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A FACILE PREPARATION OF ASYM-MONOMETHYL, SYM-MONOMETHYL AND ASYM-DIMETHYL CITRATE

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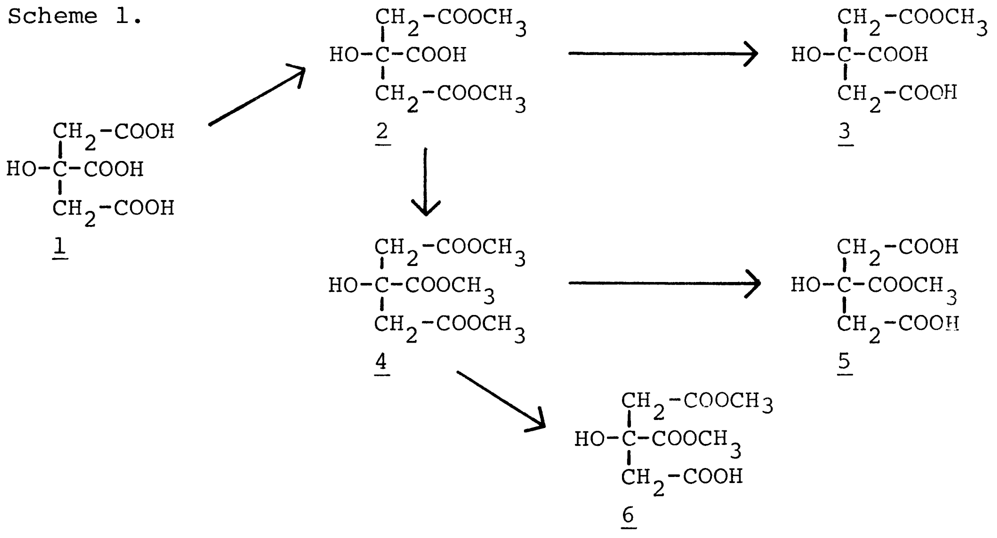
Asym-monomethyl citrate was prepared by hydrolysis of sym-dimethyl citrate. Sym-monomethyl and asym-dimethyl citrate were prepared by a selective hydrolysis of trimethyl citrate.

We wish to report a facile method for the preparation of asym-monomethyl, sym-monomethyl and asym-dimethyl citrate (3, 5 and 6). Although these compounds have previously been prepared[1,2] for the biochemical studies, the method employed were too tedious to be applied for the preparation of the compounds in substantial quantity. Our studies on the hydrolysis of various esters of citric acid (1)[3] revealed that 5 and 6, and 3 were easily obtained by the partial hydrolysis of trimethyl citrate (4) and sym-dimethyl citrate (2) respectively, under well-controlled reaction conditions (Scheme 1).

Scheme 1.



The starting materials of this study, 2[4] and 4[5], were readily obtainable by the esterification of 1 and 2, respectively.

The partial hydrolysis of 2 and 4 were performed by stirring with NaOH, until no change of pH of the reaction mixture was attained. In the reaction, 2→3, the use of 0.25 mole of NaOH to 1 mole of sodium salt of 2 gave the optimum results in giving reasonable conversion with minimum formation of 1[6]. When the desalted hydrolysate of 2 was treated with $CaCO_3$, Ca-salt of 3 precipitated. Then the removal of Ca^{++} liberated pure 3. To find out the optimum conditions of hydrolysis of 4 to 5 and 6, the relative amounts of 5 and 6 produced were plotted against the molar ratio of NaOH to 4 in the range of 0 to 4. As shown in Fig. 1, hydrolysates at the molar ratio of 2.0-3.0 and 0.5-1.2 have 5 and 6 in abundance, respectively. The preparative experiments showed that employments of each lowest value in the ranges were advantageous for the isolation of these compounds.

