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THE METHYLATION OF PYRONONES. THE STRUCTURAL CORRELATION OF AUREOTHIN AND ISOAUREOTHIN

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WE have investigated [1-6] the structure of aureothin (I), a yellow toxin isolated [7] from the culture of Streptomyces thioluteus. The substance is exceedingly sensitive towards acidic reagents and is easily demethylated with dilute acids to give desmethylisoaureothin (II). Spectral data indicate the presence of an α-pyrone rather than a γ-pyrone structure in (II), as is formulated below. Methylation of (II) with diazomethane under the usual condition yielded an isomer of aureothin, isoaureothin (III),

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[1] Y. Hirata, K. Okuhara and T. Naito, Nature 173, 1101 (1954).

[2] Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, J. Chem. Soc. Japan 78, 1700 (1957).

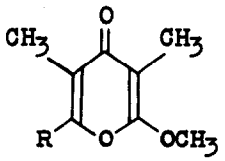
[3] T. Naito, Y. Hirata, K. Okuhara and K. Iwadare, J. Chem. Soc. Japan 79, 374 (1958).

[4] H. Nakata, Y. Hirata, K. Okuhara, K. Yamada, T. Naito and K. Iwadare, J. Chem. Soc. Japan 79, 379 (1958).

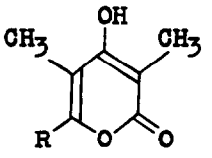
[5] K. Yamada, Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, J. Chem. Soc. Japan 79, 384 (1958).

[6] Y. Hirata, H. Nakata and K. Yamada, J. Chem. Soc. Japan 79, 390 (1958).

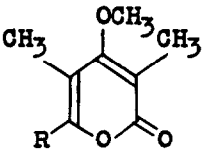
[7] K. Maeda, J. Antibiotics A 6, 137 (1953).



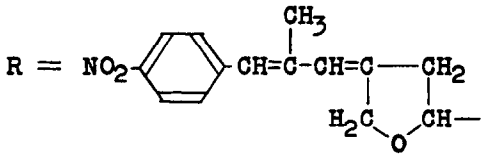
(I) aureothin



(II) desmethyl-isoaureothin



(III) isoaureothin



almost exclusively.

Recently, however, we have found that a little amount of (I) was also obtained from the reaction mixture only when a dilute ethereal solution of diazomethane was added gradually to a suspension of (II) in dry ether under the strictly anhydrous condition. The product ratio of the two isomeric ethers, (I)/(III) was 1/60.

Although literatures contain several references to the methylation reaction of 2,4-pyronone derivatives, the results obtained are still the subject of considerable controversy; thus, Arndt and Eistert [8] assigned the 6-methyl-4-methoxy-α-pyrone (A) structure for the methylation product of triacetic lactone (IV), while Arndt and Avan [9] later reported that treatment of (IV) with diazomethane yielded only one product, 6-methyl-2-methoxy-γ-pyrone (G). In 1952 Chmielewska and Cieslak [10] obtained the 1:3 mixture of two isomeric ethers, (G) and (A). Shortly thereafter, Janiszewska-Drabarek [11] re-examined this diazomethane methylation in

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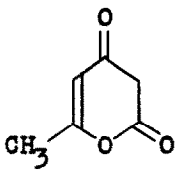
[8] F. Arndt and B. Eistert, Ber. 68, 1572 (1935).

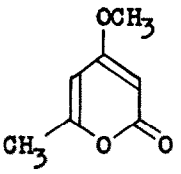
[9] F. Arndt and S. Avan, Ber. 84, 343 (1951).

[10] I. Chmielewska and J. Cieslak, Przemyst Chem. 8, 196 (1952).

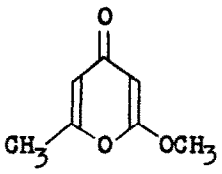
[11] S. Janiszewska-Drabarek, Roczniki Chem. 27, 456 (1953).



(IV)
triacetic lactone



(A)
6-methyl-4-methoxy-α-pyrone



(G)
6-methyl-2-methoxy-γ-pyrone

detail and concluded that both (A) (72 % yield) and (G) (20 % yield) were produced in this reaction. On the other hand, Wiley and Jarboe [12] reported that only one isomer (A) was formed. Several results in other 2,4-pyronone derivatives were also reported. [13-18]

Recently, there appeared an extensive study [19] on the methylation of triacetic lactone (IV) and it was concluded that methylation of 2,4-pyronones such as (IV) with diazomethane usually yielded mixtures of the two possible isomers, the actual proportions depending on the nature of other substituents. [20] In the case of methylation of desmethylisoaureo-

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[12] R. H. Wiley and C. H. Jarboe, J. Am. Chem. Soc. 78, 624 (1956).

