Correlation of Reaction Rates and Product Stabilities. I. The Methylation of Pyrononeswith Diazomethane[1-3]

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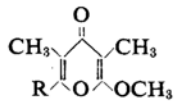
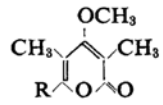
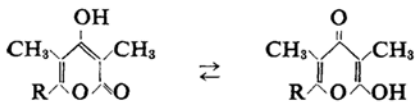
The skeletal structures of aureothin and isoaureothin have recently been established as I and II, respectively[1]. The relative stabilities of these two compounds are so different that aureothin isomerizes readily to the more stable isoaureothin derivatives especially under acidic conditions[4]. The isomerization reaction has so far been considered to be an irreversible process involving a certain drastic structural change since the reverse isomerization reaction has not been observed during the course of the structural elucidation studies.



(I) Aureothin

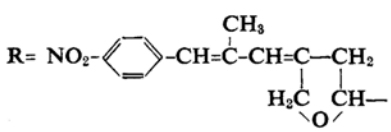


(II) Isoaureothin



(IIIα) (IIIγ)

Desmethylisoaureothin



However, as was shown in the previous paper[1], the constitutional difference between I and II is only in their pyrone rings, and therefore, two tautomeric structures of IIIα and IIIγ are possible for the demethylated product, desmethylisoaureothin. In order to confirm rigorously the structural correlation between

1) Structure of Aureothin. VIII. Part VII of this series K. Yamada, H. Nakata and Y. Hirata, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 340 (1960).

2) Presented at the 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959.

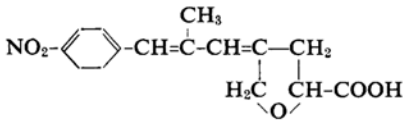
3) A preliminary communication of this work has appeared. See, H. Nakata, S. Takahashi, K. Yamada and Y. Hirata, *Tetrahedron Letters*, No. 16, 9 (1959).

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

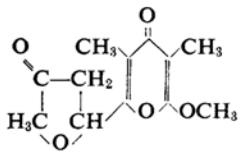
aureothin and isoaureothin, it was felt to be desirable to perform the reverse isomerization reaction.

In the present investigation, desmethylisoaureothin (IIIα) is methylated with diazomethane under the special condition derived from the theory of Arndt's kinetically interplayed methylation reaction. Satisfactory results are obtained.

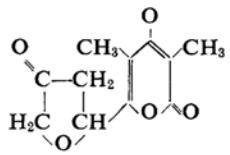
Tautomerism of Pyronone Derivatives. — Although previous studies[5] suggest the structure of desmethylisoaureothin as IIIα having an α-pyrone ring, a more definite evidence[1] is now available. Subtraction of the ultraviolet absorption curve of aureothinic acid (IV)[6] from the curve of desmethyl isoaureothin affords the spectrum of the residual pyrone



(IV) Aureothinic acid



(V) Aureonone



(VI) Isoaureonone

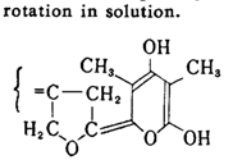
fragment. The resultant spectrum does not agree with the spectrum of aureonone (V)[1] but is well superimposable on the spectrum of isoaureonone (VI)[1]. This indicates, that the tautomeric form of the α-pyrone structure IIIα predominates desmethylisoaureothin even in solution. Data of infrared spectra of those compounds[1] also support the conclusion. Therefore, the theoretically conceivable equilibrium III$\alpha \rightleftarrows$ IIIγ lies almost at the IIIα side[7] and IIIγ is thermodynamically less stable than IIIα. The same is true for their methylated products, aureothin and isoaureothin; the former is less stable than the latter[4]. It was reported also in other pyronone derivatives that the γ-pyrone isomer is usually less stable and in solution the α-pyrone alternative predominates[9-13].

