100° *in vacuo* were unsuccessful. When the compound was heated at 111° *in vacuo*, a 77.7-mg. sample lost 39.9 mg. The theoretical loss in weight is 41.7 mg. (carbon dioxide and morpholine). The residue was soluble in water and insoluble in ethanol. It turned dark brown at about 185° and decomposed at 195–200°. This compares favorably with the physical properties reported for 5-hydroxyhydantoin.[7]

Reaction of Alloxan Hydrate with Piperidine.—The above procedure was used with piperidine in place of morpholine; yield of 1-alloxanoylpiperidine monohydrate 50%, m.p. 133–133.5°.

Anal. Calcd. for $C_9H_{13}O_4N_3 \cdot H_2O$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.06; H, 6.13; N, 17.14.

Better yields were obtained by evaporating the reaction mixture to dryness *in vacuo* and recrystallizing the residue from dry methanol–ether. This amide was prepared also from methyl alloxanate and piperidine. Mixed melting points showed no depression.

(7) H. Biltz and M. Kobel, *Ber.*, **54**, 1802 (1921).

Reaction of Alloxan Hydrate with Pyrrolidine.—The above procedure was used with pyrrolidine except that the solution was allowed to stand for two days instead of refluxing for a few minutes. Dry ethanol–ether was added to precipitate the 1-alloxanoylpyrrolidine monohydrate. The latter was recrystallized from methanol; yield 40%, m.p. 121.6–122.7°.

Anal. Calcd. for $C_8H_{11}O_4N_3 \cdot H_2O$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.49; H, 5.78; N, 18.33.

Reaction of Alloxan Hydrate with Dimethylamine.—A solution of 2 g. of alloxan monohydrate in 15 ml. of water was saturated with dimethylamine and the reaction mixture worked up by the general procedure; yield of N,N-dimethylalloxanamide monohydrate 50%, m.p. 126.4–127.3°.

Anal. Calcd. for $C_6H_9O_4N_3 \cdot H_2O$: C, 35.12; H, 5.41; N, 20.48. Found: C, 35.19; H, 5.55; N, 20.38.

This amide was prepared also from methyl alloxanate and dimethylamine. Mixed melting points showed no depression.

PHILADELPHIA 4, PENNA.

[CONTRIBUTION FROM THE U. S. NAVAL ORDNANCE LABORATORY]

The Michael Reaction in Non-alkaline Media. I. The Synthesis of 5-(2-Nitro-1-arylethyl)-barbituric Acids

BY MORTIMER J. KAMLET

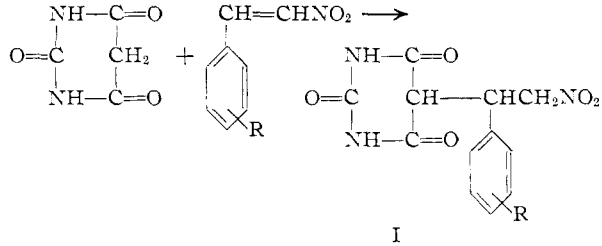
RECEIVED APRIL 2, 1955

Barbituric acid reacts with a series of substituted β-nitrostyrenes in the absence of catalysts to form the 5-(2-nitro-1-arylethyl)-barbituric acids. The structure of these compounds has been established by oxidative degradation to dialuric acid and by conversion to the corresponding arylsuccinic acids on refluxing with concentrated hydrochloric acid.

Ingold[1] has suggested that the rate-determining step in the Michael addition involves a nucleophilic attack by the anion of the adding active methylene compound at the β-carbon atom of the α,β-unsaturated molecule. Since the ionization constants of most pseudo-acidic addenda are so low that only infinitesimal amounts of the anionic species are furnished by dissociation in neutral media, the typical Michael addition requires alkaline catalysis. It would seem, however, that the addition should require no extraneous base in media of higher dielectric constant than those commonly used for this reaction and with an active methylene compound of sufficiently low pK.

