Correlation of Reaction Rates and Product Stabilities. II[1]. *The Methylation of Pyronones with Dimethyl Sulfate*[2,3]

By Hisao NAKATA

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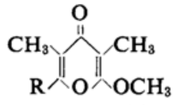
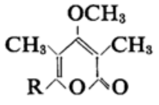
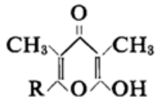
In the previous paper[1] of this series it was reported that the methylation of desmethylisoaureothin (IIIα) with diazomethane under a certain specific experimental condition afforded both aureothin (I) and isoaureothin (II). The product proportion of the two isomeric methyl ethers, viz., I : II, was 1 : 60. A more effective methylation reaction leading to a high yield of aureothin is necessary for preparative purposes since the transformation would be involved in the final stage of the total synthesis of aureothin.



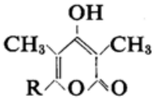
(I) Aureothin



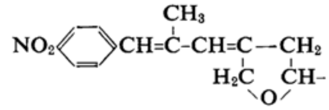
(II) Isoaureothin



(IIIγ)
Desmethylaureothin



(IIIα)
Desmethylisoaureothin

R=


The present investigation is concerned with an experiment on the methylation reaction of enolate anions of 2, 4-pyronone derivatives, the reaction that was chosen for scrutiny for reasons given in the following section. It was shown that the methylation with dimethyl sulfate was successful, and that aureothin was obtained from desmethylisoaureothin in fairly good yield. However, the product proportions of both isomers obtained were incompatible with those predicted by the general rule of this type of reaction. The scope of the reaction and some theoretical implications of the results are briefly discussed.

Theory of Kinetically Controlled Methylation

The previous investigation[4] on the tautomerism of several 2, 4-pyronones indicates that the α-pyrone derivatives are generally more stable than the isomeric γ-pyrone alternatives. This is well exemplified by the fact[1,5] that isoaureothin (II) and desmethylisoaureothin (IIIα) are, respectively, more stable than aureothin (I) and desmethylaureothin (IIIγ.)

Because of this stability sequence of I and II, no equilibrium-controlled[6] methylation reaction of either IIIγ or IIIα is expected to afford less stable aureothin (I) predominantly, since in the equilibrium-controlled reaction the proportion of the products is a function of only their relative stabilities, and is completely independent of reaction mechanism and rate. On the contrary, in a kinetically controlled reaction relative yields of the products depend only on the relative rates at which they are produced, and are independent of their relative stabilities. Accordingly, an appropriate kinetically controlled reaction must be employed for the purpose of obtaining aureothin (I) in comparatively high yield.

Even in the kinetically controlled reactions, however, there are many instances in which the most stable products are formed at the most rapid rates, and the kinetic control and the equilibrium-control of the reaction frequently give similar product proportions. The reactions of this type are in most cases endothermic processes where the products will provide the best models for the transition

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[1] Part I of this series, H. Nakata, This Bulletin, 33, 1688 (1960).

[2] Structure of Aureothin. IX. Part VIII of this series Ref. 1.

[3] Presented at the 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959. A preliminary communication of a part of this work has also appeared. See, H. Nakata, S. Takahashi, K. Yamada and Y. Hirata, *Tetrahedron Letters*, No. 16, 9 (1959).

[4] For summaries of existing data on the tautomerism of several 2,4-pyronone derivatives, see Ref. 1 and references cited therein.

[5] Y. Hirata, K. Okuhara, H. Nakata, T. Naito and K. Iwadare, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 1700 (1957).

[6] Ingold and his co-workers[7,8] have used the term "thermodynamically controlled reaction" instead of "equilibrium-controlled reaction"[9].

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

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

[9] D. J. Cram and G. S. Hammond, "Organic Chemistry", McGraw-Hill Book Co., Inc., New York (1959), p. 192.

state of the reaction[10,11]. These reactions are usually associated with the production of unstable intermediates from stable starting substances.

On the other hand, if starting substances are of highly reactive unstable species, a different situation occurs. The unstable reactant may probably be destroyed in a very fast, exothermic reaction. The activation energy is correspondingly rather small and the transition state of the reaction may resemble the reactant closely[10,11] in topology and in geometry[12].

When the reactant possesses two different reactive positions, its reaction at one or the other of its reaction centers will give two isomeric products. As is seen in ambident ions[15], such a dual reactivity is best attained when the reactant is an ion, the ionic charge of which spreads over a conjugated system covering these two reaction centers[16,17]. Moreover, the destruction of unstable organic ions, e. g., carbonium ions or carbanions, may be an exothermic process[10]. Thus, of particular importance for the reaction in question will be the fact that the reactant has ionic, conjugatively delocalized electrons distributed between its two reaction centers. Such structural requirements provide the reactant, not only with a dual reactivity, but with an enhanced reactivity as well.

Since the transition states leading to the two products in these reactions have considerable resemblance to the common starting ion, it might be expected that they would resemble each other more than do the two isomeric products[18]. Therefore, the less stable isomer will be obtained in a higher percentage in the kinetically controlled reaction than in the equilibrium-controlled one.

Consequently, the foregoing discussion leads to the conclusion that the following set of conditions is required for a given reaction in which the less stable isomeric product is obtained preferentially.

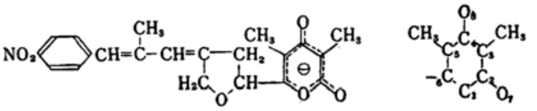
1) The reactant must have two different reactive positions mutually conjugated. The reaction upon these affords the two isomeric products.

2) The reactant must be a highly reactive unstable species so as to make its reaction exothermic.

