition Reaction of Methyl- and Methyldihydrousnic Acids. The Revised Structure for Usnic Acid Isomethoxide.

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In a previous paper of this series,[1] it was reported that methylusnic acid was degraded into the ~~metylacethhusnetol~~, methyldecarbousnic and methylusnetica cids. The present paper deals with methanolysis, ozonolysis and formolysis of methylusnic acid,[1] ozonolysis of methyldihydrousnic acid[2] and also with the correction of the previously proposed structure for monoacetylusnic acid isomethoxide.[3]

Methanolysis of methylusnic acid gave colorless crystals, $C_{18}H_{20}O_7$ (I), m.p. 86~87°, which corresponded to the methylate of methylacetusnetate. This was treated with potassium hydroxide to give the methylacetusnetol.

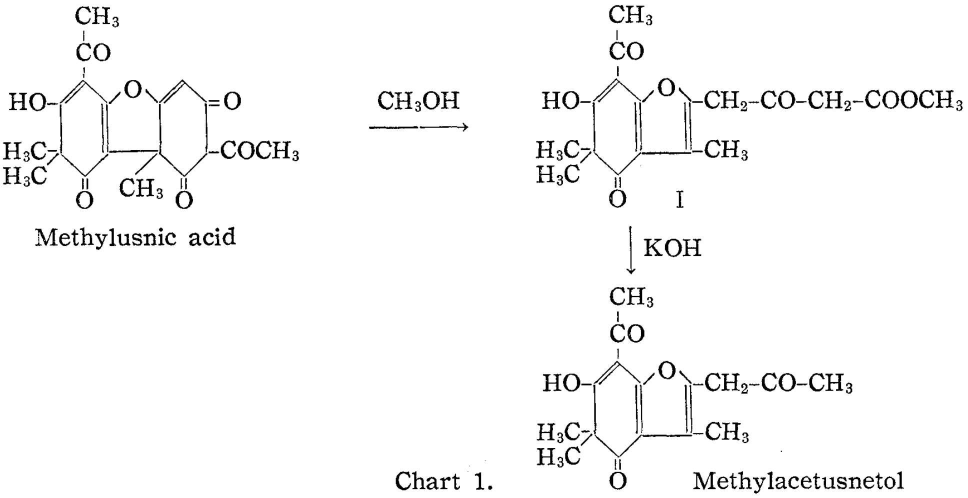

Chart 1.

Ozonolysis of methylusnic acid, followed by treatment with methanol, gave colorless crystals, $C_9H_{10}O_4$, m.p. 209°, which were proved to be identical with methylphloroacetophenone, and oxalic acid. On the other hand, methyldihydrousnic acid gave, on ozonolysis followed by distillation, 3′-methyl-2′,6′-dihydroxyacetophenone, $C_9H_{10}O_3$, m.p. 138~139°. Coupled with a previously reported fact[2] that methyldihydrousnic acid gave 3′-methyl-2′,6′-dihydroxyacetophenone, on potassium permanganate oxidation followed by vacuum distillation, these evidences indicate a possible mechanism of these ozonolysis that the phloroglucinol nucleus is derived from B ring of methylusnic acid, and the resorcinol nucleus from B ring of methyldihydrousnic acid as a result of fission of furan ring followed by dehydration of the newly formed hydroxyl and decarboxylation as shown below.

These evidences are the unambiguous experimental support for the mechanism, previously assumed by C. Schöpf, *et al.*,[4] to ozonolysis of dihydrousnic acid.

[*1] Part IV. This Bulletin, **11**, 473 (1963).

[*2] Tsutitoribanaga-machi, Kanazawa-shi, Ishikawa-ken (高橋幸太郎, 本多(旧姓上田)芳枝, 宮下修一).

1) Part II. This Bulletin, **10**, 607 (1962).

2) Part I. *Ibid.*, **10**, 603 (1962).

3) K. Takahashi : *Ibid.*, **1**, 36 (1953).

4) C. Schöpf, F. Ross : Ann., **546**, 1 (1941).