Since barbituric acid (pK 4.05 in water at 25°) fulfills the requirement set forth above, it was chosen as a model compound in a study of the kinetics of the Michael addition in neutral and acidic media.[2] The use of this compound in the Michael reaction has been recorded by Bahner,[3] who obtained a series of 5-(2-nitroalkyl)-barbiturates by treating the potassium or benzyltrimethylammonium salt with nitroölefins in boiling aqueous ethanol. Neutralization with mineral acid yielded the free 5-substituted barbituric acids. In the course of the present study it has been confirmed that where this compound adds to conjugated olefinic systems the addition occurs quite readily in the absence of catalysts while competing side reactions are minimized.

When dissolved in minimal amounts of aqueous dioxane, aqueous methanol or aqueous acetic acid, barbituric acid reacted smoothly at room temperature with β-nitrostyrene to give the 1:1 adduct, 5-(2-nitro-1-phenylethyl)-barbituric acid (I, R = H) in good yields. Analogous 1:1 adducts were

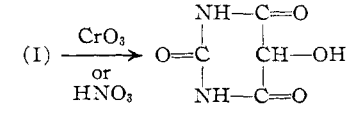


I

R = H, *p*-$(CH_3)_2N$, *p*-CH_3O, *p*-Cl, 3,4-CH_2O_2, *m*-NO_2

formed with *m*,β-dinitro-, *p*-chloro-β-nitro-, 3,4-methylenedioxy-β-nitro-, *p*-methoxy-β-nitro- and *p*-dimethylamino-β-nitrostyrene (Table I), but attempts to effect similar reactions with cinnamic acid, acrylic acid, methyl acrylate and diethyl benzalmalonate under a variety of conditions were unsuccessful as were attempts to join 5-nitrobarbituric acid or indandione-1,3- with the nitrostyrenes.

Chromic or nitric acid oxidation of I to dialuric acid indicated that addition to the nitrostyrene had occurred at the methylene carbon rather than at one of the imino nitrogens or at the hydroxyl position of an enolic tautomer, while the conversion of I to the corresponding arylsuccinic acid on prolonged refluxing with concentrated hydrochloric acid served further to confirm the assigned structure.



(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 694.

(2) M. J. Kamlet and D. J. Glover, to be published.

(3) C. T. Bahner, U. S. Patent 2,527,293 (Oct. 24, 1950).

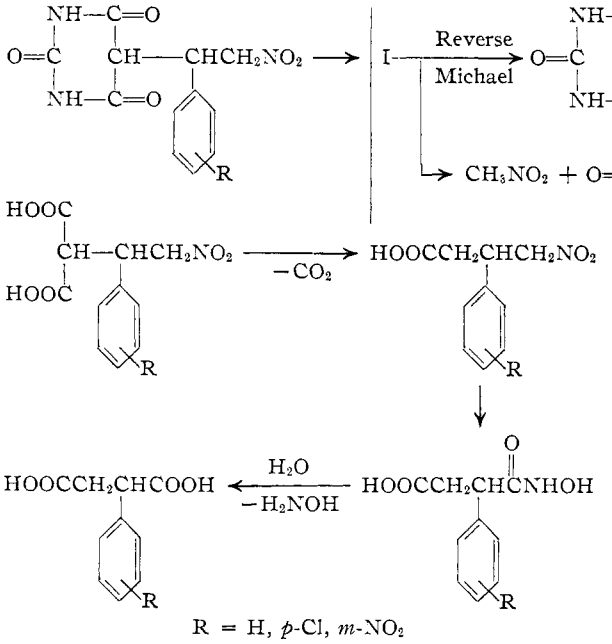
TABLE I

5-(2-NITRO-1-ARYLETHYL)-BARBITURIC ACIDS

Aryl group	M.p.,[a] °C.	Yield,[b] %	Recrystn. solvent[c]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Phenyl	181–182	(93) 70	N	51.98	51.88	4.00	4.23	15.16	15.00
					51.80		4.14		14.89
p-Dimethylaminophenyl	220	(100) 80	H	52.49	52.24	5.04	5.03	17.49	17.19
					52.46		4.97		17.72
p-Methoxyphenyl	156–157	(87) 58	NC	50.80	50.85	4.23	4.14	13.67	13.42
					51.00		4.16		13.64
3,4-Methylenedioxyphenyl	172–173	(83) 73	NC	48.60	48.72	3.43	3.35	13.09	13.27
					48.40		3.42		13.00
p-Chlorophenyl	158–159	(88) 56	NC	46.28	46.14	3.24	3.13	13.49	13.19
					46.23		3.16		13.30
m-Nitrophenyl	177–178	(85) 68	N	44.80	44.72	3.10	3.13	17.40	17.39
					44.82		3.03		

