METHYL ESTERS AND 1,3-DIOXOLAN-4-ONES DERIVED FROM SIMPLE *ALPHA*-HYDROXY CARBOXYLIC ACIDS

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The acid-catalyzed conversion of *alpha*-hydroxy carboxylic acids to methyl esters and 1,3-dioxolan-4-ones is facilitated by the use of acetone dimethyl acetal to remove the water formed. Either type of derivative of DL-malic, L-(+)-tartaric, or citric acid reacts readily with primary aliphatic amines to give the *N*-substituted amides, but under the same conditions secondary amines do not react. The compound from tartaric acid and acetone is shown to have the bi-dioxolanone structure.

Various expedients have been used in the preparative esterification of α-hydroxy carboxylic acids with methanol and ethanol to increase the yield of ester by removing water as it is formed. Thus the use of anhydrous sodium sulfate (1) and of a solution of the reagents in dichloromethane or 1,2-dichloroethane (2) has been described. Since acetone dimethyl acetal is known to be an effective reagent for removing water (3), its use has now been

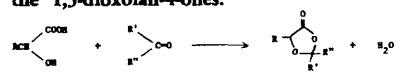
$$(CH_3)_2C(OCH_3)_2 + H_2O \xrightarrow{H+} (CH_3)_2CO + 2CH_3OH$$

extended to the esterification of L(+)-tartaric, DL-malic, and citric acids.

Mild aminolysis of the methyl esters so formed gave either the expected substituted amides (with most primary amines tried) or no reaction (with secondary amines); the difference is remarkable. Some of the amides (Tables 1 and 2) are new, such as the one illustrated for L-tartaric acid

$$CH_3OCO(CHOH)_2COOCH_3 + 2HOCH_2CH_2NH_2 \longrightarrow HOCH_2CH_2NHCO(CHOH)_2CONHCH_2CH_2OH + 2CH_3OH$$

The acid-catalyzed reaction of α-hydroxy acids with carbonyl compounds is known to yield cyclic compounds midway in structure between acetals and alkylidene esters, the 1,3-dioxolan-4-ones.



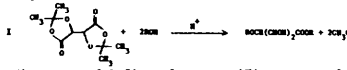
Here again it appeared useful to apply the water-removing ability of acetone dimethyl acetal. Known dioxolanones were obtained from acetone and L(+)-tartaric acid (8) or DL-mandelic acid (8,9), but DL-malic and citric acids gave products too water-

TABLE 1. *Preparation of amides.*

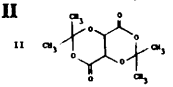
Amine	Acid	M.p., °C	Lit M.p., °C	Carbonyl absorption peak, μ	Reference
NH_3	L-(+)-Tartaric[a]	204.5[b]	208.5.209	—	(4)
CH_3NH_2	L-(+)-Tartaric[a]	195-6	189	—	(5)
$C_6H_5NH_2$	L-(+)-Tartaric[a]	213-4	215-15.5	—	(4)
o-$C_6H_5NH_2$	L-(+)-Tartaric[a]	197-8	193	—	(5)
$(CH_3)_2NH$	L-(+)-Tartaric[a,c]	186-7	—	6.19	—
$HOCH_2CH_2NH_2$	L-(+)-Tartaric[c]	143-4	—	6.11	—
cyclo-$C_6H_{11}NH_2$	L-(+)-Tartaric[c]	218-20	—	6.13	—
$C_6H_5NH_2$	DL-Malic[c]	158	—	6.14	—
$(CH_3)_2CHNH_2$	DL-Malic[c]	144-5	—	6.16	—
cyclo-$C_6H_{11}NH_2$	DL-Malic[c]	195-6	—	6.14	—
$HOCH_2CH_2NH_2$	DL-Malic[c]	125-6	—	6.16	—
$C_6H_5CH_2NH_2$	DL-Malic[c]	147-8	—	6.13	—
CH_3NH_2	Citric[c]	179-80[d]	124	6.10	(6)
$C_6H_5NH_2$	Citric	126-7[e]	—	6.10	—
o-$C_6H_5NH_2$	Citric	96-7[f]	—	6.11	—
$C_6H_5CH_2NH_2$	Citric	171-2	169-70	6.11	(7)