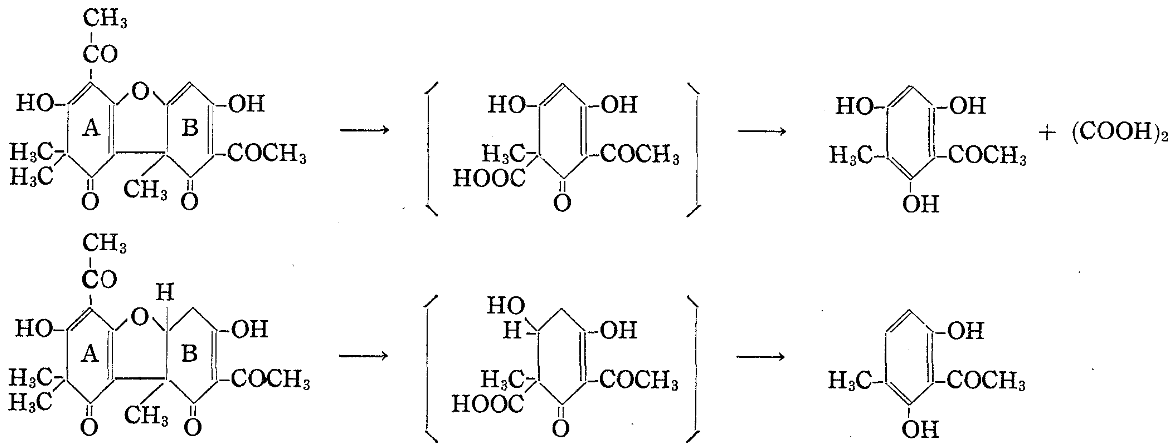

Chart 2.

On heating with 92% formic acid at 70~80°, methylusnic acid gave methyldecarbousnic acid,[1] $C_{18}H_{20}O_6$, m.p. 85°, and a product, $C_{19}H_{20}O_8$ (II), m.p. 167°, $[\alpha]_D$ +91.1°. The analytical data of the latter corresponded to hydrated methylusnic acid. Ozonolysis of II gave methylphloroacetophenone. Oximation of II gave a yellow solid, which was oxidised with hydrogen peroxide to give 4-carboxy-α,α,3-trimethyl-5-isoxazoleacetic acid,[2] m.p. 212°. These data indicate that A and B rings of methylusnic acid are still present in II. The infrared absorption spectrum of II showed bands at 3260 cm^{-1} (polymeric OH; not present in the spectrum of methylusnic acid), 1660 cm^{-1} (broad; αβ,γδ-unsatd. ketone), 1620 cm^{-1} (chelated C=O), 1560~1520 cm^{-1} (broad; triketone observed in spectra of usnic acid derivatives). The band at 1078 cm^{-1} with medium intensity could be assigned to C-O-C of furan ring, while methylusnic acid has a band at 1080 cm^{-1} due to the same system. The nuclear magnetic resonance spectrum[*3] of II showed signals at 6.85 and 6.99 p.p.m. due to -CH_2- which are present in the spectra of methyldihydrousnic acid[5] (7.05, 6.99, and 6.90 p.p.m.), isodihydrousnic acid[6] (6.90 p.p.m. (doublet)), and dihydrousnic acid[6] (6.93 p.p.m. (doublet)). Our explanation of the assignment of the two signals at 6.85 and 6.99 p.p.m. to -CH_2- is that the compound does exist in two forms due to the difference of the mode of the enolization and that such structural change results in the appearance of those signals at slightly different positions. However, a signal due to =CH-, which is present in the spectra of usnic acid[6] (4.04 p.p.m.) and methylusnic acid[5] (4.08 p.p.m.), was not observed. The above-mentioned facts indicate that the newly obtained product is formulated as II, which could be derived from methylusnic acid by addition of water to the double bond in B ring. The possibility of an alternative formula (III), which could be formed as a result of hydrolytic cleavage of -C-O-C- bond in methylusnic acid, could be ruled out by the nuclear magnetic resonance analysis as mentioned above.

