[CONTRIBUTION FROM THE RESEARCH DIVISION, ARMOUR AND CO.]

Synthesis of Deoxyalloxazines (Benzopteridines)[1]

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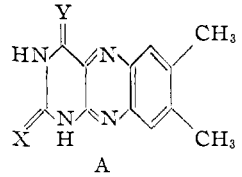
A new group of compounds, characterized as 2- and/or 4-substituted deoxyalloxazines or benzopteridines, as well as the known alloxazine derivative, lumichrome, was synthesized by the condensation of *dimeric* 4,5-dimethyl-*o*-benzoquinone with various 5,6-diaminopyrimidines. Several of the new compounds are of biological interest as antimetabolites.

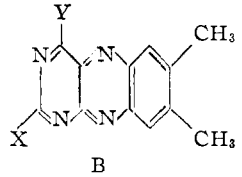
Structural analogs of B vitamins are often potent growth inhibitors, and the study of such compounds represents a promising approach in chemotherapeutic research. Many of the vitamin analogs synthesized and studied so far in various laboratories were antagonists of either riboflavin or folic acid. The new group of compounds reported in this paper appears to be of particular interest, however, because several of its members may act as "dual antagonists" of both vitamins in their respective enzyme systems.

Structurally, some of these new compounds may be derived from the known 6,7-dimethylalloxazine or lumichrome (I, formula A) by replacement of one or both alloxazine oxygens with one or two imino groups and/or a sulfur atom. Compounds II–V are shown in this manner under formula A. However, the tautomeric formula B permits a more general representation of this group of compounds (including VI, VII and VIII) which may be considered either as 2- and/or 4-substituted derivatives of 6,7-dimethyl-2,4-deoxyalloxazine or as 2- and/or 4-substituted derivatives of 6,7-[4′,5′-dimethylbenzo]-pteridine. The synthetic method described in this paper appears to be a practical procedure for the synthesis of a great variety of deoxyalloxazines (benzopteridines), a group of compounds not described in the literature, as well as for the synthesis of the known alloxazine derivative, lumichrome.



A

I, X = O; Y = O
II, X = O; Y = NH
III, X = NH; Y = O
IV, X = NH; Y = NH
V, X = S; Y = NH



B

I, X = OH; Y = OH
II, X = OH; Y = NH_2
III, X = NH_2; Y = OH
IV, X = NH_2; Y = NH_2
V, X = SH; Y = NH_2
VI, X = H; Y = NH_2
VII, X = NH_2; Y = H
VIII, X = NH_2; Y = CH_3

There are only two general methods described in the literature for the synthesis of alloxazines. The first, discovered by Kühling[2] in 1891, and later developed by Kuhn, *et al.*,[3a] and by Karrer, *et al.*,[3b] involves the condensation of alloxan with an aromatic *ortho*-diamine. The second method, by Tishler, *et al.*,[4] differs from the first only in the use of chlorobarbituric acid instead of alloxan as the pyrimidine reactant. Both of these methods can lead only to "alloxazines" (2,4-dihydroxybenzopteridines), *i.e.*, compounds in which both the 2- and 4-positions of the ring system are attached to oxygen (as in I) and are inapplicable for the synthesis of deoxyalloxazines.

Kuhn and Cook,[5] in a search for other alloxazine syntheses, explored the reaction of 5,6-diaminouracil with various 1,2-dicarbonyl compounds. Their so-called "lumazine synthesis" proved to be a versatile method which later was successfully extended by Mallette, Taylor and Cain[6] to the synthesis of several 6,7-disubstituted 2,4-diaminopteridines. However, the original aim of Kuhn and Cook's synthesis could not be accomplished by this method. While *polynuclear* *o*-quinones, such as 1,2-naphthoquinone and phenanthrenequinone, readily reacted with the diaminopyrimidine compound yielding products in which the three-ring system of alloxazine was fused with at least one additional aromatic ring, all attempts by Kuhn and Cook to obtain alloxazine by the condensation of 5,6-diaminouracil with *o*-benzoquinone failed in spite of many experiments using a great variety of reaction conditions.[5] These authors apparently concluded that the scope of this reaction was limited to 1,2-dicarbonyl compounds other than *o*-benzoquinones and that this reaction therefore could not be used for the synthesis of alloxazines.