[a] As bi-dioxolane derivative
[b] With decomposition
[c] As dimethyl ester
[d] Possibly a new crystalline form
[e] Recrystallized from carbon tetrachloride
[f] Recrystallized from isopropyl ether

soluble for convenient isolation. No crystalline dioxolanones were obtained from tartaric acid and propionaldehyde or cyclohexanone (in the absence, however, of the acetal). The bi-dioxolanone (I) from L(+)-tartaric acid and acetone upon alcoholysis gave the expected dimethyl and diethyl L-tartrates.

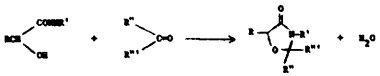


The same bi-dioxolanone (I) was aminolyzed in ethanol at room temperature to yield several *N*-substituted L-tartramides (Table 1); the only other aminolysis on record is that of the mandelic acid derivative (10). The structure shown for I, rather than the alternative II



that has been suggested (11,12), was shown to be the correct one by the infrared spectrum, which showed a carbonyl absorption peak at 1790 cm^{-1}. The corresponding dioxolanones from a number of simpler hydroxy acids, which can exist *only* as five-membered rings, showed the carbonyl peak at 1795-1815 cm^{-1} (13). The location of this peak in ordinary five-membered lactones is given as 1760-1786 cm^{-1}, whereas in six-membered lactones it appears at 1730-1750 cm^{-1} (14). This structural assignment agrees with one very recently reported for (4,4′-bi-1,3-dioxolan)-5,5-dione (14a).

Attempts to prepare 1,3-oxazolidin-4-ones (9,15,16) from L-tartramides and carbonyl compounds gave either polymers or no reaction.



EXPERIMENTAL

Preparation of esters

A mixture of L(+)-tartaric acid (150 g, 1 mole), methanol (1000 ml, 25 moles), acetone dimethyl acetal (275 ml, 2.2 moles), and concentrated sulfuric acid (5 drops) was slowly distilled through an Oldershaw fractionating column with vapor-dividing head initially set for 20% takeoff. When distillation no longer occurred at 57-59 C, and acetone was not present in the distillate (2,4-dinitrophenylhydrazine test), the most of the remaining methanol was rapidly distilled off: total time, 15 hr. The residue (225 ml) was vacuum-distilled to give 147 g (83%) of dimethyl L-tartrate, b 117/0.6 mm, lit. 158.5/12 mm (17), and 163/23 mm (18).

A run in which 1 mole of DL-malic acid was esterified similarly but with concentrated hydrochloric acid (25 drops) catalyst gave 130 g (80%) of dimethyl DL-malate, b.p. 99/1.8 mm, lit. 116/11 mm (19). Use of sulfuric acid as catalyst gave a wide-boiling distillate containing dimethyl DL-malate, dimethyl fumarate, and fumaric acid. This confirms the literature reports that sulfuric acid is unsatisfactory (15,20,21).

The similar esterification of citric acid (monohydrate) with sulfuric acid catalyst carried to the point of stripping off most of the methanol gave much crude solid from the cooled concentrate, but the product had a wide melting range and was incompletely esterified. Renewed refluxing with methanol and acetone dimethyl acetal

