

N-Cyclohexyl- β -benzoylpropionamide (XI), m.p. 109–111°, yield 50%, recrystallized from aq. ethanol. *Anal.* Calcd. for $C_{18}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.33; H, 7.79; N, 5.06.

N,N-Dimethyl- β -benzoylpropionamide (XII), m.p. 55–55.5°, recrystallized from ether; yield 69%. *Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.49; H, 7.37; N, 6.93.

N-Benzyl-N-methyl- β -benzoylpropionamide (XIII), m.p. 68–70°, recrystallized from benzene–petroleum ether; yield 98%. *Anal.* Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.00; H, 6.69; N, 4.93.

N-Cyclohexyl- γ -phenylbutyramide.—a. A 0.5-g. sample of III was dissolved in 25 ml. of methanol and shaken under 45 lb./in.² pressure of hydrogen in the presence of 10% Pd-on-charcoal catalyst. The product was recrystallized from ether, m.p. 91–92°; infrared spectrum, $\nu_{C=O}$, 1675 cm^{-1} ; ν_{N-H} , 3440 cm^{-1} (CCl_4 soln.).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.30; H, 9.45; N, 5.71. Found: C, 78.45; H, 9.42; N, 5.79.

b. This amide also was prepared from γ -phenylbutyric acid *via* the acid chloride in 53% yield according to the method previously outlined for γ -phenylbutyromorpholide.⁵ LINCOLN, NEBR.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Sodium β -Formyl- β -keto- α -nitropropionate from the Reaction of Mucochloric Acid with Sodium Nitrite¹

BY PAUL E. FANTA, ROBERT A. STEIN AND R. M. W. RICKETT

RECEIVED FEBRUARY 26, 1958

Sodium β -formyl- β -keto- α -nitropropionate (III) has been isolated from the reaction of mucochloric acid with sodium nitrite in aqueous alcohol at 35°. Evidence for the structure of III was obtained by reaction with phenylhydrazine to give a stable phenylosazone and reaction with *o*-phenylenediamine to give 2-nitromethylquinoxaline, which was oxidized to the known quinoxaline-2-carboxylic acid.

The reaction of mucobromic acid (Id, *cis*- α,β -dibromo- β -formylacrylic acid) with metal nitrites was studied many years ago by Hill and his students,² who reported in a series of papers the isolation and characterization of sodium nitromalonaldehyde (IV), several other salts of nitromalonaldehyde and the dipotassium salt of α,α,β -trinitropropionaldehyde (VI). No other products have been isolated from the reaction of the mucohalic acids (Ia-d) with nitrite.

The usefulness of sodium nitromalonaldehyde as an intermediate in synthetic organic chemistry³ later stimulated a search for a cheaper and more efficient method of preparation. A summary of the studies of the preparation of nitromalonaldehyde by the reaction of the mucohalic acids is presented in Table I. Although the yields re-

ports than the acids which have β -chloro atoms (Ia and c).

Although mucochloric acid (Ia) reacts readily with sodium nitrite in aqueous alcohol and the starting material is not recoverable, previous reports of this reaction have accounted for only a very small fraction of the starting material in the form of the product sodium nitromalonaldehyde.

In the present paper we describe the isolation and characterization of a new compound, sodium β -formyl- β -keto- α -nitropropionate (III), from the reaction of mucochloric acid with sodium nitrite, and discuss the significance of this observation with regard to a rational mechanism for the reaction of the mucohalic acids with nitrite.

Mucohalic acid treated with sodium nitrite in aq. alcohol at 54–60°, β -formylacrylic acid	Yield of sodium nitromalonaldehyde claimed, %
Ia, <i>cis</i> - α,β -Dichloro-	"Very small," ⁴ 13 ^{5,6}
Ib, <i>cis</i> - β -Bromo- α -chloro-	26, ⁵ 43 ⁶
Ic, <i>cis</i> - α -Bromo- β -chloro-	"Low" ⁴
Id, <i>cis</i> - α,β -Dibromo-	41, ⁷ 35 ⁵

ported by different authors disagree somewhat, it is evident from these data that the acids which have β -bromo atoms (Ib and d) give significantly higher

(1) This investigation was supported by a research grant CY-2240 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) H. B. Hill and J. Torrey, *Am. Chem. J.*, **22**, 89 (1899); (b) J. Torrey and O. F. Black, *ibid.*, **24**, 452 (1900).

