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γ-PYRONE DERIVATIVES

VIII. Monocyclic Bromo-γ-pyrones

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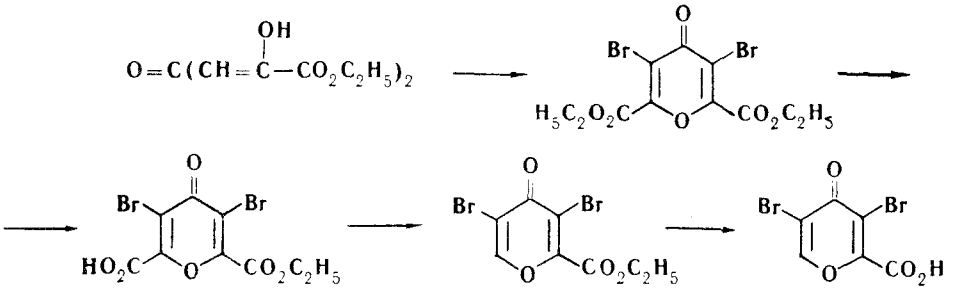
3,5-Dibromocomanic acid (3,5-dibromo-γ-pyrone-2-carboxylic acid) VI and its ethyl ester, hitherto not described in the literature, are synthesized by the following route: diethyl acetonedioxalate (I) → diethyl dibromochelidonate (III) → (mono) ethyl dibromochelidonate (IV) → diethyl 3,5-dibromocomanate (V) → VI. Direct bromination of diethyl bromochelidonate gives the ester III. 6-Bromocomenic acid and its ethyl ester are prepared, as well as 2-bromo-3-hydroxy-γ-pyrone. Bromocomanic acid (x-bromo-γ-pyrone-2-carboxylic acid) XVI is synthesized by the following route: I → (mono) ethyl chelidonate → ethyl comanate → comanic acid XVI. Oxonium salts are obtained: acid sulfates of comanic acid and ethyl comanate.

Only a few monocyclic bromo-γ-pyrones are known, on account of the difficulty of effecting direct halogenation of this heterocyclic ring system. Thus various reagents have been used in an unsuccessful attempt to brominate chelidonic acid [2]. However, it proved possible to obtain mixed diethyl bromo- and dibromochelidonates by brominating diethyl acetonedioxalate I under drastic conditions, i.e., to effect simultaneous halogenation and cyclization [2, 3, 4]. By brominating the ester I we obtained diethyl bromochelidonate (II) (free from diethyl dibromochelidonate III), or only the ester III [5]. To obtain the mono- and dibromochelidonic acids from the corresponding ethyl ethers, the latter were hydrolyzed with alkali, or, more effectively, the acid sulfates of those esters submitted to acid hydrolysis in concentrated H_2SO_4 solution [5, 6]. We realized one-stage acid hydrolysis and decarboxylation of the acid sulfate of ester II to 5-bromocomanic acid [5].

In the present work an unsuccessful attempt was made to effect simultaneous hydrolysis and decarboxylation of the acid sulfate of ester III to the hitherto undescribed 3,5-dibromocomanic acid VI. Having extended acid hydrolysis to the acid sulfates of esters III and V, by utilizing this in conjunction with the smooth decarboxylation of (mono) ethyl dibromochelidonate (IV) which takes place on dry distillation, we were able to synthesize VI by the following route:



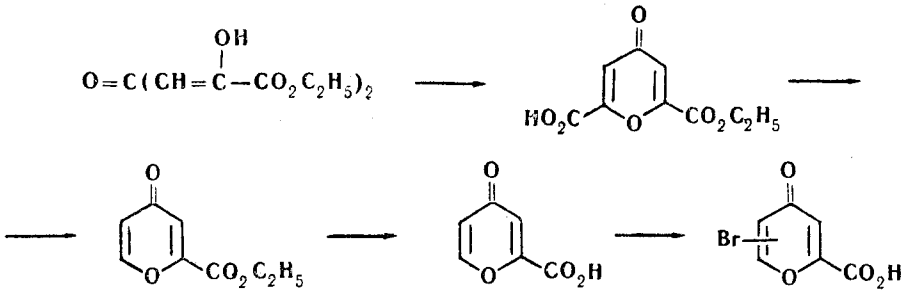
We did not succeed in effecting direct bromination of chelidonic acid with dioxane bromide [7], but the latter halogenated ester II to ester III in 50% yield. As ester III is obtained in the same yield by direct bromination of ester I, the method is of no preparative interest. Extension of the method to ethyl comenate and 3-hydroxy-γ-pyrone VIII gave low yields of the corresponding bromine substitution products, and similar results were obtained on brominating the oxonium salts of the acid sulfates of pyrones VII, VIII, and of comenic acid IX in concentrated sulfuric acid solution. However, brominating the acid sulfate of acid IX dissolved in mixed concentrated sulfuric acid-glacial acetic acid secured a 60% yield of 6-bromocomenic acid X.