Although *o*-benzoquinones are known to react with *aromatic* diamino compounds to yield quinoxalines,[7] such reactions are carried out in dry, nonpolar organic solvents, *i.e.*, under conditions which cannot be applied to the reaction of *o*-benzoquinones with 5,6-diaminopyrimidines since the latter compounds are usually quite insoluble in organic solvents. Our experiments described below were conducted in aqueous solutions.

When a solution of 4,5-dimethyl-*o*-benzoquinone in glacial acetic acid was combined with an aqueous solution of 2,4,5,6-tetraaminopyrimidine bisulfite and refluxed for 2 hr., a brown precipitate was obtained which had an ultraviolet absorption spectrum similar to that of lumichrome. This crude product was obtained in 20–30% yield, but purification was extremely difficult. The small amount of pure substance which was obtained was tentatively identified as 2,4-diamino-6,7-dimethyl-2,4-deoxyalloxazine (IV) by microanalysis. The

(1) Presented in part before the Division of Medicinal Chemistry, 129th National Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(2) O. Kühling, *Ber.*, **24**, 2363 (1891).

(3) (a) R. Kuhn and F. Weygand, *ibid.*, **67**, 1409 (1934); (b) P. Karrer, H. Salomon, K. Schöpf, E. Schlitter and H. Fritzsche, *Helv. Chim. Acta*, **17**, 1010 (1934).

(4) M. Tishler, J. W. Wellman and K. Ladenburg, THIS JOURNAL, **67**, 2165 (1945).

(5) R. Kuhn and A. H. Cook, *Ber.*, **70**, 761 (1937).

(6) M. F. Mallette, E. C. Taylor, Jr., and C. K. Cain, THIS JOURNAL, **69**, 1814 (1947).

(7) F. Kehrmann and C. Mermod, *Helv. Chim. Acta*, **10**, 62 (1927).

yield and the purity of the crude condensation product varied considerably with the reaction conditions and with the quality of the reactants used. When the pyrimidine sulfate was used instead of the bisulfite, only 10–15% of very crude product was obtained.

Apparently the main factor which influenced the condensation was the quality of the 4,5-dimethyl-*o*-benzoquinone. This compound, first prepared by Diepolder[8] and characterized as a deep-red-colored mixture of two crystalline modifications (a red and a yellow) melting at 101°, was obtained by us in varying shades of red and yellow with different melting points. When the oxidation of 2-amino-4,5-dimethylphenol[8,9] and recrystallization of the resulting quinone from ether were carried out rapidly, a deep-red crystalline substance was obtained which melted at 91–93°. However, when the ethereal solution was allowed to stand overnight, red-brown to yellow products precipitated which melted as high as 110–130°. In one experiment the oxidation was carried out in the presence of ethyl acetate, and the organic layer was dried over magnesium sulfate for several days. Evaporation of the solvent left an oily residue which upon trituration with ether and recrystallization from isopropyl alcohol gave a yellow crystalline substance melting at 173–174°. Elementary analyses and molecular-weight determinations suggested that this compound was a dimer of 4,5-dimethyl-*o*-benzoquinone (a dimer of 4-methyl-*o*-benzoquinone had been described by Willstätter, *et al.*[9]), which was confirmed by examination of spectra and chemical reactions.[10] Subsequent experiments also showed that conversion of monomeric quinone to the dimer may be brought about in a variety of ways, which include gentle heating in aqueous acetic acid, wet ether or 2-propanol solution, or in aqueous suspension. In these cases dimerization occurs within an hour. At room temperature, dimerization progresses at a slower rate, requiring several days or weeks, but the resulting dimer is often more pure. The dimer is less soluble in these solvents than the monomer and usually precipitates as a yellow powder which may be recrystallized from 2-propanol. Chromatography on Florisil is helpful in removing the last traces of impurities, and the chromatographically pure dimer melts at 179–180°.

Mixtures of the monomeric and the dimeric quinones have melting points between 91 and 179°, and through most of this temperature range the melting points appear to approximate a linear function of the percentage composition.

