

Anal. Calcd. for $C_8H_{11}O_2N_2Br$: C, 38.86; H, 4.49; N, 11.34. Found: C, 39.12; H, 4.28; N, 11.17.

4-Keto-3,4-dihydro-2-ethoxy-5-bromopyrimidine.—To a solution of 16.5 g. of 2,4-dichloro-5-bromopyrimidine in 10 cc. of absolute ethyl alcohol was carefully added 5.89 g. of sodium in 50 cc. of alcohol. After the vigorous reaction had subsided, the reaction mixture was refluxed for two hours, filtered, and the alcohol removed under diminished pressure on a steam-bath. The residue was diluted with water and extracted with ether; the ether extract yielded 2.5 g. of 2,4-diethoxy-5-bromopyrimidine. On acidification of the aqueous extract with acetic acid 4-keto-3,4-dihydro-2-ethoxy-5-bromopyrimidine immediately precipitated. This was filtered and recrystallized from water; it separated as colorless needles; yield 8.4 g.; sintered at 160° and melted at 163° . It gave a Wheeler-Johnson color test similar to that of isocytosine when the bromine was removed by aspiration in the cold.

Anal. Calcd. for $C_8H_{11}O_2N_2Br$: C, 32.88; H, 3.22; N, 12.78; OC_2H_5 , 20.57. Found: C, 33.28; H, 3.17; N, 12.93; OC_2H_5 , 20.53.

Summary

The alkoxy groups in 2,4-dialkoxypyrimidines have been found to be sensitive toward alkali and in the particular case of 2,4-dialkoxy-5-bromopyrimidine, the alkoxy group in the 4 position was hydrolyzed to give the intermediate lactam, 4-keto-3,4-dihydro-2-alkoxy-5-bromopyrimidine, which under the alkaline conditions suffered ring rupture to yield the sodium salt of α -bromo- β -alkylisoureidoacrylic acid. This salt was readily cyclized to the lactam by acid. Ammonia was also found to interact with 2,4-dialkoxypyrimidines and with 2,4-dimethoxy-5-bromopyrimidine; replacement of the methoxy group in 4 position by an amino group was effected. These reactions suggest new methods of approach for the synthesis of naturally occurring pyrimidines.

WASHINGTON, D. C.

RECEIVED JULY 24, 1933

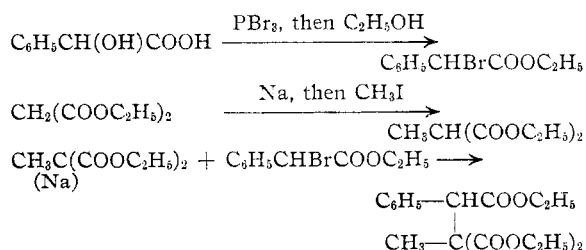
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VASSAR COLLEGE]

α, α' -Dimethyl- α -phenylsuccinic Acid

BY H. MARJORIE CRAWFORD

In some earlier work, Smith and Crawford¹ obtained by the oxidation of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4 an acid which they regarded as α, α' -dimethyl- α -phenylsuccinic acid. This acid was not previously known, and the present paper is the result of attempts to synthesize it.

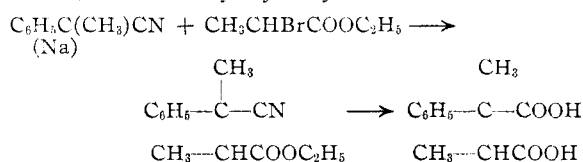
Bone and Sprankling² give a review of methods for the preparation of substituted succinic acids. Two of the methods they mention were tried without success. The first method, heating the corresponding dibromide with potassium cyanide, gave only tars. In the second trial the following series of reactions was carried out



This triester, which was not known, was identified by analysis, molecular weight determinations, and by hydrolysis to α -methyl- α' -phenylsuccinic acid

which had previously been made.³ Attempts to introduce another methyl group by means of sodium and methyl iodide were unsuccessful.

The method which finally gave the desired acid was the reaction between α -bromopropionic ester and the sodium derivative of α -phenylpropionitrile, followed by hydrolysis.



The acid, as first obtained by hydrolysis, melted around 145° . The two racemic forms, when finally separated, melted at 170 – 172° and 159 – 160° . The higher melting form is identical with the acid obtained by the oxidation of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4.¹

No attempt was made to resolve the two acids into optically active forms.