Theory of Kinetically Interplayed Methylation. — When a proton transfers from tautomeric acids to bases, it has been observed[14,15] that the proton is lost most quickly from a least stable tautomer. This proton mobility is characterized as the *dynamic acidity*[16,17] and should be differentiated from the so-called acidity in the equilibrium state (*static acidity* in the strict sense)[18,19]. The dynamic acidity correlates with the activation energy of the proton transfer process and the static acidity correlates with the free energy difference between the acid and its conjugated base[20]. The reactivity of a given acid depends on the dynamic acidity of the acid particularly in the reaction, where the proton plays a dominant role; thus, it may be concluded that the reactivity of the acid towards diazomethane is proportional to its dynamic acidity[17,18,23-28]. The less stable isomeric acid has a larger dynamic acidity and is methylated with diazomethane more quickly than the stable isomer,

5) T. Naito, Y. Hirata, K. Okuhara and K. Iwadare, ibid., 374 (1958).

6) Y. Hirata, H. Nakata and K. Yamada, ibid., 79, 390 (1958).

7) Recently, Yamazaki[8] has ascertained the percentage of enol of desmethylisoaureothin in various solvents. Although she reported the values 46.0 and 41.5% in ethanol and 25.0 and 22.2% in chloroform, no indications of such a result are observed from the infrared spectra[1] of desmethylisoaureothin, and our present conclusion that desmethylisoaureothin exists largely as IIIα (one of the enol forms) also does not agree with her. Moreover, the reported values in formic acid and in methanol are over 100%, the reason of which attributed to the presence of the dienol form of desmethylisoaureothin. However, it is unlikely to consider any dienol form of this compound. If we were forced to assume the following dienol structure, this would contradict with our previous observation[4] that desmethylisoaureothin is optically active and has a definite sign of rotation in solution.



8) F. Yamazaki, ibid., 79, 1204 (1958).

9) I. Chmielewska and J. Cieslak, *Przemysl. Chem.*, 8, 196 (1952).

10) R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, 78, 624 (1956).

11) J. Cieslak, *Roczniki Chem.*, 32, 837 (1958).

12) I. Chmielewaka, J. Cieslak, K. Gorczynska, B. Kontnik and K. Pitakowska, *Tetrahedron*, 4, 36 (1958).

13) D. Herbst, W. B. Mors, O. R. Gottlieb and C. Djerassi, *J. Am. Chem. Soc.*, 81, 2427 (1959).

14) A. G. Catchpole, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 1948, 11.

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

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

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

18) C. Gustafsson, *Suomen Kemistilehti*, 18B, 11 (1945).

19) F. Arndt, "Statische und Dynamische Acidität", Vol. VIII, Abhandlungen der Braunschweigischen Wissenschaftlichen Gesellschaft (1956), p. 1.

20) Parallelisms between dynamic acidity and static acidity have frequently been observed. See Refs. 15, 21, 22 and 33.

21) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry", Interscience Publishers Inc., New York (1956), p. 187.

22) R. W. Taft, Jr., *J. Am. Chem. Soc.*, 79, 5075 (1957).

23) B. Eistert, "Tautomerie und Mesomerie", Ferdinand Enke, Stuttgart (1938), p. 43.

24) J. D. Roberts, W. Watanabe and R. E. McMahon, *J. Am. Chem. Soc.*, 73, 760 (1951).

25) J. D. Roberts and J. A. Yancey, ibid., 73, 1011 (1951).

26) C. K. Hancock and J. S. Westmoreland, ibid., 80, 545 (1958).

27) J. Hine and W. C. Bailey, Jr., ibid., 81, 2075 (1959).

28) Ref. 16, p. 202.

though the equilibrium concentration of the former is less than that of the latter in the solution.

Since the methylation reaction with diazomethane produces an exceedingly stable nitrogen molecule, the process undoubtedly does not have high energy requirements and, indeed, may even be somewhat exothermic[29-31]. The activation energy is correspondingly rather small and the transition state of the methylation reaction would resemble the starting material closely[32,33] in topology[34] and in geometry[34].