It is more effective to add bromine, or a solution of bromine in 85% acetic acid, to the γ-pyrone derivative dissolved in 50% (aqueous) dioxane held at 0°-100° C, formation of oxonium salts with γ-pyrone derivatives, and their perbromides, being excluded. Thus meconic acid and ester VII gave respectively 85% and 76% yields of acid X and ethyl 6-bromomeconate, (XI), this latter ester being obtained in almost the same yield by brominating ester VII dissolved in mixed chloroform-glacial acetic acid, a less convenient method.

Halogenation of VII in aqueous dioxane gave 2-bromo-3-hydroxy-γ-pyrone (XII) in yield as high as that obtained by brominating using the best variant of method [8], i.e., using a buffered mixture. In our view, the authors started

* For Part VII [1].

with the oxonium salt of the acid orthophosphate of pyrone VIII but during reaction, due to addition of a solution of bromine in 85% acetic acid and excess sodium acetate, the oxonium salt decomposed. Repetition of the work of the authors [8] showed that the 84% yield of pyrone which they indicated was for the product untreated with sodium bicarbonate. With bicarbonate treatment it is 65%, i.e., the same as when using aqueous dioxane. Comanic acid XV was halogenated in aqueous dioxane; our synthetic route to that acid was: ester I → (mono) ethyl chelidonate (XIII) → ethyl comanate XIV → XV. The acid sulfate of ethyl comanate (XVII), prepared from XIV by the method of [4], was hydrolyzed with concentrated sulfuric acid; the acid sulfate of comanic acid XVIII was prepared similarly. The preparation of acid XVI by direct bromination of acid XV shows that a generalization which has been made by some authors [2] does not extend to it. We have not established the position of the bromine in XVI. Despite a published opinion to the contrary [9], copper powder can be successfully used as a catalyst for decarboxylating ester XIII.



Experimental

Diethyl dibromochelidonate (3,5-dibromo-γ-pyrone-2,6-dicarboxylate) (III). A solution of 1.6 g (0.005 mole) II in 10 ml dioxane was heated on a boiling water bath, and 2.4 g (0.015 mole) bromine in 6 ml dioxane added dropwise over 1.5 hr. Then the dioxane was distilled off under reduced pressure, at room temperature, to leave a syrup, water added, and the precipitate filtered off and washed with water. Mass 1 g, yield 50%, mp 122°-124° C (EtOH) [4,5].

Ethyl 3,5-dibromocomanate (ethyl 3,5-dibromo-γ-pyrone-2-carboxylate) (V). A flask fitted with a thermometer had sealed into it, low down, a wide-necked exit tube, to which was connected a wide tube, the other end of the latter going to a water pump, and 5.7 g ester IV was placed in the flask. On heating at 225°-240° C (inside flask) for 30 min, vacuum 5-10 mm, an oily distillate separated and gradually solidified. Yield 4.0 g (80%), mp 114°-116° C (EtOH). The compound was readily soluble in $CHCl_3$, Et_2O, dioxane, benzene, slightly soluble in water. Found: C 29.00; H 1.80; Br 48.60%. Calculated for $C_8H_6Br_2O_4$: C 29.44; H 1.84; Br 49.08%.

3,5-Dibromocomanic acid (3,5-dibromo-γ-pyrone-2-carboxylic acid) (VI). A solution of 4 g ester V and 8 ml H_2SO_4 (d 1.84) was stirred and heated for 5 hr at 100° C, then the products decomposed with ice. Next day the precipitate was filtered off, washed with water, then with $CHCl_3$. Yield: 2.7 g (75%), mp 219°-220° C (EtOH). Readily soluble in EtOH, and dioxane, less soluble in boiling water. Found: C 23.70; H 1.00; Br 54.04%. Equiv. 296. Calculated for $C_6H_2Br_2O_4$: C 24.16; H 0.67; Br 53.69%. Equiv. 298.

6-Bromocomenic acid (5-hydroxy-6-bromo-γ-pyrone-2-carboxylic acid) (X). a) A solution of 12.5 g (0.08 mole) dry comenic acid of the highest purity [10] in 38 ml H_2SO_4 (d 1.84) was prepared by heating the mixture on a boiling water bath, after which it was cooled to 60° C, 60 ml glacial AcOH added, followed by 14.0 g (0.088 mole) Br_2 in 30 ml glacial AcOH plus 10 ml $CHCl_3$ added at a uniform rate over 6 hr to the mixture held at 30° C. Excess solvent was distilled off under reduced pressure at 35°-40° C, the residue decomposed with ice, the precipitate filtered off next day, washed with ice water, dissolved in cold water plus 10% Na_2CO_3 solution (bromothymol blue), the solution acidified with HCl (1:1), the the precipitate filtered off. Yield 13.6 g (60%), mp 190° C (ex H_2O) [11]. The compound gave a red color with 1% aqueous $FeCl_3$.

b) 40 g (0.2 mole) maximum purity dry meconic acid [12] was dissolved in 80 ml 50% aqueous dioxane, and 48 g (0.3 mole) Br_2 added dropwise over 3 hr to the solution held at 15° C, stirring continued for 2 hr more, the solvent distilled off under reduced pressure at 30° C, the solid filtered off, washed with water, and purified as in (a). Yield 40.0 g (85%). Found: equiv. (using methyl red) 237. Calculated for $C_6H_3BrO_5$: equiv. 235.