3) The reaction employed must be kinetically controlled.

In the present case, methylation of the sodium salt of desmethylisoaureothin seems to be advantageous for the following three reasons.

1) As is the case in other enolate ions of β-dicarbonyl derivatives, the anion of the salt will probably have the structure IV in which the ionic, conjugatively delocalized electrons are distributed over the pyronone skeleton including the two exocyclic oxygen atoms, O_7 and O_8. The methylation reaction at one or the other of these oxygens will give either of the two isomeric methyl ethers, viz., I or II.



(IV) Enolate ion of desmethylisoaureothin

2) Although the sodium salt of desmethylisoaureothin is prepared easily and is considerably stable in alkaline solution[5,19], the enolate ion is at any rate a kind of organic ion, and it will have an enhanced reactivity towards any electrophilic reagents[20]. As in ionic inorganic reactions the destruction process of such a reactive ionic species is expected to be a very fast and, presumably, exothermic reaction.

3) Since the methyl ether groupings of aureothin (I) and isoaureothin (II) are relatively stable in neutral or in weakly alkaline mediums[5], no demethylation reaction of either compound will take place under such mild conditions. Therefore, if the methylation reaction is carried out under these conditions, it will be an irreversible, and thus will be a kinetically controlled process.

The next problem was to decide the actual experimental conditions, i. e., the reagent, the

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10) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

11) J. E. Leffler, *Science*, **117**, 340 (1953).

12) The terms *topology* and *geometry* of the transition state[11,13,14] have been defined previously[1], differentiating from the term *structure* of reactants or of products. The *topology* represents the linkage of atoms of the reacting molecules in the transition state, and may correspond to the *constitution* of the molecule in the static state. The *geometry* represents the spacial orientations of atoms of the reacting molecules in the transition state, and may correspond to the *configuration* and the *conformation* of the molecule in the static state. The topology and the geometry reflect the *dynamic* aspect of molecules.

13) J. E. Leffler and E. Grunwald, in S. L. Friess and A. Weissberger ed., "Technique of Organic Chemistry", Vol. VIII (Investigation of Rates and Mechanism of Reactions), Interscience Publishers Inc., New York (1953), p. 326 and 329.

14) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry", Interscience Publishers., Inc., New York (1956), p. 116.

15) N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

16) A. N. Nesmeyanov and M. I. Kabachnik, *Zhur. Obshchei Khim.*, **25**, 41 (1955).

17) A. N. Nesmeyanov and M. I. Kabachnik, *Experientia, Suppl.*, No. 2, 49 (1955).

18) J. Hine, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York (1956), p. 232.

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

20) It should be noted that generally there is no necessary relation among the synthetic ease of the compound, its reactivity, and its stability[21].

21) G. W. Wheland, "Advanced Organic Chemistry", 2nd Ed., John Wiley & Sons Inc., New York (1949), p. 366.

solvent, and the reaction temperature, of the methylation.

In general the alkylation of β-diketones and β-keto-esters is complicated by the possibility that the alkyl group may be introduced either on an oxygen atom (O-alkylation) or on a carbon atom (C-alkylation). As is expected from the structural formula IV, the pyronone enolate ion has at least three reactive positions of C_3, O_7 and O_8. For the present purpose the predominant O-alkylation is desirable and the methylation at the carbon atom C_3 must be avoided.

The most important factor affecting the nature of oxygen versus carbon alkylation is the electrophilicity of the alkylating agent. It has been reported[16,17] that when a bond between oxygen and a metal is strongly ionized, e. g., in a typical sodium enolate, a cationic reagent having a strongly electrophilic character will react preferentially at the oxygen atom. This can be generalized[15] in the following way. In the reaction of an ambident ion, the greater is the electrophilicity of the reagent, the greater is the preference for covalency formation with the atom of higher electronegativity[22].

Of available methylating agents, dimethyl sulfate was preferred to methyl iodide on this basis. The fact[25] that dimethyl sulfate usually attacks the more electronegative atom of ambident anions reveals the strongly electrophilic character of the reagent[32].

In the reaction of IV with dimethyl sulfate, the magnitude of the anionic charge will be more or less reduced as the reaction proceeds. Therefore, the less polar solvent, and thus the solvent having a smaller *Y*-value[33,34], may promote the reaction[35,36]. Anhydrous acetone is considered to be a good solvent in this connection[37]. Furthermore, acetone is an aprotic solvent[39] and may prevent solvolytic decomposition of dimethyl sulfate.

The reaction temperature should be low enough to keep the reaction condition mild and less drastic. This is a direct consequence of the requirement that the methylation reaction must be kinetically controlled[40].

Results

The sodium salt of desmethylisoaureothin was prepared by dissolving the enol IIIα into 2 N sodium hydroxide solution, and was separated as light yellow needles. The salt had no distinct melting point and decomposed at about 207～210°C without melting. It was insoluble in non-hydroxylic solvents such as benzene. These properties indicated the ionic character of the salt[23,42] as was formulated in IV.

