20 cc. of abs. EtOH, 2 cc. of 80% hydrazine hydrate was added, then evolution of N_2 began. The reaction mixture was evaporated under reduced pressure after standing over nignt. The residue was dissolved in a mixture of $CHCl_3$–EtOH (50 cc.+20 cc.), chromatographed over Al_2O_3 and developed with same solvent. After evaporation of the solvent, a orange crystalline solid was obtained, m.p. 262° (decomp.). The IR spectrum was identical with that of 4-aminoquinoline 1-oxide. Yield, 0.23 g. (53%).

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai, Prof. T. Okamoto of the University of Tokyo, and Dr. T. Itai of this Institute for their kind and helpful guidance through the course of this work, and to Dr. T. Kariyone, the Director of this Institute for his encouragement. He is also thankful to Dr. T. Oba and Mr. G. Kawabata for the measurement of IR spectra, and to Miss Y. Urushibata and Miss E. Shimizu of Kowa Chemical Laboratories for elemental microanalysis. This investigation was supported in part by a scientific research grant in aid of the Ministry of Health and Welfare.

Summary

Several reactions of the azido group in 4-azidoquinoline 1-oxide were examined. It was found out that they could generally be classified under-mentioned three groups. 1. A radical reaction after the loss of the two nitrogen atoms, i.e., dimerization and hydrogen abstraction reactions of produced diradical. 2. A substitution reaction with the loss of azido group, i.e., ionic reaction. 3. An addition reaction to formation of tetrazole.

(Received March 29, 1961)

UDC 547.979-07

76. Shoji Shibata,[*1] Junzo Shoji,[*1] Norio Tokutake,[*2] Yoshiyuki Kaneko,[*2] Hiroshi Shimizu,[*1] and Hsüch-Ching Chiang[*1]: Decomposition of Usnic Acid. VI.[*3] Studies on the Ozonolytic Products of O,O-Diacetylusnic Acid.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

Usnic acid, whose structure (III) had long been discussed[1] was synthesized by Barton *et al.*[2] by oxidative coupling of methylphloroacetophenone (I) in an analogous way of formation of Pummerer's ketone from *p*-cresol. However, the condensation mechanism shows an alternative possibility of formation of a product formulated (IV).

The possibility of formula (IV) of usnic acid was suggested once by Yanagita,[3] though it would obviously be difficult, if not impossible, to explain the degradation products of usnic acid, most of which were synthetically established.

Nevertheless, the formula (IV) could not be ruled out until the ambiguity of ozonolytic products of O,O-diacetylusnic acid would have completely been solved. The present study

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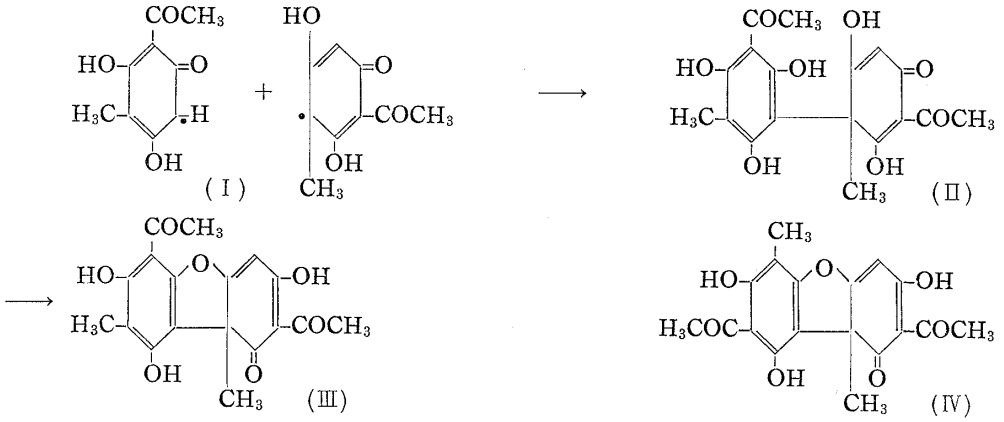
*3 Part V: S. Shibata, K. Takahashi, Y. Tanaka: Pharm. Bull., 4, 65 (1956).

