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CHEMISTRY OF 2-BROMO 3-TRICHLOROMETHYL SUCCINIC ANHYDRIDE AND DIMETHYL ESTER : PREPARATION OF VARIOUS HALOGENATED SUCCINIC, MALEIC, FUMARIC AND MALIC ACID DERIVATIVES

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ABSTRACT - Various reactions of the readily available adducts of bromotrichloromethane with maleic anhydride and dimethyl maleate and fumarate leading to halogenated derivatives of succinic, maleic, fumaric or malic acids and/or esters are described.

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Free-radical addition of $BrCCl_3$ to maleic or fumaric diesters leads to a 1:1 adduct (1) which has been used as synthon in further free-radical additions[1] and studied also as possible precursor of "trihalogenated compounds of potential therapeutic interest"[2]. Although the isolated adduct is a stable solid, it easily looses HBr in either basic or acidic medium. For that reason BOWMAN et al[2] failed to prepare the 2-trichloromethyl succinic acid (8b) they aimed at.

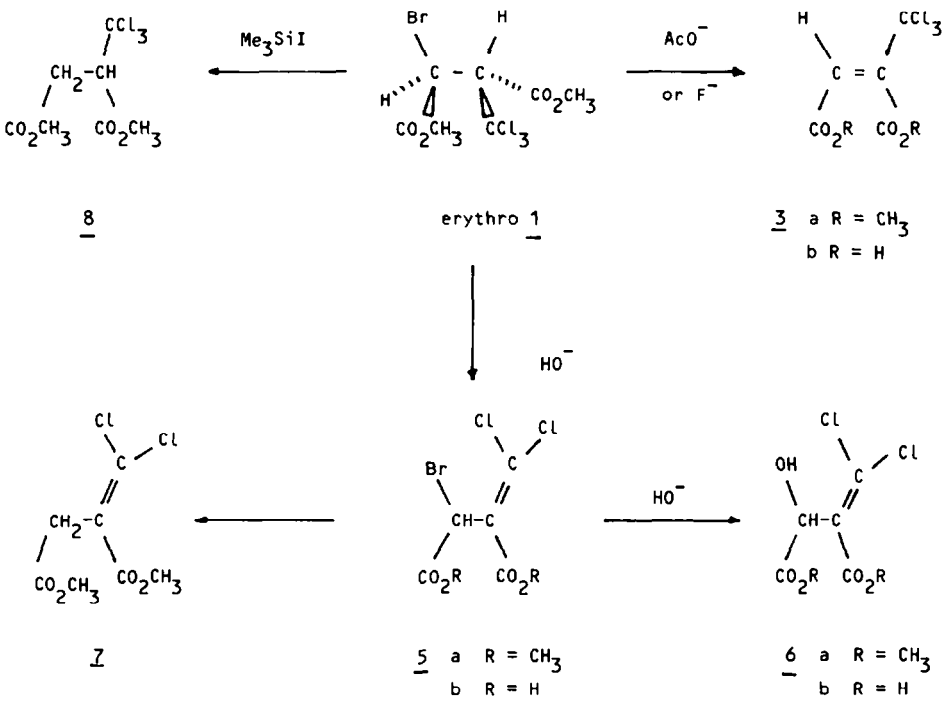
Despite seemingly having been overlooked in the past, this adduct remains an attractive synthon in view of its ready availability. We therefore decided to reinvestigate the preparation and the chemistry of dimethyl 2-bromo 3-trichloromethyl succinate (1) and 2-bromo 3-trichloromethyl succinic anhydride (2). The stereochemistry of the free-radical additions leading to these products will be reported separately[3] : we have found that the addition of $BrCCl_3$ to either maleate or fumarate dimethyl esters mainly gives the erythro 1:1 adduct (1), whereas threo adduct (2) is obtained from maleic anhydride.