When two tautometric acids, A-OH and G-OH, are methylated with diazomethane, the reaction may proceed according to the following mechanistic scheme[16,37] where $A\text{-}OCH_3$ is produced only from A-OH and $G\text{-}OCH_3$ only from G-OH. Because of the resemblance of the transition state to the starting materials it

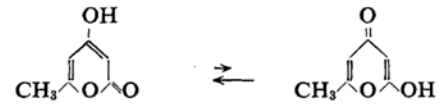
$$\begin{array}{ccc} CH_2N_2 + A\text{-}OH & \underset{k_-}{\overset{k_+}{\rightleftarrows}} & G\text{-}OH + CH_2N_2 \\ \downarrow k_a & & \downarrow k_g \\ A\text{-}OCH_3 & & G\text{-}OCH_3 \end{array}$$

seems unlikely to consider any other reaction processes of indirect methylation involving the rearrangement of the reaction centre.

Arndt[16,19,38] has discussed in detail the kinetic interplay between methylation reactions (velocities k_a and k_g) and prototropic rearrangement reactions (velocities k_+ and k_-), and drawn the following conclusions. If the concentrated diazomethane solution is added to the tautomeric mixture of A-OH and G-OH, the product proportions $G\text{-}OCH_3/A\text{-}OCH_3$ are not very different from the ratio of G-OH/A-OH, which is the ratio of the initial equilibrium concentrations of the respective acids. On the other hand, if the concentration of diazomethane is maintained at a low level, the ratio of $G\text{-}OCH_3/A\text{-}OCH_3$ will be larger than G-OH/A-OH, provided that G-OH has a larger dynamic acidity than A-OH.

Consequently, it may be expected that the product proportions of the two isomeric methyl ethers depend on the time required for the addition of the diazomethane solution, the more gradually the addition of the diazomethane solution, the more will increase the proportions of the methylated product of the less stable isomeric acid having the larger dynamic acidity.

Diazomethane Methylation of Pyronone Derivatives. — Although literatures contain several references to the diazomethane methylation of 2, 4-pyronone derivatives such as 6-methyl-2, 4-pyronone (triacetic lactone) (VII), the results obtained have been the subject of considerable controversy[9,10,39-41].



(VIIα) (VIIγ)

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

(VIIIα) 6-Methyl-4-methoxy-α-pyrone

(VIIIγ) 6M-ethyl-2-methoxy-γ-pyrone

Recently, there appeared an extensive study[13] of this methylation reaction and it was concluded that the products were usually mixtures of two possible isomers, the actual proportions depending on the nature of other substituents[42]. Several results in other 2, 4-pyronone derivatives were also reported[11,12,43-47]. However,

29) D. J. Cram and J. Allinger, *J. Am. Chem. Soc.*, **79**, 2866 (1957).
30) A. Streitwieser, Jr., and W. D. Schaeffer, ibid., **79**, 2888 (1957).
31) A. Streitwieser, Jr. *J. Org. Chem.*, **22**, 861 (1957).
32) J. E. Leffler, *Science*, **117**, 340 (1953).
33) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
34) It seems reasonable to distinguish the terms *topology* and *geometry* of the transition state from the term *structure* of reactants or of products, as seen in Refs. 32, 35 and 36. Although the transition state lies somewhere between the reactants and the products, it may not have any definite structure in the ordinary sense, since the arrangement of atoms of the reacting molecules varies with the time in passing over the transition state. 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.
35) J. E. Leffler and E. Grunwald, in S. L. Friess and A. Weissberger ed., "Technique of Organic Chemistry", Vol. VIII (Investigation of Rates and Mechanisms of Reactions), Interscience Publishers Inc., New York (1953), pp. 326, 329.
36) Ref. 21, p. 116.
37) R. Huisgen, *Angew. Chem.*, **67**, 445 (1955).
38) F. Arndt, ibid., **61**, 397 (1949).
39) F. Arndt and B. Eistert, *Ber.*, **68**, 1572 (1935).
40) F. Arndt and S. Avan, ibid., **84**, 343 (1951).
41) S. Janiszewska-Drabarek, *Roczniki Chem.*, **27**, 456 (1953).
42) 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 that product proportions were distinctly affected by the type of substituent in position 3. The author is indebted to Professor I. Chmielewska of Warsaw University for her kind information of this result (private communication to K. Yamada of this Institute). See, J. Cieslak, S. Lewak and I. Chmielewska, *Roczniki Chem.*, **33**, 349 (1959).
43) W. Borsche and C. K. Bodenstein, *Ber.*, **62**, 2515 (1929).
44) I. Chmielewska and J. Cieslak, *Roczniki Chem.*, **28**, 38 (1954).
45) R. B. Woodward and G. Small, Jr., *J. Am. Chem. Soc.*, **72**, 1297 (1950).
46) H. Stetter and C. W. Schellhammer, *Ann.*, **605**, 58 (1957).
47) E. Ziegler and E. Nolken, *Monatsh.*, **89**, 391 (1958).

