The Structure of Aureothin. XI[1]. *On the Structure of Some of the Isoaureothin Derivatives*

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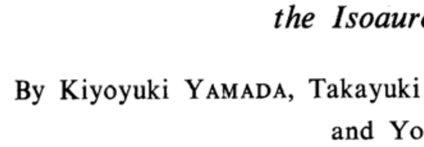
Among many derivatives obtained from isoaureothin (I)[2], there are several, the structures of which has not yet been disclosed. These derivatives, owing to their unexpected behavior, made the investigation of isoaureothin rather complicated. In this paper, the structures of these derivatives are put forward. They are well related to isoaureothin (I) and, of course account for all their properties. Further, the aspect of these reactions is briefly discussed. Of these derivatives, some descriptions were already made as to the nature of the products obtained by complex metal hydride reduction[3].



(I)

On the Structures of Aminol Compounds

Structure of Aminol H (IIIa).—The reduction of the nitro group in isoaureothin (I) by ferrous hydroxide afforded a corresponding amino derivative $C_{22}H_{25}O_4N$ (IIa), which in turn was treated with lithium borohydride in tetrahydrofuran to give an acidic compound named "aminol H", $C_{22}H_{27}O_4N$[3]. As regards the acidic nature of aminol H, the infrared evidence (broad band at 2600~2700 cm^{-1} in aminol H: bands at 1795, 1712 cm^{-1} in *N*,*O*-diacetyl aminol H (IIId)), coupled with the result of the methoxyl analysis[4], showed that it might be due to a carboxyl group. *p*-Bromophenacyl ester of aminol H (m. p. 85~87°C) was obtained. Taking account of the fact that aminol H is optically active and has two more hydrogen atoms than isoaureothamine (IIa), it seems reasonable to deduce the occurrence of the hydrogenolytic cleavage in α-pyrone ring,

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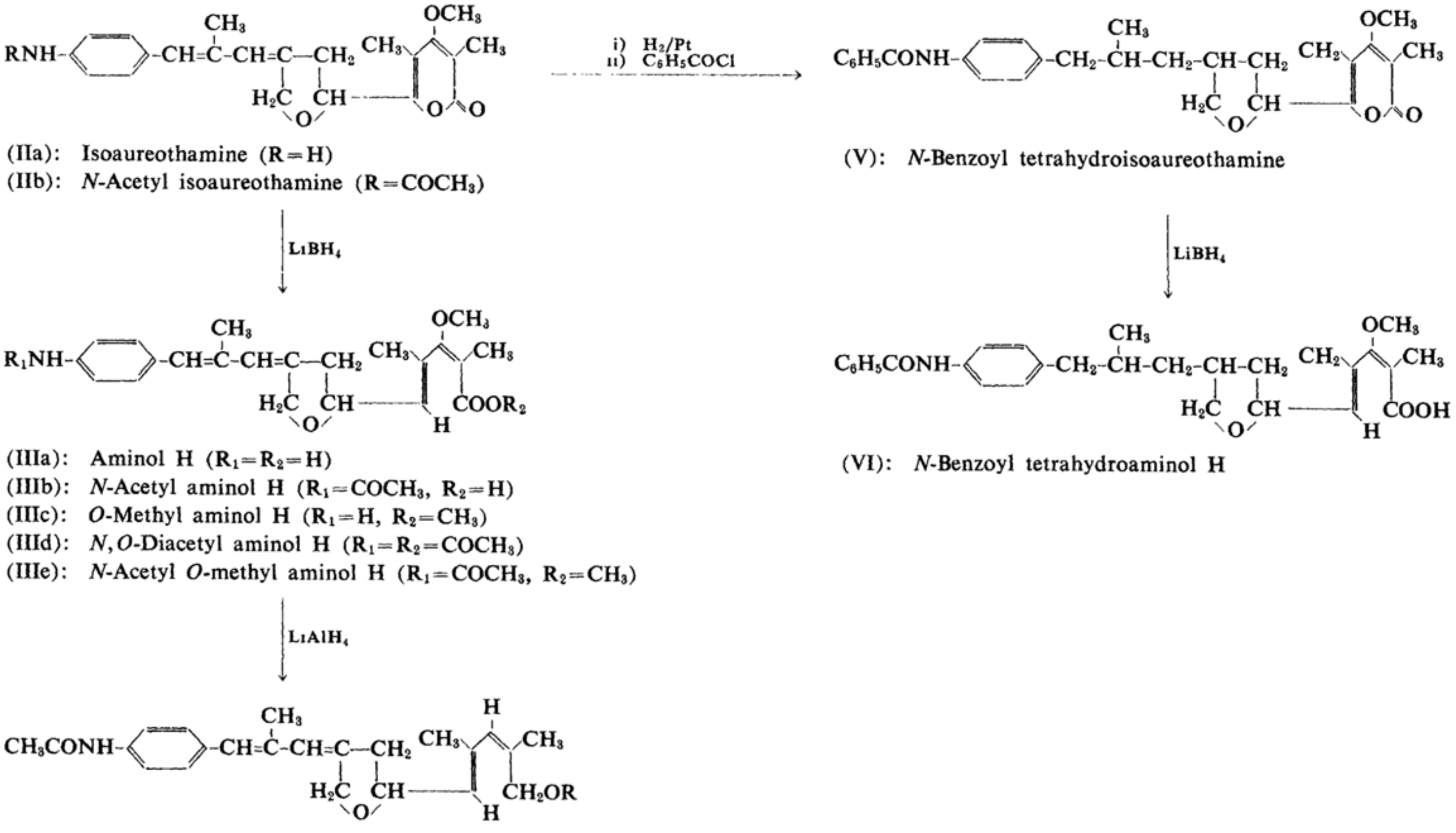
[1] Part X. K. Yamada. H. Nakata and Y. Hirata, This Bulletin, 33, 1298 (1960).