TABLE 2. *Analytical data for amides.*

R	R′	Molecular formula	N, Calcd.	N, Found[a]
	L-Tartramides,	$RR'NCO(CHOH)_2CONRR'$		
CH_3	CH_3	$C_6H_{12}N_2O_4$	13.72	13.44
HOCH-CH_3	H	$C_5H_{10}N_2O_5$	11.86	11.32
Cyclo-C_6H_{11}	H	$C_{16}H_{28}N_2O_4$	8.97	8.57
	DL-Malamides,	$RR'NCOCH_2CHOHCONRR'$		
C_2H_5	H	$C_8H_{16}N_2O_3$	14.89	14.91
$(CH_3)_2CH$	H	$C_{10}H_{20}N_2O_3$	12.96	12.53
$HOCH_2CH_2$	H	$C_8H_{16}N_2O_5$	12.72	12.20
Cyclo-C_6H_{11}	H	$C_{14}H_{24}N_2O_3$	9.45	9.00
$C_6H_5CH_2$	H	$C_{18}H_{20}N_2O_3$	8.97	8.62
	Citramides,	$(RR'NCOCH_2)_2C(OH)CONRR'$		
C_2H_5	H	$C_{18}H_{32}N_2O_4$	15.38	14.92
n-C_3H_7	H	$C_{21}H_{38}N_2O_4$	11.76	11.20

[a] By Kjeldahl analysis

did not complete the conversion. However, a run in which 1 mole of the citric acid was esterified with hydrochloric acid catalyst produced 188 g (80%) of trimethyl citrate, b.p. 154-5/3.4 mm, m.p. 76-7 C; lit. m.p. 79 (2), 75-76.5 (22), 78-80 (23), or 78.5-79 C (24).

Aminolysis of esters. Dimethyl L-tartrate (III) or DL-malate (IV) or trimethyl citrate (V) (5.0 g) in 10 ml of methanol was treated with a slight excess of the amine and the mixture kept for two days. The amide that had then crystallized was isolated and recrystallized from ethanol.

The results of successful preparations are shown in Tables I and 2. The following combinations gave only sirups: III and diethylamine, diisopropylamine, dibutylamine, or morpholine; IV and dimethylamine, diethylamine, dipropylamine, dibutylamine, morpholine, piperidine, or 1-naphthylamine; V and 2-hydroxyethylamine, piperidine, or 1-naphthylamine. No reaction occurred between IV and isopropylamine, dimethylamine, diethylamine, dibutylamine, cyclohexylamine or morpholine; even refluxing a mixture of V and diethylamine containing some diethylammonium chloride catalyst and distilling off the amine in vacuo left V unchanged. III and IV gave unrecrystallizable solids, undoubtedly polymeric, by reaction with ethylenediamine.

Preparation of 1,3-Dioxolan-4-ones

A mixture of L(+)-tartaric acid (40.0 g, 0.266 mole), acetone (400 ml, 5.5 moles), and acetone dimethyl acetal (200 ml, 1.6 moles) was cooled to 0 C, treated with 50% boron trifluoride etherate in ether (2 ml), and stirred 4 hr at 0 C. The mixture was evaporated to a sirup on a rotary evaporator, dissolved in 200 ml ethyl ether, and washed with two 100-ml portions of cold water, and the ether evaporated to leave a residue that was recrystallized from isopropyl ether to give 2,2-dimethyl-(4,4'-bi-1,3-dioxolan)-5,5'-dione (I) (37.1 g, 60.7%), m.p. 99-100 C; a recrystallization from ethanol gave material melting at 101 C; lit. 102 C (8). Other catalysts (sulfuric acid, Dowex 50W ion-exchange resin, and *p*-toluenesulfonic acid) gave poorer yields.

In a very similar procedure DL-mandelic acid (10 g) was treated with acetone, acetone dimethyl acetal, and a little concentrated sulfuric acid for 15 min. at −7 C. The mixture was poured into cold aqueous sodium bicarbonate and the crude product filtered out, washed, dried, and recrystallized from ligroin: yield 9.34 g (73%), m.p. 45-6 C; lit. 47.5 C (8, 9).

When the procedure used for L-tartaric acid was applied to DL-malic and citric acids, extraction of the concentrated reaction mixture with ethyl ether, washing the ether layer with water, and evaporation of the ether gave no useful product.

Refluxing a mixture of L(+)-tartaric acid with cyclohexanone and sulfuric acid catalyst, or stirring the organic acid with propionaldehyde and boron trifluoride etherate catalyst at room temperature, produced mixtures that gave only sirups on workup. An attempt to cause acid-catalyzed interchange between cyclohexanone and I, to displace acetone and produce the cyclohexanone derivative, gave no evidence of reaction.