as far as the author is aware, little attention has been paid to investigate the relation between the product proportions and the reaction condition employed[48]. Thus, the diazomethane methylation of 6-methyl-2, 4-pyronone (VII) was first examined.

Results and Discussion

The methylation was carried out by addition of ethereal solution of diazomethane[49] to a suspension of VII in dry ether, and the two isomeric methyl ethers, VIIIα and VIIIγ, were separated by the technique of Polish workers[9,50]. Product proportions are calculated as the percentage of the total weight of the methylated products isolated. The results are summarized in Table I.

TABLE I. PRODUCT PROPORTIONS OF DIAZOMETHANE METHYLATION

The time required for the addition of the diazomethane solution	Average product proportions	
i) 6-Methyl-2,4-pyronone (VII):	VIIIγ %	VIIIα %
Very rapidly	0	100
4 hr.	26	74
8 hr.	31	69
18 hr.	33	67
ii) Desmethylisoaureothin (III):	I, %	II, %
Very rapidly	0	100
2~4 hr.	0	100
18 hr.	2	98

On the basis of these data, it should be emphasized that the more gradually the addition of the diazomethane solution, the more will increase the proportions of the γ-pyrone methyl ether, VIIIγ.

6-Methyl-2, 4-pyronone (VII) would exist in solution as a tautomeric mixture of VIIα and VIIγ. Spectral data[9,10] suggest, that in either solution the tautomeric form of an α-pyrone structure (VIIα) predominates. This means VIIγ is thermodynamically less stable, and has a larger dynamic acidity, than VIIα. The observed results presented in Table I are therefore in good agreement with the theoretical prediction that the gradual addition of diazomethane will give rise to the increase of percentages of the less stable isomeric methyl ether in the over-all product.

The same is true in the case of methylation of desmethylisoaureothin (III). As is shown in Table I, aureothin (I) was obtained only when the diazomethane solution was added very gradually. Accordingly, the reverse isomerization reaction was also solved satisfactorily.

From these data the structural correlation of aureothin (I) and isoaureothin (II) was confirmed. It is also indicated that the desmethyl derivative of aureothin does exist in solution as a tautomeric mixture of IIIα and IIIγ[51]. Desmethylaureothin (IIIγ) has not been known so far, since its concentration in solution is presumably very small as compared with that of the stable isomer, desmethylisoaureothin (IIIα).

Moreover, the present results support the conclusion[1] that desmethylisoaureothin has the structure IIIα also in the solid state, since the methylation reaction was carried out for the ether suspension of desmethylisoaureothin[52].

The skeletal structure of aureothin (I) thus being established rigorously, emphasis must be given for the structural peculiarity of this compound. Aureothin has a nitro group which is as yet a rather rare function in natural products. Only few other examples were known, including chloramphenicol[60], hiptagenic acid[61], azomycin[62], and aristolochic acid[63]. Among

48) Herbst et al.[13] reported the product ratio, VIIIα: VIIIγ as 64 : 19, which did not agree with the ratio 72 : 20 of Janiszewaka-Drabarek[41]. They also noticed that different proportions were observed under the condition described by Wiley and Jarboe[10] but no explanation of this result was given.