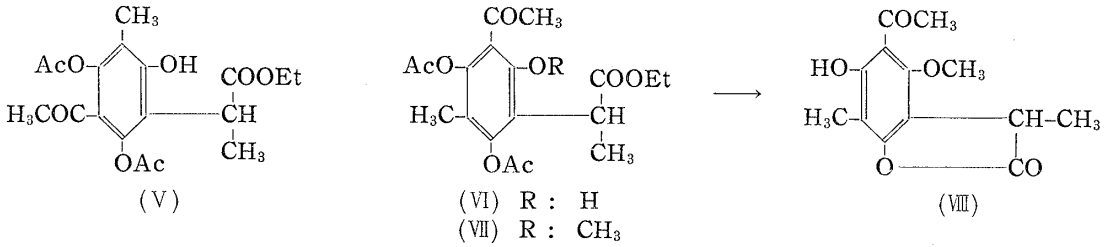
1) See Y. Asahina, S. Shibata: Chemistry of Lichen Substances, p. 172~197 (Japan Society of Promotion for the Sciences, Tokyo (1954); "Especial Compounds of Lichens" in Encyclopedia of Plant Physiology, Vol. X, p. 600~612 (Springer Verlag (Berlin-Göttingen-Heidelberg), 1958) cited earlier references.
2) D. H. R. Barton, A. M. Deflorin, O. E. Edwards: J. Chem. Soc., **1956**, 530.
3) M. Yanagita: Meeting of Pharm. Soc. Japan, Nov., 1958 (unpublished.).



has dealt with the presentation of an unequivocal evidence for the structure of ozonolytic products of O,O-diacetylusnic acid.[4,5]

Asahina and Okazaki[5] obtained an ethyl ester, $C_{18}H_{22}O_8$, m.p. 116°, by the alcoholysis of ozonide of O,O-diacetylusnic acid.

If the structure (IV) is adopted for usnic acid, the ethyl ester must be (V), while it was proposed as being (VI) by Asahina and Okazaki who accepted Robertson-Schöpf's formula (III) of usnic acid.



The establishment of the structure of the ozonolytic product (V) or (VI) has been performed by the infrared spectral analysis.

The infrared spectra of 2′-hydroxyacetophenone and 4′-hydroxyacetophenone derivatives were measured in chloroform solution changing its concentration. The C=O stretching infrared absorption band of methylketone chelated with 2′-hydroxyl appeared at 1630~1640 cm^{-1}, whose intensity was stronger than the absorption of phenyl at 1600 cm^{-1} and the position was not affected by dilution of the solution, while 4′-hydroxyacetophenone derivative in higher concentration showed a shift of C=O band at nearly 1635 cm^{-1} by the intermolecular association, which was moved towards higher frequencies on dilution and gave weaker intensity than that of phenyl band.[6] The OH- stretching band of 2′-hydroxyacetophenone derivatives was shifted by hydrogen bonding, while that of 4′-hydroxyacetophenone derivatives appeared at 3600 cm^{-1}.

The infrared absorption of the ethyl ester derived from the ozonide of O,O-diacetylusnic acid showed the C=O band of methyl ketone at 1630 cm^{-1} (in $CHCl_3$) which was not shifted on dilution and the intensity was stronger than that of phenyl absorption (1608 cm^{-1}).

Consequently, the ethyl ester should be represented by the formula (VI) as originally forwarded by Asahina and Okazaki[5], and this was confirmed further by converting into the methyl ether of lactone, which was proved to be identical with 4-methoxy-5-

4) C. Schöpf, F. Ross: Ann., **546**, 1 (1941).
5) Y. Asahina, K. Okazaki: Yakugaku Zasshi, **63**, 626 (1943); C. A., **45**, 5037.
6) L. J. Bellamy: The Infrared Spectra of Complex Molecules, p. 74 (1952). (Methuen & Co. Ltd. London (1958)).

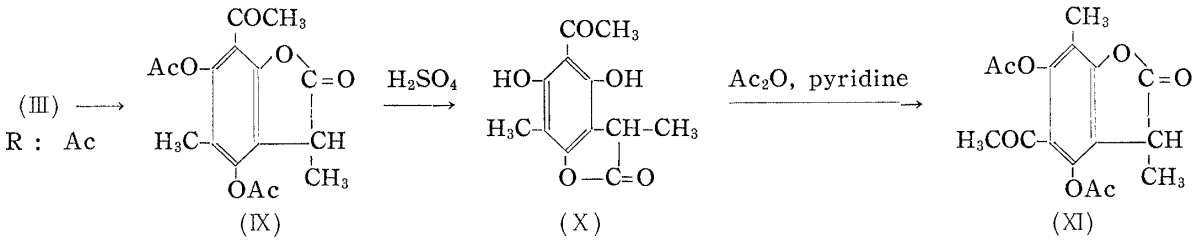
acetyl-6-hydroxy-3,7-dimethyl-2-coumaranone (Ⅷ) synthesized by Dean and Robertson[7] by an unequivocal method.

