action which according to conditions may break sooner or later. The final state of the system depends on kinetic factors. The process of oxidation in our example is a reversible process. Provided benzoin is fed with the oxidizing agent continuously at a sufficiently slow rate, the gradual oxidation of benzoin to benzil is a continuous shift of thermodynamical equilibria.

Summary

The purple substance on an oxidation level between benzil and benzoin is a radical of the same molecular size as benzil and benzoin. Its stability is due to resonance. The oxidation of benzoin to benzil on adding an oxidizing agent such as oxygen or iodine proceeds in two successive univalent steps. Oxidation does not proceed at all unless the conditions, especially those of alkalinity, are such as to allow the existence of the radical in equilibrium with benzoin and benzil.

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[CONTRIBUTION FROM THE BURROUGHS WELLCOME AND CO., U. S. A., EXPERIMENTAL RESEARCH LABORATORIES]

Some N-Aryl Barbituric Acids. III

BY JOHANNES S. BUCK

There has recently appeared in this Journal[1] a description of some colored barbituric acids, the object of the work being to obtain a hypnotic which would preferentially stain certain tissues. In the paper mentioned it is the 5-carbon atom which carries the chromophore. The author has been working recently with N-aryl barbituric acids[2] and it seemed that these offered greater possibilities in the way of colored hypnotics, as there would be less chance of destroying the pharmacological properties if substitution were carried out on the N-aryl group.

1-Phenyl-5,5-diethylbarbituric acid[2,3] was nitrated, and gave approximately equal amounts of the meta- and para-nitro derivatives. These were readily reducible to the corresponding amino compounds. These latter behave as typical aromatic amines, the amino group being acylated and diazotized readily. The diazonium group is replaceable by hydroxyl, chlorine, etc., and may also be coupled with a variety of amines and phenolic compounds to give typical azo dyes. 1-*p*-(Phenylazo)-phenyl-5,5-diethylbarbituric acid (prepared by condensation) is included for check in the pharmacological work, which will be reported elsewhere.

Dox[4] has described an ethylene-N,N'-bis-(5,5-diethylbarbituric acid), prepared from ethylene diurea and ethyl diethylmalonate. The analogous *m*-phenylene- and the *p*-phenylene-N,N'-bis-(5,5-diethylbarbituric acid) have been made by condensing 1-*m*- and 1-*p*-ureidophenyl-5,5-diethylbarbituric acids with the same ester, and these are described in the present work.

Experimental

1-Nitrophenyl-5,5-diethylbarbituric Acids.—Twenty-six grams of 1-phenyl-5,5-diethylbarbituric acid was ground up and dissolved in 100 cc. of concd. sulfuric acid at −5°. During one hour a solution of 4.30 cc. of fuming nitric acid (sp. gr. 1.50) in 25 cc. of concd. sulfuric acid was dropped in. After a further hour the solution was poured onto crushed ice and, after standing, the solid was filtered off and washed with water. The reaction mixture was stirred mechanically throughout, and the temperature held at −3 to −5°, by means of ice–salt cooling. The conditions given are critical.[5]

Prolonged fractional crystallization from alcohol gave small amounts of the meta and paranitro compounds, the major portion being inseparable by any reasonable amount of effort. The nitro compounds were orientated by reduction to the corresponding amino compounds, whose structure was known. For practical purposes the mixed nitro compounds, after one recrystallization from alcohol, were reduced directly and the amino compounds then separated by fractional crystallization.

1-Aminophenyl-5,5-diethylbarbituric Acids.—Eighteen and three-tenths grams of the mixed nitro compounds, ground up and suspended in 150 cc. of 95% alcohol, was reduced catalytically (platinum oxide at room temperature). A considerable proportion of the crude para compound separates toward the end of the reduction and is filtered off. This product and the material obtained from the filtrate are then crystallized fractionally until pure, a laborious operation in view of the close similarity between the meta and para compounds. There is so obtained approximately equal amounts of two compounds melting at 226 and 234° when pure. No third isomer was found.

The compound of m. p. 234° was identified as the para compound by direct comparison (mixed m. p., etc.) with

(1) Pierce and Rising, THIS JOURNAL, **58**, 1361 (1936).
(2) Buck, *ibid.*, **58**, 1284, 2059 (1936).
(3) Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929).
(4) Dox, THIS JOURNAL, **55**, 1230 (1933).
(5) *Cf.* Bousquet and Adams, *ibid.*, **52**, 224 (1930).

a specimen of 1-*p*-aminophenyl-5,5-diethylbarbituric acid, prepared in another, and unambiguous, way (see below). In addition it was converted into 1-*p*-chlorophenyl-5,5-diethylbarbituric acid, which was identified by direct comparison with a specimen prepared in another way.