Experimental

Mandelic Acid.—This was prepared from benzaldehyde and sodium cyanide by the method outlined in "Organic Syntheses."⁴

(3) Zelinsky, *Ber.*, **24**, 1878 (1891).

(4) "Organic Syntheses," John Wiley and Sons, Inc., New York, Vol. VI, p. 58.

(1) Smith and Crawford, *THIS JOURNAL*, **50**, 860 (1928).

(2) Bone and Sprankling, *J. Chem. Soc.*, **75**, 839 (1899).

Ethyl Ester of α -Bromophenylacetic Acid.—This was prepared from mandelic acid by the method of Hell.⁵

Methylmalonic Ester.—This was prepared from methyl iodide, sodium and malonic ester.⁶

1-Phenylpropane-1,2,2-tricarboxylic Acid, Triethyl Ester.—This ester was obtained from methylmalonic ester, sodium and the ethyl ester of α -bromophenylacetic acid in 45% yield, b. p. 210–217° (17 mm.).

Anal. Calcd. for $C_{15}H_{24}O_8$ (336.2): C, 64.3; H, 7.2. Found: C, 64.0, 64.0; H, 6.9, 7.0. *Mol. wt.* Subs., 0.1606, 0.1606; benzene, 14.728, 23.857; ΔT , 0.166, 0.108. *Mol. wt.*, 336.3, 319.3.

α -Methyl- α' -phenylsuccinic Acid.—The triester, 6.5 g., was hydrolyzed by boiling for five hours with 30 cc. of alcohol, 12 g. of potassium hydroxide and 15 cc. of water. A white acid resulted which melts at 169–172°, the melting point recorded for this acid which had been obtained by a different method.³

Anal. Calcd. for $C_{11}H_{12}O_4$ (208.1): C, 63.4; H, 5.8. Found: C, 63.9, 63.5; H, 5.9, 5.9. *Eq. wt.* Subs., 0.1500; NaOH (0.09361 *N*) 16.8 cc. = 0.06295 g. NaOH. *Eq. wt.*, 95.5.

2-Phenylbutane-2,3,3-tricarboxylic Acid, Triethyl Ester.—The reaction of the triester prepared above with sodium and methyl iodide was carried out in the usual manner. There resulted a 50% yield of a compound boiling at 213–216° (20 mm.).

Anal. Calcd. for $C_{19}H_{26}O_6$ (350.2): C, 65.1; H, 7.5. Calcd. for $C_{18}H_{24}O_6$ (336.2): C, 64.3; H, 7.2. Found: C, 64.7; H, 7.2 (average of five analyses). *Mol. wt.* Subs., 0.18055, 0.18055; benzene, 13.812, 19.129; ΔT , 0.199, 0.152. *Mol. wt.*, 336.8, 318.0.

Hydrolysis of this ester by potassium hydroxide in alcohol and water gave an acid melting at 166–167°, which by mixed melting point (166–168°), analyses (C, 63.6; H, 6.2, average of five), and equivalent weight determinations (99.9, average of five) proved to be identical with the acid obtained from the triester which had not been methylated.

α -Bromopropionic Ester.—The ester was prepared according to the method of Zelinsky.⁷

Phenylacetonitrile.—This was prepared from benzyl chloride and sodium cyanide by the method described in "Organic Syntheses."⁸

α -Phenylpropionitrile.—After several unsuccessful attempts to introduce a methyl group into phenylacetonitrile by means of methyl iodide and sodium or sodium ethylate, a modification of the methods of Bodroux and Taboury⁹ and of Meyer¹⁰ gave a 66% yield of α -phenylpropionitrile. A stream of nitrogen (dried by sulfuric acid and potassium hydroxide) was passed through the reaction flask to provide an inert atmosphere. A motor stirrer was used to assure complete reaction. 60 g. (1.5 moles) of powdered sodamide was suspended in 400 cc. of dry ether and 117 g. (1 mole) of phenylacetonitrile in 100 cc. of dry ether was added, the addition requiring about forty-five minutes.