Thus it has been established that the condensation of methylphloroacetophenone proceeded as presented by Barton *et al.*,[2] and the alternative structure (Ⅳ) of usnic acid has completely been ruled out.

The ozonolysis of O,O-diacetylusnic acid provided an important evidence for the structure of usnic acid (Ⅲ) which was reported by Schöpf and Ross.[4] On treatment of crystalline ozonide of O,O-diacetylusnic acid with alcohol, a lactonic compound, $C_{16}H_{16}O_7$, m.p. 132° (Lactone A) and ethyl acetoneoxalate were obtained. In addition to these products, as has been referred above, Asahina and Okazaki[5] obtained the ethyl ester, $C_{18}H_{22}O_8$, m.p. 116°, whose structure (Ⅵ) has now been confirmed by the present study.

The structure of lactone A was represented by Schöpf and Ross,[4] without established evidence, as being 7-acetyl-3,5-dimethyl-4,6-dihydroxy-2-coumaranone diacetate (Ⅸ). Reacetylation of deacetylated lactone A, $C_{12}H_{12}O_5$, m.p. 233°, furnished a compound, lactone B, which also showed m.p. 132°, and thought to have the same molecular formula as lactone A, giving, however, an obvious depression of melting point (⊿-20°) on mixed fusion with the original lactone A.

Schöpf and Ross suggested that the reacetylated lactone B would be a rearranged product of lactone A as formulated (Ⅺ).



(Ⅸ) (Ⅹ) (Ⅺ)

Asahina and Okazaki,[3] and Asahina and Yanagita[8] obtained a lactone monoacetate, $C_{14}H_{14}O_6$, m.p. 190°, as an ozonolytic product of O,O-diacetylusnic acid, which was also afforded by partial deacetylation of the lactone B with sodium carbonate.

Asahina and Okazaki[5] described that on seeding a small fragment of crystals of the original lactone A to the alcoholic solution of the lactone B, only crystals of lactone A separated, which was proved by mixed fusion giving no depression of melting point. Thus they concluded that the lactone B is not a rearranged product but a crystallographic dimorphic state of lactone A.

Afterwards, Dean and Robertson[7] synthesized the deacetylated lactone, m.p. 233°, and its monoacetate, m.p. 190°, but failed to obtain the diacetate (lactone A or B), though they tried acetylation by Schöpf's method. In the course of synthetical process, they assumed a rearrangement of lactone ring on demethylation of an intermediate product, 4-methoxy-5-acetyl-6-hydroxy-3,7-dimethyl-2-coumaranone.

In repeated trials we have failed to convert the lactone B into the lactone A by seeding alcoholic solution of lactone B with crystals of lactone A.

On reexamination of this confused problem, we observed that all the former workers employed acetic anhydride and pyridine as the reagent of reacetylation of the deacetylated lactone A to result lactone B.

Using acetic anhydride and conc. H_2SO_4, instead of pyridine, in the reacetylation process, we obtained only the lactone A. Employing pyridine as indicated by the former workers, we confirmed that the lactone B is a main product of reacetylation of deacetylated lactone A.

7) F. M. Dean, A. Robertson : J. Chem. Soc., **1955**, 2166.
8) Y. Asahina, M. Yanagita : unpublished data referred in Rf. 5).

In some cases we found that the lactone A was also formed using acetic anhydride and pyridine. Thus Asahina and Okazaki might have obtained pure lactone A by seeding it from a mixture of lactones A and B.

The infrared absorption spectrum of lactone B, but not that of lactone A showed a characteristic band in the C:O region at 1733 cm^{-1} ($CHCl_3$).

This is incompatible with the former explanation suggesting dimorphism or rearrangement of lactone ring.

We concluded therefore that the reacetylation with acetic anhydride and pyridine resulted mainly C-acetylation at the 3-position of 2-coumaranone ring together with the ordinary O-acetylation at the 4- and 6-hydroxyls.