Reaction of twice recristallised diester 1 with MeONa followed by hydrolysis with 70 % H_2SO_4 has been said by KHARASCH[1] to give 2-trichloromethyl fumaric acid (4b)[4]. Some years later BOWMAN[2] reported that reaction of diethyl 2-bromo 3-trichloromethyl succinate with triethylamine in ether followed by hydrolysis with "boiling hydrochloric acid" afforded 2-trichloromethyl maleic acid (3b). The stereochemical discrepancy between those two results will be examined later.

We report here some reactions of diester 1 and anhydride 2 summarized in schemes I and II.

Our findings were that dimethyl 2-trichloromethyl maleate (3a) was obtained in moderate yield by reacting diester 1 with AcONa in AcOH at room temperature for 24 h. Alternatively reaction of 1 with Bu_4NF in THF at 0° C afforded 3a in good yield.

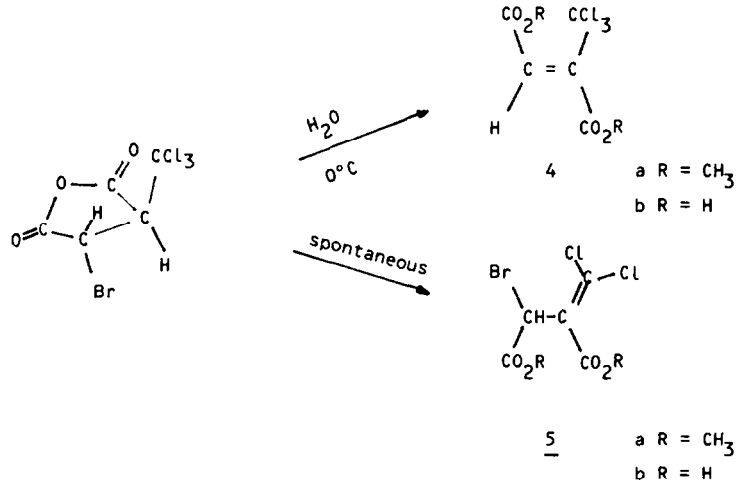
SCHEME I



8 erythro 1 3 a R = CH_3 b R = H

7 5 a R = CH_3 b R = H 6 a R = CH_3 b R = H

SCHEME II



4 a R = CH_3 b R = H

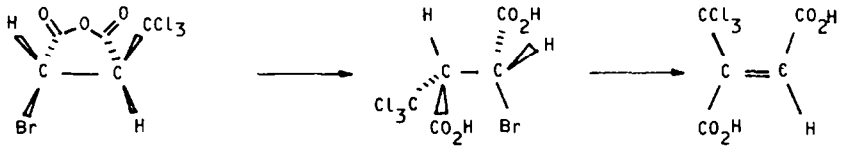
5 a R = CH_3 b R = H

Diester 3a is expected from erythro 1 under conditions of anti-elimination which is the most probable mechanism with either AcO^- in AcOH of F^- in THF and also with MeO^- in Kharasch's study[1] and with Et_3N in Bowman's work[2].

erythro 1 3a

Threo 1 was not isolated ; nevertheless it was found that reaction of a 50:50 mixture of erythro and threo 1 with Bu_4NF in THF led to a 50:50 mixture of diesters 3a and 4a.

The same stereoselectivity was observed with anhydride 2 which is threo. Reaction of the crude adduct 2 with water at 0°C gave essentially diacid 4b along with small amounts of the isomer 3a and of dehydrochlorination product 5b. We suppose that the anhydride was first hydrolysed to the corresponding threo acid and then converted into 4b



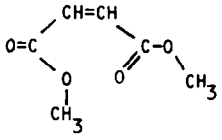
2 4b

When attempting to hydrolyse diester 3a in 1 M H_2SO_4 to obtain 3b, we isolated the fumaric derivative 4b. Only very mild acidic conditions, ie in HCO_2H with catalytic amounts of CH_3SO_3H at 50° C, afforded a mixture of isomeric diacids 3b and 4b ; but sofar 3b has not been isolated. Then we can question if 2-trichloromethyl maleic acid 3b was really obtained in BOWMAN's work[2] ; in addition, the reported melting point for 3b is identical to that one we attributed to 4b.