(3) The literature has been surveyed by R. A. Stein, Ph.D. Thesis, Illinois Institute of Technology, June, 1955.

(4) E. Kuh and R. L. Shepard, *THIS JOURNAL*, **75**, 4597 (1953).

(5) C. C. Price and T. L. V. Ulbricht, *J. Org. Chem.*, **22**, 235 (1957).

(6) E. Kuh and H. W. Steward, U. S. Patent 2,606,931 (Aug. 12, 1952).

(7) P. E. Fanta, *Org. Syntheses*, **32**, 95 (1952).

(8) Dr. C. Stuckwisch reported in a private communication to the author that a better yield of nitromalonaldehyde was obtained from mucochloric acid by operating at 45–50°, according to directions appearing in the Ph.D. Thesis of N. M. Sandberg, University of Wichita.

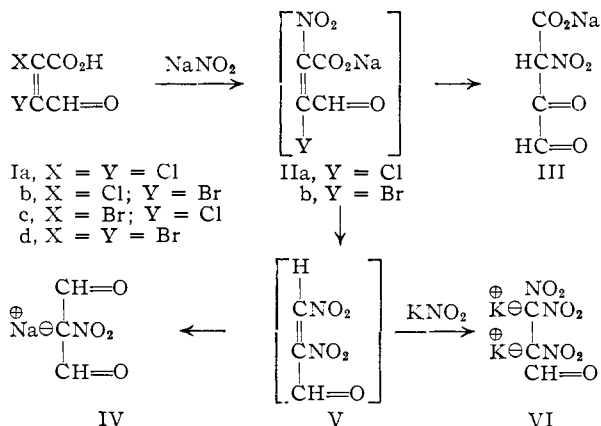
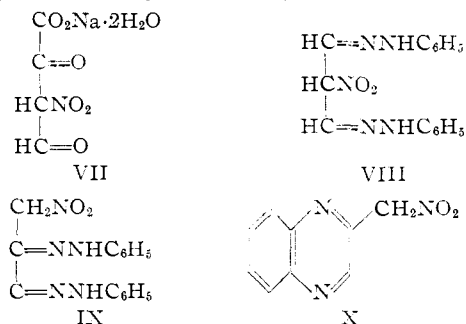


Fig. 1.—Condensed scheme for the reactions of the mucohalic acids with nitrite. Hypothetical intermediates are in brackets.

From the reaction of mucochloric acid with sodium nitrite in dilute alcohol at 35°, a white solid was obtained which had no definite melting point below 300°, and exploded when heated on a spatula over an open flame. Analysis of the material was in agreement with the formula $C_4H_2NO_6Na \cdot 2H_2O$ and the infrared absorption spectrum in a Nujol

mull showed maxima characteristic of H_2O , aldehyde or ketone $C=O$, COO^- and NO_2 .

With S-benzylisothiuronium chloride, the sodium salt gave a good yield of a crystalline product which analyzed for $C_4H_3NO_6 \cdot C_6H_5N_2S$ and had a decomposition point of 114° , which is distinctly different from the 121.5° decomposition point of the S-benzylisothiuronium salt of nitromalonaldehyde. These data suggested that the sodium salt was either III or the isomer, sodium formyl-nitropruvate dihydrate (VII).

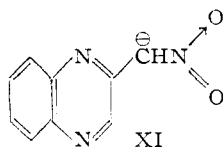


Evidence in favor of structure III was obtained by the reaction with phenylhydrazine in dilute hydrochloric acid to give a crystalline product whose analysis corresponded to the formula $C_{15}H_{15}O_2N_5$. This compound cannot be nitromalonaldehyde bis-(phenylhydrazone), since it is stable in an acidic medium and was recrystallized from boiling alcohol, whereas VIII is reported to be an unstable compound which cyclizes under these conditions to form 4-nitro-3-phenylpyrazole.^{2a} Therefore the phenylhydrazine derivative must be nitropruvate phenyllosazone (IX), obtained from III by decarboxylation preceding or following the reaction with the phenylhydrazine.