The mixture was then heated on a hot-plate for three hours, cooled, and 213 g. (1.5 moles) of methyl iodide in 100 cc. of dry ether dropped in very slowly. On standing overnight the dark brown color of the sodium derivative faded to tan. Water was added cautiously to dissolve the heavy precipitate of sodium iodide. The ether solution, after drying over calcium chloride, was treated with 4 g. of sodium dissolved in 75 cc. of absolute alcohol, and 50 g. of benzaldehyde. After standing for two days, the yellow gelatinous mass was treated with water, and the ether extract dried. After removing the ether on a steam-bath, the material was fractionated under reduced pressure. The condensation product of benzaldehyde and unchanged phenylacetonitrile (the nitrile of α -phenylcinnamic acid) remained as a high boiling residue (above 130° (20 mm.)). The low boiling material was then fractionated at atmospheric pressure, a typical run being: I, up to 192°, 4.5 g. (discarded); II, 192–220°, 62.0 g.; III, 220–230°, 62.5 g. Fraction II was then washed with sodium bisulfite solution and on refractionation gave 24.0 g. of material boiling at 220–230°. This made a total of 86.5 g., or 66% of α -phenylpropionitrile recovered.

Anal. Calcd. for C_9H_9N : N, 10.7. Found: N, 10.9.

The nitrile was hydrolyzed to the corresponding acid and the silver salt prepared.

Anal. Calcd. for $C_9H_9O_2Ag$: Ag, 42.0. Found: Ag, 41.5. *Eq. wt.* Subs., 0.5149; NaOH (0.1031 *N*) 31.4 cc. = 0.1295 g. NaOH. *Eq. wt.*, 159. Calcd. for $C_9H_9O_2$: 150.

α -Methyl- β -phenyl- β -cyanobutyric Acid, Ethyl Ester.—This compound was prepared in the same way as α -phenylpropionitrile from 32 g. (0.8 mole) of powdered sodamide in 300 cc. of dry ether, 78.6 g. (0.6 mole) of α -phenylpropionitrile in 100 cc. of dry ether, and 145 g. (0.8 mole) of α -bromopropionic ester. The mixture was heated for two hours after the addition of the α -bromopropionic ester, and allowed to stand overnight. After dissolving the sodium bromide with water, the ether extract was dried over anhydrous sodium sulfate, the ether removed on a steam-bath, and the mixture fractionated under reduced pressure. The nitrile ester boils at 172–173° (14 mm.) and has a specific gravity of 1.0591 at 15°; yield 15%.

Anal. Calcd. for $C_{14}H_{17}NO_2$ (231.1): N, 6.1. Found: N, 7.2 (average of five analyses). *Mol. wt.* Subs., 0.2050, 0.3757; benzene, 17.580, 17.580; ΔT , 0.261, 0.443; *mol. wt.*, 228.5, 246.8.

α, α' -Dimethyl- α -phenylsuccinic Acid.—Hydrolysis of the half ester half nitrile was accomplished very easily by boiling for about eighteen hours with constant boiling hydrobromic acid. The yields were from 90–97%. The acid obtained was chemically pure, as was shown by analyses and equivalent weight determinations, but since it consisted of a mixture of two racemic acids, the melting points varied, and recrystallization was not sufficient to separate them. This separation is best brought about by converting the acids to their calcium salts and fractionally crystallizing these. The first fourth of the salt separating, on reconversion to the acid, gives the lower melting compound, and the last fourth gives the higher melting compound. The middle half can be worked over to yield more of the acids. After numerous recrystallizations from 25% alcohol

(5) Hell, *Ber.*, **28**, 2447 (1895).

(6) Michael, *J. prakt. Chem.*, [2] **72**, 551 (1905).

(7) Zelinsky, *Ber.*, **20**, 2026 (1887).

(8) "Organic Syntheses," 1922, Vol. II, p. 9.

(9) Bodroux and Taboury, *Compt. rend.*, **150**, 531 (1910).

(10) Meyer, *Ann.*, **250**, 124 (1889).

the two compounds were obtained pure. They are both very soluble in alcohol and ether, slightly soluble in benzene, and soluble in water only on boiling for considerable time. They then crystallize from the water very slowly. The higher melting form is a white powder or small, hard spheres. The lower melting form is distinctly crystalline.