Monomeric quinone is usually contaminated with dimer owing to some dimerization in the course of its preparation, and the usual melting point is about 95°. Recrystallization from ether, as employed by Diepolder, raises the melting point to 100–102°, but this is probably due to further dimerization rather than to purification. A preparation substantially free of dimer (as verified by infrared spectrum[11]) was obtained by partition chromatography on Celite, and this material melted at 91°. Since the higher-melting quinone preparations appeared to give better results in the condensation reactions, the use of pure dimeric quinone was investigated.

When dimeric 4,5-dimethyl-*o*-benzoquinone was treated with 2,4,5,6-tetraaminopyrimidine bisulfite (*or* sulfate) under the reaction conditions described above, a large amount of yellow condensation product was obtained which could be readily purified by recrystallization to give IV in good yield. Even better results were obtained when aqueous alkaline solutions of dimeric quinone and the pyrimidine were combined in stoichiometric (1:2 molar) ratio and allowed to stand at room temperature for 1–3 days. In this case, IV precipitated in almost analytically pure form. If monomeric quinone was treated with the bisulfite of the pyrimidine compound under these alkaline conditions, only a small amount of crude condensation product could be obtained, and no product could be isolated when the sulfate salt of the pyrimidine compound was used (see Table I).

In a series of experiments, dimeric 4,5-dimethyl-*o*-benzoquinone was treated with various other 5,6-diaminopyrimidines to give compounds I, II, III and V–VIII in similarly good yields. In some cases the condensation reaction was carried out with best results under neutral conditions. The deoxyalloxazines were obtained in pure form by recrystallization from pyridine, DMF or aqueous formic acid. The ultraviolet spectra of these compounds show two characteristic absorption bands in the 260 and 360 mμ regions (see Table II).

It is apparent that each molecule of dimeric quinone reacts as a *pair* of true 1,2-dicarbonyl compounds with two molecules of diaminopyrimidine and that depolymerization of the dimer occurs in the course of this condensation reaction. No evidence of dimeric condensation products or of reaction intermediates containing two structural units derived from 4,5-dimethyl-*o*-benzoquinone could be found in any of these reactions. Since the alkaline or neutral condensations proceed at room temperature, it seems reasonable to assume that the energy required for depolymerization is supplied by aromatization of the quinone nucleus (the pyrimidine ring loses its partially aromatic character[12]).

(8) E. Diepolder, *Ber.*, **42**, 2921 (1909); **44**, 2502 (1911).

(9) R. Willstätter and F. Müller, *ibid.*, **44**, 2171 (1911).

(10) Two German research groups have recently described dimeric and polymeric forms of *o*-benzoquinones; H. J. Teuber and G. Staiger, *Chem. Ber.*, **88**, 802 (1955), and L. Horner and K. Sturm, *Ann.*, **597**, 1 (1955). These articles were published or became available in this country after the work reported here was completed and submitted by abstract for presentation at the 1956 Spring A.C.S. Meeting. However, the present paper omits those observations or experiments which would duplicate those reported by the German authors.

(11) The infrared spectrum of the dimer is characterized by two very strong "carbonyl" absorption bands at 1735 and 1640 cm.$^{-1}$ and by a strong band at 1610 cm.$^{-1}$ corresponding to an α,β-double bond. There is also a third, much weaker "carbonyl" absorption peak at 1683 cm.$^{-1}$. The monomeric quinone has only one strong, but broader, absorption band in this region, at 1660 cm.$^{-1}$. Another very strong and broad absorption band, conspicuous in the spectrum of the dimer and absent in that of the monomer, is in the 1230 cm.$^{-1}$ region.

(12) This explanation seems to be substantiated by the reaction of dimeric 4,5-dimethyl-*o*-benzoquinone with *o*-phenylenediamine as reported by Horner and Sturm (ref. 10). In this case a quinoxaline was isolated which contained the elements of one molecule of dimeric quinone and one molecule of *o*-phenylenediamine (minus two molecules of water). That is, in the quinoxaline-type condensations, dimeric quinone does not depolymerize because the quinone nucleus

TABLE I

COMPARATIVE CONDENSATION EXPERIMENTS USING CHROMATOGRAPHICALLY PURIFIED MONOMERIC AND DIMERIC 4,5-DIMETHYL-*o*-BENZOQUINONES WITH THE SULFATE AND BISULFITE SALTS OF 2,4,5,6-TETRAAMINOPYRIMIDINE