It has been reported[3] that diacetylusnic acid gave, on treatment with 10% methanolic hydrochloric acid, monoacetylusnic acid isomethoxide, and one of the authors (K. T.) forwarded a formula (IV) for the compound. The formula has been assumed to be formed by the cleavage of the oxygen bridge in diacetylusnic acid followed by partial deacetylation. Later, S. Shibata[7] suggested the possibility of an alternative

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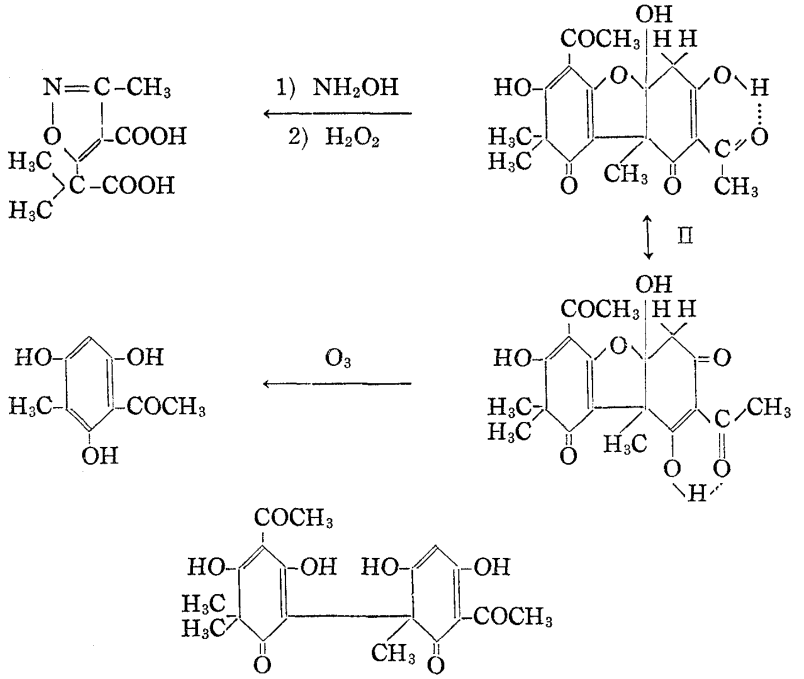
[*3] The nuclear magnetic resonance spectra were measured using JNM-III spectrometer (Japan Electron Optics Laboratory Co., Ltd.), operating at 40 Mc. The position of resonances were measured by the side band technique and given as τ-values which were obtained in chloroform solution by using chloroform or tetramethylsilane as internal reference. The τ-value of chloroform was assumed to be 2.75 p.p.m.

5) Details will be reported later.

6) J. Shōji: This Bulletin, **10**, 483 (1962).

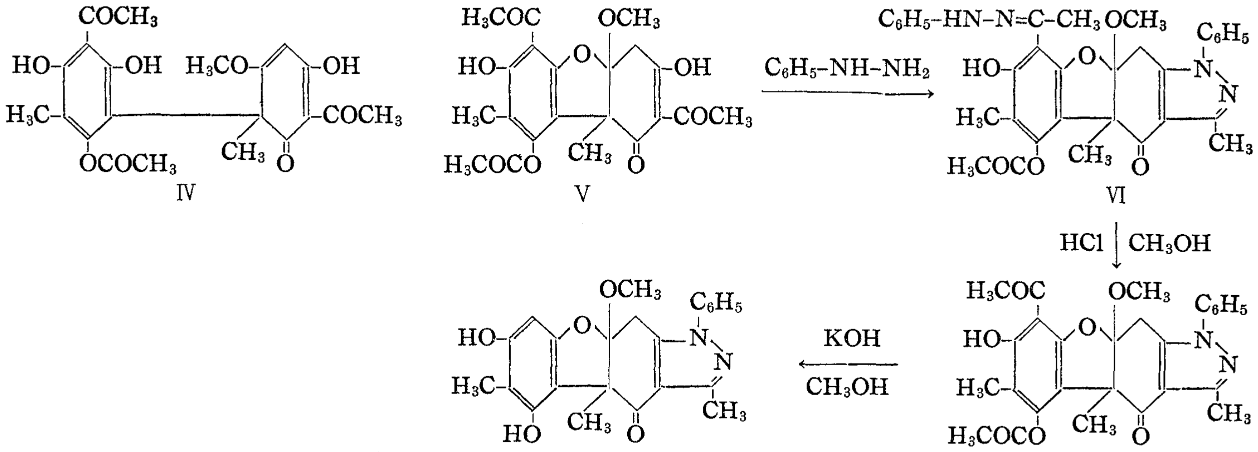
7) Y. Asahina, S. Shibata: The Chemistry of Lichen Substances, Page 190, Japan Society for the Promotion of Science, Tokyo, Japan, **1954**.