Ethyl 6-bromocomenate (ethyl 5-hydroxy-6-bromo-γ-pyrone-2-carboxylate) (XI). a) 15.6 g (0.1 mole) ester VII (mp 126° C), dissolved in 240 ml $CHCl_3$ plus 16 ml glacial AcOH was held at 30° C, and a solution of 16.0 g (0.1 mole) Br_2 in 18 ml $CHCl_3$ added over 5 hr. The solvent was distilled off under reduced pressure at 40° C, the solid separated off, and washed with water, yield 19 g (80%), mp 142° C ($CHCl_3$) [11]. The compound gave a red color with 1% aqueous $FeCl_3$.

b) 1.84 g (0.01 mole) ester VII was dissolved in 30 ml 50% aqueous dioxane, and 2.4 g (0.015 mole) Br_2 in 4 ml 85% AcOH added with stirring over 2 hr. The solvents were then distilled off under reduced pressure. The solid was then separated off, washed with water, recrystallized from 50% EtOH with the addition of Na_2CO_3 (bromothymol blue) followed by acidification with HCl. Yield 2.0 g (76%). Identified by mixed mp.

2-Bromo-3-hydroxy-γ-prone. 1.12 g (0.01 mole) VIII was dissolved in 11 ml 50% aqueous dioxane, and held at 0°, 2.4 g (0.015 mole) Br_2 in 1.0 ml 85% AcOH containing 1.2 g fused NaOAc, added over a period of 2.5 hr, the reaction products treated with 1% aqueous $NaHCO_3$, and the solvent then distilled off under reduced pressure. The solid was separated off and washed with water, yield 1.24 g (65%), mp 182° C (decomp) [8]. It gave a red color with 1% aqueous $FeCl_3$, and a reddish violet color with an ethanolic solution of $FeCl_3$.

Ethyl comanate (ethyl-γ-pyrone-2-carboxylate) (XIV). The starting monoethyl ester of chelidonic acid XIII was prepared as described in [9]. In the flask of the apparatus (see synthesis of ester VII) was put a dry mixture of 20 g XIII and 2.5 Cu powder, which was then heated for 2 hr in a metal bath, a cut bp 220°-230° C (5-10 mm) being taken, and crystallized from 50% EtOH. Yield 6.8 g (60%), mp 102° C [9, 13].

The acid sulfate of ethyl comanate XVII was prepared from a solution of 0.84 g ester XIV in 15 ml benzene, 0.28 ml H_2SO_4 (d 1.84) being added, and the whole heated and boiled to give a viscous transparent mass. The products were kept under petrol ether for 1.5 months in a refrigerator, the petrol ether being decanted off from time to time, and the white solid precipitate formed was separated and worked up as described in [5]. The salt was highly hygroscopic Yield 1.0 g (80%). Found: equiv. 260. Calculated for $C_8H_8O_4H_2SO_4$: equiv. 266.

Comanic acid (γ-pyrone-2-carboxylic acid) (XV). A solution of 8.0 g XIV in 12 ml H_2SO_4 (d 1.84) was heated for 4 hr on a boiling water bath, the reaction products then decomposed with ice, and the solid recrystallized from EtOH-dioxane (1:1), yield 4.1 g (63%), mp 250° C (water) [13]. The compound was soluble in boiling EtOH and dioxane, slightly soluble in cold water. Found: equiv. 138. Calculated for $C_6H_4O_4$: equiv. 140.

Acid sulfate of comanic acid (XVIII). A solution of 1.4 g XV in 2.1 ml H_2SO_4 (d 1.84) was heated at 120° C. The white precipitate was separated after keeping the reaction products under petrol ether in a refrigerator for 3 days, after which it was worked up as described in [5]. Yield 0.9 g (85%). Found: equiv. 236. Calculated for $C_6H_4O_4H_2SO_4$: equiv. 238.

Brominated acid (x-bromo-γ-pyrone-2-carboxylic acid) (XVI). 2.8 g (0.02 mole) XV was dissolved in 56 ml 50% dioxane, held at 60° C (bath) and 3.2 g (0.02 mole) Br_2 in 5 ml AcOH added over 6 hr. Excess solvent was then distilled off under reduced pressure, at room temperature, the solid separated off next day, and washed with water. Yield 1.3 g (30%), mp 230° C (decomp, 50% EtOH). Found: C 32.60; H 1.65; Br 35.80%. Equiv. 217. Calculated for $C_6H_3BrO_4$: C 32.87; H 1.36; Br 36.53%. Equiv. 219.

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