	Quinone			Pyrimidine				Product (crude IV)				
								Yield		U.v. absorp. $E_1^{1\%}$ cm.		
No.	Form	Gram	Mole	Salt	Gram	Mole	Method of condensation	Gram	% Theor.	260 mμ	365 mμ	Calcd. purity %
1	Monomer	0.243	0.0018	Sulfate(·2H₂O)	0.493	0.0018	Acetic acid	0.051	12	370	234	22
2	Monomer	.185	.0014	Bisulfite	.311	.0014	Acetic acid	.080	24	482	205	28
3	Dimer	.200	.00075	Sulfate(·2H₂O)	.411	.0015	Acetic acid	.200	56	800	277	46
4	Dimer	.200	.00075	Bisulfite	.333	.0015	Acetic acid	.304	85	900	318	53
5	Monomer	.061	.00045	Sulfate(·2H₂O)	.123	.00045	Alkaline	.001	<1	..	..	..
6	Monomer	.057	.00042	Bisulfite	.093	.00042	Alkaline	.032	32	740	472	44
7	Dimer	.200	.00075	Sulfate(·2H₂O)	.411	.0015	Alkaline	.238	66	1400	497	84
8	Dimer	.200	.00075	Bisulfite	.333	.0015	Alkaline	.194	54	1620	582	98
9	Dimer	.272	.0010	Sulfate(·2H₂O)	.274	.0010	Alkaline	.135	56.5[a] 113	1450	522	87
10	Dimer	.136	.0005	Sulfate(·2H₂O)	.548	.0020	Alkaline	.094	78.5[a] 39.2	1490	546	91

[a] In experiments 9 and 10, the dimer:pyrimidine molar ratios were 1:1 and 1:4, respectively. Two yields are given, based on the dimer (left) and the pyrimidine (right), but still assuming that one molecule of dimer reacts with two molecules of pyrimidine to give two molecules of product. In the other experiments, the molar ratios are the theoretically equivalent ratios.

TABLE II

SUMMARY OF CONDENSATIONS OF DIMERIC 4,5-DIMETHYL-*o*-BENZOQUINONE WITH THE SULFATE SALTS OF VARIOUS 5,6-DIAMINOPYRIMIDINES

	5,6-Diaminopyrimidine reactant substd. in positions					Microanalyses[b]						
						Carbon %	Hydrogen %	Nitrogen %	U.v. absorption[c]			
Compound	2	4	Condensation method	Yield[a] % theoret.	Recrystn. solvent	Calcd. Found	Calcd. Found	Calcd. Found	Maximum mμ	log ε	Minimum mμ	log ε
I	OH	OH	Alkaline	68	Acetic acid	59.50	4.13	23.18	263	4.64	300	3.54
						59.18	4.29	23.43	340	3.88	375	3.68
II	OH	NH_2	Neutral	90	Formic acid	59.72	4.60	29.04	261	4.72	297	3.26
					+ water	59.68	4.78	28.93	366	4.33		
III	NH_2	OH	Alkaline	66	Formic acid	59.72	4.60	29.04	266	4.59	303	3.07
					+ water	59.21	4.71	28.60	362	4.03		
IV	NH_2	NH_2	Alkaline	66	DMF	59.98	5.04	34.98	260	4.61	295	3.58
						60.28	5.07	34.81	365	4.15		
V	SH	NH_2	Neutral	100	Pyridine	56.01	4.31	27.63	300	4.66	340	3.77
						56.19	4.62	27.50	387	4.17		
VI	H	NH_2	Neutral	88	DMF	63.96	4.92	31.09	262	4.32	320	3.06
						63.91	5.10	30.94	381	4.00		
VII	NH_2	H[d]	Neutral	86	Pyridine	63.96	4.92	31.09	259	4.63	295	3.59
						64.23	4.82	30.46	354	4.11		
VIII	NH_2	CH_3[d]	Neutral	75	Pyridine	65.25	5.47	29.27	260	4.69	314	3.85
						65.25	5.53	28.28	383	4.24		

[a] These are the "crude" condensation yields; however, in most cases the products were obtained in 80–95% purity, and one recrystallization gave the analytically pure compound. [b] Microanalyses by Midwest Microlab, Indianapolis, Ind. The samples were heated at 140° and 1–2 mm. vacuum for 4 hr. [c] In 0.1 *N* hydrochloric acid, except for I and VIII. I, in 0.1 *N* NaOH; VIII, in 97% formic acid. [d] Used as the free amine.