III Chart 3.

formula (V), which can be derived from usnic acid by addition of methanol to the double bond in the $\alpha\beta$-position of the ketonic group, without any experimental proof. Now we have found that the results of some decomposition reactions, infrared spectra and nuclear magnetic resonance analysis of the compound support formula (V) previously assumed by Shibata.

l-Monoacetylusnic acid isomethoxide gave *d*-monoacetylusnic acid isomethoxide bisphenylhydrazone monoanhydride,[3] $C_{33}H_{32}O_6N_4$ (VI), m.p. 276° (decomp.), $[\alpha]_D$ +381°. The inversion of the sign of optical rotation was observed at this stage. VI was then treated with methanolic hydrochloric acid to give monoacetylusnic acid isomethoxide phenylhydrazone monoanhydride, $C_{27}H_{26}O_7N_2$ (VII), m.p. 197~199°, $[\alpha]_D$ +312°. On boiling with methanolic potassium hydroxide, VII gave colorless crystals, $C_{23}H_{22}O_5N_2$ (VIII), m.p. 205~206°, $[\alpha]_D$ +303°, which were proved to be identical with Barton's compound,[8] obtained from usnic acid phenylhydrazone monoanhydride by treatment with methanolic potassium hydroxide, by the mixed melting point determination and comparison of ultraviolet and infrared spectra.



IV V VI VII VIII

Chart 4.

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[8] D.H.R. Barton, T. Bruun: J. Chem. Soc., **1953**, 603.

The infrared spectrum of monoacetylusnic acid isomethoxide does not show a band at 3200~3600 cm^{-1} (in Nujol) due to polymeric OH and shows at 1750 cm^{-1} (phenolic acetate), 1670 cm^{-1} ($\alpha\beta$-unsatd. C=O) and 1540~1570 cm^{-1} (broad, triketone).

The unambiguity of the newly proposed structure (V) for monoacetylusnic acid isomethoxide was eventually examined by the nuclear magnetic resonance analysis (Fig. 1).

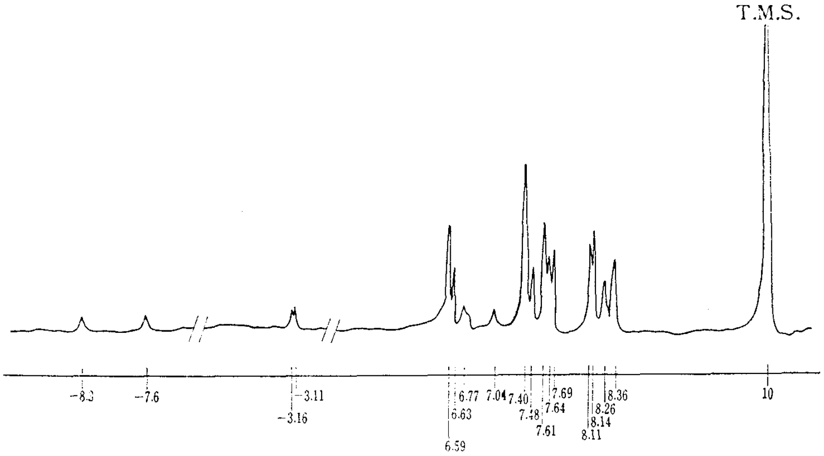

Fig. 1. The Nuclear Magnetic Resonance Spectrum*⁴ of Monoacetylusnic Acid Isomethoxide

Firstly, it was presumed that monoacetylusnic acid isomethoxide is present in the tautomeric formula A and B, regarding the location of hydrogen bonds, as it has two chelated enol OH signals at −7.60 p.p.m. and −8.30 p.p.m. and the intensity of $COCH_3$ signal of A ring at 7.37 p.p.m. is almost equal to the sum of two $COCH_3$ signals of B ring at 7.58 and 7.46 p.p.m. Signals might be assigned as follows.

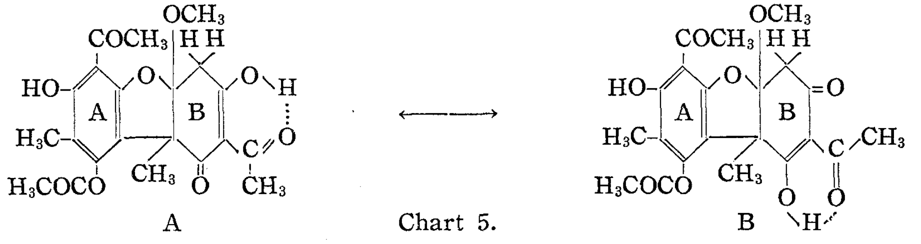

Chart 5.