[2] K. Yamada, H. Nakata and Y. Hirata, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 81, 340 (1960).

[3] K. Yamada, Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, ibid., 79, 384 (1958).

[4] Aminol H (IIIa) contains one methoxyl group, whereas two such groups present in the methylated product, *O*-methyl aminol H (IIIc).

Chart 1. Derivatives of isoaureothin.



(IIa): Isoaureothamine (R=H)
(IIb): *N*-Acetyl isoaureothamine ($R=COCH_3$)

(IIIa): Aminol H ($R_1=R_2=H$)
(IIIb): *N*-Acetyl aminol H ($R_1=COCH_3$, $R_2=H$)
(IIIc): *O*-Methyl aminol H ($R_1=H$, $R_2=CH_3$)
(IIId): *N,O*-Diacetyl aminol H ($R_1=R_2=COCH_3$)
(IIIe): *N*-Acetyl *O*-methyl aminol H ($R_1=COCH_3$, $R_2=CH_3$)

(IVa): *N*-Acetyl aminol A (R=H)
(IVb): *N,O*-Diacetyl aminol A ($R=COCH_3$)

(V): *N*-Benzoyl tetrahydroisoaureothamine

(VI): *N*-Benzoyl tetrahydroaminol H

TABLE I. YIELD OF METHYL PYRUVATE

Compound	Sample mg.	$CH_3COCOOCH_3$[a] mg.	Equiv. mol.
Isoaureothin (I)	940	130	0.19
N-Acetyl isoaureothamine (IIb)	300	40	0.21
N-Benzoyl tetrahydroisoaureothamine (V)	470	32	0.15
N-Acetyl aminol H (IIIb)	250	38	0.22
N-Benzoyl tetrahydroaminol H (VI)[b]	620	80	0.22
N-Acetyl *O*-methyl aminol H (IIIe)	450	311	1.05

a) Determined as 2,4-dinitrophenylhydrazone.

b) Crude sample (m. p. 78∼83°C) was used without recrystallisation.

to produce a carboxyl group[5]. The various properties previously described[3] (infrared and ultraviolet spectra etc.), thus can best be accounted for by assigning the structure IIIa to aminol H. Furthermore, the following experiment supports the correctness of formula IIIa; ozonisation of compounds belonging to the isoaureothin- and aminol-series always afforded methyl pyruvate, the yield of which in each case is listed in Table I. An essentially equal amount of methyl pyruvate (ca., 0.2 equivalent mole) was produced in every case[6], except the largely enhanced amount (1.05 equivalent moles) in the case of *N*-acetyl *O*-methyl aminol H (IIIe). Therefore, in *N*-acetyl *O*-methyl aminol H (IIIe), it becomes evident that there exist in one molecule two such units, from which methyl pyruvate is formed: in addition, one of such units should originate from the newly formed carbomethoxyl group by complex metal hydride reduction and subsequent methylation (cf. methoxyl analysis[4]).