[13] W. Borsche and C. K. Bodenstein, Ber. 62, 2515 (1929).

[14] I. Chmielewska and J. Cieslak, Roczniki Chem. 28, 38 (1954).

[15] J. Cieslak, Roczniki Chem. 32, 837 (1958).

[16] I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik and K. Pitakowska, Tetrahedron 4, 36 (1958).

[17] R. B. Woodward and G. Small, Jr., J. Am. Chem. Soc. 72, 1297 (1950).

[18] E. Ziegler and E. Nolken, Monatsh. 89, 391 (1958).

[19] E. Herbst, W. B. Mors, O. R. Gottlieb and C. Djerassi, J. Am. Chem. Soc. 81, 2427 (1959).

[20] Chmielewska and co-workers observed that two series of isomeric methyl ethers were obtained on the methylation of 3-substituted 4-hydroxycoumarins with diazomethane and the product proportions were distinctly affected by the type of substituent in position 3. We are indebted to Professor I. Chmielewska of Warsaw University for his kind information of this result (private communication to K. Y.). See, J. Cieslak, S. Lewak and I. Chmielewska, Roczniki Chem. 33, 349 (1959).

thin (II), however, the product ratio of the two isomeric ethers seemed to depend also on the reaction condition employed. [21]

Since it appeared of interest to investigate further the scope and mechanism of this reaction, the methylation reaction of triacetic lactone with diazomethane was re-examined in order to elucidate the relation between the reaction condition and the product proportions. Consequently, a dilute ethereal solution of diazomethane prepared [22] from 10 g of nitrosomethylurea was added, with vigorous stirring, to a suspension of 1 g of triacetic lactone (IV) in dry ether over various periods. All traces of atmospheric moisture were excluded and the temperature of the reaction mixture was maintained at 10 - 15° during the addition of the diazomethane solution. The resulting mixture was separated using the technique of Polish workers. [10,23] Product proportions are calculated as the percentage of the total weight of methylated products isolated. The results are summarized in Table 1.

On the basis of these data, it may be concluded that the product proportions of two isomeric ethers depend on the time required for the addition of the diazomethane solution; thus, the more gradually the addition of the diazomethane solution, the more will increase the proportions of the γ-pyrone methyl ether.

Triacetic lactone (IV) would exist in solution as a tautomeric mixture of (IVα) and (IVγ). Spectral data [10] suggest that in ether

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[21] Djerassi and co-workers [19] also noticed that different proportions were observed under the condition described by Wiley and Jarboe.[12]

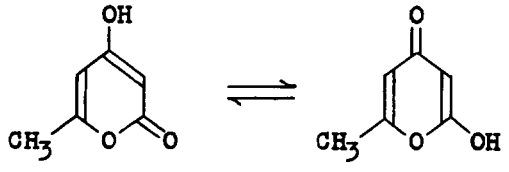
[22] F. Arndt, in Organic Syntheses Coll. Vol. II, p. 165. John Wiley and Sons Inc., New York (1943).

[23] I. Chmielewska, J. Cieslak and T. Kraczkiewicz, Roczniki Chem. 30, 1009 (1956).

Table 1

	The time required for the addition of the diazomethane solution	Average product proportions	
i) Triacetic lactone (IV):		(G) %	(A) %
	very rapidly	0	100
	2 - 4 hours	26	74
	18 hours	33	67
ii) Desmethylisoaureothin (II):		(I) %	(III) %
	very rapidly	0	100
	2 - 4 hours	0	100
	18 hours	2	98

solution the tautomeric form of an α-pyrone structure (IVα) predominates. This means (IVγ) is thermodynamically less stable than (IVα). According to the general theory [24,25] proposed by Ingold in 1948, a proton is transferred more quickly to bases from the less stable tautomer than from the stable tautomer. This proton mobility is characterized as the "dynamic



(IVα) (IVγ)

[24] A. G. Catchpole, E. D. Hughes and C. K. Ingold, J. Chem. Soc. 1948, 11.