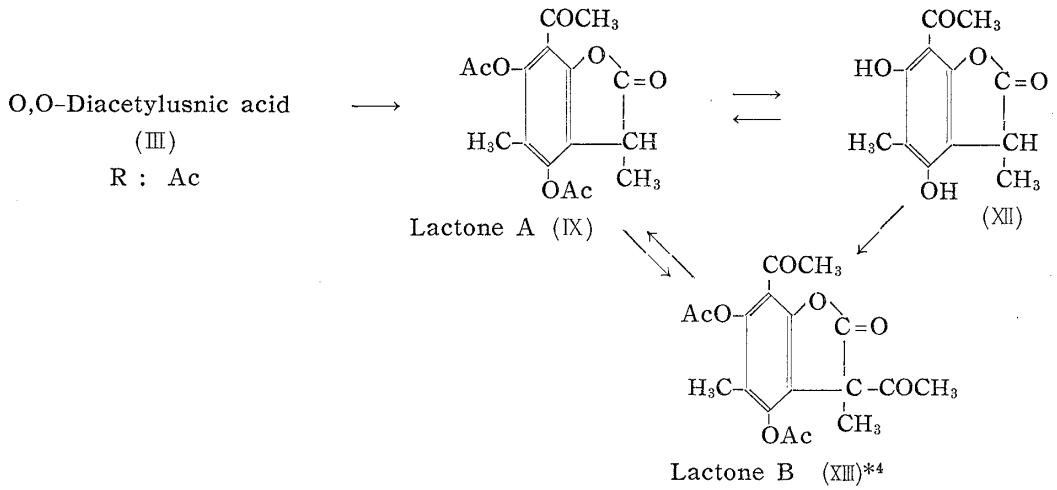
The band of infrared absorption at 1733 cm^{-1} given by the lactone B must be attributed to a non-conjugated $COCH_3$ group at the 3-position. Moreover, it was observed that the original lactone A is converted directly into the lactone B by treatment with acetic anhydride and pyridine.

Table I.

Compound	Infrared Absorption Bands in the C=O Region (cm^{-1}, in $CHCl_3$)	
Lactone A	1813	$\beta\gamma$-Unsaturated γ-lactone
	1770	Phenolic acetate
	1696	Aryl acetyl
Lactone B	1810	$\beta\gamma$-Unsaturated γ-lactone
	1775	Phenolic acetate
	1733	Non-conjugated acetyl
	1696	Aryl acetyl

The lactones A and B could not be distinguished by analytical results: lactone A (Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.01. Found: C, 60.26; H, 5.11) and lactone B (Calcd. for $C_{18}H_{18}O_8$: C, 59.67; H, 4.97. Found: C, 60.07; H, 5.06).

Thus the relationship between lactone A and lactone B, and the structures of these compounds are explained as shown below:



This conclusion was confirmed by the nuclear magnetic resonance spectra which showed the presence of a $-\underset{|}{CH}-CH_3$ grouping in the lactone A (Fig. 1 A), and the absence of such a system in the lactone B (Fig. 1 B).

*4 The formula (XIII) was once given by Takahashi and Shibata (Yakugaku Zasshi, **71**, 1083 (1951)) for the oxidation product of O,O-diacetylusnic acid, which however was corrected by Barton *et al.* (J, Chem. Soc. **1953**, 603) as being a dimer of lactone A.