Conclusive evidence for structure III was obtained by the reaction with *o*-phenylenediamine in dilute acetic acid to give 2-nitromethylquinoxaline (X). The structure of X, in turn, was demonstrated by oxidation to the known quinoxaline-2-carboxylic acid.

The decarboxylation of III on reaction with either phenylhydrazine or *o*-phenylenediamine is not unexpected, since III is an α -nitro- as well as a β -ketocarboxylic acid. The α -nitrocarboxylic acids are decarboxylated most readily in the form of the anion, while the β -ketocarboxylic acids are decarboxylated most rapidly in the form of the free acid.⁹ Since both mechanisms are available to III, it should undergo decarboxylation with particular readiness, as shown in Fig. 2.

The quinoxaline X is a fairly strong acid, which dissolves in 5% aqueous sodium bicarbonate solution and gives a sharp end-point on titration with 0.1 *N* sodium hydroxide in aqueous alcohol. Such high stability of the anion XI was not anticipated



(9) B. R. Brown, *Quart. Revs.*, 131 (1951).

from the previous literature on the quinoxalines.^{10a,b}

The significance of III with regard to the mechanism of the reaction of nitrite with the mucohalic acids, Ia-d, is illustrated in Fig. 1. Since the mucohalic acids react by substitution at the α -carbon atom with aniline, phenylate ion and hydroxide ion,¹¹ it is reasonable to expect that IIa or b is the initial product of the reaction of Ia-d with nitrite ion.¹² The isolation of III now provides direct evidence for this assumption, since III must be formed by the hydrolysis of IIa.

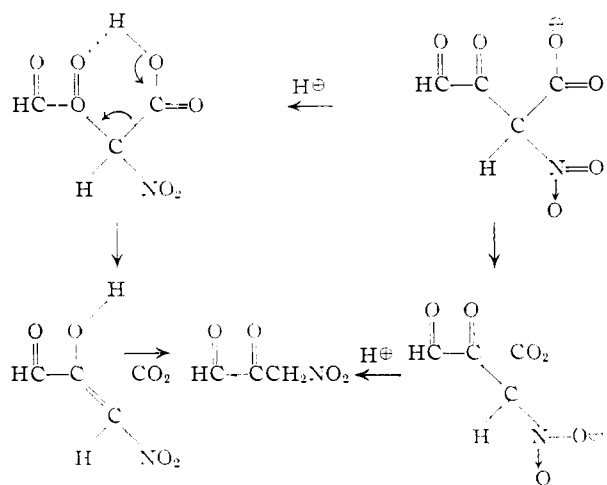


Fig. 2.—Scheme for the decarboxylation of β -formyl- β -keto- α -nitropropionic acid.

The formation of nitromalonaldehyde from IIa or b is a much more complicated reaction, since a decarboxylation, substitution and hydrolysis are required. In such a series of reactions a variety of paths are possible, and research now in progress is designed to elucidate the steps of the reaction leading to the formation of nitromalonaldehyde. Tentatively, it is suggested that intermediate V accounts for the formation of products IV and VI and utilizes most effectively the activation provided by the α -nitro group in the decarboxylation and substitution steps.

In summary, the scheme outlined here for the reaction of a mucohalic acid with nitrite involves first the substitution of a nitro group for the α -halogen, after which the path is determined by the nature of the remaining β -halogen and the conditions of the reaction. Previous studies have shown that where the β -halogen is bromine, the preferred path at 55° leads to nitromalonaldehyde. We have now found that if the β -halogen is chlorine, at 35° in aqueous solution it is hydrolyzed to give sodium β -formyl- β -keto- α -nitropropionate.