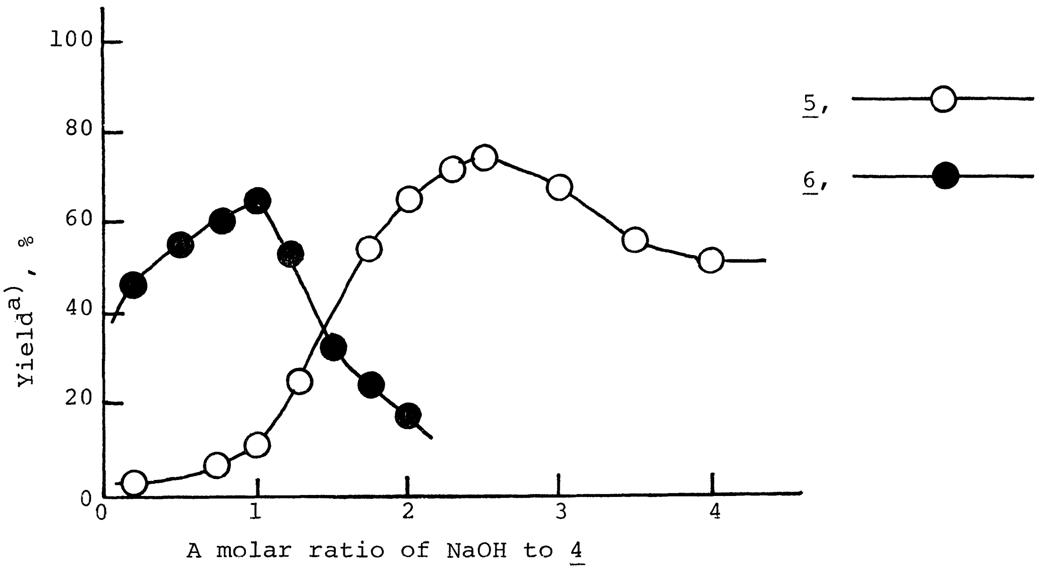


Fig. 1. Plots of the approximate yields of 5 and 6 at fixed amounts of NaOH.

Trimethyl citrate (117.1 mg, 0.5 mmol) was suspended in water and known quantities of NaOH were mixed. The reaction mixture (17 ml) was stirred for 30 min at room temperature. The resulted solution was desalted by addition of air-dried Diaion SK-1 resin (H-type) and concentrated to dryness under reduced pressure. The residue dissolved in methanol was charged to TLC-plate (silica gel) and developed with a solvent system of B (see below). The corresponding zone was scrapped off and extracted with 1 N NaOH. The extract was heated for 0.5 h at 90°C and 1 produced was determined by pentabromoacetone method$^{7)}$. a) Based on 4.

All compounds listed in Scheme 1 can be well resolved on TLC. Thus, the homogenity of each reaction product was easily determined by TLC method$^{8)}$ on silica gel ($60F_{254}$, Merck) using the following solvents;A: 1,2-dichloroethane-methanol-formic acid (10:3:0.5), B: 1,2-dichloroethane-methanol-formic acid (7:3:0.5).

An aqueous solution and solids of all these esters were quite stable on storage at room temperature without the hydrolysis and rearrangements of the ester groups.

Preparation of 3. To a methanol solution (700 ml) of 2·H_2O[4)] (83.4 g, 0.35 mol) was added a 50% methanol solution (450 ml) containing NaOH (0.437 mol) for 4.5 h with vigorous stirring at room temperature. After the addition the stirring was continued until the mixture became neutral. The mixture was concentrated to about half of the volume under reduced pressure, and then stirred for 0.5 h with Diaion SK-1 resin (H-type, 400 ml). The resin was removed by filtration and washed with hot water several times. The filtrate and washing were concentrated to a volume of 300 ml and kept in a refrigerator overnight. The precipitate of 2 (58.52 g) was recovered on a filter. The filtrate was treated with $CaCO_3$ and stirred at 80-90°C for 20 min to precipitate Ca-salt of 3. The precipitate was again desalted by the treatment with Diaion SK-1 resin (H-type). The desalted solution removed from the resin was concentrated to dryness to give colorless syrup which crystallized when kept in vacuum desiccator. Recrystallization from ethyl acetate gave 3 (8.27 g) in a yield of 38% on the basis of the amount of 2 consumed during the reaction: mp 116.5-117.5°C (lit.[1)] mp 119-121°C). TLC showed only one spot (Rf; A: 0.13, B: 0.40). Found: C, 40.78; H, 4.99%. Calcd for $C_7H_{10}O_7$: C, 40.78; H, 4.89%. MNR (d_6-DMSO): 3.56 (3H, s, CH_3), 2.70-2.79 (4H, m, CH_2).