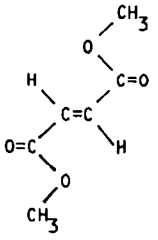
The relative stereochemistry of the isomers 3 and 4 was determined on the basis of the NMR data of the diacids 3b and 4b and of the IR data of the diesters 3a and 4a.

The chemical shifts for the vinyl hydrogen at C-3 of the diacids 3b and 4b are respectively 6.9 and 5.8 ppm in CF_3CO_2H. Addition of $(CF_3CO)_2O$ shifted the 6.9 signal to 7.19 ppm and the 5.8 signal to 5.5 ppm. This observation parallels what happens with maleic and fumaric acids : down-field shift with maleic acid (from 6.6 to 7.1 ppm), indicating the formation of maleic anhydride, and upfield shift with fumaric acid. We made similar NMR observations with citraconic and mesaconic acids.

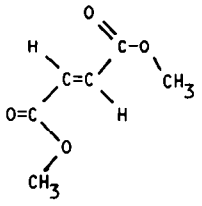
In confirmation of the NMR based stereochemical assignement for the diacids 3b and 4b, a comparative IR study of the diesters 3a and 4a on one hand, and dimethyl maleate and fumarate on the other hand, allowed characterization of the isomers on the basis of the C-H bending vibration of the CH_3 groups. W.O. George et al.[5] interpreted the IR spectra of dimethyl maleate and fumarate on considering preferred cis-trans form (I) for dimethyl maleate and trans-trans (II) and trans-cis (III) forms for the fumarate derivative.



(I)



(II)

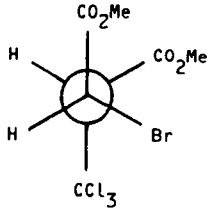


(III)

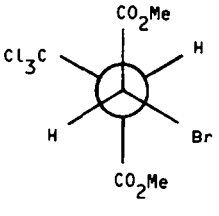
This infers two alkyl C-H bending modes for dimethyl maleate (bands at 1435 and 1387 cm^{-1}) and only one alkyl C-H bending mode for dimethyl fumarate (band at 1438 cm^{-1}). Similar IR differences were observed with diester 3a (bands at 1440 and 1355 cm^{-1}) and 4a (band at 1480 cm^{-1}) allowing us to state 3a as dimethyl 2-trichloromethyl maleate.

2-bromo 3-dichloromethylene succinic acid (5b) was easily obtained from 2 simply on standing the crude dry anhydride 2 for two days in the air at room temperature. In contrast to the reaction of 2 with water leading to diacid 4b, in the absence of water the anhydride is stable enough and then the dehydrochlorination is the only anti-elimination which is possible. Diester 5a, was then readily obtained by reacting 5b in MeOH with H_2SO_4 as catalyst. Alternatively 5a was formed by reaction of erythro 1 with KOH in 70:30 water-dioxane at room temperature ; nevertheless the reaction product was a mixture from which 5a was not easily isolated. However this reaction proved to be useful for the preparation of 6a from 1 using between 3 and 4 equivalents of HO^-. In those conditions the first step is supposed to be the elimination of HCl followed by the substitution of Br by OH. The esters qroups being partially hydrolysed, the product was treated with $MeOH-H_2SO_4$ to give 6a.

The medium dependance of the dehydrohalogenation in erythro diester 1 is surprising : HBr elimination in AcOH, HCl elimination in water-dioxane. Assuming an anti-elimination in both implies that the favoured conformation is not the same in both solvents : (IV) would be favoured in the acid medium and (V) in water dioxane. We have not attempted to clarify this striking difference.



IV



V

Reduction of α-halogenated esters or ketones with Me_3SiI has been well documented[6]. This reaction has been used to prepare 7 and 8. Thus reaction of 1 with $(Me_3Si)_2$ and I_2 in $HCCl_3$ gave 8 in good yield. Better results were obtained however with Me_3SiCl and NaI in CH_3CN. Those latter conditions were used to obtain 7 from 5 in high yield.