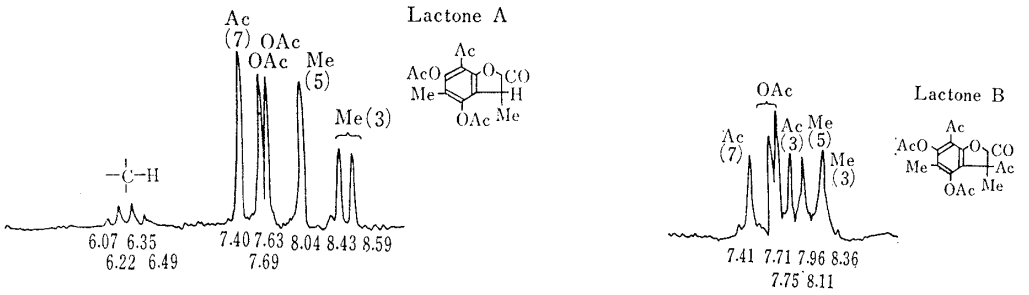
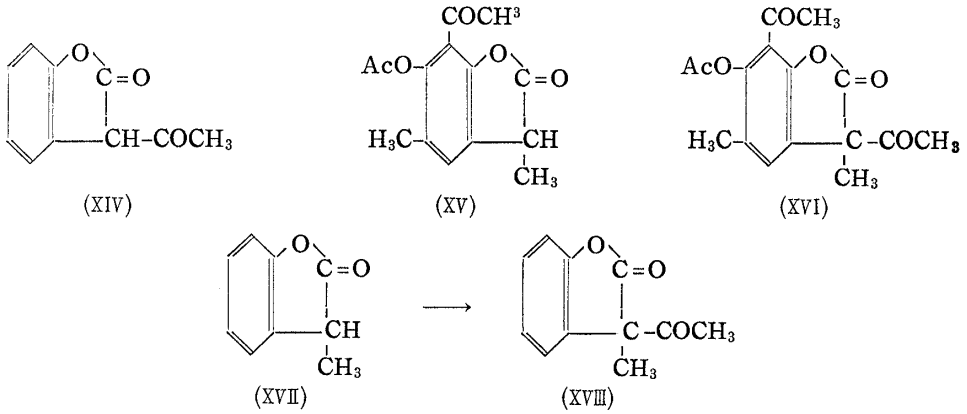


Fig. 1. N.M.R. Spectra of Lactone A and Lactone B (in $CHCl_3$)
(The spectra were obtained with a Varian Associates 4300 C spectrometer operating at 56.4 Mc. The positions of resonances are measured by the side band technique and expressed as values of τ.)

3-Acetyl-2-coumaranone (XIV) was reported by Geissman *et al.*,[9] who prepared it from (*o*-hydroxyphenyl)acetic acid by treatment with acetic anhydride and pyridine. This provides a support to our above conclusion, though the explanation of mechanism assuming an acid anhydride as an intermediate stage of this reaction seems to be improbable, since the lactone A (IX) is directly subjected to C-acetylation giving the lactone B.



As a model compound, 3-methyl-2-coumaranone (XVII) was prepared and acetylated with acetic anhydride and pyridine to yield 3-acetyl-3-methyl-2-coumaranone (XVIII).

6-Hydroxy-7-acetyl-3,5-dimethyl-2-coumaranone which was afforded by Asahina and Yanagita[10] by the thermal decomposition of dihydrousnic acid in the presence of calcium chloride also yielded by the acetylation with acetic anhydride and pyridine a C-acetylated product, m.p. 108° (XVI), which showed the characteristic absorption band at 1733 cm^{-1} ($CHCl_3$), while O-acetate (XV), m.p. 102°, was yielded by the action of acetic anhydride and conc. H_2SO_4.[10]

Thus the proposals forwarded by the former workers dealing with the ozonolytic products of O,O-diacetylusnic acid have been corrected and all the ambiguities related to this reaction have clearly been solved.

Experimental

Ethyl 2-(2-Hydroxy-3-acetyl-5-methyl-4,6-diacetoxyphenyl)propionate (VI. R=H)——Ozonolysis of O,O-diacetylusnic acid was carried out by the method of Asahina and Okazaki[5] : Ozonized O_2 was passed through the solution of (+) O,O-diacetylusnic acid (5 g.) in CCl_4 (100 ml.) for 3 hr., when the yellow color of solution was discharged, and crystals of ozonide separated out. 95% EtOH (50 ml.) was added and the solvent was removed below 45° *in vacuo*. The syrupy residue was allowed to stand

9) T. A. Geissman, A. Armen : J. Am. Chem. Soc., **77**, 1623 (1955).
10) Y. Asahina, M. Yanagita : Ber., **71**, 2260 (1938).

in a cool place to separate faintly yellowish crystals (2 g.) which were recrystallized from MeOH to give m.p. 115~116°. *Anal.* Calcd. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.01; H, 5.97.
Acetate (VI, R=Ac): Colorless prisms, m.p. 102.5~103.5°. *Anal.* Calcd. for $C_{20}H_{24}O_9$: C, 58.82; H, 5.92. Found: C, 59.20; H, 5.68.
Methyl ether (VII, R=Me): The above ethyl ester (VI, R=H) (300 mg.) was mixed with anhydr. K_2CO_3 (3 g.), MeI (4 ml.), and Me_2CO (12 ml.). The mixture was kept at 25° under occasional shaking for 18 hr. The solvent was removed, and 50% MeOH was added to separate colorless crystals, which were recrystallized from MeOH to m.p. 91°. *Anal.* Calcd. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.86; H, 6.05.