Structure of N-Acetyl Aminol A (IVa).—Reduction of *N*-acetyl *O*-methyl aminol H (IIIe) with lithium aluminum hydride gave a neutral product, *N*-acetyl aminol A, $C_{23}H_{28}O_3N$ in poor yield[3]; no other crystalline products than this were isolated. Elemental and methoxyl analysis showed, during the reduction of IIIe, the occurrence of unusual hydrogenolysis of methoxyl group (enol ether), originally present in isoaureothin (I), in addition to the expected transformation of the ester group into alcohol.

Aspect of Complex Metal Hydride Reduction.—As described above, plausible structural assignments were made to the reduction products, aminol H (IIIa) and *N*-acetyl aminol A (IVa), on a basis of their chemical and spectroscopic properties. These would, at first sight, be regarded as unusual reduction products.

In the case of aminol H, however, it is expected that α-pyrone shows peculiar reactivity far different from that of lactone toward hydride reagents, owing to the high conjugation of α-pyrone and a possible effect of substituents of the ring. So far, very little is known about the reduction of α- and γ-pyrones with various complex metal hydrides, except for limited examples of xanthone[7], benzo-α-[8] and benzo-γ-pyrones[9], where not unexpected results were recorded. In contrast to the reduction of such benzopyrones, a situation, however, would be unique in the case of pyrones if no aromatic ring was fused to them. Investigation on the reactivity of pyrones toward complex metal hydrides is desirable.

Of particular interest is a hydrogenolytic cleavage of enol-ether (methoxyl group), during the formation of *N*-acetyl aminol A (IVa). In general, enol ethers are inert to complex metal hydride reduction[10], and so is a β-alkoxy-α, β-unsaturated ester[11]. An exception[12] was reported; reduction of dihydrocorynantheine (A) with lithium aluminum hydride led to demethoxylated products B and C. Sarett and his coworkers reported a similar exception[13], found in β-alkoxy-α, β-unsaturated

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[5] On catalytic hydrogenation, aminol H absorbed quantitatively two moles of hydrogen, with which the double bonds conjugated with aminophenyl group were saturated[3]. From this result, it is tempting to consider the possibility of the existence of an α-pyrone ring in aminol H. However, this view is untenable on the ground that a band near 1575 cm⁻¹, characteristic of α-pyrone, is absent in all of the aminol compounds studied.

[6] Ozonisation was carried out repeatedly, in order to ascertain the reproducible yield of methyl pyruvate in each case.

[7] A. Mustafa and M. K. Hilmy, *J. Chem. Soc.*, **1952**, 1343.

[8] (a) F. A. Hochstein, *J. Am. Chem. Soc.*, **71**, 305 (1949); (b) P. Karrer and P. Banerjea, *Helv. Chim. Acta*, **32**, 1692 (1949). (c) S. Siegel and S. Coburn, *J. Am. Chem. Soc.*, **73**, 5494 (1951); (d) J. P. Freeman and M. F. Hawthorne, ibid., **78**, 3366 (1956).

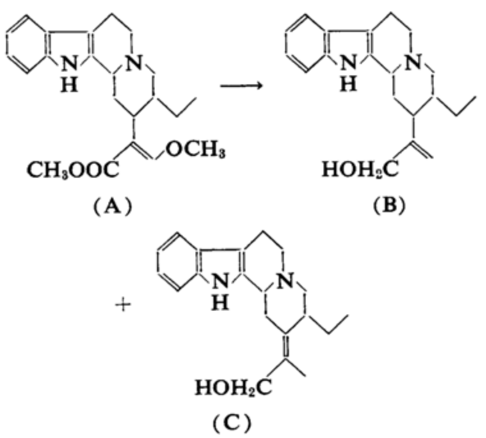
[9] (a) R. Robinson and R. Mirza, *Nature*, **166**, 929 (1950); (b) R. Mirza and R. Robinson, ibid., **166**, 997 (1950); (c) M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2044 (1958).

[10] N. G. Gaylord, "Reduction with Complex Metal Hydrides", Interscience Publishers, Inc., New York (1956), p. 695.