The compound, m. p. 226°, was identified as meta by acetylation and comparison of the acetyl compound with a specimen of 1-*m*-acetaminophenyl-5,5-diethylbarbituric acid prepared by direct condensation. Similarly, on replacing the amino group by chlorine, the product formed was identical with 1-*m*-chlorophenyl-5,5-diethylbarbituric acid, obtained by an unambiguous reaction.

The hydrochlorides were prepared from the bases by means of concd. hydrochloric acid. The (dried) meta compound crystallizes slowly from ether–alcohol mixture while the para compound crystallizes readily from dilute hydrochloric acid.

The compounds subsequently described were prepared from the separated amino compounds so that their orientation follows automatically.

1-Acetaminophenyl-5,5-diethylbarbituric Acids.—These may be prepared by acetylation of the corresponding amino compounds by means of acetic anhydride. The meta compound is also prepared readily by the condensation of *m*-acetaminophenyl urea[6] with ethyl diethylmalonate, by means of sodium ethylate. *p*-Acetaminophenyl urea,[6] condensed with the same ester, in the same manner, gave a small yield of 1-*p*-aminophenyl-5,5-diethylbarbituric acid, sufficient, however, for orientation purposes. The above two products of condensation were identical with those prepared via the nitro compounds. *o*-Acetaminophenyl urea, with ethyl diethylmalonate and sodium ethylate, gave no isolable product.

1-Ureidophenyl-5,5-diethylbarbituric Acids.—The respective amino compounds were converted into the ureas by means of nitrourea in 95% alcohol, after the method of Buck and Ferry.[6]

1-Carbethoxyaminophenyl-5,5-diethylbarbituric Acids.—The carbethoxy derivatives of the amino compounds were prepared by treating them, in alkaline solution, with ethyl chlorocarbonate and sodium hydroxide solution, the total alkali and the chlorocarbonate being accurately 3 moles of each. The product separates without further treatment and is purified readily by recrystallization.

Phenylene-N,N'-bis-(5,5-diethylbarbituric Acids).—These two derivatives were prepared by condensing the corresponding 1-ureidophenyl-5,5-diethylbarbituric acid with ethyl diethylmalonate, in the presence of sodium ethylate, in the usual manner.

1-Chlorophenyl-5,5-diethylbarbituric Acids.[7]—The three (*o*-, *m*-, and *p*-) isomers were prepared (the ortho compound as an additional orientation check) by condensing the corresponding chlorophenyl urea[8] with ethyl diethylmalonate, in the presence of sodium ethylate. The meta and para compounds are also produced, in mediocre yields, from the corresponding amino compounds by the Sandmeyer method, using the ordinary technique, and are identical (mixed m. p., etc.) with those prepared by condensation.

1-*p*-(Phenylazo)-phenyl-5,5-diethylbarbituric Acid.—This was prepared by condensing *p*-ureidoazobenzene[9] with ethyl diethylmalonate by means of sodium ethylate, as with other barbituric acids. The compound was purified by solution in dilute sodium hydroxide, precipitation by carbon dioxide, digestion with alcohol, and recrystallization from ethyl acetate. It forms small, glittering orange-brown needles, melting at 244°. It is insoluble in water, moderately soluble in hot alcohol, soluble in ethyl acetate, and soluble in cold 5% sodium hydroxide solution.

Anal. Calcd. for $C_{20}H_{20}O_3N_4$: N, 15.38. Found: N, 15.34.

***o*-Acetaminophenyl Urea.**—This compound, not previously reported, is produced readily by reducing *o*-nitroacetanilide catalytically, by the Adams method, and then converting the amine into the urea by means of nitrourea in alcohol. The product is recrystallized from water until pure. It forms small, white needles, moderately soluble in hot alcohol, somewhat more soluble in hot water, sparingly soluble in ether, ethyl acetate, and benzene, and insoluble in petroleum ether. It melts at 188° with frothing.

Anal. Calcd. for $C_9H_{11}O_2N_3$: N, 21.75. Found: N, 22.05.

Diazotization Experiments.—The diazonium solution was prepared by dissolving the respective amino compound in dilute hydrochloric acid, cooling, and adding the theoretical amount of sodium nitrite solution. With cuprous chloride, chlorine is introduced in place of the diazonium group, but a considerable amount of gum is formed in the reaction. By running the diazonium solution into boiling 40% sulfuric acid, the corresponding phenolic derivative is produced smoothly.