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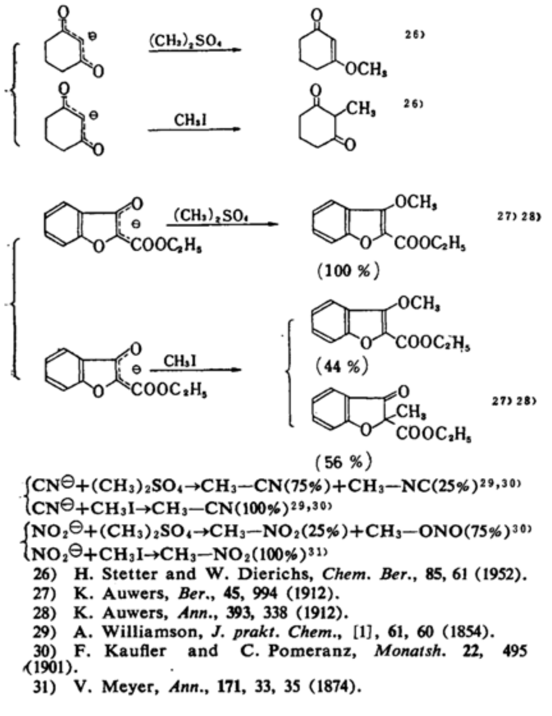
[22] The alkylation of ambident anions has been discussed comprehensively but in a completely different way by Brändström[23,24].

[23] A. Brändström, *Arkiv Kemi*, 6, 155 (1953).

[24] A. Brändström, *Arkiv Kemi*, 7, 81 (1954).

[25] Some typical examples are found in the literature[26-31].



$\left\{\begin{array}{l} CN^{\ominus}+(CH_3)_2SO_4 \rightarrow CH_3-CN(75\%)+CH_3-NC(25\%)^{29,30)} \\ CN^{\ominus}+CH_3I \rightarrow CH_3-CN(100\%)^{29,30)} \end{array}\right.$

$\left\{\begin{array}{l} NO_2^{\ominus}+(CH_3)_2SO_4 \rightarrow CH_3-NO_2(25\%)+CH_3-ONO(75\%)^{30)} \\ NO_2^{\ominus}+CH_3I \rightarrow CH_3-NO_2(100\%)^{31)} \end{array}\right.$

[26] H. Stetter and W. Dierichs, *Chem. Ber.*, 85, 61 (1952).

[27] K. Auwers, *Ber.*, 45, 994 (1912).

[28] K. Auwers, *Ann.*, 393, 338 (1912).

[29] A. Williamson, *J. prakt. Chem.*, [1], 61, 60 (1854).

[30] F. Kaufler and C. Pomeranz, *Monatsh.* 22, 495 (1901).

[31] V. Meyer, *Ann.*, 171, 33, 35 (1874).

[32] Nesmeyanov and Kabachnik[16,17] also reported that dimethyl sulfate has greater electrophilicity than methyl iodide.

[33] E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, 70, 846 (1948).

[34] A. H. Fainberg and S. Winstein, ibid., 78, 2770 (1956).

[35] Ref. 8, pp. 345～355.

[36] A. E. Remick, "Electronic Interpretations of Organic Chemistry", 2nd Ed., John Wiley & Sons Inc., New York (1949), pp. 272～284.

[37] The selection of acetone as a solvent might give rise to a slight disadvantage to the preferential O-alkylation[15-17, 23,24]. As was reported in Ref. 38 recently, however, this is not necessarily the case.

[38] D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, 80, 6016 (1958).

[39] L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co., Inc., New York (1940), p. 288.

[40] Selectivity of oxygen versus carbon alkylation may probably be affected by temperature. The corresponding rate equation becomes $\ln(k_o/k_c)=-(\Delta\Delta H^{\ddagger}/RT)+(\Delta\Delta S^{\ddagger}/R)$. where $\Delta\Delta H^{\ddagger}=\Delta H_o^{\ddagger}-\Delta H_c^{\ddagger}$ and $\Delta\Delta S^{\ddagger}=\Delta S_o^{\ddagger}-\Delta S_c^{\ddagger}$, the subscripts o and c referring to O- and C-alkylation, respectively. In the present case, k_o/k_c will presumably decrease with the increase of the reaction temperature since the choice of the reagent would enable one to assume $\Delta H_o^{\ddagger}<\Delta H_c^{\ddagger}$. Accordingly, the low temperature is favored. Dewar[41] has suggested that for very reactive cationic reagents the quantity $\Delta\Delta H^{\ddagger}$ will be small. If this is actually the case, then the selectivity will have a relatively small temperature dependence. For further detailed discussion and criticism of Dewar's argument, see Ref. 23.

[41] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry", Oxford University Press, London (1949), p. 104.

[42] Sidgwick and Brewer[43] have classified many alkali metal derivatives of β-dicarbonyl compounds into salts and covalent compounds from observations of melting point and of solubility in benzene.

[43] N. V. Sidgwick and F. M. Brewer, *J. Chem. Soc.*, 1925, 2379.

TABLE I. METHYLATION OF DESMETHYLISOAUREOTHIN (IIIα) WITH DIMETHYL SULFATE

	Solvent	Time of refluxing hr.	Total yield %	Product proportions %	
				I	II
IIIα-sodium salt	Acetone	6	62	41	59
IIIα-sodium salt	Acetone	5	63	27	73
IIIα-sodium salt+K_2CO_3	Acetone	6	41	38	62
IIIα-sodium salt+K_2CO_3	Acetone	6	68	29[a]	71[a]
IIIα+K_2CO_3	Acetone	6	46	18[a]	82[a]
IIIα+I[b]+K_2CO_3	Acetone	6	72	16[a]	84[a]

a) Data from the infrared analysis.
b) Recovery of added I was estimated as 83% from a separate experiment. See experimental section.