	Signals of A ring (τ-value) at 40 Mc.*³ (p.p.m.)	at 60 Mc.*⁴ (p.p.m.)
$OCOCH_3$	7.66 and 7.62	7.69 and 7.64
aromatic CH_3	8.14 〃 8.12	8.14 〃 8.11
chelated arom. OH	not measured	−3.11 〃 −3.16
$COCH_3$	7.37	7.40
	Signals of B sing	
chelated enol OH	not measured	−7.60 and −8.30
$COCH_3$	7.58 and 7.46	7.61 〃 7.48
angular CH_3	8.38 〃 8.26	8.36 〃 8.26
OCH_3	6.60 〃 6.56	6.63 〃 6.59
$-CH_2-$	6.98 〃 6.75	7.04 〃 6.77

The facts that the nuclear magnetic resonance spectra of V at 40 Mc. and 60 Mc. showed essentially no change in τ-values of signals indicate that the splitting of bands of radicals are due to chemical shifts, not to spin-spin coupling. It could further

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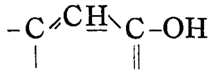
*⁴ The NMR spectrum was measured by JNM-3H-60 spectrometer (Japan Electron Opticus Laboratory Co., Ltd.) in $CDCl_3$ solution at 60 Mc., using tetramethyl silane as internal reference.

mentioned that the difference of the mode of enolization, mentioned before, does make influence on the chemical shift of bands, for instance, due to $-CH_2-$ of V and II by 0.23 p.p.m. and 0.14 p.p.m. respectively, as in the case of 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione[9] (0.16 p.p.m.).

The possibility of IV in which the -C-O-C- bridge is cleaved can be excluded because of absence of signal  $-\underset{|}{C}{=}\overset{CH}{}{-}\underset{\|}{C}-OH$ at about 4.0 p.p.m., which is present in the spectra of usnic acid[6] (4.04 p.p.m.) and methylusnic acid[5] (4.08 p.p.m.).

The another possibility of the structural formula (C) for monoacetylusnic acid isomethoxide which might be explained by the nuclear magnetic resonance analysis, if it would be present in the tautomeric formula C, C′, and C″, can be excluded by the formation of 7-acetyl-3,5-dimethyl-4,6-dihydroxy-2-coumaranone 4-acetate (D) on pyrolysis.[3] The absence of signal of methine $-\overset{|}{C}H-$ at about 5.2 p.p.m., which is present in dihydrousnic acid[6] (5.22 p.p.m.), isodihydrousnic acid[6] (5.20 p.p.m.) and methyldihydrousnic acid[5] (5.22 p.p.m.) ruled out the possibility of formulation (E).

It is of interest that the addition of methanol to the double bond in the usnic acid molecule takes place in methanolysis both with methanolic hydrochloric acid and methanolic potassium hydroxide.[8]