[a] These compounds melt with decomposition in all cases. [b] Yield of crude product in parentheses. [c] N = nitromethane, NC = nitromethane–chloroform mixture, H = dilute hydrochloric acid.

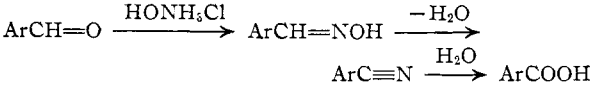
Although no evidence is available regarding the sequence of steps, the latter degradation probably involves the transformations



The Victor Meyer reaction, in which a primary nitro compound is converted to a carboxylic acid on treatment with hot aqueous mineral acids, hitherto has been used mainly in the synthesis of the simple fatty acids or, under milder conditions, of the hydroxamic acids. While here the yields ran below 50%, the simplicity of the reaction and ease of isolation of the products recommend this route (omitting the isolation of the intermediate) as a somewhat more facile method for the preparation of the arylsuccinic acids than those hitherto described.[4]

As by-products in the degradation described above, slight amounts of the correspondingly substituting benzoic acids were always obtained. A probable precursor to *p*-chlorobenzoic acid, *p*-chlorobenzonitrile, also was isolated in the decomposition of 5-[2-nitro-1-(*p*-chlorophenyl)-ethyl]-barbituric acid. In view of the known reversibility of the Michael reaction[5] it is likely that benzaldehyde, was formed in the reaction mixture by one or both of the following routes

and reacted with the hydroxylamine hydrochloride (formed by hydrolysis of the hydroxamic acid in the Victor Meyer reaction) to give the aldoxime. This then was dehydrated to the nitrile which, in turn, was hydrolyzed to the free benzoic acid.

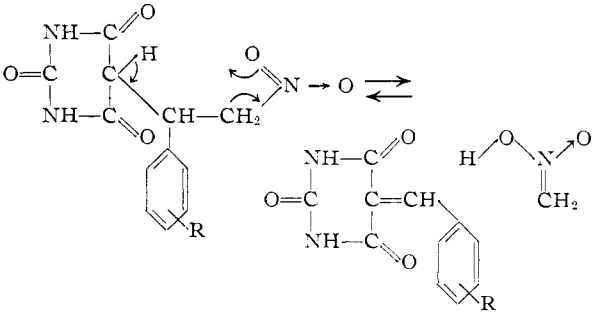


These reverse Michael reactions also probably accounted for the extreme difficulty encountered in attempting to purify the adducts by recrystallization. Only on recrystallization from nitromethane or nitromethane–carbon tetrachloride mixtures were consistantly suitable analytical samples obtainable. This fact indicated that the decomposition to nitromethane and benzalbarbituric acid was the predominant side reaction and that with a large excess of nitromethane the equilibrium was shifted far in the direction of the undecomposed adduct.[6]

(4) C. F. H. Allen and H. B. Johnson, *Org. Syntheses*, **30**, 83 (1950).

(5) Reference 1, p. 692.

(6) The occurrence of this reaction in essentially non-polar or acidic media may be rationalized by assuming that a non-ionic mechanism such as the following obtains concurrently with the ionic mechanism commonly postulated for the reverse Michael reaction.



The poor recrystallization yields derive from the unfortunate solubility characteristics of most of the adducts in nitromethane.