TABLE II. METHYLATION OF 6-METHYL-2,4-PYRONONE (V) AND OF 4-HYDROXYCOUMARIN (VI) WITH DIMETHYL SULFATE

	Solvent	Time of refluxing hr.	Total yield %	Product proportions %	
i) 6-Methyl-2,4-pyronone (V):				VIIγ	VIIα
V-sodium salt+K_2CO_3	Acetone	1	58	0	100
V-sodium salt+K_2CO_3	Acetone	6	35	0	100
V-sodium salt+K_2CO_3	Ether	6	>26[a]	0	100
V-triethylammonium salt +K_2CO_3	Acetone	6	34	0	100
V-silver salt+K_2CO_3	Acetone	6	16	0	100
V+K_2CO_3	Acetone	6	69	0	100
V-sodium salt+VIIγ+K_2CO_3	Acetone	4	69	0[b]	100
V-sodium salt+VIIγ+K_2CO_3	Ether	6	36[c]	0[d]	100
ii) 4-Hydroxycoumarin (VI):				VIIIγ	VIIIα
VI-sodium salt+K_2CO_3	Acetone	6	85	0	100

a) A small amount of V was recovered.
b) Recovery of added VIIγ was 90%.
c) About 40% of V was recovered unchanged.
d) Recovery of added VIIγ was 71%.

Since the sodium salt was practically insoluble in anhydrous acetone the methylation reaction was first attempted in water-acetone mixture (4:1) at 0°C for 1.5 hr. Under these conditions, however, only the starting material IIIα was recovered unchanged. Consequently, it seemed desirable to employ the more forced condition. Thus, the salt was suspended in anhydrous acetone and the mixture was refluxed with dimethyl sulfate for 6 hr.[44]. Upon employing the fractional crystallization of the resulting mixture, there were actually isolated both aureothin (I) (25% yield) and isoaureothin (II) (37% yield).

This result provided an additional and unambiguous evidence for the reverse isomerization reaction[1] of desmethylisoaureothin derivatives into aureothin, and accordingly, the structural correlation between them was rigorously established.

As might be anticipated from the scrutiny for the reaction conditions discussed in the preceding section, the yield of the less stable isomeric methyl ether I was satisfactory in this methylation reaction. However, attention was called to the relative product proportions of both methyl ethers.

The separation of two isomeric methyl ether derivatives of 2,4-pyronones is usually accomplished by taking advantage of the fact that γ-pyrones form ether-insoluble hydrochlorides[47,48]. In the present case, however, the hydrochloride of aureothin (I) could not be formed, and both isomers were separated by the fractional crystallization from alcohol.

In order to determine more accurately, the relative amounts of isomeric I and II in a

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[44] Since the reaction was carried out in acetone suspension, the selectivity of oxygen versus carbon alkylation might be affected by the so-called heterogeneity factor[45,46].

45) G. A. Russell, *J. Am. Chem. Soc.*, **81**, 2017 (1959).

46) N. Kornblum and A. P. Lurie, ibid., **81**, 2705 (1959).

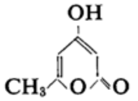
47) I. Chmielewska and J. Cieslak, *Przemystl. Chem.*, **8**, 196 (1952).

48) I. Chmielewska and J. Cieslak and T·Kraczkiewicz, *Roczniki Chem.*, **30**, 1009 (1956).

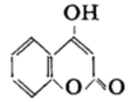
reaction mixture, it seems desirable to use an analytical technique by infrared spectra rather than the troublesome fractional crystallization. Essentially the same method as that described by Zimmerman and his co-workers[49-51] was employed here. The method proved to be accurate to ±2% of aureothin (note Table III in the Experimental Section for analysis of known mixtures of I and II).

Repetition of the methylation experiments showed that the relative amounts of aureothin (I) were always less than those of isoaureothin (II) (Table I). This is incompatible with the general rule of the kinetically controlled reaction[7,8]. The rule states that the less stable isomeric product is formed more rapidly from a given ambident ion, i. e., the less stable isomer should be obtained in a higher percentage over-all product.

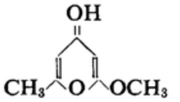
Since it appeared of interest to investigate further the general feature of this reaction, the methylations of 6-methyl-2, 4-pyronone (triacetic lactone, V)[4] and of 4-hydroxycoumarin (VI)[52] with dimethyl sulfate were examined. These compounds may probably serve as good models of desmethylisoaureothin (IIIα). 6-Methyl-2, 4-pyrone (V) is expected to afford two possible isomeric methyl ethers, VIIγ and VIIα, of which the latter is more stable[4]. Similarly, 4-hydroxycoumarin (VI) will give both VIIIγ and VIIIα. The method for quantitative separation of each isomeric methyl ether has been established[47,48], utilizing the hydrochloride formation of VIIγ and of VIIIγ. The results are shown in Table II.



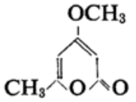
(V)
6-Methyl-2, 4-pyronone
(triacetic lactone)



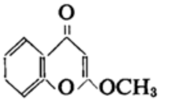
(VI)
4-Hydroxycoumarin



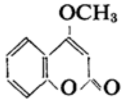
(VIIγ)
6-Methyl-2-methoxy-γ-pyrone



(VIIα)
6-Methyl-4-methoxy-α-pyrone



(VIIIγ)
2-Methoxy-γ-chromone



(VIIIα)
4-Methoxy-α-chromone

The most striking aspect of the results of the methylation experiments summarized in Table II is the exclusive formation of the more stable methyl ethers under all conditions. This is again quite contrary to the general rule of Ingold[7,8].

Prior to discussion of these contrasted results of methylation reactions, an important point must be established. It is to demonstrate that the methylation reaction is undoubtedly a kinetically controlled process. If the reaction are, not kinetically, but equilibrium-controlled, the preferential formation of the more stable product is understandable, and the results are, of course, far from our problem.