4-Methoxy-5-acetyl-6-hydroxy-3,7-dimethyl-2-coumaranone (VIII)——The methyl ether of the above ester (VII, R=Me) (30 mg.) was dissolved in conc. H_2SO_4 (4 ml.). The mixture was kept for 10 mins. at room temperature, and then poured into ice-water (50 ml.). The precipitates were recrystallized from MeOH to give faintly yellowish plates, m.p. 126°. The substance was proved to be identical with Robertson and Dean's authentic sample of 4-methoxy-5-acetyl-6-hydroxy-3,7-dimetyl-2-coumaranone, m.p. 126°, on a mixed fusion.

7-Acetyl-3,5-dimethyl-4,6-dihydroxy-2-coumaranone diacetate (IX)——Ozonolysis of O,O-diacetylusnic acid was then carried out by the method of Barton and Bruun[11]: The ozonide of O,O-diacetylusnic acid in CCl_4 was decomposed by addition of water, and the mixture was refluxed on a boiling water bath for 15 min. The CCl_4 solution was extracted with 5% $NaHCO_3$ solution and the neutral portion was obtained by removing the solvent. On recrystallization from EtOH, it gave m.p. 130~132° (Lactone A). UV λ_{max}^{EtOH} mμ (ε): 218 (29,000), 297 (3,700). *Anal.* Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.01. Found: C, 60.19; H, 5.36.

7-Acetyl-3,5-dimethyl-4,6-dihydroxy-2-coumaranone (XII)——Prepared by hydrolysis of Lactone A (IX) with *N*-NaOH or conc. H_2SO_4. Faint yellow needles, m.p. 223~224° (Deacetyl-lactone A).

Acetylation of Deacetyl-lactone A——i) Acetylation with Ac_2O and conc. H_2SO_4: The acetate obtained was recrystallized from EtOH to give m.p. 130~131°, which showed no depression on admixture with lactone A.
ii) Acetylation with Ac_2O and pyridine: The acetate obtained was recrystallized from EtOH to give m.p. 132~132.5° (Lactone B). On admixture with lactone A, it showed a depression of melting point (*Δ*-20°). UV λ_{max}^{EtOH} mμ (ε) 220 (31,000), 297 (4,100). *Anal.* Calcd. for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01. Found: C, 60.07; H, 5.06.

Synthesis of 3-Methyl-2-coumaranone (XVII)——Methyl 3-methyl-2-coumarone-carboxylate[12], m.p. 70°, (820 mg.) was dissolved in EtOH and added with $NH_2OH \cdot H_2O$ (1.5 ml.). The mixture was refluxed on a boiling water bath for 1 hr. On concentration of the reaction mixture, the crystals of hydrazide, m.p. 139~141° (820 mg.) separated out. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.87; H, 5.39; N, 14.51.

The hydrazide (1 g.) was dissolved in glacial AcOH (20 ml.) and ice water (10 ml.) was added. Aq. $NaNO_2$ solution (0.2 g. in 5 ml. H_2O) was dropped under stirring and the mixture was kept further for 5 mins.

Thus the crystals of azide, m.p. 105~106.5° (decomp.) separated out. A mixture of azide (1 g.) and abs. EtOH (5 ml.) was boiled on a bath giving brown solution liberating N_2 vigorously. After 1 hr. boiling, the mixture was filtered and the filtrate was evaporated to give dark brown syrup, which formed crystals on standing. The product, urethane, was treated with hot ligroin to remove resinous substance, and recrystallized from ligroin to give colorless crystals, m.p. 81~82° (0.7 g.).

A solution of the urethane (0.6 g.) dissolved in 10% KOH was boiled for 30~60 min. The reaction mixture was concentrated *in vacuo* and acidified with dil. HCl to separate resinous substance. Salting out by the addition of NaCl the mixture was extracted with Et_2O. The residue obtained by removing Et_2O was distilled *in vacuo* (bath temp. 128~130°, 3~4 mm-Hg) to give colorless oil (3-methyl-2-coumaranone (XVII)). *Anal.* Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.93; H, 5.34.