It should be mentioned that, in the absence of the diaminopyrimidines, dimeric quinone is quite stable in aqueous alkali or acetic acid solutions. It does not depolymerize under conditions similar to those employed in the condensation reactions. In the solid state, it sublimes without depolymerization at 130–140° *in vacuo*, giving a sublimate which is identical with the pure dimer (m.p. 179°).

We do not wish to propose a structure for the dimeric quinone at this time because available evidence does not permit unequivocal interpretation.[13] With regard to the deoxyalloxazine synthesis, any acceptable structural formula for dimeric quinone must be consistent with two important properties of this compound. These are that (1), in contrast to the monomeric quinone, the dimer has no oxidizing properties (*e.g.*, it does not liberate iodine from acidified aqueous potassium iodide solution or KI–starch paper); and (2) it reacts with 5,6-diaminopyrimidines in the manner discussed above. The first fact implies that the quinone–hydroquinone (catechol) conversion is hindered in the dimeric structure, whereas the second emphasizes the reactive α-diketone character of the dimeric quinone. The α-diketone character is also apparent from the infrared spectrum of this compound.[11]

It is suggested that the failure of monomeric *o*-benzoquinones to give satisfactory condensation reactions with 5,6-diaminopyrimidine compounds is due to the powerful oxidizing properties (high oxidation potential[14]) of these monomers. In aqueous solutions, the oxidation of oxidation-susceptible heterocyclic amines by the quinone may proceed at a much faster rate than the condensation reaction, especially under alkaline conditions

can aromatize only if the benzene ring of the *o*-phenylenediamine becomes quinoid instead, which would result in no net energy change.

(13) The structure of a Diels–Alder adduct has been proposed by the German research group (ref. 10).

(14) L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1944, pp. 726–731.

The relatively better condensation results obtained with the bisulfite salt are probably due to the protective effect of the bisulfite ion on the amino compounds.[15] In the acetic acid method the conditions are such that the quinone may partially dimerize and react as the dimer. However, in all cases where monomeric quinone is used in aqueous solution,[16] the condensation product is contaminated with a high percentage of oxidation products.

Only a brief summary of the microbiological experiments will be given here; details will be published elsewhere. Several of the new compounds were found active as inhibitors in *L. leichmannii* as well as in *L. arabinosus*,[17] IV having the highest activity. In *L. leichmannii*, IV gives complete growth inhibition at a concentration of 0.2 μg. per ml., and this inhibition can be reversed effectively by folinic acid (not folic acid) or thymine (or thymidine). Thus, at low concentrations, IV behaves like other anti-folinic compounds of the 2,4-diaminopteridine and -pyrimidine types.[17] However, at higher concentrations of IV (2–5 μg. per ml.), the above metabolites are capable of reversing the inhibition only if large, additional amounts of riboflavin (200–400 μg. per ml.) are added to the growth medium. Neither folinic acid, thymine, thymidine nor riboflavin alone is capable of reversing the inhibition at these higher levels of IV, but the two vitamins together are effective.

Similarly, in *L. arabinosus* the inhibitory action of IV at low levels may be reversed with thymidine, which is the only effective reversing agent of antifolic compounds in this microbiological system.[17] At higher levels of IV, thymidine is effective only in the presence of excess amounts of riboflavin.

Thus, IV appears to be an active "anti-metabolite" of both the folic acid and the riboflavin enzyme systems.

