257. *Substitution in the γ-Pyrone Nucleus: Derivatives of Pyromeconic Acid.*

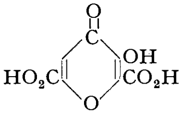
By Edwin L. Shimmin and Frederick Challenger.

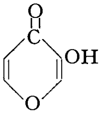
The bromo- and amino-derivatives of pyromeconic acid have been examined with regard to their possible use as synthetic reagents.

An improved method of bromination is described and evidence suggested for the orientation of the nitro- and amino-derivatives of pyromeconic acid.

The acetyl, benzoyl, and benzenesulphonyl derivatives of aminopyromeconic acid have also been prepared.

Dry distillation of anhydrous meconic acid (I) with copper-bronze causes the loss of two carboxyl groups from one molecule of the acid (Robiquet, *Annalen*, 1833, **5**, 102; Ihlée, *ibid.*, 1877, **188**, 31; Borsche, *Ber.*, 1916, **49**, 2544; Peratoner and Leone, *Gazzetta*, 1894, **24**, ii, 78) producing at best a 45% yield of pyromeconic acid (II). We find that, under reduced pressure, a mixture of 43% pyromeconic acid and 57% comenic acid (III) results, which is analogous to the increase in yield of comanic acid when chelidonic acid (IV) is also distilled in vacuum (Haitinger and Lieben, *Monatsh.*, 1885, **6**, 279). Bromopyromeconic acid was prepared by the methods of Brown (*Annalen*, 1852, **84**, 41) and Compagno (*Atti R. Accad. Lincei*, 1908, **17**, i, 78), and by numerous variations of the known methods of bromination, but the extremely low yields indicated that oxidation rather than bromination was favoured by acid solutions. By the use of buffer solutions the pH was adjusted to give yields as high as 85%, a result of importance in view of the high cost of meconic acid. This method has also been successfully applied to the preparation of bromokojic acid (Barnard, Thesis, Leeds, 1947).


(I.)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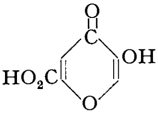
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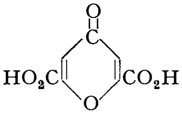
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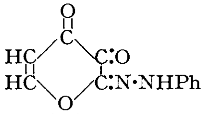
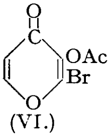
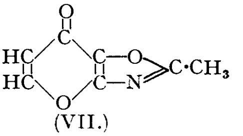

(V.)

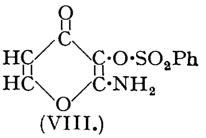
The bromine atom in bromopyromeconic acid is completely inert, owing to the pronounced effect of the unsaturated ring, disintegration taking place in all cases before any reaction occurred. The hydroxyl group behaves normally, yielding an *acetyl* derivative (VI).

The nitration of pyromeconic acid was studied, nitric acid of various concentrations and nitrous fumes in various media and at different temperatures being employed. The yield was not improved by the use of fuming nitric acid, and concentrated sulphuric acid increased the rate of oxidation at the expense of nitration. Also, oxidation and not nitration occurred at temperatures below 34°, while partial nitration took place during the course of the violent reaction above this temperature. Urea (0·1 g. to 1 g. of pyromeconic acid) moderated the violence of the reaction to some extent but gave no increase in yield, whilst if 0·2 g. or more of urea was present the vigorous reaction did not take place below 36° or higher, and oxidation was favoured. The method finally adopted was a modification of that of Ost (*J. pr. Chem.*, 1879, **19**, 189), who had already prepared the explosive sodium and silver salts (*loc. cit.*). The *ferric* salt was also found to be explosive. The silver atom in silver nitropyromeconate resisted all attempts at substitution. The O-*methyl* derivative was prepared by means of diazomethane.

Electrolytic and catalytic methods of reduction of nitropyromeconic acid to the amino-compound being found unsuitable, this compound was isolated as the hydrochloride by Ost's method (*loc. cit.*), which, though laborious, gave a 75% yield. The usual methods of diazotisation were tried without success, resulting only in oxidation and disintegration of the molecule. There was no evidence of the formation of an internal diazo-oxide which might have been expected owing to the presence of the *o*-hydroxyl group.


(VI.)


(VII.)


(VIII.)

Aminopyromeconic acid reacts readily with acetic anhydride and, as would be expected, both the hydroxyl and the amino-group are involved. The product appears to be 2-*methyl-*

oxazolo(4 : 5-2′ : 3′)*pyrone* (VII). Benzoylation of both groups proceeded normally in very weak alkaline solution, though in pyridine a tar was produced. Mild hydrolysis with dilute alkali removed the acyl group attached to the hydroxyl, but prolonged alkaline hydrolysis was required to remove the *N*-benzoyl group, in the course of which there was some fission of the ring.