Solvolysis of I

Excess methanol, I (10.0 g, 0.0435 mole), and sulfuric acid catalyst were slowly distilled until no more acetone appeared in the distillate. The residue was treated with sodium methoxide to neutralize the sulfuric acid and fractionally distilled to yield dimethyl L-tartrate (5.0 g, 65%). A similar ethanolysis produced diethyl L-tartrate in 74% yield.

A solution of I in absolute ethanol was treated with an excess of an amine at room temperature, the mixture chilled and filtered after two days, and the crystalline product recrystallized from absolute ethanol. The amines used and amides obtained are presented in Table 1.

Attempted preparation of 1,3-oxazolidin-4-ones

Treatment of L-tartramide with (a) acetone, acetone dimethyl acetal, and sulfuric acid, (b) cyclohexanone and sulfuric acid, and (c) aqueous formaldehyde and hydrochloric acid gave no crystalline products. The same was true for *N,N'*-diethyltartramide and formaldehyde; as with L-tartramide, an insoluble white paste was formed.

REFERENCES

1. P. F. Frankland and F. W. Aston, J. Chem. Soc. 79: 511-20 (1901).
2. N. R. Campbell and E. P. Taylor, J. Pharm. Pharmacol. 2: 229-30 (1950).
3. N. B. Lorette and J. H. Brown, J. Org. Chem. 24: 261-9 (1959).
4. J. Coops and P. E. Verkade, Recl. Trav. Chim. Pays-Bas 44: 983-1011 (1925).
5. P. F. Frankland and D. F. Twiss, J. Chem. Soc. 89: 1852-9 (1906).
6. H. Hecht, Ber. 19: 2614-8 (1886).
7. O. C. Dermer and J. King, J. Org. Chem. 8: 168-73 (1943).
8. H. O. L. Fischer and C. Taube, Ber. 60: 485-90 (1927).
9. R. Willstaetter and F. Koenigsberger, Ber. 56B: 2107-9 (1923).
10. K. Freudenberg, J. Todd, and R. Seidler, Justus Liebigs Ann. Chem. 501: 199-219 (1933).
11. P. C. Austin and V. A. Carpenter, J. Chem. Soc. 125: 1939-46 (1924).
12. Y. Tsuzuki, Bull. Chem. Soc. Japan 10: 255-6 (1935).
13. M. Farines and J. Soulier, Bull. Soc. Chim. Fr. 332-40 (1970).
14. L. Bellamy, *The infrared spectra of complex molecules*, 2d ed., J. Wiley and Sons, New York, 1958, p. 179.
14a. L. A. Cart and R. A. Stewart, J. Chem. Soc. C, 1386-9 (1971).
15. H. O. L. Fischer, G. Dangschat, and H. Stettiner, Ber. 65B: 1032-7 (1932).
16. J. B. Bicking, S. F. Kwong, M. H. Fisher, and W. H. Nicholson, J. Med. Chem. 8: 95-100 (1965).
17. R. Anschuetz, Ber. 18: 1949-53 (1885).
18. R. Anschuetz and A. Pictet, Ber. 13: 1175-8 (1880).
19. I. G. Farbenindustrie, A.-G. (H. Havekoss, O. Bayer, and H. Wolz, inventors), Ger. Pat. 738,922 (1943); via Chem. Abstr. 39, 308.
20. J. Demondesir, Compt. Rend., Acad. Sci. Paris 33: 227-30 (1851).
21. E. Fischer and A. Speier, Ber. 28: 3252-8 (1895).
22. W. E. Donaldson, R. F. McCleary, and Ed. F. Degering, J. Amer. Chem. Soc. 56: 459-60 (1934).
23. P. K. Bose and S. N. Bhattacharyya, Sci. and Cult. 2: 162 (1936).
24. A. S. Sadykov and N. I. Salit, Uzbeksk. Khim Zh. 6 (5): 68-74 (1962); via Chem. Abstr. 59, 432.