(X). *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.75; H, 11.25. Found: C, 79.00; H, 11.02.

A mixture of both methyl esters melted without depression.

Summary

By successive oxidation with selenium dioxide and sodium dichromate followed by introdution of a hydroxymethylene group, a partial structure $-C=C-CH_2-CH_2-$ was given for a diterpenic acid $C_{20}H_{30}O_2$ (II) which was isolated from the fruits of Japanese juniper. Further, as the acid (II) gave tetrahydro-7-isodextropimaric acid after consumption of two moles of hydrogen, the structure of (II) was concluded to be represented by $\Delta^{13,14}$-7-isodextropimaric acid.

The structure of a doubly unsaturated compound obtainable from a hydroxymethyl ester (VI), an oxidation product of (V), was proposed to be $\Delta^{5,13\cdot 9,14}$-7-isodextropimaric acid.

(Received Aug. 26, 1955)

---

87. **Masaichiro Masui and Takami Teshima**: High Frequency Titration. XIV.* Estimation of the Distance between the Two Carboxyl Groups of a Dicarboxylic Acid by High Frequency Titration.

(*Pharmaceutical Faculty, University of Osaka***)

The theoretical relation between the dissociation constants and the distance, r, of the two carboxyl groups in a dicarboxylic acid was first studied by Bjerrum.[1] His expression was based upon a rather simple calculation but the data obtained by his method using the dissociation constant of a dicarboxylic acid were unsuitable, especially where r was small. The modified method[2] or the same calculation with the different dissociation constants[3] were reported later, but the values of r were still somewhat doubtful, because some assumptions included in the method were not suited to the actual conditions. The most reliable theoretical method of calculation for r was presented by Kirkwood, Westheimer, and Shookhoff,[4~7] though it was, in its true object, an argument for the electrostatic influence of substituents on the dissociation constants of organic acids. Therefore, their method was rather complicated by the use of the factor D_E (effective dielectric constant), K_1 and K_2 (the first and second dissociation constants), and $\cos \xi$ (the angle between the dipole and the line which combines the center and the ionized proton).

In our study of the high frequency titration of organic acids in nonaqueous medium,[8] one of the present writers (M) found that some dicarboxylic acids showed an N-shaped titration curve in a certain medium, and a simple estimation method of the distance r between the two carboxyl groups in dicarboxylic acids was deduced

---

* This work is a part of series entitled "High Frequency Titration" by M. Ishidate. Part XIII.: J. Pharm. Soc. Japan, **75**, 1519 (1955).

** Kitatoneyame, Toyonaka, Osaka-fu (桝井雅一郎, 手島孝美).

1) N. Bjerrum: Z. physik. Chem., **106**, 219 (1923).
2) R. Gane, C. K. Ingold: J. Chem. Soc., **1928**, 2267; **1931**, 2153.
3) Y. Yamaguchi: "Kiso Denki Kagaku," Shokabo Co., Tokyo, 256 (1952).
4) J. G. Kirkwood, F. H. Westheimer: J. Chem. Phys., **6**, 506 (1938).
5) J. G. Kirkwood, F. H. Westheimer: *Ibid.*, **6**, 513 (1938).
6) F. H. Westheimer, M. W. Shookhoff: J. Am. Chem. Soc., **61**, 555 (1939).
7) F. H. Westheimer: *Ibid.*, **61**, 1977 (1939).
8) M. Ishidate, M. Masui: J. Pharm. Soc. Japan, **73**, 487 (1953).

from the interpretation9) of these curves.

Basis of Estmation The foundation of this method is based on the equation(4)*** in the preceding paper,9) which was deduced from Coulomb's force between the two carboxyl groups in a dicarboxylic acid. Once the value of K is determined by using both values of r of some acid and of its D_C9) which are determined by titration, then distance r of other acids can be easily calculated from the value of D_C determined by the high frequency or conductimetric titration. In the present series of experiments, acetylene-dicarboxylic acid was also used as a standard acid. The estimated values are shown in Table I. For the sake of comparison other workers' data are also listed in the table. There can be seen considerable differences between the data of four workers, but Gane and Ingold's, and Kirkwood and Westheimer's data (calcd.) are thought to be the most reliable.