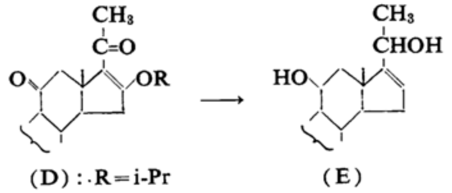
[11] (a) J. C. Seaton and LeoMarion, *Can. J. Chem.*, **35**, 1102 (1957); (b) J. C. Seaton, R. Tondeur and LeoMarion, ibid., **36**, 1031 (1958).

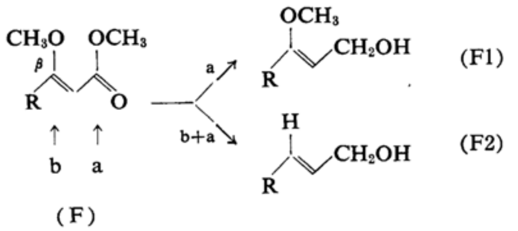
[12] P. Karrer, R. Schwyzer and A. Flam, *Helv. Chim. Acta*, **35**, 851 (1952): cf. A. Chatterjee and P. Karrer, ibid., **33**, 802 (1950).

[13] G. E. Arth, G. I. Poos and L. H. Sarett, *J. Am. Chem. Soc.*, **77**, 3834 (1955).



ketone (D), which afforded product E lacking in alkoxyl group. Such an apparent anomaly of β-alkoxyl group in α, β-unsaturated carbonyl system, encountered in the exceptions, can be interpreted in terms of vinylogy in reaction (see F); since β-carbon is regarded as a vinylogous position of carbonyl carbon, the reactivity of two methoxyl groups would be expected to be comparable.





Therefore, the mode of attack of the hydride reagent would be possible in two directions, as indicated by arrows in F, to give a normal product F1 and/or anomalous product F2. The subtle difference of the reactivity between two such positions would be influenced by structural variations and experimental conditions, neither of which, however, have yet been examined systematically.

Structure of "Lactol"

Property of Lactol (VIII). — *N*-Acetyl isoaureothamine (IIb) was converted to Lactol $C_{24}H_{29}O_6N$ (VIII), by the action of aqueous alkali[14]. The product, Lactol, is soluble in alkali and optically inactive, while the starting material IIb shows remarkable optical activity, $[\alpha]_D^{28^\circ}$ +140°.

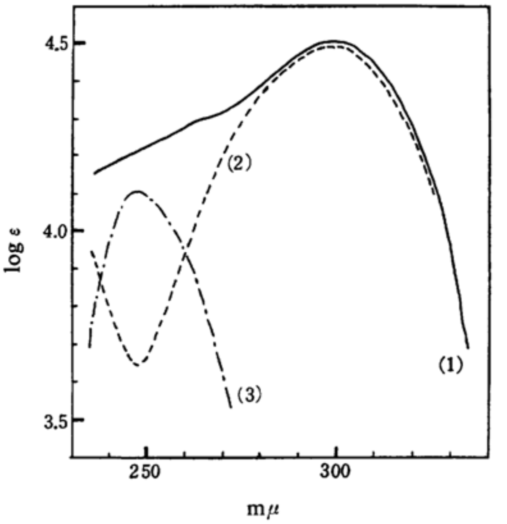
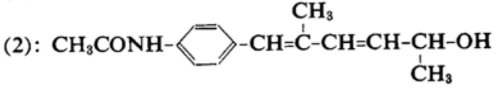


Fig. 1. Ultraviolet spectra (in ethanol)
(1): Lactol


(2): $CH_3CONH-C_6H_4-CH=C(CH_3)-CH=CH-CH(CH_3)-OH$

(3): Subtraction curve, (1) — (2)

The ultraviolet spectrum of Lactol shows the absence of α-pyrone chromophore (Fig. 1); the subtraction of ultraviolet spectrum of conjugated *p*-acetylaminophenyl group from that of Lactol gives a curve, which shows its maximum near 248 mμ and should correspond to that of α-pyrone ring (λ_{max} 295 mμ) of *N*-acetyl isoaureothamine (IIb). This outstanding hypsochromic shift, observed in the transformation of IIb to Lactol proves the destruction of α-pyrone chromophore in the latter[15]. There were observed bands at 1708(sh.), 1675 (s), 1645(s), 1599(s), 1530(s) and 1516(s)cm^{-1} in the 1800~1500cm^{-1} range of the infrared spectrum (KBr). The presence of a hydroxyl group in Lactol was detected from a broad band near 3200 cm^{-1} and a band at 1150 cm^{-1}. Lactol was neutralized by sodium hydroxide[16], to afford its sodium salt with bands located at 1717, 1672, 1640, 1595(s. and br.), 1530 and 1510 cm^{-1} (KBr). In order to clarify the nature of this hydroxyl group, acetylation with pyridine-acetic anhydride was carried out; an unexpected product, racemic *N*-acetyl isoaureothamine (IIb) was obtained. Methylation