(10) (a) Y. T. Pratt, "Heterocyclic Compounds," Vol. 6, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 455; (b) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953, p. 203.

(11) H. H. Wasserman and F. M. Precopio, *THIS JOURNAL*, **74**, 326 (1952); H. H. Wasserman, F. M. Precopio and T. C. Liu, *ibid.*, **75**, 2527 (1953); H. H. Wasserman and F. M. Precopio, *ibid.*, **76**, 1242 (1954).

(12) One of the referees suggested that the reaction may proceed by addition of oxides of nitrogen to the olefinic system. This mechanism seems less likely than nucleophilic attack by nitrite ion, but is not excluded by the presently available data.

Experimental¹³

Mucochloric acid (technical grade) was obtained from the Quaker Oats Co. through the courtesy of Dr. A. P. Dunlop. Two recrystallizations from water (charcoal) gave white plates, m.p. 124–126°.

Sodium β -Formyl- β -keto- α -nitropropionate Dihydrate (III).—A solution of 65.7 g. (0.90 mole) of sodium nitrite in 80 ml. of water was stirred in a 1-l. r.b. flask while a solution of 50.7 g. (0.30 mole) of mucochloric acid in 250 ml. of 95% alcohol was added during the course of 30 minutes. The temperature was maintained at $35 \pm 2^\circ$ by intermittent application of an ice-bath. After stirring for an additional 1.5 hours at 35° , the reaction mixture was cooled to -5° in a salt-ice-bath and the pale yellow solid product was collected on a Buchner funnel and finally dried in a vacuum desiccator over anhydrous calcium chloride. The yield of crude product was 65.7 g. (96% yield). Two recrystallizations from dilute ethanol gave an analytical sample which had no melting point below 300° and exploded when heated on a spatula over an open flame.

Anal. Calcd. for $C_4H_6NO_5Na$: C, 21.93; H, 2.76; N, 6.39. Found: C, 21.63; H, 2.70; N, 6.37.

S-Benzylisothiuronium β -Formyl- β -keto- α -nitropropionate.—A solution of 1.01 g. of S-benzylisothiuronium chloride in 20 ml. of water was added to a solution of 0.91 g. of crude III in 20 ml. of water. The solution was filtered to remove a trace of brown solid and then stored in the refrigerator for 0.5 hour. Scratching the walls of the flask initiated the precipitation of a mass of fine, pale yellow crystals, which were collected and washed with two 5-ml. portions of water. Drying in air gave 0.92 g. of the salt (62% yield), in the form of fine, very light tan clusters. A reproducible decomposition point was obtained on this material by placing the capillary in the melting point bath at 70° , heating it up to 100° in three minutes, then to 110° in two more minutes and finally continuing to raise the temperature at the rate of 2° /minute. In this way a vigorous decomposition was obtained at 114° .

Anal. Calcd. for $C_{12}H_{13}O_5N_3S$: C, 44.03; H, 4.00; N, 12.84. Found: C, 43.73; H, 4.28; N, 13.10.

S-Benzylisothiuronium Nitromalonaldehyde.—A warm solution of 0.78 g. of sodium nitromalonaldehyde monohydrate in 10 ml. of water was mixed with a warm solution of 1.01 g. of S-benzylisothiuronium chloride in 10 ml. of water. Cooling in the refrigerator gave short, thick, light-

(13) All melting points are corrected, unless otherwise stated. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

tan prisms which were collected, washed with two 10-ml. portions of cold water and dried overnight in a vacuum pistol at room temperature, m.p. 120.5 – 121.5° dec.

Anal. Calcd. for $C_{11}H_{13}O_4N_3S$: C, 46.64; H, 4.62; N, 14.83. Found: C, 46.50; H, 4.66; N, 14.91.