Table I. Comparison of Distance r in Dicarboxylic Acids

Acid	r (Å)								
	This Method		Bjerrum1)		Gane, Ingold2)		Kirkwood, Westheimer4)		Yamaguchi
	obs.[a]	calc.[c]	obs.[a]	calc.[c]	obs.[a]	calc.[c]	obs.[a]	calc.[c]	obs.[a]
Oxalic	3.4		1.33	3.5	3.37	3.54	3.85	3.50~4.44	
Malonic	4.0[d] 4.6		1.35	5.0	3.43	4.26	4.10	4.12~4.87	2.44
Dimethylmalonic	4.9		(1.34)[e]				4.15	4.12~4.87	
Succinic	4.9[d] 5.6	5.58	3.8	6.5	5.58	5.87	5.85	4.66~6.66	4.52
Malic	5.15								
Tartaric	5.15		(4.09)[e]				6.00	4.66~6.66	
Glutaric	7.2[d] 6.5	7.23	5.3	8.0	7.11	6.84	7.00	5.15~7.39	6.50
β-Methylglutaric	6.2		(5.48)[e]				6.85	5.15~7.59	
ββ-Dimethylglutaric	5.25		(1.56)[e]				5.25	5.15~7.59	
Camphoric	7.8								
1,8-Naphthalic	7.8								
Adipic	9.0[d]	7.53			8.22	8.36	7.75	5.59~9.02	7.85
Diphenic	5.5								
Phthalic	4.4[d] 4.4	4.49							
Quinolinic	4.6								
Maleic	4.5[d] 4.7	4.63							
Fumaric	5.8[d]	5.02							
Acetylenedicarboxylic	5.75 (stand.)	5.71							
α-Methylhomophthalic	5.05								
Citric	(4.5) 5.5								
3,5-Dinitrosalicylic	(5.3)								

a. "obs." means the estimated value from their theoretical equation using dissociation constants.

b. Mean value of the maximum and minimum distances of plausible molecular structures, but of many acids the values cannot be calculated as the bond angles are unknown.

c. "calc." means the calculation value from bond lengths and bond angles.

d. Estimated by using $LiOCH_3$. Others by $NaOCH_3$.

e. Estimated by Kirkwood *et al.*, using Bjerrum's equation.

*** $K=\frac{D_C(r^2+3\Delta rr+2\Delta r^2)^2}{2r+3\Delta r}$ where $K=-\frac{\varepsilon^2\Delta r}{f}$

9) M. Masui: J. Pharm. Soc. Japan, **75**, 1519(1955).

Experimental

Procedures of titrations and of determining D_c values were entirely the same as those described in the preceding paper.[9] The calculations were made from the following equations:

For Na salt $$6540=\frac{D_c(r^2+7.05r+11.05)}{2r+7.05}\cdots\cdots(1)$$

For Li salt $$5200=\frac{D_c(r^2+6.00r+8)}{2r+6.00}\cdots\cdots(2)$$

Discussion

Other methods, which need dissociation constants and other factors, may be useless for the acids that are insoluble or very sparingly soluble in water, and the determination of the dissociation constants of dicarboxlic acid is fairly tedious. Present method does not need such constants and, instead, uses the dielectric constant of a medium, which, in general, need not be necessarily critical, and in spite of the simple theory and simple procedure,[9] it gives a considerably good results as shown in Table I. Ordinary conductimetric titration will also be effective for this purpose as well as high frequency titration. One of its limitations is also the solubility of acids and their salts. In most cases, the concentration of the solution to be titrated is desirable to be less than about 0.001~0.002 *M*.

The theoretical upper limit of r that can be estimated by this method will be determined by the lowest value of dielectric constant of the available medium, it would probably be 2.1 of dioxane, therefore it may be about 15 Å. In practice, the limitation by solubility of acids and their salts and sensitivity of the instrument will make the limit very small, and in the present work it has been within 9 Å of adipic acid.

Only lithium methoxide can be used to estimate the D_C of adipic and fumaric acids, and it is also difficult to determine D_C, since precipitation disturbs the steady meter readings. Though the molecular structures and distances r are not known, the estimated r of camphoric and 1,8-naphthalic acid are somewhat larger than those expected. In the medium of $D_C=28$, citric acid——tricarboxylic acid——shows an increasing curve till the second equivalence point is reached, and then it becomes horizontal until the end point. From the $D_C=28$ and equation (1) r becomes 4.5 Å.

Now, if citric acid could be considered as shown in Fig. 1, $r_2=r_3<r_1$, and therefore, the mutual electrostatic effect of r_1 may be neglected, since the effect of r_2 or r_3 is larger than that of r_1. When the former two effects (between r_2 or r_3) are independent of each other, the equation (1) may be adequate, but because of the associated electrostatic effect between the center and the terminal two carboxyl groups, the strength is larger than equation(1)[9] but samller than twice that. If calculation is made by using the strength of 1.5 times the equation (1),[9] which is the mean value of one and two folds, $r_2=r_3=5.5$ Å. It is interesting that the value is close to the mean value of the Kirkwood and Westheimer's calculated value for tartaric acid, listed in the Table I.