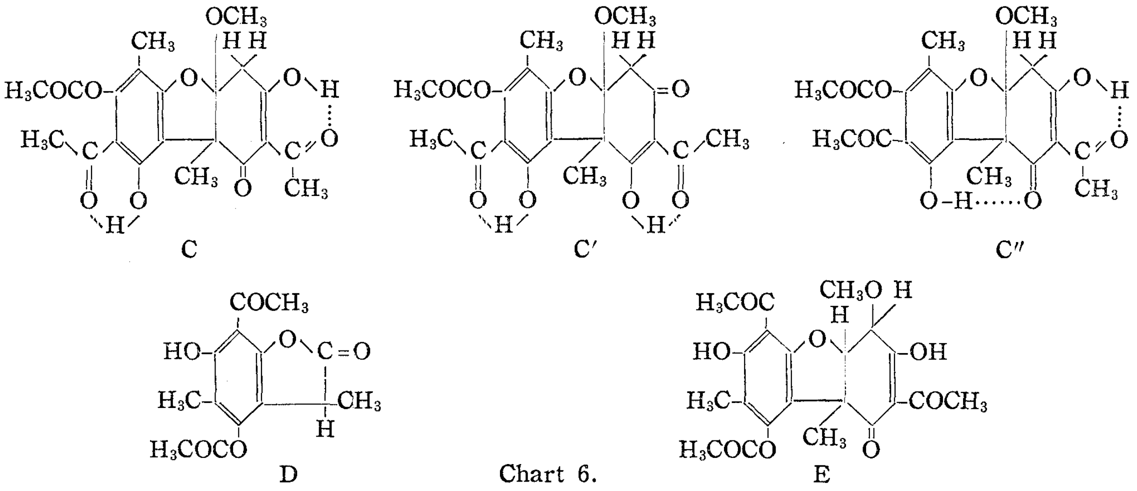


Chart 6.

Experimental[*5]

Methanolysis of Methylusnic Acid——Methylusnic acid (4 g.) in MeOH (40 ml.) was boiled on steam bath for 6 hr. and half volume of MeOH was distilled off and the mixture was allowed to stand at room temperature to give pale yellow crystals which were recrystallised from hexane, giving colourless needles, $C_{18}H_{20}O_7$ (I), m.p. 86~87°. Yield 1.5 g. They were soluble in $NaHCO_3$ solution and gave blue-violet colouration with $FeCl_3$. *Anal.* Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79; O-CH_3, 9.49. Found : C, 62.11; H, 5.84; O-CH_3, 9.48. UV λ_{max} mμ : 224.5, 235 (shoulder), 330. IR ν_{max} cm^{-1} : 1740 (β-keto-ester), 1710 (C=O), 1655 (αβ,γδ-unsatd. C=O), 1595 (chelated C=O).

Alkaline Decomposition of I——I (1 g.) in 20% KOH solution (10 ml.) was warmed at 70~80° in H_2 stream for 40 min. and the solution was acidified with dil. HCl and precipitated resinous substance was filtered, dried and treated with benzene. The benzene-soluble fraction gave pale yellow needles (from 50% MeOH), m.p. 87°. $FeCl_3$ reaction : brown. They were proved to be identical with methylacetusnetol by the mixed melting point determination and the comparison of IR spectra. *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found : C, 66.28; H, 5.98.

[*5] Ultraviolet absorption spectra were taken in ethanol solution using Hitachi EPU-2A spectrophotometer. Infrared absorption spectra were taken in KBr pellet, if not otherwise stated, by Nippon Bunko Model IRS infra code.

9) J. Shōji : This Bulletin, **10**, 485 (1962).

Ozonolysis of Methylusnic Acid——Methylusnic acid (3 g.) was dissolved in $CHCl_3$ (20 ml.) and ozonized O_2 was passed through under ice cooling for 2 hr. and then MeOH (10 ml.) was added to the $CHCl_3$ solution and the solution was allowed to stand overnight. Then the solvent was distilled off to give resinous substance, which was dissolved in Et_2O and the Et_2O solution was shaken with 5% $NaHCO_3$ solution. The neutral portion formed colourless crystals, m.p. 209°, which were proved to be identical with methylphloroacetophenone by the mixed melting point determination and the comparison of IR and UV spectra. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found : C, 59.29; H, 5.41.

From acidic portion, after acidification with dil. HCl, colourless crystals were obtained which gave no melting point depression on admixture with oxalic acid and gave bisphenylhydrazide m.p. 253°. *Anal.* Calcd. for $C_{14}H_{14}O_2N_4$: C, 62.21; H, 5.22; N, 20.73. Found : C, 62.15; H, 4.91; N, 20.15.

Ozonolysis of Methyldihydrousnic Acid——Methyldihydrousnic acid (3 g.) was dissolved in $CHCl_3$ (20 ml.) and ozonized O_2 was passed through for 40 min. under ice cooling and MeOH (10 ml.) was added to the $CHCl_3$ solution and the mixture was warmed on steam bath at 60° for 30 min. and the solvent was distilled off *in vacuo* to give resinous substance, which was distilled at 4 mm. Hg (bath temp. 140~220°) to give yellow crystals, m.p. 138~139°. Yield 0.2 g. They were proved to be identical with 3′-methyl-2′,6′-dihydroxyacetophenone by the mixed melting point determination and the comparison of IR and UV spectra. *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found : C, 65.30; H, 6.10.