In conclusion we have shown that 1 and 2 are precursors of various halogenated derivatives of succinic, maleic fumaric and malic acids or esters.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 577 spectrometer. ^1H NMR spectra were recorded on a Varian T-60 or Brucker WH-90 spectrometer and ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer. UV spectra were obtained with a Beckman ACTA-III spectrometer. Mass spectra were obtained on a Nermag R-10-10 spectrometer coupled with a Girdel gas chromatography instrument with a 25 m CPSIL 5 capillary column at Department de Chimie Organique, Orsay.

The preparation and characterization of 1 and 2 will be reported separately[3].

Dimethyl 2-trichloromethyl maleate (3a)

a) A mixture of erythro 1 (2 g, 5.8 mmol) and sodium acetate (0.5 g, 6.1 mmol) in AcOH (10 ml) was stirred at room temperature for 24 h. AcOH was removed by distillation under partial vacuum. Ether was then added to the residue and the solution was washed with water, dried over $MgSO_4$ and evaporated. GC analysis indicated that the crude product consisted of a mixture of 3a and 5a in a 6:1 ratio, and very small amount of 4a. Chromatography on silica gel with pentane-diethyl ether (95:5) gave 3a (0.76 g, yield 50 %) as an oil : IR ($CDCl_3$) 1740, 1650, 1440, 1355, 1205, 1175 cm^{-1} ; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.87 (s, 3H), 3.97(s,3H), 6.78 (s,1H) ; ^{13}C NMR 52.74, 53.4, 91.45, 123.28 (C-3), 128.4 (C-2), 148.53, 163.82 ; mass spectrum (CI with NH_3) m/e 278, 280, 282, 284 (MNH^+_4), 261, 263, 265, 267 (MH^+).

b) 0.2 g of erythro 1 was stirred with 1 M Bu_4N F solution in THF (2 ml) for 1 h at 0° C. CH_2Cl_2 (10 ml) was then added and the solution was extracted with 1 N HCl, dried over $MgSO_4$ and evaporated. Chromatography on silica gel with pentane-diethyl ether (95:5) gave 3a (0.11 g; 72 %).

Dimethyl 2-trichloromethyl fumarate (4a)

a) 0.1 g of 3a was refluxed in 1 M H_2SO_4 (2 ml) for 24 h. The reaction product was isolated by continuous extraction with diethylether, dried over $MgSO_4$ and evaporated to give 4b as a white solid (0.085 g, 95 % yield) : mp 145-146° C ; ^1H NMR (TFA, 60 MHz) 5.8 ppm (s). 4b was then refluxed with MeOH (2 ml) and conc. H_2SO_4 (0.1 ml) for 3 h. MeOH was then partially removed by distillation, CH_2Cl_2 (5 ml) was added to the residue and the solution was extracted with 1 % $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to give 4a as an oil (0.08 g, 80 % yield from 3a) : IR ($CDCl_3$) 1765, 1740, 1600, 1480, 1315, 1200, 1150, 1100, 1010 cm^{-1} ; ^1H NMR ($CDCl_3$, 60 MHz) 3.80 (s, 3H), 3.83 (s, 3H), 5.57 (s, 1H) ppm ; mass spectrum (CI with NH_3) identical with that of 3a.

b) Portionwise addition of ice to a portion of crude 2 (0.5 g) at ice-bath temperature with stirring followed by continuous extraction with ether and evaporation gave a white solid. Reaction with MeOH-conc. H_2SO_4 (10:1) followed by usual work-up and chromatography on silica gel with pentane-ether (95:5) gave 4a as an oil (0.2 g).