Coupling of the diazonium chlorides takes place readily with aniline, α-naphthylamine, α-naphthol, 1-naphthol-5-sulfonic acid (Cleve's acid) and other amino and phenolic compounds, under the usual conditions, that is to say, when the diazonium solution is run into the amines in hydrochloric acid solution and the phenols in sodium hydroxide solution. Excess of acid inhibits coupling, which, however, takes place on the addition of sodium acetate. The products of the coupling are typical azo dyes, and, as they are not particularly stable, no attempt was made to recrystallize them, although every effort was made to obtain pure products.

The azo dyes are practically insoluble in water, except nos. 4 and 8, which are moderately soluble. They are all soluble in alcohol and in cold 5% sodium hydroxide solution. Nos. 1, 2, 5 and 6 are moderately soluble in hot 5% hydrochloric acid, nos. 4 and 8 very slightly soluble and nos. 3 and 7 insoluble. Silk and wool are dyed by the compounds, nos. 1 and 5 giving bright yellow, nos. 2 and 6 red-brown, nos. 3 and 7 light orange-brown, and nos. 4 and 8 red-brown and light brown, respectively. The behavior on heating is not characteristic, gradual softening or sudden decomposition taking place.

(6) Prepared by reducing the corresponding nitroacetanilide catalytically and then treating the resulting amine with nitrourea. *Cf.* Buck and Ferry, THIS JOURNAL, **58**, 854 (1936); Beilstein's "Handbuch," 4 Auf., Vol. XIII, pp. 49, 103.

(7) The para compound has been described by Hjort and Dox,[3] who give the melting point as 135–136°, as against 181° given in this paper.

(8) The ureas were prepared from the corresponding chloroanilines by the nitrourea method. *Cf.* Beilstein's "Handbuch," 4 Auf., Vol. XII, pp. 600, 606, 615.

(9) Prepared by treating azobenzene with nitrourea, in alcohol solution. *Cf.* Pierron, *Compt. rend.*, **143**, 340 (1906).

TABLE I

NUCLEAR-SUBSTITUTED 1-PHENYL-5,5-DIETHYLBARBITURIC ACIDS

A = alcohol; a = aqueous; Ac = acetic acid; B = benzene; c = cold; E = ether; F = with froth and decomp.; h = hot; i = very slightly sol. to insol.; m = moderately; S = after softening; s = soluble; sl = slightly; W = water.

Substituent on phenyl group	Appearance	Formula	M. p., °C.	Solv., recryst.	Solubilities E	W	5% HCl	A	B	Ac	Analyses, % N Calcd.	Found
m-Nitro	Glitt. flat prisms	$C_{14}H_{15}O_5N_3$	189	A	i	i	i	sh	slsh	sh	13.76	13.93
p-Nitro	Glitt. stout prisms	$C_{14}H_{15}O_5N_3$	208	A	i	i	i	msh	slsh	sh	13.76	13.80
m-Amino	Small glitt. leaves	$C_{14}H_{17}O_3N_3$	226	A	i	i	sc	msh	slsh	sc	15.26	15.23
p-Amino	Leafy prisms	$C_{14}H_{17}O_3N_3$	234	A	i	i	sc	msh	slsh	msc	15.26	15.11
m-Amino (hydrochloride)	Dull powdered crusts	$C_{14}H_{18}O_3N_3Cl$	242F	AE	i	sc	sc	s	i	sh	13.48	13.64
p-Amino (hydrochloride)	Dull powder of plates	$C_{14}H_{18}O_3N_3Cl$	256F	aHCl	i	sh	sc	s	i	sh	13.48	13.70
m-Acetamino	Glitt. small leaves	$C_{16}H_{19}O_4N_3$	285	Ac	i	i	i	i	i	msh	13.24	13.25
p-Acetamino	Glitt. leaves	$C_{16}H_{19}O_4N_3$	174	aA	i	slsh	slsh	sh	sh	sc	13.24	13.09
m-Ureido	Crusts of broken prisms	$C_{15}H_{18}O_4N_4$	ca206	A	i	slsh	slsh	ms	i	sc	17.60	17.45
p-Ureido	Powdery crusts	$C_{15}H_{18}O_4N_4$	ca221	A	i	slsh	slsh	s	i	sc	17.60	17.80
m-Carbethoxyamino	Dull powdery spindles	$C_{17}H_{21}O_5N_3$	242	aAc	i	i	i	i	i	msh	12.09	12.23
p-Carbethoxyamino	Glitt. silky leaves	$C_{17}H_{21}O_5N_3$	203.5	aAc	ms	slsh	slsh	msc	sh	msc	12.09	12.35
m-Hydroxy	Glitt. silky leaves	$C_{14}H_{16}O_4N_2$	222.5	W	i	slsh	slsh	sh	i	sh	10.14	10.30
p-Hydroxy	Dull leafy prisms	$C_{14}H_{16}O_4N_2$	191S	W	ms	msh	msh	sc	slsh	sc	10.14	10.39
m-Barbital[a]	Tiny slender needles	$C_{22}H_{26}O_6N_4$	ca345S	Ac	i	i	i	i	i	slsh	12.66	12.79
p-Barbital[b]	Glitt. tiny plates	$C_{22}H_{26}O_6N_4$	ca352S	Ac	i	i	i	i	i	msh	12.66	12.47
o-Chloro	Small glitt. prisms	$C_{14}H_{15}O_3N_2Cl$	169	aA	s	i	i	s	sh	sc	9.51	9.56
m-Chloro	Small flat glitt. prisms	$C_{14}H_{15}O_3N_2Cl$	152.5	aA	s	i	i	s	sh	sc	9.51	9.68
p-Chloro	Large prisms	$C_{14}H_{15}O_3N_2Cl$	181	A	s	i	i	s	sh	sc	9.51	9.63