Decomposition of Methylusnic Acid by Formic Acid——Methylusnic acid (3 g.) in 92% formic acid (30 ml.) was warmed on steam bath for 1.5 hr. and the solvent was distilled off *in vacuo* to give red crystals. On recrystallisation from 80% MeOH, colorless crystals were obtained, $C_{19}H_{20}O_8$ (II), m.p. 167°. $[\alpha]_D$ +91.1° (c=0.735, chloroform). Yield 1 g. $FeCl_3$ reaction : brown. UV λ_{max} mμ (ε) : 225 (22,400), 283 (13,800), 320 (13,500). *Anal.* Calcd. for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36. Found : C, 60.71; H, 5.45.

From mother liquor of crystallisation, after standing, pale yellow needles, m.p. 85°, was obtained which were proved to be identical with methyldecarbousnic acid[1] by the mixed melting point determination and the comparison of IR and UV spectra. Yield 0.6 g.

Formation of 4-Carboxy-*α*,*α*,3-trimethyl-5-isoxazoleacetic Acid from II——To a solution of NH_2OH-HCl (0.6 g.) and anhyd. AcONa (0.6 g.) in H_2O (1 ml.), II (0.5 g.) in MeOH (15 ml.) was added and warmed on steam bath at 70° for 3 hr. The solvent was distilled off and H_2O was added to give yellow powder. To a solution of the yellow powder (0.6 g.) in 10% KOH (20 ml.) was added 30% H_2O_2 (10 ml.) three times and 30% H_2O_2 (2 ml.) ten times at the interval of 30 min. and then 30% H_2O_2 (6 ml.) four times at the interval of 1 hr. at 80°. The color of the solution turned from red to pale yellow. The solution was acidified with dil. HCl and salted out with NaCl and extracted with Et_2O. After evaporation of Et_2O, colourlesscrystals were obtained on recrystallisation from H_2O, m.p. 213°. It was proved to be identical with 4-carboxy-α,α,3-trimethyl-5-isoxazoleacetic acid by the mixed melting point determination and the comparison of IR spectra. *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70; H, 5.20. Found : C, 50.91; H, 5.08.

Ozonolysis of II——II (1 g.) was dissolved in $CHCl_3$ (25 ml.) and ozonized O_2 was passed through under ice cooling for 4 hr. and then MeOH (5 ml.) was added and the solution was warmed at 45° for 20 min. Then the solvent was distilled off to give resinous substance which was dissolved in Et_2O and Et_2O was shaken with 10% $NaHCO_3$ solution. The neutral portion forms crystals, m.p. 208° (decomp.), by recrystallisation from H_2O. It was proved to be identical with methylphloroacetophenone by the mixed melting point determination and the comparison of IR spectrum. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found : C, 59.16; H, 5.30.

***d*-Monoacetylusnic Acid Isomethoxide Phenylhydrazone Monoanhydride (VII)**——*d*-Monoacetylusnic acid isomethoxide bisphenylhydrazone monoanhydride (VI)[3] (2 g.) ($[\alpha]_D$ +381° (c=0.734, $CHCl_3$)), obtained from l-monoacetylusnic acid isomethoxide, in methanolic HCl (130 ml.) (35% HCl 40 ml.+MeOH 90 ml.) was boiled on steam bath for 1 hr. and after evaporation of the solvent *in vacuo*, pale yellow crystals were obtained, which were recrystallised from 70% MeOH to give pale yellow crystals, $C_{27}H_{26}O_7N_2$ (VII), m.p. 197~199°, $[\alpha]_D$ +303° (c=0.749, $CHCl_3$). UV λ_{max} mμ (log ε) : 224 (shoulder) (4.46), 267 (4.42), 352 (3.64). *Anal.* Calcd. for $C_{27}H_{26}O_7N_2$: C, 66.11; H, 5.34; N, 5.71. Found : C, 66.24; H, 5.28; N, 5.95. From cyclohexane, it forms pale yellow crystals, $C_{27}H_{26}O_7N_2 \cdot \frac{1}{2}C_6H_{12}$, m.p. 115° (decomp.), $[\alpha]_D$ +312° (c=0.627, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{26}O_7N_2 \cdot \frac{1}{2}C_6H_{12}$: C, 67.65; H, 6.06; N, 5.26. Found : C, 67.59; H, 6.00; N, 5.37. The UV spectra of both compounds were identical.