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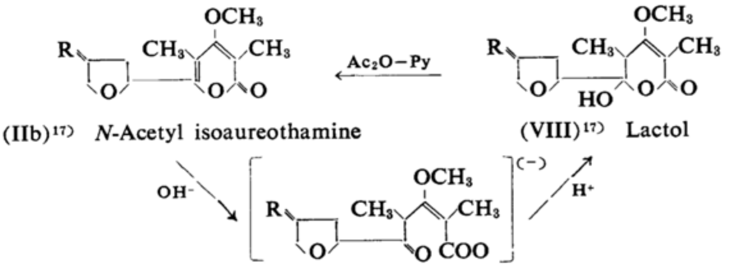
[14] In the same treatment of isoaureothin (I) and isoaureothamine (IIa), amorphous products were obtained showing properties similar to that of Lactol.

[15] This view was also supported by the lack of the characteristic band of α-pyrone at 1575 cm^{-1} in Lactol.

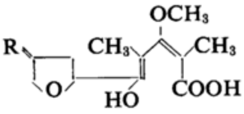
[16] The addition of excessive sodium hydroxide did not significantly after the infrared spectrum of the salt.



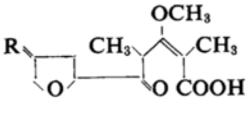
(IIb)$^{17)}$ *N*-Acetyl isoaureothamine

(VIII)$^{17)}$ Lactol

(VII)$^{17)}$



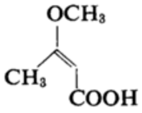
(IX)$^{17)}$



(X)$^{17)}$

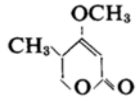
with diazomethane brought out the same result obtained in acetylation. In spite of careful scrutiny of the reaction products, no methylated substance was obtained in crystalline state. Since the formation of sodium salt suggests an acidic nature of Lactol, measurement of acidity constant (pK_a) by titration method was undertaken. No consumption of alkali by sample was observed below pH 10.5, implying the absence or masked state of carboxyl group under the conditions studied.

Structure of Lactol.—By comparison of the molecular formula between Lactol $C_{24}H_{29}O_6N$ and *N*-acetyl isoaureothamine $C_{24}H_{27}O_5N$, it is at once evident that hydrolysis of α-pyrone took place, leading to a product soluble in alkali. Since alcoholic part formed is an enol, it would exist enolate under strongly alkaline condition. Assuming the anion in alkaline solution to be expressed approximately as VII, disappearance of optical activity would naturally result. Examination of the properties of Lactol secures structure VIII for this product and excludes another possibility such as tautomeric α,β-γ,δ-unsaturated carboxylic acid IX and α,β-unsaturated ketocarboxylic acid X. Thinking of the result on the titration of Lactol, carboxylic acid structures are clearly ruled out and the structure VIII is assigned to Lactol in solution. The use of ultraviolet spectrum is not reliable for the discrimination between lactol structure (VIII) and carboxylic acid structure X[18]; an absorption maximum in question is located near 245 mμ (Fig. 1), which would be reasonable both for Lactol (VIII) and α,β-unsaturated carboxylic acid (IX), considering the spectra of models G[19] and H[20].



$\lambda_{\max}$ 234 mμ

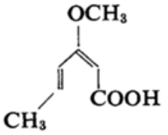
(G)



$\lambda_{\max}$ 234 mμ

(H)

From the position and the shape of hydroxyl stretching vibration which appeared in 3000 cm^{-1} region of the infrared spectrum, it becomes highly probable that there is no hydroxyl group of carboxylic nature. There was observed a band at 1708 cm^{-1}, the overlapping of which with a strong amide I band (1675 cm^{-1}) rendered the former to be a shoulder band of the latter. Utilizing this shoulder band, in conjunction with bands which appeared in sodium salt, it is possible to discriminate a structure VIII from IX and X. First, form IX is taken into account. Considering the infrared spectrum of model J, >C=O vibration of IX is expected to occur near 1660 cm^{-1}, which is not an actual case (band observed is at 1708 cm^{-1}).