Experimental[7]

Preparation of the Nitrostyrenes.—The substituted β-nitrostyrenes were prepared by two general methods from the corresponding benzaldehydes and nitromethane. β-Nitrostyrene was prepared by the method of Worrall,[8] while minor modifications of this procedure furnished the *m*,β-dinitro-, *p*-chloro-β-nitro- and *p*-methoxy-β-nitrostyrenes in good yields. The *p*-dimethylamino-β-nitro- and 3,4-methylenedioxy-β-nitrostyrenes were prepared by the following variation of an azeotropic method used by Pratt and Werble[9] to carry out the Knoevenagel condensation: A solution of 0.25 mole each of the aldehyde and nitromethane, 1 g. of caproic acid and 2 ml. of piperidine in 500 ml. of benzene was refluxed until the theoretical amount of water had been collected in a graduated Dean–Stark trap. The crude products which separated on cooling the solutions were filtered off and recrystallized from the solvents indicated below.

The products, preferred recrystallization solvents and melting points were as follows: β-nitrostyrene, ethanol, 57–58°; *m*,β-dinitrostyrene, ethanol, 124.5–125.5°; 3,4-methylenedioxy-β-nitrostyrene, ethanol–benzene, 160.5–161°; *p*-chloro-β-nitrostyrene, ethanol, 112–112.5°; *p*-dimethylamino-β-nitrostyrene, benzene, 182–183.5°; *p*-methoxy-β-nitrostyrene, ethanol, 86–87°.

5-(2-Nitro-1-phenylethyl)-barbituric Acid (I) (R = H). **(a) In 80% Dioxane.**—To a solution of 25.6 g. (0.20 mole) of barbituric acid in 200 ml. of dioxane was added 30.0 g. (0.20 mole) of β-nitrostyrene and 100 ml. of water. After standing overnight at room temperature the red solution was added dropwise with vigorous stirring to 500 ml. of cold water. There was thus obtained in two crops 51.5 g. (93% yield) of crude 5-(2-nitro-1-phenylethyl)-barbituric acid as a light yellow powder, melting at 175–179° dec.

(b) In 75% Methanol.—A solution of 0.02 mole each of barbituric acid and β-nitrostyrene in 100 ml. of 75% methanol was allowed to stand 4 hours at room temperature after which time a vacuum was applied and the methanol slowly removed. The solid which separated was filtered off in three successive crops and a total of 5.04 g. (91% yield) of crude 5-(2-nitro-1-phenylethyl)-barbituric acid melting at 168–173° dec. was collected.

Recrystallization of 4.1 g. of this material from nitromethane afforded 3.1 g. (68% over-all yield) of the purified material as tiny white bars melting at 180–181°. A further recrystallization from nitromethane raised the melting point to 181–182° dec.

The following compounds were prepared by procedure (b) with the modifications noted: **5-[2-nitro-1-(*p*-methoxyphenyl)-ethyl]-barbituric acid**: refluxed 2.5 hours, crude product melted at 145–150°; **5-[2-nitro-1-(*p*-chlorophenyl)-ethyl]-barbituric acid**: 4 hours at room temperature, crude product melted at 145–152°; **5-[2-nitro-1-(*p*-dimethylaminophenyl)-ethyl]-barbituric acid**: refluxed 2.25 hours then stood overnight at room temperature, crude product melted at 215°; **5-[2-nitro-1-(3,4-methylenedioxyphenyl)-ethyl]-barbituric acid**: refluxed 1.75 hours, crude product melted at 155–160°.

5-[2-Nitro-1-(*m*-nitrophenyl)-ethyl]-barbituric Acid (I) (R = *m*-NO_2).—To a solution of 3.88 g. of *m*,β-dinitrostyrene (0.02 mole) in 30 ml. of acetic acid was added 2.56 g. (0.02 mole) of barbituric acid in 20 ml. of 50% aqueous acetic acid, then 50 ml. of water. After 30 minutes at room temperature the solution was added to 200 ml. of cold 1% sulfuric acid. On standing in the ice-box, two crops of crude 5-[2-nitro-1-(*m*-nitrophenyl)-ethyl]-barbituric acid totaling 5.49 g. and melting at 164–167° precipitated. Recrystallization of 2.0 g. of this material from nitromethane yielded 1.6 g. of tiny white diamond-shaped platelets melting at 177–178° dec.