***d*-Desacetylusnic Acid Isomethoxide Phenylhydrazone Monoanhydride (VIII)**——VII (0.4 g.) in methanolic KOH solution (MeOH 20 ml.+KOH 4 g.) was warmed at 70° for 3 hr. in H_2 stream and after cooling, H_2O (40 ml.) was added and the solution was acidified with dil. HCl to give colourless crystals, which were recrystallised from $CHCl_3$-petr. ether or $CHCl_3$ to give colorless crystals, $C_{23}H_{22}O_5N_2$ (VIII), m.p. 205~206°, $[\alpha]_D$ +303°*6 (c=0.785, $CHCl_3$). UV λ_{max} mμ (ε) : 261.5 (20,580), 326 (2,470). *Anal.* Calcd. for $C_{23}H_{22}O_5N_2$: C, 67.96; H, 5.46, N, 6.89. Found : C, 67.82; H, 5.79; N, 6.47. It was proved to be identical

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*6 $[\alpha]_D$ of VIII, obtained from usnic acid was recorded as +376° by Barton,[8] whereas it was observed by us as +307° (c=0.717, $CHCl_3$).

with Barton's compound[8] obtained from usnic acid phenylhydrazone monoanhydride on treatment with methanolic KOH, by the mixed melting point determination and the comparison of UV and IR spectra.

The authors wish to express their deep gratitude to Dr. Y. Asahina, Emeritus Professor of University of Tokyo, for his encouragement throughout the course of this study and Dr. S. Shibata, Professor of University of Tokyo, for the gift of usnic acid. The authors are indebted to Mr. S. Matsuoka of this university and Japan Electron Optics Laboratory Co. Ltd. for measurement of NMR spectra. Thanks are due to Mr. Y. Itatani for elemental analysis and Miss E. Katarao for co-operation.

Summary

1) The ozonolysis of methyl- and methyldihydrousnic acid was discussed.

2) The structure of the formolysis product of methylusnic acid was elucidated as being II.

3) The structure of monoacetylusnic acid isomethoxide was reinvestigated and established as being V.

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198. **Shunsaku Noguchi and Katsura Morita**: Aldol-Condensation of Corticoids with Formaldehyde.[*1] Syntheses of 21-Hydroxymethyl-corticoids and 21-Methyl-11β,17α-dihydroxypregna-1,4-diene-3,20,21-trione 17-Acetate.

(*Research Laboratories, Takeda Chemical Industries, Ltd.*[*2])

While many corticoids have been prepared which are modified by the addition of a methyl[1] or a hydroxyl[2] group at various positions in the molecules, and their biological properties noted, no hydroxymethyl[3]-substituted corticoids have been reported. In the present paper we describe the synthesis of 21-hydroxymethyl-prednisolone and -hydrocortisone by the aldol condensation of the parent steroids with formaldehyde.

When prednisolone (I) was treated with aqueous formaldehyde in the presence of sodium acetate as catalyst, the addition of a hydroxymethyl group to the methylene at C-21 resulted and 21-hydroxymethylprednisolone (II) was obtained in about 50% yield as amorphous hydrated crystals, from which the crystalline water was hardly removed by the ordinary drying conditions. Anhydrous crystals of II were obtained by repeating the following procedure: the amorphous hydrated crystals were dissolved in methanol-ethyl acetate and the solvent evaporated under azeotropic conditions.[4] II gave the diacetate (III) by the usual acetylation with acetic anhydride and pyridine. On treatment

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[*1] This paper constitutes Part XXX of Takeda Laboratories' series entitled "Steroids"; Part XXIX: This Bulletin, 11, 144 (1963).

[*2] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (野口俊作, 森田 桂).

1) E. Toromanoff: Bull. soc. chim. France, **1960**, 888.

2) S. Bernstein: Recent Progress in Hormone Research, **14**, 1 (1958).

3) cf. A.L. Nussbaum, T.L. Poper, E.P. Oliveto, S. Friedman, I. Wender: J. Am. Chem. Soc., **81**, 1228 (1959); P.F. Beal, M.A. Rebenstore, J.E. Pike: *Ibid.*, **81**, 1231 (1959) (6-hydroxymethylation by oxo reaction).

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