Nitropyruvaldehyde Phenylsazone (IX).—To a solution of 1.44 g. of phenylhydrazine hydrochloride in a mixture of 20 ml. of water, 1.5 ml. of concentrated hydrochloric acid and 2 ml. of ethanol was added a solution of 0.66 g. of crude sodium β -formyl- β -keto- α -nitropropionate dihydrate (III) in 10 ml. of water. After 0.5 hour at room temperature a small amount of gummy material was removed by filtration and the solution was allowed to stand for 18 hours at room temperature. The flask then contained a mass of fine, tan, crystalline material. On drying in air this weighed 0.54 (60% yield). It was recrystallized from 20 ml. of 95% ethanol to give flat, tan needles of IX, m.p. 150 – 151° dec.

Anal. Calcd. for $C_{15}H_{15}O_2N_3$: C, 60.59; H, 5.09; N, 23.56. Found: C, 60.95; H, 5.18; N, 23.02.

2-Nitromethylquinoxaline (X).—A solution of 8.64 g. of crude sodium β -formyl- β -keto- α -nitropropionate dihydrate in 160 ml. of water was mixed with a solution of 4.8 g. of *o*-phenylenediamine in a mixture of 16 ml. of acetic acid and 64 ml. of water. The mixture was heated in a steam-chest at 65 – 75° for 1.5 hours and then cooled and filtered to give 3.4 g. (46% over-all yield from mucochloric acid) of crude, tan 2-nitromethylquinoxaline. A sample purified by vacuum sublimation formed bright yellow clusters which turned orange in the m.p. capillary at 100 – 110° and melted to a dark red liquid at 122 – 123° .

Anal. Calcd. for $C_8H_7O_2N_3$: C, 57.14; H, 3.73; N, 22.21; neut. equiv., 189. Found: C, 57.25; H, 3.65; N, 22.39; neut. equiv. by titration in 50% aq. alcohol with 0.1 N aq. sodium hydroxide, using a glass electrode, 192.

Quinoxaline-2-carboxylic Acid.—A mixture of 1.9 g. of crude 2-nitro-methylquinoxaline, 7 g. of potassium permanganate, 1 g. of sodium hydroxide and 200 ml. of water was heated on the steam-bath for one hour. The manganese dioxide was removed by filtration and the filtrate was acidified with concentrated hydrochloric acid to give a precipitate of quinoxaline-2-carboxylic acid, m.p. 210° (the literature value¹⁴ is variously reported as 208–209, 210 and 212°).

(14) Reference 10b, p. 251.

CHICAGO 16, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. XXI. Effect of 3-Substituents on the Optical Stability of Some N-Benzenesulfonyl-N-carboxymethylmesidines

BY ROGER ADAMS AND J. S. DIX¹

RECEIVED FEBRUARY 15, 1958

Expansion of the study of the optical activity of 3-substituted N-benzenesulfonyl-N-carboxymethylmesidines to include the 3-*t*-butyl and 3-methyl derivatives indicates that any inductive effect of an alkyl group apparently is minor. The low optical stability of the *t*-butyl compound may be an unexpected result of steric effects.

The influence of a 4-substituent on the optical stability of N-benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalenes has been demonstrated by previous investigations of these compounds.^{2–4}

To determine the extent to which field effects alone might influence the optical stability of such systems, a series of five compounds having various

m-substituted benzyl groups attached to the 3-position of N-benzenesulfonyl-N-carboxymethylmesidine (I) has previously been studied.⁵ Apparently there is little variation of optical stability with change in field. The minimum and maximum half-lives observed in the various substituted benzyl derivatives studied were 11.3 and 12.3 hr. and the two examples of extreme difference of electronic character of the groups gave essentially the same values; X = CN, half-life 12.1 hr.; and X = CH₃O, half-life 12.3 hr.

(1) University of Illinois Fellow, 1954–1955; Standard Oil of California Fellow, 1955–1957.

(2) R. Adams and R. H. Mattson, *THIS JOURNAL*, **76**, 4925 (1954).

(3) R. Adams and K. V. Y. Sundstrom, *ibid.*, **76**, 5474 (1954).

(4) R. Adams and H. H. Gibbs, *ibid.*, **79**, 170 (1957).

(5) R. Adams and K. R. Brower, *ibid.*, **78**, 663 (1956).