The O-*benzenesulphonyl* derivative (VIII) has the acyl group attached to hydroxyl. The acylation was carried out in a saturated solution of sodium hydrogen carbonate, it being found that the sensitive γ-pyrone ring was rendered even more so in this compound; the use of pyridine as a medium caused vigorous decomposition and formation of a tar. Very dilute sodium hydroxide, of a concentration usually without action on these compounds, produced immediate disintegration giving hydroxyacetone.

Since many derivatives of pyromeconic acid contain the substituent in the 2-position (Files and Challenger, *J.*, 1940, 665), it seemed probable that the nitro- and the amino-group also occupy this 2-position. The composition of the acetyl derivative is in agreement with the formula (VII) which requires the NH_2 in the 2-position. Nitropyromeconic acid was decomposed on heating with acetyl chloride for 1 hour or on warming with acetic anhydride. The yellow colour, like that of 2-nitro-3-hydroxyfuran (Hodgson and Davies, *J.*, **1939**, **1013**), suggests chelation. The methyl ether was readily prepared by using diazomethane.

More conclusive evidence is afforded by an examination of the scarlet compound $C_{11}H_8O_3N_2$ prepared by Peratoner (*Atti R. Accad. Lincei*, 1902, **11**, i, 250) from pyromeconic acid and benzenediazonium acetate, and considered by him to be a hydrazine derivative with the structure (V). Reaction of 3-hydroxy-γ-pyrones with nitrous acid and diazonium salts occurs in the 2-position and is accepted as a proof of the C(OH)⁚CH structure of allomaltol (Yabuta, *J.*, 1924, **125**, 576) and of kojic acid (Corbellini and Gregorini, *Gazzetta*, 1930, **60**, 244). Maltol, containing the group C(OH)⁚C(CH_3), does not react with these reagents (Peratoner and Tamburello, *ibid.*, 1906, **36**, i, 41).

The scarlet compound, on reduction with tin and hydrochloric acid, gave aminopyromeconic acid, identified by its colour reaction with ferric chloride and by the m. p. (182°) of its dibenzoyl derivative. It is therefore concluded that both the amino- and the nitro-group occupy the 2-position.

EXPERIMENTAL.

2-*Bromopyromeconic Acid.*—(A) Bromine (3·5 g.) was dissolved in saturated sodium acetate solution (100 c.c.) and 75 c.c. of this solution added at 0° to a solution of pyromeconic acid (2 g.) in glacial acetic acid (5 c.c.). After 1 hour the bromopyromeconic acid (1·8 g.) was filtered off and recrystallised from alcohol.

(B) A solution of pyromeconic acid (2 g.) in orthophosphoric acid (12 c.c.) was treated at 0° with the above bromine solution (85 c.c.). The yield after recrystallising from alcohol was 2·87 g. Attempts to remove the bromine atom or to cause ring-linkage by reaction with silver, silver oxide, silver cyanide, copper-bronze, sodium thiocyanate, sodium and methyl iodide, and aniline failed, although various solvents, temperatures and conditions, including heating in sealed tubes, were tried.

2-*Bromo*-O-*acetylpyromeconic Acid.*—2-Bromopyromeconic acid (0·5 g.) and acetyl chloride (5 c.c.) were refluxed for 5 hours, and most of the excess acetyl chloride distilled off. The colourless solid obtained on cooling, when recrystallised from benzene–light petroleum, had m. p. 99°, and was very soluble in chloroform, benzene, and water but sparingly soluble in ether; long boiling with water was required before hydrolysis was effected, and a coloration obtained with ferric chloride (Found: Br, 33·7; Ac, 18·4. $C_7H_5O_4Br$ requires Br, 34·4; Ac, 18·45%).

2-*Nitropyromeconic Acid.*—Ost's method (*loc. cit.*) was modified to obtain consistent yields; pyromeconic acid (2 g.) was dissolved in glacial acetic acid (6 c.c.) in a large tube (roughly 9″ × 1″) and immersed in ice–salt, nitric acid (*d* 1·41; 1·5 c.c.) being added with shaking until the nitrate had been precipitated. The tube was then cautiously warmed over a small flame to start a strictly localised reaction, the tube being again plunged into the freezing mixture as soon as brown fumes were observed. The reaction, though very violent, was not explosive and gave a yield of 0·8 g. The *ferric* salt was obtained by adding a concentrated aqueous solution of ferric chloride to a cold saturated solution of the sodium salt. Great care must be exercised, since the precipitate is very soluble in slight excess of ferric chloride. The dry red salt is explosive on warming, soluble in alcohol, but sparingly in water.