In order to test this possibility, the methylation reaction of the sodium salt of V in acetone and in ether solvent was repeated in the presence of 6-methyl-2-methoxy-γ-pyrone (VIIγ). From each run there was obtained nearly the same amount of VIIα as in the previous experiments and the added VIIγ was almost quantitatively recovered unchanged (Table II, footnotes b and d). If the methylation reaction had been reversible, the less stable, added VIIγ would be converted into the more stable VIIα by demethylation, isomerization, followed by re-methylation. However, the recovery of VIIγ and the material balance indicated that this was not the case. Therefore, the two possible products are not interconvertible under the reaction condition, and the possibility that the reaction might be an equilibrium-controlled process is rigorously excluded. Furthermore, it was also shown by these experiments that the absence of VIIγ in a reaction mixture was not due to any decomposition of it during working-up processes.

Some additional data on the exclusive formation of the more stable methyl ether in 2, 4-pyronone derivatives are available from the literature, though each reaction was not specified as a kinetically controlled process[55-57].

Discussion

Ingold's rule[7,8] of the kinetically controlled reaction is acceptable for a wide variety of reactions including the recombination of allylic

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[49] H. E. Zimmerman, *J. Am. Chem. Soc.*, **78**, 1168 (1956).

[50] H. E. Zimmerman and H. J. Giallombardo, ibid., **78**, 6259 (1956).

[51] H. E. Zimmerman and T. W. Cutshall, ibid., **81**, 4305 (1959).

[52] Two tautomeric structures are possible for 4-hydroxycoumarin. As in other 2,4-pyronone derivatives[4], the α-chromone structure VI is more stable than the alternative γ-chromone structure[53,54].

[53] F. Arndt, L. Loewe, R. Ün and E. Ayca, *Ber.*, **84**, 319 (1951).

[54] R. A. Abramovitch and J. R. Gear, *Can. J. Chem.*, **36**, 1501 (1958).

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

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

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

carbonium ions with anions, the protonation of anions of aliphatic nitro compounds, and those of β-dicarbonyl compounds. From the present results, however, one might conclude that the rule has not entirely general applicability. It will be of interest to re-examine the scope and limitations of the rule in connection with the correlation between reaction rates and product stabilities. This point will be discussed in detail in a subsequent publication of this series, but a brief discussion is given here.

Ingold's rule is based on the consideration[8] that the least stable starting ambident ion is converted into the energetically less different unstable isomeric product with a less drastic electronic reorganization involving less activation energy, than into the electronically and energetically very different stable isomeric product. This seems to be in accordance with Hammond's postulate[10], which states that an interconversion of two states will involve only a small reorganization of the molecular structures if these two states occur consecutively during a reaction process and have nearly the same energy content.

In fact, in most reactions which have so far been associated with the rule, the structure of a given ambident ion has close resemblance to the less stable product. For example, the enolate ion of ethyl acetoacetate has a structure similar to that of the enol[58-60], and thus, treatment of it with dry hydrogen chloride actually gives almost exclusively the less stable enol[61].

If, however, the least stable ambident ion structurally resembles more the stable product than the unstable one, the reverse situation can occur; the most stable isomer will be formed more rapidly than the less stable isomer. The present results of the preferential formation of the more stable methyl ethers in all reactions may be explicable if one considers that the structure of the pyronone enolate ion resembles more the structure of the more stable α-pyrone isomer than that of γ-pyrone isomer. The simple molecular orbital calculation of the charge distributions in the pyronone enolate ion supported this consideration. The details will be reported in a forthcoming paper.

Although the above formulation is in agreement with the orignial idea of Ingold and of Hammond, i. e., the less drastic the structural change the less will be the activation energy of the reaction, it is worthy to note that the structure of the least stable ambident ion does not always resemble the structure of the less stable isomer.

Finally, it may require comment as to why the structure of the ambident ion has resemblance to the more stable isomer in the present special type of compound. Generally, the stabilities of two tautomeric substances depend on two competitive factors[62-65], i. e., *prototropic expenditure of work* and *electronic delocalization*[66], the former being a dominant factor in most keto-enol systems[67]. On the contrary, in the α-pyrone-γ-pyrone system, it seems reasonable to assume that this factor will be more or less of minor importance, since both isomers of a given 2, 4-pyronone have similar O–H functions. Therefore, the relative stabilities of the two isomers will probably be due to the electronic delocalization. This means that the more stable α-pyrone structure is more favorable for the electronic delocalization than the less stable γ-pyrone structure. On the other hand, the electrons should be most favorably distributed in the pyronone enolate ion. Accordingly, the structural resemblance between the ion and the more stable α-pyrone isomer is expected to exist.

Experimental

Sodium Salt of Desmethylisoaureothin (IIIα).— Desmethylisoaureothin (IIIα,) m. p. 196~198°C[5] (1 g.) was dissolved in 30 ml. of hot 2 N sodium hydroxide solution. A clear brown solution was obtained. The crystals which separate on cooling were collected, washed with a small amount of cold alcohol, and dried. Light yellow needles. Yield 1.1 g. The salt had no distinct melting point and decomposed at about 207~210°C without melting.

Methylation of Sodium Salt of IIIα. — The sodium salt (1.1 g.) prepared from 1 g. of desmethylisoaureothin (IIIα) was suspended in 40 ml. of anhydrous acetone. Dimethyl sulfate (0.7 g.) was added to the suspension and the mixture was refluxed for 6 hr., and was then set aside overnight. The mixture was again warmed on water bath for 5 min. and was filtered. By concentration of the filtrate to 5 ml. in vacuo a yellow crystalline solid separated, which was filtered. Twice recrystallizations from alcohol gave yellow needles, m. p. 146°C, undepressed upon admixture with an authentic

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[58] B. Eistert, "Tautomerie und Mesomerie", Ferdinand Enke, Stuttgart (1938), p. 125.