Acetylation of 3-Methyl-2-coumaranone——3-Methyl-2-coumaranone was acetylated with Ac_2O (1 ml.) and pyridine (7 ml.) to give oily acetate. The IR spectrum of the acetate showed a characteristic band of nonconjugated $COCH_3$ at 1733 cm^{-1} ($CHCl_3$) to indicate that the product is 3-acetyl-3-methyl-2-coumaranone (XVIII).

The authors wish to thank Dr. I. Yamaguchi and Mr. N. Hayakawa of Japan Institute for Atomic Energy for the measurement of n. m. r. spectra, Miss M. Ninomiya and Mrs. E. Tanaka for the measurement of infrared spectra and the members of microanalytical laboratory of the Institute of Applied Microbiology, and this Faculty, University of Tokyo, for microanalyses. The authors are also indebted to Dr. F. M. Dean, University of Liverpool, for the gift of the sample.

11) D. H. R. Barton, T. Bruun: J. Chem. Soc., **1953**, 603.
12) A. Hantsch: Ber., **19**, 1292 (1886).

Summary

The structure of the ethyl ester, $C_{18}H_{22}O_8$, m.p. 116°, which was obtained from O,O-diacetylusnic acid by the ozonolysis followed by alcoholysis was established by infrared spectral analyses as being ethyl 2-(2-hydroxy-3-acetyl-5-methyl-4,6-diacetoxy-phenyl)-propionate (VI). An alternative possible structure of usnic acid (IV) has therefore been excluded, and the structure of usnic acid (III) has been confirmed.

The behaviors of lactone A, m.p. 132°, an ozonolytic product of O,O-diacetylusnic acid was reëxamined. It was proved by infrared and nuclear magnetic resonance spectra, that reacetylation of deacetyl-lactone A with acetic anhydride and pyridine was affected at the 3-position of 2-coumaranone ring to furnish lactone B, m.p. 132°. Acetylating with acetic anhydride and conc. H_2SO_4, lactone A was regenerated from deacetyl-lactone A. Thus the earlier conclusions concerning with the lactones A and B have been corrected.

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77. Junzo Shoji*1 : Decomposition of Usnic Acid. VII.*2 Pyrolysis of Dihydrousnic Acid. (3).*3 Isodihydrousnic Acid.

(*Faculty of Pharmaceutical Sciences, University of Tokyo**1)

Shibata, Takahashi and Tanaka*3 found that on heating above 200°, *in vacuo*, dihydrousnic acid (DHU), m.p. 149°, was converted into an isomeric compound named isodihydrousnic acid (IDHU), m.p. 128°, before it was completely decomposed into 6-hydroxy-7-acetyl-3,5-dimethyl-2-coumaranone and acetylacetone. DHU and IDHU could be distinguished neither by the color reactions nor by their infrared and ultraviolet absorption spectra. The both compounds, however, gave different optical rotations and migration distances on paper electrophoresis using buffer solution at pH 8.8.

$$\begin{array}{lcl} (-)\ \text{DHU m.p. } 149^\circ & \longrightarrow & (+)\ \text{IDHU m.p. } 128^\circ \\ [\alpha]_D\ -86.8^\circ & & [\alpha]_D\ +57.5^\circ \end{array}$$

In the previous report,*3 it was suggested that DHU and IDHU would be *cis-trans* isomers at B/C ring fusion. On renewed investigation on this transformation of DHU, it has been found that the earlier suggestion would not be probable to elucidate the relation of DHU and IDHU.

All the attempts to obtain acetate of IDHU were failed, and the product of acetylation of IDHU was identical with the diacetate of DHU. DHU and IDHU were, however, differentiated by the individual Cu-complex salt having different color and optical rotation (DHU Cu-salt : $[\alpha]_D$ $-123\pm10°$; IDHU Cu-salt : $[\alpha]_D$ $0\pm10°$).

Observing the change of optical rotation, it has been shown that DHU and IDHU are interconvertible in pyridine or in aq. alkali solution to form an equilibrium (approx. 50:50)

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*1 Hongo, Tokyo (庄司順三).

*2 Part VI : S. Shibata, J. Shoji, N. Tokutake, Y. Kaneko, H. Shimizu, H. C. Chiang : This Bulletin, **10**, 477 (1962).

*3 (2) : S. Shibata, K. Takahashi, Y. Tanaka (nee Hiizumi) : This Bulletin, **4**, 65 (1956).