Anal. Calcd. for $C_{12}H_{14}O_4$ (222.1): C, 64.8; H, 6.35. (*Mixture of two forms*) Found: C, 64.4, 64.7, 64.8; H, 6.4, 6.4, 6.7. *Eq. wt.* Subs., 0.3017; NaOH (0.1013 *N*) 26.8 cc. = 0.1086 g. NaOH. *Eq. wt.*, 111.1. Silver salt: 0.4099 g. gave 0.2002 g. Ag. *Eq. wt.*, 113. (*Lower melting form*, m. p. 159–160°.) Found: C, 64.5, 64.7; H, 6.4, 6.5. Silver salt: 0.5001 g. gave 0.2436 g. Ag. *Eq. wt.*, 113.6. (*Higher melting form*, m. p. 170–172°.) Found: C, 64.3, 64.3; H, 6.4, 6.3. Silver salt: 0.3333 g. gave 0.1628 g. Ag. *Eq. wt.*, 113. *Eq. wt.* Subs., 0.2011; NaOH (0.1031 *N*) 18.1 cc. = 0.0746 g. NaOH. *Eq. wt.*, 107.8.

Acid from the oxidation¹ of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4, m. p. 170–172°; synthetic acid, m. p. 170–172°; mixed melting point, m. p. 170–171°.

The author wishes to thank Dr. W. L. Evans and the Department of Chemistry of the Ohio State University for the use of their laboratory during the last week of experimental work on this problem.

Summary

The identity of the acid obtained by the oxidation of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4 has been established.

The two racemic forms of α, α' -dimethyl- α -phenylsuccinic acid have been prepared and characterized.

Two other new compounds, 1-phenylpropane-1,2,2-tricarboxylic acid, triethyl ester and α -methyl- β -phenyl- β -cyanobutyric acid, ethyl ester, have been prepared and described.

POUGHKEEPSIE, N. Y.

RECEIVED AUGUST 2, 1933

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diarsyls. VI. 3,3',3'',3'''-Tetranitro-, 3,3',3'',3'''-Tetra-amino- and 3,3',3'',3'''-Tetra-(acetylamino)-tetraphenyldiarsyl

By F. F. BLICKE, U. O. OAKDALE¹ AND J. F. ONETO

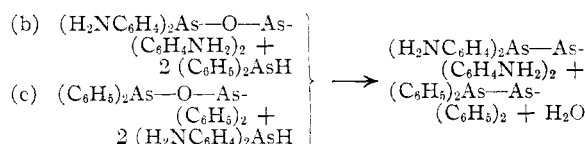
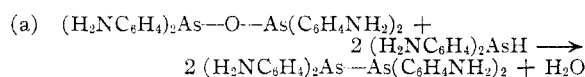
A number of years ago Michaelis² heated 3,3'-dinitrodiphenylarsinic acid with phosphorous acid for a short time and stated that he obtained 3,3',3'',3'''-tetranitrotetraphenyldiarsyl; a longer period of interaction, according to him, yielded the corresponding tetraamino diarsyl which he then acetylated to the tetraacetyl derivative.

While Michaelis undoubtedly obtained the tetranitrodiarsyl, although his method is an unsatisfactory one since at elevated temperatures the nitro groups also are reduced, it is certain in view of our experiments that he was mistaken in his claims regarding the isolation of the other two diarsyls.

3,3'-Dinitrodiphenylarsinic acid was converted into the dinitrodiphenylchloroarsine and the latter into the corresponding hydroxy arsine. This substance, dissolved in acetic acid, is transformed rapidly into the diarsyl when treated with hypophosphorous acid at ordinary temperature.

3,3',3'',3'''-Tetraaminotetraphenyldiarsyl was prepared by four methods: (a) reaction between 3,3',3'',3'''-tetraaminotetraphenylarsyl oxide and 3,3'-diaminodiphenylarsine; (b) interaction be-

tween the above mentioned oxide and diphenylarsine; (c) reaction of tetraphenylarsyl oxide and 3,3'-diaminodiphenylarsine; (d) reduction of 3,3'-diaminodiphenylarsinic acid with hypophosphorous acid.



In methods b and c a mixture of 3,3',3'',3'''-tetraaminotetraphenyldiarsyl and tetraphenyldiarsyl was obtained. However, separation of the two compounds was easily carried out by extraction of the mixture in the presence of benzene with dilute hydrochloric acid; the amino compound dissolved in the aqueous acidic layer in the form of a water-soluble hydrochloride while the tetraphenyldiarsyl entered into the benzene layer. The isolation of the two diarsyls in yields as high as 85% proves that the unsymmetrical diarsyl, 3,3'-diaminotetraphenyldiarsyl, which might be

(1) Parke, Davis and Company Fellow.

(2) Michaelis, *Ann.* **321**, 149 (1902).