49) F. Arndt, "Organic Syntheses", Coll. Vol. II, John Wiley and Sons Inc., New York (1943), p. 165.

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

51) If IIIγ does not exist in solution, aureothin (I) will not be obtained and the sole product, independently of the reaction condition, will be II, since I is considered to be produced only through IIIγ in the above mechanistic scheme.

52) It seems reasonable to assume that the equilibrium A—OH $\rightleftarrows$ G—OH is not held in the solid state. If the crystal consists from the less stable G—OH, the tautomer is first formed when the crystal is dissolved into solution must be G—OH. The next step of the reaction will be either the methylation of this newly formed G—OH to G—OCH_3 or its rearrangement to the more stable A—OH. Since G—OH is methylated more rapidly than A—OH, when the methylation takes place immediately by the addition of the concentrated diazomethane solution, the methylation reaction should occur preferentially and the rearrangement reaction will lag behind, so that diazomethane will have little chance to react with A—OH. In this case, therefore, the percentage of the less stable methyl ether, G—OCH_3, will increase in the over-all product, when the concentrated diazomethane solution is added rapidly. This is quite contrary to the observed tendency. The method used in Ref. 53 may generally be utilized to show which possible tautomeric structure is represented by the crystals. Several applications have recently been reported. See Refs. 54—59.

53) Ref. 16, p. 217 and 239.

54) F. Arndt, L. Ergener and O. Kutlu, *Chem. & Ind.*, 1950, 565.

55) L. Ergener, *Rev. faculte sci. univ. Istanbul*, **A15**, 96, 103 (1950).

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

57) F. Arndt, L. Loewe and E. Ayca, ibid., **84**, 329 (1951).

58) F. Arndt, L. Ergener and L. Kutlu, *Chem. Ber.*, **86**, 951, 957 (1953).

59) Ref. 17, pp. 290, 291 and 294.

60) M. C. Rebstock, H. M. Crooks, Jr., J. Contoulis and Q. R. Bartz, *J. Am. Chem. Soc.*, **71**, 2458 (1949).

61) C. L. Carter and W. J. McChesney, *Nature*, **164**, 575 (1949).

62) S. Nakamura, *Pharm. Bull.*, **3**, 379 (1955).

them, aureothin is the third nitro compound obtained from nature[64]. Moreover, aureothin has the substituted 2-methoxy-γ-pyrone structure. All other methylated 2, 4-pyronones which have so far been encountered in nature are 4-methoxy-α-pyrones, such as yangonin[11,12,43,44], anibine[65], 4-methoxyparacotoin[65,66] and 5, 6-dehydrokavain[66].

Experimental

6-Methyl-2, 4-pyronone (VII). — 6-Methyl-2, 4-pyronone was prepared from dehydroacetic acid[67].