Experimental

2-Amino-4,5-dimethylphenol.—This compound was prepared according to Diepolder,[8] by reduction of 2-phenylazo-4,5-dimethylphenol with sodium hydrosulfite, in 89% yield. However, the following catalytic reduction procedure appeared to be more convenient:

To a suspension of 22.6 g. (0.1 mole) of 2-phenylazo-4,5-dimethylphenol in 300 ml. of 95% ethanol was added 2.0 g. of Raney nickel catalyst and the mixture was hydrogenated in a Parr hydrogenation apparatus at an initial hydrogen pressure of 40 p.s.i. When the theoretical volume of hydrogen had been consumed as calculated from the pressure drop, the catalyst was removed by filtration and the alcohol by vacuum distillation. The residue was washed with 100 ml. of cold toluene and recrystallized from hot toluene to yield 12.1 g. (88%) of 2-amino-4,5-dimethylphenol, m.p. 173–175°.

4,5-Dimethyl-*o*-benzoquinone (Monomer).—Diepolder's[8] and Willstätter's[9] methods were used in the following modified form:

2-Amino-4,5-dimethylphenol, 7.4 g. (0.053 mole), was dissolved in 500 ml. of water and 13 ml. of concentrated sulfuric acid. This solution was poured rapidly, with stirring, into a solution of 12 g. (0.04 mole) of potassium dichromate in 500 ml. of water. The deep-red-brown solution was extracted immediately with 200 ml. of chloroform. The chloroform layer was separated and dried over anhydrous sodium sulfate, and the clear solution was concentrated to dryness under reduced pressure. The deep-red crystals of (monomeric) 4,5-dimethyl-*o*-benzoquinone which remained were washed with cold ether and dried; m.p. 95°, yield 2.9 g. (40%).

Anal. Calcd. for $C_8H_8O_2$: C, 70.55; H, 5.93; mol. wt., 136. Found: C, 69.91; H, 6.10; mol. wt., 110.[18]

Dimerization of 4,5-Dimethyl-*o*-benzoquinone.—Six grams of monomeric 4,5-dimethyl-*o*-benzoquinone was dissolved with heating in 20 ml. of glacial acetic acid, and 80 ml. of water was then added. After this mixture stood at room temperature for 8 days, 3.6 g. of precipitated dimer was collected, washed with water and dried. An additional 0.4 g. was recovered from the filtrate upon standing after further dilution with water. The combined precipitates were recrystallized several times from 2-propanol; m.p. of the recrystallized, yellow dimeric 4,5-dimethyl-*o*-benzoquinone was 178–180°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.55; H, 5.93; mol. wt., 272. Found: C, 70.30; H, 6.10; mol. wt., 284.[18]

To obtain *pure monomeric* and *pure dimeric* samples of 4,5-dimethyl-*o*-benzoquinone for spectroscopic studies and for the comparative condensation experiments given in Table I, the following chromatographic techniques were developed:

Purification of the Monomer by Partition Chromatography on Celite.—A solvent system and technique described by Kissman, *et al.*,[19] were applied with appropriate modifications. Fifty grams of acid-washed Celite 545 was thoroughly mixed with 25 ml. of the aqueous layer (used as the "stationary phase") from a solvent system consisting of water, methanol, *n*-heptane and benzene (1:2:3:1.5), and this was packed in layers into a chromatographic column of 50 mm. diameter. A solution of 0.3 g. of monomeric quinone in 4 ml. of "stationary phase," plus a few drops of methanol necessary for solution, was mixed with an additional 8 g. of acid-washed Celite and packed on top of the column. The column was then eluted with the "mobile phase" (*i.e.*, the organic layer from the above solvent mixture). After an initial 100–150 ml. forerun, a red band was eluted. This eluate gave, after evaporation of the solvent *in vacuo* at 30°, 0.1–0.2 g. of brilliant red needles, m.p. 91–93°.

Purification of the Dimer by Adsorption Chromatography on Florisil.—A column was prepared with 100 g. of Florisil (100–200 mesh) and ethyl acetate as the solvent. One gram of dimeric quinone was dissolved in a minimum volume of ethyl acetate and chromatographed through the column with the same solvent. Chromatography was continued until the yellow-colored eluate became colorless. (Any trace of reactive monomeric quinone remained on the column.) The residue after evaporation of the solvent was recrystallized from 2-propanol to give pure dimeric quinone, m.p. 179–180°.