Nitropyromeconic Acid Methyl Ether.—Nitropyromeconic acid (8 g.) was suspended in dry ether. excess of diazomethane in ether (160 c.c.) added with shaking, and the mixture left in the refrigerator overnight. An orange powder (8·4 g.) was obtained, m. p. 88° (decomp.), insoluble in ether and benzene, sparingly soluble in water but more soluble in alcohol and acetone (Found: C, 41·9; H, 3·4; N, 8·7, $C_6H_5O_5N$ requires C, 42·1; H, 2·9; N, 8·2%).

2-*Methyloxazolo*(4 : 5-2′ : 3′)*γ-pyrone* (VII).—Aminopyromeconic acid hydrochloride (0·7 g.) was dissolved in acetic anhydride (8 c.c.) and refluxed for 3 hours, the excess acetic anhydride being then distilled off, leaving a mass of colourless crystals which were dried in a vacuum desiccator and recrystallised from chloroform; m. p. 137° (Found: C, 55·82; H, 3·3; N, 9·25; Ac, 27·8. $C_7H_5O_3N$ requires C, 55·65; H, 3·3; N, 9·3; Ac, 28·5%). They were insoluble in benzene, ether, and light petroleum, but easily soluble in acetone, chloroform, alcohol, and water. The cold aqueous solution gave no coloration with ferric chloride even after long standing, and at least 30 minutes' boiling with water was required before hydrolysis was noticeable. Refluxing for 3 hours in presence of hydrochloric acid produced crystals of the original amine hydrochloride.

ON-*Dibenzoylaminopyromeconic Acid.*—The hydrochloride (0·5 g.) was dissolved in ice-water (20 c.c.), and benzoyl chloride added with vigorous shaking. An ice-cold N-solution of sodium hydroxide was added dropwise to maintain faint alkalinity. The white precipitate obtained after 20 minutes was redissolved in a few drops of alkali, and the mixture filtered and acidified with dilute hydrochloric acid, a white solid being obtained. This was separated, shaken several times with ether, and recrystallised from alcohol. The colourless crystals, m. p. 182°, were very soluble in acetone, sparingly in hot water, and insoluble in ether and benzene; yield, 0·54 g. (Found: C, 68·6; H, 3·9; N, 4·1. $C_{19}H_{13}O_5N$ requires C, 68·1; H, 3·9; N, 4·1%).

Benzamidopyromeconic Acid.—The dibenzoyl derivative was dissolved in very dilute sodium hydroxide, heated for 10 minutes on the steam-bath, giving a bright yellow solution, and then acidified with dilute hydrochloric acid, giving a white crystalline solid on cooling. This was recrystallised from alcohol in which it was sparingly soluble; m. p. 232° (decomp.). The aqueous solution gave a strong violet coloration with ferric chloride, indicating the presence of phenolic hydroxyl (Found: C, 61·95; H, 4·1; N, 5·5. $C_{12}H_9O_4N$ requires C, 62·3; H, 3·9; N, 6·06%). Treatment with benzoyl chloride and alkali reconverted this compound into the dibenzoyl derivative.

O-*Benzenesulphonylaminopyromeconic Acid* (VIII).—Aminopyromeconic acid hydrochloride (0·5 g.) in ice-water (5 c.c.) and cold saturated sodium hydrogen carbonate solution (10 c.c.) was treated with benzenesulphonyl chloride (1·5 c.c.), the mixture being kept in ice–salt. The white precipitate, when recrystallised from hot dilute hydrochloric acid and again from water, had m. p. 169° (yield 0·64 g.). With pyridine as solvent there was no reaction in the cold, but at room temperature vigorous decomposition occurred with production of tar. Prolonged acid hydrolysis liberated the parent amine from the compound, which, since it gave no coloration with ferric chloride, was clearly an O-*benzenesulphonyl* derivative (Found: C, 49·8; H, 3·4; S, 12·0; N, 5·6. $C_{11}H_9O_5NS$ requires C, 49·45; H, 3·4; S, 12·0; N, 5·25%).

The benzenesulphonyl derivative in water was boiled under reflux, and sodium hydroxide added dropwise during 10 minutes. The mixture was then acidified and concentrated. It gave a yellow dinitrophenylhydrazone, which was washed with aqueous sodium carbonate to remove any pyruvic acid 2 : 4-dinitrophenylhydrazone. It then had m. p. 299° and gave a deep blue-violet colour with alcoholic sodium hydroxide. These reactions indicate the presence of hydroxyacetone. Under the same conditions aminopyromeconic acid was stable during 30 minutes.

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