[a] *m*-Phenylene-N,N′-bis-(5,5-diethylbarbituric acid). [b] *p*-Phenylene-N,N′-bis-(5,5-diethylbarbituric acid).

TABLE II

AZO DYES FROM 1-AMINOPHENYL-5,5-DIETHYLBARBITURIC ACIDS

No.	Compound -phenyl-5,5-diethylbarbituric acid	Appearance	Color In alcohol	Color In 5% NaOH	Formula	Analyses, % N Calcd.	Found
1	1-*m*-(4-aminophenylazo)	Bright yellow powder	Bright yellow	Orange-red	$C_{20}H_{21}O_2N_5$	18.46	18.87
2	1-*m*-(4-aminonaphthylazo)	Orange-brown powder	Deep orange-red	Deep orange-red	$C_{24}H_{23}O_2N_5$	16.31	16.79
3	1-*m*-(4-hydroxynaphthylazo)	Dark chocolate powder	Deep red-brown	Intense deep red	$C_{24}H_{22}O_4N_4$	13.02	13.43
4	1-*m*-(2-azo-α-naphthol-5-sulfonic acid)[a]	Dark red-black powder with weak green iridescence	Deep orange-red	Deep clear red	$C_{24}H_{22}O_7N_5S$	10.98	10.45[b]
5	1-*p*-(4-aminophenylazo)	Yellow powder	Bright yellow	Orange-red	$C_{20}H_{21}O_2N_5$	18.46	18.26
6	1-*p*-(4-aminonaphthylazo)	Red-brown powder	Orange-red	Deep orange-red	$C_{24}H_{23}O_2N_5$	16.31	16.13
7	1-*p*-(4-hydroxynaphthylazo)	Dark chocolate powder	Deep red-brown	Intense deep red	$C_{24}H_{22}O_4N_4$	13.02	13.51
8	1-*p*-(2-azo-α-naphthol-5-sulfonic acid)[a]	Dark red-black powder with weak green iridescence	Deep orange-red	Deep clear red	$C_{24}H_{22}O_7N_4S$	10.98	10.84[b]

[a] Coupling position inferred from Cochineal Scarlet G, Chromotrope F4B, etc. [b] Dried *in vacuo* for three and one-half hours at 95°.

The compounds other than azo dyes, if not described above, are given in Table I; the azo dyes are described separately in Table II. All melting points are corrected. Nitrogen determinations were carried out by a micro-Dumas method, and were frequently checked by carbon-hydrogen determinations (not recorded here). The analyses were carried out by Mr. W. S. Ide. Unless otherwise stated, the yields were good to very good. All the compounds in both tables are soluble in cold 5% sodium hydroxide solution.

Summary

1-*m*-Aminophenyl-5,5-diethylbarbituric acid and 1-*p*-aminophenyl-5,5-diethylbarbituric acid have been prepared *via* the nitro compounds. Compounds derived from these aminobarbituric acids are described. In addition, the amino group has been replaced, via the diazonium chloride, by chlorine and hydroxyl, and the diazonium chloride has also been coupled with some phenolic and amino compounds, giving typical azo dyes. Two phenylene-N,N′-bis-(5,5-diethylbarbituric acid) compounds have been obtained from the amino compounds, via the ureido derivatives.

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