$\nu_{C=O}$: 1665 cm^{-1}

(J)

Secondly, if Lactol took form X, it should, in addition to a band due to carboxylic acid, exhibit a band of isolated ketone at 1717 cm^{-1} (observed in sodium salt), which is absent in Lactol itself. Carboxylic acid structures are, in any event, inconsistent with the observation about ν_{O-H} region as described before.

Structure VIII can, in every respect, be re-

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[17] R=*p*-acetylamino-α-methyl cinnamylidene.

[18] The possibility of IX is clearly excluded, since this should show an absorption at much longer wavelengths.

[19] K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, **1946**, 948.

[20] E. R. H. Jones and M. C. Whiting, ibid., **1949**, 1419.

conciled with the infrared spectra of Lactol and of its sodium salt. Looking upon α, β-unsaturated lactone ($\nu_{C=O}$: 1717~1730 cm^{-1}) as the fundamental system, the structure VIII is constructed by attaching hydroxyl and methoxyl group to the fundamental system. These two substituents, in this case, cause opposite effects on the position of carbonyl absorption in the α, β-unsaturated ester system; i.e., carbonyl frequency tends to be lowered by the mesomeric effect due to the methoxyl group and to be raised by the inductive effect of the hydroxyl group. A slight lowering of carbonyl frequency would be expected as a net result, according to the estimation of two such effects based on the data[21] so far available. Thus, it is reasonable to ascribe a band at 1708 cm^{-1} to the lactonic carbonyl group in structure VIII. Furthermore, the appearance of a band at 1717 cm^{-1} in sodium salt is quite consonant with structure VIII.

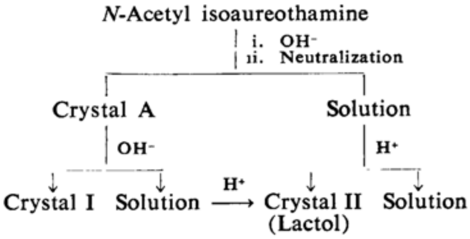
Chemical and spectral evidence now substantiates lactol structure VIII and rules out other possibilities, both in solution and solid state.

Experimental

Ozonization of Isoaureothin Derivatives. — In order to estimate the amount of methyl pyruvate produced by ozonization, the following procedure was applied in each run. Through a solution of ca. 500 mg. of sample in 10~15 ml. of chloroform, ozone was passed at −5~−10°C, until the uptake of ozone by sample ceased. On removal of the solvent at reduced pressure, a viscous syrup was obtained which was then treated at 60°C with 10~15 ml. of water in a flask equipped with a condenser. The aqueous fraction was separated, and a solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid was added to it. The crude hydrazone was collected, dried, dissolved in benzene and chromatographed on alumina. 2,4-Dinitrophenylhydrazone of methyl pyruvate, eluted with benzene-ether was collected and weighed, m.p. above 140°C, m.p. 145~147°C after recrystallization from benzene. Formaldehyde was also detected in every sample, except in the cases of *N*-acetyl aminol H (IIIb) and *N*-acetyl *O*-methyl aminol H (IIIe).

Lactol (VIII). — To a mixture of 110 ml. of ethanol and 55 ml. of 3 N aqueous sodium hydroxide, 2 g. of *N*-acetyl isoaureothamine was added. The flask was equipped with a reflux condenser and the suspension was warmed on a water bath at about 80°C for ten min., when the mixture became clear and of an orange color. After rapid cooling, the solution was neutralized with dilute hydrochloric acid; the solution turned yellow immediately at the neutralization point (pH 7). The solution was concentrated to 50 ml. under reduced pressure to yield fine crystals ("crystal A"). The yellow filtrate from "crystal A" was acidified gradually with dilute hydrochloric acid and the resultant precipitates (in part oily material) were collected and recrystallized from ethanol to yield almost colorless needles ("crystal II"), named Lactol, m.p. 170~171°C, 500 mg. When "crystal A" was dissolved in aqueous sodium hydroxide solution, a small part was insoluble in alkali. The alkali-insoluble crystals ("crystal I") were collected and recrystallized from ethanol repeatedly, m.p. 223~225°C, 40 mg.