[59] H. Henecka, "Chemie der Beta-Dicarbonyl-Verbindungen", Springer Verlag, Berlin (1950), p. 29.

[60] W. Hückel, "Theoretische Grundlagen der Organischen Chemie", Vol. I, 8th Ed., Akademische Verlagsgesellschaft, Leipzig (1956), pp. 280 and 322.

[61] L. Knorr, O. Rothe and H. Averbeck, *Ber.*, **44**, 1143 (1911).

[62] F. Arndt and C. Martius, *Ann.*, **499**, 228 (1932).

[63] Ref. 59, pp. 15~20.

[64] Ref. 60, pp. 301~313.

[65] G. Briegleb and W. Strohmeier, *Angew. Chem.*, **64**, 409 (1952).

[66] In Arndt's terminology[62], these are "Prototropie" (prototroper Arbeitsaufwand) and "Enotropie" (elektromerer Effekt), respectively. See also, *Chem. Abstr.*, **27**, 2132 (1933).

[67] Ref. 21, p. 613.

sample of isoaureothin II. Yield 200 mg. Spontaneous evaporation of each mother liquor of this recrystallization gave 60 mg. of brownish yellow prisms, m. p. 151∼152°C, undepressed on admixture with an authentic sample of aureothin I. The infrared spectrum of this material was identical with that of I. The above acetone filtrate was diluted with 30 ml. of water. The separated brown oil crystallized after 2 days. Recrystallization from alcohol gave additional 180 mg. of isoaureothin (II). The mother liquor was evaporated as above, and 205 mg. of aureothin I, m. p. 150∼151°C was obtained as brownish yellow prisms. Total yield 62% (aureothin, 265 mg.; isoaureothin, 380 mg.). When the reaction mixture was refluxed for 5 hr., there was obtained 40 mg. of I and 110 mg. of II from 230 mg. of IIIα (total yield 63%). In another run, the reaction mixture was refluxed with 2 g. of anhydrous potassium carbonate. From 1 g. of the sodium salt, 150 mg. of I and 250 mg. of II were obtained (total yield 41%). In each case, none of the starting material of IIIα was recovered.

Attempt on Methylation of Sodium Salt of IIIα at Low Temperature. — The sodium salt of IIIα (500 mg.) was dissolved in 25 ml. of water-acetone mixture (4 : 1). This yellow solution was cooled below 0°C and 4 drops of dimethyl sulfate was added. The mixture was stirred for 30 min. at 0°C and then for another 1 hr. at room temperature. The solution was concentrated to 10 ml. in vacuo and neutralized with dilute acetic acid. A precipitated yellow solid was collected and washed with cold water. Recrystallization from alcohol gave yellow needles, m. p. 195∼198°C, undepressed upon admixture with an authentic desmethylisoaureothin IIIα. Recovery 230 mg.

Quantitative Infrared Analyses.—Essentially the same analytical technique as that described by Zimmerman and his co-workers[49-51] was employed. All spectra were measured as potassium bromide pellets. It was found that aureothin I exhibited a sharp maximum at 1260 cm^{-1} (optical density= 0.5528 ; 1.05 mg.-sample) while isoaureothin II had a minimum at this frequency (optical density= 0.0603 ; 1.06 mg. -sample). The spectrum of isoaureothin II possessed a sharp maximum at 1230 cm^{-1} (optical density=0.3098 ; 1.06 mg.-sample) while aureothin I had a minimum at this frequency (optical density=0.0969 ; 1.05 mg.-sample). These two bands were well separated and were selected as the key bands for analysis. Desmethylisoaureothin IIIα had no intense band in the range 1300∼1220 cm^{-1}.

The following equation was used : $R=Q\times F$. Here R is the ratio of aureothin I to isoaureothin II, viz., R=I/II.

$$Q=\frac{D_m{}'D_i{}''-D_m{}''D_i{}'}{D_m{}''D_a{}'-D_m{}'D_a{}''}$$

The D_m's, D_a's and D_i's are optical densities of a given mixture, pure aureothin, and pure isoaureothin, respectively. The superscripts refer to the analytical frequencies of 1260 (′) and 1230 (″) cm^{-1}. F was determined empirically from the values of Q and R for known mixtures as shown in Table III. The average value of F=0.848 was used in calculating the results in the last two columns of Table III. The optical densities used were calculated from the transmittances directly without any consideration of background absorption.

In each case the unknown was prepared by grinding evenly the isomeric mixture with double portions of potassium bromide. An appreciable amount of this well ground mixture was taken as an analytical sample. The sample was ground evenly with 150 mg. of potassium bromide for 5 min. and the mixture was placed under 8 ton/cm^2 in a 1.30 cm. diameter casing. The spectra were recorded on a Koken IR-S double beam instrument equipped with sodium chloride optics. The optical density of all mixtures, known and unknown, was taken as zero at 1850 cm^{-1}. The best results were obtained when the percentage transmission of both key bands of mixtures was in the range 25∼80%. Analyses were made in duplicate in nearly all experiments.

Repetition of the Methylation Experiment. — Desmethylisoaureothin IIIα was converted into its sodium salt (from 400 mg. of IIIα). The salt was suspended in 25 ml. of dry acetone. Nine drops of dimethyl sulfate and 2 g. of anhydrous potassium carbonate were added and the mixture was refluxed for 6 hr. The reaction mixture was worked up as in the foregoing experiment. There was obtained 280 mg. (total yield 68%) of isomeric mixture, which was used for infrared analysis.