Methylation of 6-Methyl-2,4-pyronone. — About 100 ml. of a dilute ethereal solution of diazomethane prepared[49] from 10 g. of nitrosomethylurea was added, with vigorous stirring, to a suspension of 1 g. of 6-methyl-2, 4-pyronone (VII) 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°C during the addition of the diazomethane solution. After all the diazomethane had been added, stirring was continued for about one hour. All solids gradually dissolved, and finally a light yellow solution was obtained. The resulting mixture was evaporated to dryness in vacuo. The solid was then extracted with seven 50 ml. portions of petroleum ether (b. p. 30~60°C). A small amount of a dark sticky solid remained. The combined extracts were filtered to remove any insoluble impurities and were again evaporated to dryness in vacuo. The crystals thus obtained were dried in a vacuum desiccator over calcium chloride. The procedure for the separation of the two isomeric methyl ethers was the same as that described by Chmielewska et al.[9,50]. The above crystals were dissolved in 50 ml. of anhydrous ether and the solution was cooled below 0°C and was treated with dry hydrogen chloride. The insoluble hydrochloride of VIIIγ separated immediately and was filtered and dried. The isomeric VIIIα remained in solution and was obtained after evaporation of the solvent. The crude 6-methyl-4-methoxy-α-pyrone (VIIIα) exhibited m. p. 84~88°C. Recrystallization from petroleum ether gave pure material, m. p. 87~88°C. The hydrochloride of VIIIγ was suspended in anhydrous ether, and about 0.5 ml. of diethylamine was added and the mixture was set aside overnight. Insoluble diethylamine hydrochloride was then filtered and the evaporation of the solvent gave free 6-methyl-2-methoxy-γ-pyrone (VIIIγ), m. p. 88~93°C. After recrystallization from petroleum ether it melted at 94~95°C.

The product proportions shown in Table I are calculated as the percentage of the total weight of the methylated products isolated, data of which are listed in Table II.

TABLE II. PRODUCT YIELDS OF DIAZOMETHANE METHYLATION OF 6-METHYL-2, 4-PYRONONE (VII)

The time required for the addition of the diazomethane solution	Solvent	Product yields mg.	
		VIIIγ	VIIIα
Very rapidly	Ether	0	600
4 hr.	Ether	180	550
8 hr.	Ether	190	430
18 hr.	Ether	250	500
Very rapidly	Acetone	0	400
4 hr.	Acetone	120	330

Table II includes some additional data of the methylation in acetone solvent. The results are essentially the same with those in ether except for the recovery of about 300 mg. of the unchanged starting material (VII).

Methylation of Desmethylisoaureothin (III).— To a suspension of 870 mg. of desmethylisoaureothin (III) in 30 ml. of dry ether was added, dropwise, 50 ml. of ethereal diazomethane solution prepared[49] from 1 g. of nitrosomethylurea over a period of 18 hr. with vigorous stirring. During this period, the temperature of the reaction mixture was maintained at 10~15°C and all traces of atmospheric moisture were excluded. After all the diazomethane solution had been added, stirring was continued for 2 hr. The light yellow crystalline solid was then filtered and washed with three 10 ml. portions of ether. The ether washings were combined with the filtrate. The solid separated was recrystallized from ethanol and there was obtained 620 mg. of isoaureothin (II), light yellow needles, m. p. 146~147°C, undepressed upon admixture with an authentic sample.

It is interesting to note that aureothin does not form a hydrochloride, though it has a γ-pyrone structure. Therefore, two isomeric methyl ethers, I and II, were separated by fractional crystallization from ethanol. Thus, the above ether filtrate and washings were combined and were evaporated to dryness in vacuo. Recrystallization of the resulting solid from ethanol gave a mixture of crystals of yellow prisms and of a small amount of light yellow needles. Two additional recrystallizations from ethanol gave 10 mg. of aureothin (I), yellow prisms, m. p. 152~153°C, undepressed upon admixture with an authentic sample.

The author is indebted to Professor Yoshimasa Hirata of this University for his valuable discussions and encouragement during this investigation. The author wishes to express his gratitude to Mr. Sho Takahashi for technical assistance in some of the experiments reported here. He is also grateful to Mr. Kiyoyuki Yamada for kindly calling the Professor Chmielewska's paper to his attention.

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63) M. Pailer, L. Belohlave and E. Simonitsh, *Monatsh.*, 87, 249 (1956).
64) Y. Hirata, K. Okuhara and T. Naito, *Nature*, 173, 1101 (1954).
65) W. B. Mors, O. R. Gottlieb and C. Djerassi, *J. Am. Chem. Soc.*, 79, 4507 (1957).
66) O. R. Gottlieb and W. B. Mors, *J. Org. Chem.*, 24, 17 (1959).
67) J. Collie, *J. Chem. Soc.*, 59, 607 (1891).