Preparation of 5. To a 70% methanol solution (150 ml) of 4[5)] (23.4 g, 0.1 mol) was added 1 N NaOH (200 ml) during 2 h with vigorous stirring. The solution was concentrated to about 50 ml and then applied to a column of Diaion SK-1 resin (H-type). The acidic eluate was collected and concentrated to dryness under reduced pressure. The residue was recrystallized from acetone to give 5 (12.3 g). By the concentration of the mother liquor, a second crop (2.7 g) was obtained. The total yield of 5 amounted to 73% on the basis of the starting ester: mp 174-175°C (lit.[1)] mp 167°C). TLC showed only one spot (Rf; A: 0.27, B: 0.55). Found: C, 40.72; H, 4.92%. Calcd for $C_7H_{10}O_7$: C, 40.78; H, 4.89%. NMR (d_6-DMSO): 3.62 (3H, s, CH_3), 2.62 and 2.82 (4H, each 2H, d, J= 15.4 Hz, CH_2).

Preparation of 6. To a 50% methanol solution (200 ml) of 4[5)] (10 g, 0.043 mol) was added 0.1 N NaOH (215 ml) during 2 h with vigorous stirring at room temperature. Trimethyl citrate (3.9 g) was recovered by the extraction with ethyl acetate. An aqueous solution was concentrated to about 50 ml, and desalted with a column of Diaion SK-1 resin (H-type). The acidic eluate was collected and concentrated to dryness. The residue was dried over P_2O_5 desiccator, and recrystallized from toluene to give 6 (3.27 g) in a yield of 57% on the basis of the amount of 4 consumed during the reaction: mp 80-81°C (lit.[2)] syrup). TLC showed only one spot (Rf; A: 0.60, B: 0.73). Found: C, 43.26; H, 5.48%. Calcd for $C_8H_{12}O_7$: C, 43.64; H, 5.45%. MNR (d_6-DMSO): 3.63 and 3.56 (each 3H, s, CH_3), 2.61-2.96 (4H, m, CH_2).

REFERENCES AND NOTES

1) W. Buckel and H. Eggerer, Z. Physiol. Chem., 350, 1367 (1969).

2) M. Miyake, Y. Kamimoto, and M. Sorimachi, Biochim. Biophys. Acta, 544, 656 (1978).

3) Details of the study will be published elsewhere.

4) A by-product of 4 in the preparation of 2 with the method previously reported (G. Schroeter and L. Schmits, Chem. Ber., 35, 2085 (1902)) caused difficulties in the purification of 3. Thus, a slight modification was taken as follows. Anhydrous 1 (350 g) was refluxed with methanol (2000 ml) and H_2SO_4 (10 ml) for 1 h. The reaction mixture was diluted with water (1000 ml), and then neutralized with $Ca(OH)_2$. The resulted precipitate was filtered off, and the filtrate was dried up. The residue was suspended in acetone (600 ml), filtered to remove 4, and again suspended in water (400 ml). To the suspension, concentrated hydrochloric acid (200 ml) was added at 0-5°C. After stirring for 10 min, the precipitate was collected on a filter, and recrystallized from 30% methanol to give $2\cdot H_2O$ (111.6 g) in a yield of 25%: mp 122-124°C (lit.2) mp 116-121°C). TLC showed only one spot (Rf; A: 0.46, B: 0.69). NMR (d_6-DMSO): 3.56 (6H, s, CH_3), 2.71 and 2.89 (each 2H, d, J=15.0 Hz, CH_2).

5) In the preparation of 4, the esterification of 2 provided more satisfactory results with the rapid purification as well as with the yield than the direct esterification of 1 with hydrogen chloride (W. E. Donaldson, R. F. McCleary, and E. F. Degering, J. Am. Chem. Soc., 56, 459 (1934)). To a methanol solution (1500 ml) of $2\cdot H_2O$ (125 g) were added 2,2-dimethoxypropane (80 ml) and H_2SO_4 (10 ml), and the mixture was refluxed for 7 h. The solvent was distilled off and the residue was recrystallized from water to give 4 (108 g) in a yield of 88%. TLC showed only one spot (Rf; A: 0.77, B: 0.83).

6) The formation of a large quantity of 1 caused difficulties in the purification of 3, because Ca-salt of 1 coprecipitated with that of 3.

7) K. Kuratomi and N. Hosoya, Seikagaku, 27, 72 (1955).

8) The detection on TLC was carried out with the spray of 0.1% ethanol solution of bromocresol green and the vapor of iodine. All esters (2-6) can be separated from 1 with a Rf-value of 0.02 and 0.25 in a solvent system A and B, respectively.

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