No. 1 $D_m{}'=0.2148$, $D_m{}''=0.2365$, $Q=0.474$,
Calcd. $R=0.402$, Calcd. I %=28.6%

Nd. 2 $D_m{}'=0.5688$, $D_m{}''=0.6196$, $Q=0.483$,
Calcd. $R=0.409$, Calcd. I %=29.1%
Average I %=28.9%

TABLE III. ANALYSIS OF KNOWN MIXTURES OF AUREOTHIN AND ISOAUREOTHIN

Actual I, %	$D_m{}'$	$D_m{}''$	Q	Actual R	Calcd. F	Calcd. R	Calcd. I, %
0.0	0.0603	0.3098	—	—	—	—	—
14.0	0.2148	0.4200	0.194	0.163	0.836	0.165	14.2
22.4	0.1939	0.2756	0.325	0.289	0.889	0.275	21.6
30.6	0.2758	0.3189	0.508	0.439	0.864	0.432	30.2
32.6	0.4560	0.4319	0.592	0.485	0.820	0.502	33.4
41.9	0.3768	0.2677	0.902	0.721	0.800	0.765	43.3
47.1	0.4322	0.2842	1.009	0.889	0.889	0.856	46.2
61.4	0.6375	0.3100	1.786	1.595	0.894	1.515	60.3
84.2	0.4684	0.1192	6.690	5.300	0.793	5.671	85.2
100.0	0.5528	0.0969	—	—	—	—	—

The infrared spectrum of this mixture did not exhibit a band at 1195 cm^{-1}, indicating the absence of IIIα.

Methylation of IIIα with Dimethyl Sulfate and Potassium Carbonate. — A solution of desmethylisoaureothin IIIα in anhydrous acetone (500 mg. in 30 ml.) was refluxed with 20 drops of dimethyl sulfate and 2 g. of potassium carbonate for 6 hr. The resulting yellow solution was evaporated to dryness in vacuo. A yellow crystalline solid was obtained. Three recrystallizations from alcohol gave 150 mg. of pure isoaureothin II. From mother liquors of the recrystallization, there was isolated 90 mg. of isomeric mixture, which was subjected to infrared analysis.

No. 1 $D_m'=0.2923$, $D_m''=0.1937$, $Q=1.071$,
Calcd. $R=0.909$, Calcd. I $\%=47.7\%$

No. 2 $D_m'=0.4202$, $D_m''=0.2679$, $Q=1.062$,
Calcd. $R=0.900$, Calcd. I $\%=47.3\%$

Average I $\%=47.5\%$

The infrared spectrum of this mixture did not exhibit a band at 1195 cm^{-1}, indicating the absence of IIIα. Therefore, the total yield was 46%, 43 mg. of I and 197 mg. of II.

Methylation of IIIα in the Presence of I. — Desmethylisoaureothin (IIIα) (300 mg.) was methylated as above in the presence of 200 mg. of aureothin (I). There was isolated 390 mg. of isomeric mixture, which was subjected to infrared analysis.

No. 1 $D_m'=0.4953$, $D_m''=0.2840$, $Q=1.252$,
Calcd. $R=1.062$, Calcd. I $\%=51.4\%$

No. 2 $D_m'=0.2365$, $D_m''=0.1367$, $Q=1.236$,
Calcd. $R=1.049$, Calcd. I $\%=51.2\%$

Average I $\%=51.3\%$

The infrared spectrum of the mixture did not exhibit a band at 1195 cm^{-1}, indicating the absence of IIIα. The analysis showed that the mixture contained 202 mg. of I and 188 mg. of II. In a separate experiment, 200 mg. of I alone was treated under the same reaction condition as above. It resulted in 83% recovery (165 mg.) of I. Thus, the actual methylation products were 37 mg. of I and 188 mg. of II. Total Yield 72%.

6-Methyl-2,4-pyronone (V). — 6-Methyl-2,4-pyronone was prepared from dehydroacetic acid[68].

Sodium Salt of 6-Methyl-2, 4-pyronone. — The general procedure for preparation of sodium salts of β-dicarbonyl compounds was used[69]. Alcoholic sodium ethoxide solution prepared from 0.5 g. of metallic sodium and 15 ml. of ethanol was added to a solution of 3 g. of V in 30 ml. of ethanol. The mixture was concentrated to 20 ml. in vacuo and then 100 ml. of ether was added. The precipitated white solid was collected, washed with acetone, and dried. Yield 2.5 g.

Methylation of Sodium Salt of V in Acetone.— One gram of the sodium salt and 2 g. of anhydrous potassium carbonate was suspended in anhydrous acetone, and 1.8 ml. of dimethyl sulfate was added to the suspension. The mixture was refluxed for 1 hr. with occasional shaking. The reaction mixture was filtered while still hot, and the filtrate was evaporated to dryness in vacuo. The resulting solid was extracted with seven 50 ml. portions of petroleum ether (b. p. 30~60°C). A relatively large amount of dark solid remained. The combined extracts were filtered to remove any insoluble impurities and were evaporated to dryness in vacuo, and finally dried in a vacuum desiccator over calcium chloride. The crystalline solid thus obtained was dissolved in 50 ml. of anhydrous ether. The solution was cooled below 0°C and was treated with dry hydrogen chloride. None of the hydrochloride of 6-methyl-2-methoxy-γ-pyrone (VIIγ) was precipitated. After evaporation of the solvent crude 6-methyl-4-methoxy-α-pyrone (VIIα) was obtained. Recrystallization from petroleum ether gave pure material, m. p. 87~88°C, undepressed upon admixture with an authentic sample[1]. Yield 550 mg. (58%). The above dark solid, which remained from the petroleum ether extraction, was again extracted with anhydrous ether. Treatment of the extracts with dry hydrogen chloride gave no precipitate.