The filtrate from "crystal I" was acidified and the resulting crystals were identified as "crystal II"; yield 250 mg., combined amount of "crystal II", 750 mg. The ultraviolet spectrum of "crystal II" showed λ_{max} 299 mμ (log ε 4.52) (in ethanol). $[\alpha]^{27}_{D}$, 0±1.5° (methanol, c=0.75). Titration was carried out in 66% aqueous ethanol solution.



Analysis was carried out on "crystal II" (Lactol): Found: C, 67.06; H, 7.19; N, 3.63. Calcd. for $C_{24}H_{29}O_6N$: C, 67.43; H, 6.84; N, 3.28%.

Action of Diazomethane on Lactol.—Crystalline Lactol was added to ethereal diazomethane, but no reaction took place under the heterogeneous condition and the starting material was recovered. To 20 ml. of ethereal diazomethane was added 100 mg. of Lactol, dissolved in 20 ml. of methanol and the mixture was allowed to stand overnight. After removal of about two-thirds of the volume of solvent at reduced pressure, the precipitated crystals were filtered and recrystallized from ethanol to give colorless needles, m.p. 191~193°C, 25 mg., $[\alpha]^{28}_{D}$, 0±2° (c=0.8 in a mixture of chloroform and methanol (1:2)). The infrared spectrum taken in solid state (KBr) was identical with that of *N*-acetyl isoaureothamine (m.p. 209~211°C; $[\alpha]^{28}_{D}$ +140 ±1.5° in a mixture of chloroform and methanol (1:2)), the starting material of Lactol. Mixing two species of *N*-acetyl isoaureothamine (optical active and inactive species), no depression of the melting point was observed; mixted melting point, 193~200°C. Further concentration of filtrate gave a small amount of oily material, the infrared spectrum of which included bands at 1701(sh), 1690(s), 1606(m), 1592(m) and 1512(s)cm^{-1} (in chloroform). The main portion of the product might be an ester.

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[21] Literatures for the estimation of mesomeric effect of methoxyl group; (a) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954); (b) R. S. Rasmussen and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949); (c) H. Heyman, S. S. Bhatnagar and L. F. Fieser, ibid., **76**, 3689 (1954).

Literatures as to inductive effect of hydroxyl (and alkoxyl) group: (d) R. B. Woodward and E. G. Kovach, *J. Am. Chem. Soc.*, **72**, 1009 (1950); (e) J. F. Grove and G. A. Willis, *J. Chem. Soc.*, **1951**, 877; (f) J. F. Grove ibid., **1952**, 3345; (g) L. A. Duncanson, J. F. Grove and J. Zealley, ibid., **1953**, 1331, 3637.

Action of Acetic Anhydride on Lactol.—To a mixture of 1 ml. of pyridine and 5 ml. of acetic anhydride was added 50 mg. of Lactol. It was kept at 70°C for ten minutes and after cooling, water was added to the solution, the resultant crystals were collected, recrystallized from ethanol and identified as the starting material, Lactol. Again, the same procedure was applied with prolonged heating (one hour); the resultant crystals, differing from Lactol, were recrystallized from ethanol and were identified as *N*-acetyl isoaureothamine by the comparison of the infrared spectra, m.p. 193~194°C.

Found: C, 70.59; H, 6.50. Calcd. for $C_{24}H_{27}O_5N$: C, 70.40; H, 6.50%.

All melting points were uncorrected. The ultraviolet spectra were measured with a Hitachi spectrophotometer and the infrared spectra with a Hilger H 800 spectrometer, equipped with rock-salt prisms. The optical rotations were measured with a Rudolf polarimeter.

Summary

During the course of the investigation of isoaureothin (I), several derivatives were obtained, the structure of which still remains unknown. The structure of these derivatives is presented in this paper on a basis of spectral and chemical evidence. The reduction of isoaureothamine (IIa) with lithium borohydride yielded an unexpected acidic substance, aminol H (IIIa) the formation of which, taken in conjunction with that of *N*-acetyl aminol A (IVa), provides an unusual type of reduction by complex metal hydride. Treatment of *N*-acetyl isoaureothamine (IIb) with alkali yielded an optically inactive substance, Lactol, which was formulated as VIII. The action of acetic anhydride on Lactol resulted in the formation of racemate of *N*-acetyl isoaureothamine (IIb).

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