Chromic Acid Oxidation of I (R = H).—A solution of 4.7 g. (0.017 mole) of the adduct and 10 g. (0.1 mole) of chromic oxide in 50 ml. of 60% aqueous acetic acid was allowed to stand overnight at room temperature, then added to an equal volume of water. Sodium bisulfite was added till the color was deep green and the solution was extracted several times with ether. Evaporation of the combined ether extracts yielded 1.4 g. of a white solid melting at 196–198° dec. Recrystallization of this material from acetone–benzene furnished 1.0 g. (41% yield) of dialuric acid, m.p. 210–212° dec., neut. equiv. 141 (calcd. 144), which did not depress the melting point of an authentic sample, m.p. 214° dec. Oxidation of the adduct with 90% fuming nitric acid afforded the same product in 25% yield.

Conversion of I (R = *m*-NO_2) **to *m*-Nitrophenylsuccinic Acid.**—A suspension of 1.62 g. (0.005 mole) of the adduct in 35 ml. of concentrated hydrochloric acid was refluxed 18 hours and the resultant mixture extracted several times with ether. Evaporation of the ether and recrystallization of the residual solid from ethanol–water furnished 0.51 g. (43% yield) of *m*-nitrophenylsuccinic acid as clusters of tiny white needles melting at 203–205° (lit.[10] 204°); neut. equiv., 121.5 (calcd. 119.5). Concentration of the combined mother liquors yielded 0.02 g. of *m*-nitrobenzoic acid, m.p. 140°, which did not depress the melting point of an authentic sample. By a similar procedure I (R = H), was converted to phenylsuccinic acid, m.p. 163–166° (lit.[4] 165.5–166°), neut. equiv. 98 (calcd. 97.5), in 17% yield. In addition small amounts of benzoic acid were recovered.

Direct Preparation of *p*-Chlorophenylsuccinic Acid from Barbituric Acid and *p*-Chloro-β-nitrostyrene.—A solution of 3.67 g. (0.02 mole) of *p*-chloro-β-nitrostyrene and 2.56 g. (0.02 mole) of barbituric acid in 100 ml. of 75% methanol was allowed to stand 20 hours at room temperature (after heating first to effect solution) and the solvent then was evaporated off *in vacuo*. The residual oil, when treated as above, yielded 1.35 g. (30% yield) of *p*-chlorophenylsuccinic acid as tiny white needles melting at 198–200°.

Anal. Calcd. for $C_{10}H_9O_4Cl$: C, 52.52; H, 3.97; Cl, 15.51; neut. equiv., 114.3. Found: C, 52.30, 52.46; H, 3.76, 3.83; Cl, 15.15, 15.34; neut. equiv., 112.5.

A white solid which had formed on the walls of the condenser was triturated with hexane and filtered. The hexane-insoluble material (0.05 g., m.p. 241–243°) did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid (m.p. 243°). Evaporation of the hexane solution yielded 0.33 g. of tiny fluffy white needles, m.p. 91–92°, which did not depress the melting point of an authentic sample of *p*-chlorobenzonitrile (m.p. 92°).

Acknowledgments.—The author wishes to thank Dr. D. V. Sickman for his interest and advice and Dr. O. H. Johnson, of these laboratories, who suggested refluxing the adducts with concentrated hydrochloric acid as a method of degradation.

SILVER SPRING, MARYLAND

(7) All melting points are uncorrected. Microanalyses by Dr. M. H. Aldrich and Miss K. Gerdeman, University of Maryland, College Park, Md.

(8) D. E. Worrall in "Organic Syntheses," edited by H. Gilman and A. H. Blatt, Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 513.

(9) E. F. Pratt and E. Werble, THIS JOURNAL, **72**, 4638 (1950).

(10) J. Stanek and J. Urban, *Collection Czechoslov. Chem. Communs.*, **15**, 371 (1950); *C. A.*, **45**, 3824 (1951).