In another run, after the filtration of the initial reaction mixture, the filtrate was concentrated in vacuo over 1 g. of freshly added anhydrous potassium carbonate to prevent any possible acid-catalyzed decomposition of VIIγ during the working-up process. The final results were essentially the same as those described above, and no VIIγ was obtained.

When the reaction mixture was refluxed for 6 hr., only VIIα was obtained. Yield 330 mg. (35%).

Methylation of Sodium Salt of V in Ether.—In 20 ml. of anhydrous ether 1 g. of the sodium salt and 2 g. of potassium carbonate was suspended, to which 2 g. of dimethyl sulfate was added. The mixture was refluxed for 6 hr. After removing the potassium carbonate, the ether filtrate was treated with dry hydrogen chloride. No precipitate was formed. The solution was then concentrated in vacuo. Recrystallization of the resulting solid from petroleum ether gave 250 mg. of VIIα. Since V was sparingly soluble in ether, unchanged V remained in potassium carbonate residue. The above filtrated solid was dissolved in water and the solution was acidified with dilute sulfuric acid. A small amount of V separated as fine needles, m. p. 186~188°C.

Triethylammonium Salt of V. — About 2 ml. of triethylamine was added to a solution of 1 g. of V in 5 ml. of ethanol. Evaporation of the solvent in vacuo gave a colorless oil. Attempts to crystallize the salt from the oil were unsuccessful, and the oil was used without further purification. When the oil was dissolved in water, the initial V was precipitated as a white crystal.

Methylation of Triethylammonium Salt of V.— The above oily material (1 g.) was methylated. The procedures used for separation and purification of products were essentially the same as those described above. Only VIIα was obtained. Yield 210 mg. (34%).

Methylation of Silver Salt of V.—The silver

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[68] J. Collie, *J. Chem. Soc.*, **59**, 607 (1891).

[69] S. M. McElvain and K. H. Weber, *J. Am. Chem. Soc.*, **63**, 2192 (1941).

salt of V was prepared according to the directions of Janiszewska-Drabarek[55]. Methylation was carried out as above. The yield was low, VIIα 150 mg. (16%).

Methylation of V with Dimethyl Sulfate and Potassium Carbonate. — In 15 ml. of anhydrous acetone 850 mg. of V was dissolved. The solution was refluxed with 5 g. of potassium carbonate and 2 ml. of dimethyl sulfate for 6 hr. Concentration of the filtrate of the reaction mixture gave an oily material containing crystals. The procedures for separation of the isomeric methyl ethers were essentially the same as those described above. Only VIIα was obtained. Yield 650 mg. (69%).

Methylation of Sodium Salt of V in the Presence of VIIγ.—The mixture of 1 g. of the sodium salt, 100 mg. of 6-methyl-2-methoxy-γ-pyronoe (VIIγ)[1], 2 g. of potassium carbonate, and 2 ml. of dimethyl sulfate was refluxed in anhydrous acetone for 4 hr. The filtrate of the reaction mixture was concentrated in vacuo and the resulting solid was dissolved in 60 ml. of dry ether. A small amount of insoluble material remained and was discarded. The ether solution was cooled and was treated with dry hydrogen chloride. The hydrochloride of VIIγ was precipitated immediately, and was collected and dried (120 mg.). The isomeric VIIα remained in solution and was obtained after evaporation of the solvent. Yield 650 mg. (69%). The free VIIγ was recovered from the above hydrochloride on treatment with diethylamine[47,48]. Yield 90 mg. (recovery 90%).

In another run, the mixture of 1 g. of the sodium salt, 140 mg. of VIIγ, 2 g. of potassium carbonate, and 2 ml. of dimethyl sulfate was refluxed in anhydrous ether for 6 hr. The ether layer of the reaction mixture was cooled and treated with dry hydrogen chloride. About 130 mg. of hydrochloride of VIIγ was obtained. This was transformed to free VIIγ as above. Yield 100 mg. (recovery 71%). The ehter solution was concentrated and the solid thus obtained was recrystallized from petroleum ether. Yield 200 mg. VIIα (36%). The filtrated potassium carbonate residue was dissolved in 20 ml. of water. Acidifying with dilute sulfuric acid gave white needles, m. p. 187～189°C, undepressed upon admixture with an authentic sample of V. Recovery 350 mg. (40%).

4-Hydroxycoumarin (VI). — Acetylation of 75 g. of methyl salicylate with 75 g. of acetic anhydride in 20 ml. of pyridine gave 80 g. of methyl acetyl salicylate. Treatment of this methyl acetyl salicylate with 9.6 g. of metallic sodium yielded 26 g. of 4-hydroxycoumarin (VI[70].) After recrystallization from water it exhibited m. p. 204～205°C.

Sodium Salt of 4-Hydroxycoumarin (VI). — 4-Hydroxycoumarin (VI) (4 g.) was dissolved in 20 ml. of ethanol and alcoholic sodium ethoxide solution prepared from 0.5 g. of metallic sodium and 10 ml. of ethanol was added. The mixture was concentrated in vacuo to 15 ml. and then 100 ml. of ether was added. The precipitated white solid was filtered and dried. Yield 3.4 g.

Methylation of Sodium Salt of VI. — One gram of the sodium salt of VI and 2 g. of potassium carbonate were suspended in anhydrous acetone, and the mixture was refluxed with 1.5 ml. of dimethyl sulfate for 6 hr. The acetone layer was treated as described in the literature[55] to separate each isomeric methyl ether. Only 4-methoxy-α-chromone (VIIIα) was obtained. m. p. 125～126°C. Yield 810 mg. (85%).

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[70] H. Pauly and K. Lockemann, *Ber.*, **48**, 28 (1915).