Dimethyl 2-bromo 3-dichloromethylene succinate (5a)

After standing at room temperature for 2-3 days, 0.5 g of crude 2 were treated as follows : water was added, and the aqueous layer was first washed with CH_2Cl_2 and then extracted with diethyl-ether to give 5b (0.32 g) : ^1H NMR (TFA, 60 MHz) 5.9 ppm. The obtained product was then esterified with MeOH-conc. H_2SO_4 (10:1). Chromatography on silica gel with pentane-ether (9:1) gave 5a as a yellow oil : IR($CDCl_3$) 1740, 1585, 1440, 1265, 1155 cm^{-1} ; mass spectrum (CI with NH_3) 322, 324, 326, 328 (MNH^+_4 305, 307, 309, 311 (MH^+) 244, 246, 248 (MNH^+_4 - Br) 227, 229, 231 (MNH^+_4 - NH_4Br) ; ^1H NMR ($CDCl_3$, 60 MHz) 3.8 (s, 3H), 3.85 (s, 3H), 5.66 (s, 1H).

(±)-Dimethyl 2-hydroxy 3-dichloromethylene succinate (6a)

A mixture of 1 (2 g, 5.8 mmol) and KOH (1.3 g, 23.2 mmol) in (30:70) dioxane-water (10 ml) was stirred at room temperature for 24 h. The solution was then acidified to pH 5 with 1 M H_2SO_4 and extracted with ether. After evaporation the crude product (1.42 g) was refluxed with MeOH (50 ml) and conc. H_2SO_4 (4 ml) for 3 h. MeOH was partially distilled and CH_2Cl_2 (30 ml) was added to the residue. The solution was washed with 1 % Na_2CO_3, dried over $MgSO_4$ and evaporated. Chromatography on silicagel with pentane:diethyl ether (70:30) gave 6a as an oil (0.53 g, 36 % yield) : IR (neat) 2960, 1750, 1610, 1590, 1440, 1310, 1140, 1100 cm^{-1} ; ^1H NMR ($CDCl_3$, 90 MHz) 3.43 (OH), 3.83 (s, 3H), 3.86 (s, 3H), 5.28 (s, 1H) ; ^{13}C NMR ($CDCl_3$) 52.77, 53.49, 7041, 130.34, 133.88, 163.57, 171.68 mass spectrum (CI with NH_3) m/e 260, 262, 264 (MNH^+_4), 243, 245, 247 (MH^+).

Dimethyl 2-dichloromethylene succinate (7)

To a mixture of NaI (0.75 g, 5 mmol) and 5a (0.5 g, 1.6 mmol) in CH_3CN (15 ml) was added Me_3SiCl (0.6 ml, 5 mmol) with stirring and the reaction mixture was heated at reflux for 24 h. After cooling the mixture was filtered, CH_2Cl_2 (15 ml) was added, and the solution was extracted with 10 % $NaHCO_3$ and with 0.1 N $Na_2S_2O_4$, dried over $MgSO_4$ and evaporated. Chromatography on silica gel with pentane-ether (90:10) afforded 7 (0.28 g, yield 75 %) : IR ($CDCl_3$) 1740, 1600, 1438, 1345, 1275, 1205, 1175, 1100 cm^{-1} ; ^1H NMR ($CDCl_3$) 3.62 (s, 2H), 3.7 (s, 3H), 3.8 (s, 3H).

(±)-Dimethyl 2-trichloromethyl succinate (8)

To a solution of $MeSiSiMe_3$ (0.28 g, 3.3 mmol) and I_2 (0.83 g, 3.3 mmol) in chloroform (10 ml) was added 1 g (3 mmol) of 1 with continuous stirring under argon. The reaction mixture was heated at reflux for 4 h. After cooling the mixture was extracted with $Na_2S_2O_4$ to remove the unreacted I_2, dried over $MgSO_4$ and evaporated. The crude product was chromatographed on silica gel with pentane-diethyl ether (9:1) to give 0.4 g of 8 as an oil (yield 51 %) : ^1H NMR 3.21 (m, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 4 (m, 1H) : ^{13}C NMR ($CDCl_3$) 35.10, 52.32, 52.90, 60.89, 96.80, 168.08, 170.44 ; mass spectrum (CI with NH_3) m/e 280, 282, 284, 286 (MNH^+_4) 263, 265, 267, 269 (MH^+).

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(4) According to our stereochemical assignements (ref. 3), erythro was certainly the major isomer in KHARASCH's experiments.

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