[25] C. K. Ingold, Structure and Mechanism in Organic Chemistry p. 565. Cornell University Press, New York (1953).

acidity",[26,27] and therefore, (IVγ) has a larger dynamic acidity than that of (IVα). Since the reactivity towards diazomethane is proportional to this dynamic acidity, (IVγ) would react more rapidly than (IVα), though the equilibrium concentration of the former is much less than that of the latter in the solution.

When this solution reacts with a solution of diazomethane and only the direct methylation is possible, the following kinetic scheme can be written for the course of the reaction.

$$\begin{array}{ccccccc} CH_2N_2 & + & (IV\alpha) & \underset{k_-}{\overset{k_+}{\rightleftharpoons}} & (IV\gamma) & + & CH_2N_2 \\ & & \downarrow k_\alpha & & k_\gamma \downarrow & & \\ & & (A) & & (G) & & \end{array}$$

The velocity k_γ is larger than k_α so that the equilibrium quantity of (IVγ) will be used up more quickly than that of (IVα). Therefore, the prototropic rearrangement reaction (IVα)⟶(IVγ) will take place in favour of the formation of (G).

Arndt [26] has discussed in detail the "kinetic interplay" between methylation reactions (velocities k_α and k_γ) and prototropic rearrangement reactions (velocities k_+ and k_-), and drawn the following conclusions. If the concentration of diazomethane is maintained at a low level by gradual addition of a dilute diazomethane solution to the reaction mixture, and all traces of water exerting catalytic influences are excluded, velocities k_α

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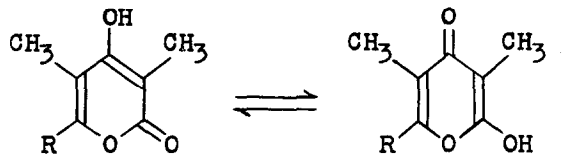
[26] F. G. Arndt, in J. Mitchell, Jr., I. M. Kolthoff, E. S. Proskauer and A. Weissberger ed., Organic Analysis Vol. I, p. 197. Interscience Publishers Inc., New York (1953).

[27] W. Hückel, Theoretische Grundlagen der Organischen Chemie Vol. I, 8th Ed., p. 306. Akademische Verlagsgesellschaft, Leipzig (1956).

and k_γ will decrease without a decrease in velocities k_+ and k_-; thus, there will be more time for the rearrangement (IVα)⟶(IVγ) to occur, and the condition will favour the formation of (G), i.e., its percentage will increase in the over-all product. This is in good agreement with our observations.

The same is true in the case of methylation of desmethylisoaureothin (II). As is shown in Table 1, aureothin (I) was obtained only when the diazomethane solution was added very gradually.

These data confirm the structural correlation of aureothin (I) and isoaureothin (III), and suggest that desmethyl derivative does exist in solution as a tautomeric mixture of (II) and (II'). Desmethylaureothin (II') has not been known so far, since its concentration in solution is very small as compared with that of the stable isomer, desmethylisoaureothin (II). It is interesting to note that aureothin (I) does not form a hydrochloride, though it has a γ-pyrone structure. Therefore, two isomers (I) and (III) were separated by fractional crystallization from alcohol.



(II) desmethyl-isoaureothin (II') desmethyl-aureothin

The more effective methylation reaction leading to a high yield of aureothin is neccessary for preparative purposes since the transformation would be involved in the final stage of the total synthesis of aureothin. Methylation with dimethyl sulfate gave satisfactory results; thus, the sodium salt of (II) prepared from 1 g of (II) was suspended in 40 ml dry

acetone and refluxed with 0.7 g of dimethyl sulfate for 6 hours. Upon employing the fractional crystallization of the resulting mixture, there was isolated 300 mg of aureothin (I) and 400 mg of isoaureothin (III).

As the methoxyl group can not be hydrolized under the reaction condition, the methylation reaction would be an irreversible process. The starting material is the least stable enolate anion and the kinetically controlled [24,25] methylation reaction would give the thermodynamically less stable isomer, aureothin (I). However, the methylation of the sodium salt of triacetic lactone (IV) under the same condition afforded only the stable isomer, 6-methyl-4-methoxy-α-pyrone (A).

The more detailed discussion of above results will be submitted for publication to the Journal of the Chemical Society of Japan in the near future.