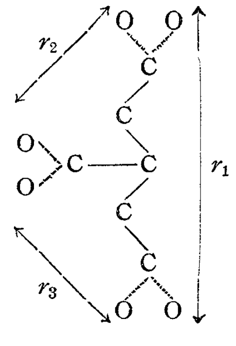


Fig. 1. Citric Acid

Phenols which have strong acidity also behave as a carboxylic acid, but in that case, the value of ε[9] and f[9] must be different from those of ordinary carboxylic acids.

In the case of comparing some analogous compounds, for instance, stereoisomers, especially in large r, it is not always necessary to evaluate their distance r, and only comparing slopes of their titration curves in the same solvent between 1st and 2nd equivalence points, may be sufficient. The steeper slope means a larger r.

However, if one selects a larger D and consequently a steeper slope, the more difficult the comparison will be. In comparing the slopes, the sensibility of high frequency titrator must be maintained constant throughout all titrations.

The authors are indebted to Prof. M. Ishidate of the University of Tokyo and Prof. K. Takiura of the University of Osaka for valuable suggestions and encouragements. The authors also wish to thank Messrs. K. Kawaguchi, K. Koizumi, I. Nakagawa, and Y. Tamura for gifts of samples of some of the acids used in the present series of experiments.

Summary

A new simple estimation method of the distance r between the two carboxyl groups of a dicarboxylic acid by high frequency titration in nonaqueous medium is described. This method is based on the Coulomb's force between the two groups. In spite of its being very simple, relatively good results were obtained.

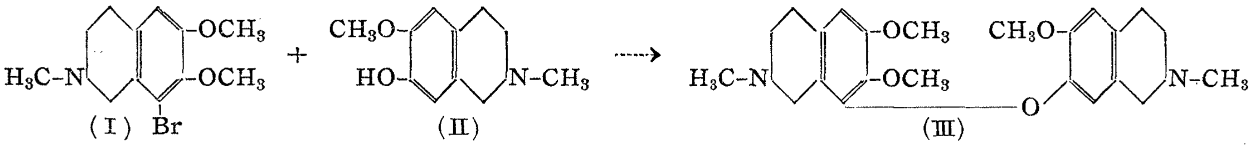
(Received September, 2, 1955)

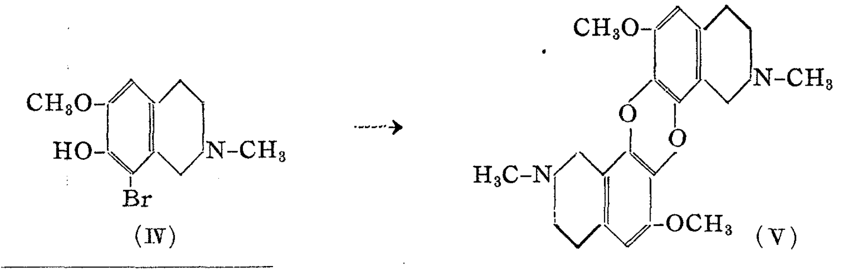
---

88. **Masao Tomita, Kazuo Itō, and Hideo Yamaguchi**: Studies on the Alkaloids of Menispermaceous Plants. CXXX.[1] Synthesis of O-Methyldauricine by Ullmann Reaction.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

One of the authors, Tomita,[2] had previously performed some preliminary experiments with the intention of synthesizing the biscoclaurine alkaloids. Among his projected syntheses was included the Ullmann reaction of 6,7-dimethoxy-8-bromo-N-methyl-1,2,3,4-tetrahydroisoquinoline (I) and 6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (corypalline) (II). In this reaction, however, debromination of (I) occurred as a side reaction, only to yield 6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (O-methylcorypalline), and no trace of the desired product (III) was found. A similar attempt to synthesize the diphenylene dioxide derivative (V) by the condensation of two molecules of 8-bromocorypalline (IV) by the Ullmann method was also found unsuccessful, since debromination of (IV) occurred, merely yielding corypalline (II) and O-methylcorypalline. The observation during these experiments was that the bromine at 8-position of the





---

* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 伊藤一男, 山口秀夫).

1) Part CXXIX. H. Kondo, K. Takeda: Ann. Rept. ITSUU Lab. (Tokyo), **6**, 34(1955).

2) M. Tomita, H. Watanabe: J. Pharm. Soc. Japan, **58**, 783(1938).