Preparation of Compounds I–VIII.—The following general methods of condensation were employed: (a) **Acetic Acid Method.**—A solution of 1.8 meq. of 4,5-dimethyl-*o*-benzoquinone (*i.e.*, 0.9 millimole of dimer or 1.8 millimoles of monomer) in 5 ml. of glacial acetic acid was added to a boiling suspension of 1.8 millimoles of the pyrimidine (sulfate or bisulfite)[20] in 15 ml. of water. The mixture was refluxed for 2 hr., allowed to stand overnight at room temperature and then neutralized with concentrated NH_4OH. The precipitated solid was collected by centrifugation or filtration, washed with water and ethanol and dried.

(b) **Alkaline Method.**—A solution of 1.5 meq. of quinone in 10 ml. of water and 1 ml. of 10% sodium hydroxide was prepared without heating, and a solution of 1.5 millimoles of pyrimidine salt[20] was prepared similarly. The two clear solutions were combined and allowed to stand at room tem-

(15) It is also possible that bisulfite stabilizes the "diketone form" of the monomeric *o*-benzoquinone and prevents its conversion to the "peroxide form" postulated by Willstätter (ref. 9).

(16) In contrast to the quinoxaline syntheses in which the condensation between *o*-benzoquinones and aromatic diamines can be carried out in non-polar organic solvents.

(17) Both microbiological systems are described by T. J. Bardos, G. M. Levin, R. R. Herr and H. L. Gordon, THIS JOURNAL, **77**, 4279 (1955).

(18) Microanalyses and molecular weight determinations (in camphor) were performed by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. The monomeric quinone could not be dried completely because of its instability.

(19) H. M. Kissman, C. D. Pidacks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

(20) The pyrimidine sulfates (or the free amines) listed in Table II were obtained from commercial sources. The bisulfite of 2,4,5,6-tetraaminopyrimidine was prepared according to Mallette, *et al.* (ref. 6).

perature for 3 days. Precipitate was collected by filtration. (In the preparation of compounds I and III (Table II), neutralization with hydrochloric acid was necessary for the precipitation of the condensation products.) The almost pure products were washed with water and ethanol and dried. One recrystallization from a suitable solvent, as given in Table II, gave the analytically pure compounds.

(c) **Neutral Method.**—A solution of 1.5 millimoles of dimeric 4,5-dimethyl-*o*-benzoquinone in 20 ml. of 95% ethanol was added to 3.0 millimoles of the pyrimidine sulfate[20] dissolved in 100 ml. of water and neutralized with 10% sodium hydroxide. The final *p*H of the combined solutions was adjusted to 7.0, and the mixture was heated on the steam-bath for 4 hr. and then allowed to stand at room temperature for 1–3 days. The precipitate was collected, washed and dried, as above. One recrystallization from the appropriate solvent (Table II) gave the analytically pure product.

CHICAGO 9, ILLINOIS

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Various Reactions of Organic Bases with 1,1,1-Trinitroethane and 1-Halo-1,1-Dinitroethanes. 1,1-Dinitroethene as a Reaction Intermediate[1]

BY LAWRENCE ZELDIN[2] AND HAROLD SHECHTER[3]

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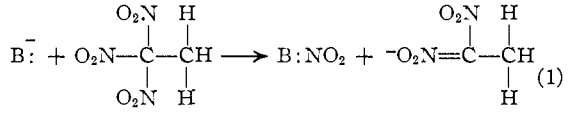
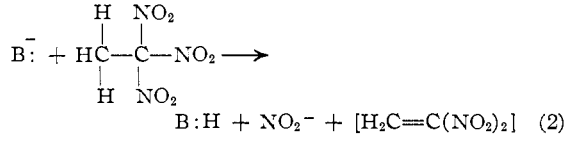
Bases undergo two reactions with 1,1,1-trinitroethane: (1) nucleophilic attack on one of the nitro groups effecting displacement of the 1,1-dinitroethane anion and (2) elimination of nitrous acid to give 1,1-dinitroethene, a reactive intermediate; 1,1-dinitroethene undergoes addition of the bases to yield β-substituted derivatives of 1,1-dinitroethane. Bases which react with 1,1,1-trinitroethane by sequence 1 are potassium salts of 2-nitropropane, 2,4-pentanedione and 1-butanethiol, respectively, and *n*-butyllithium. Bases which react by sequence 2 are potassium diethyl malonate, guanidine, piperidine and trimethylamine (and triethylamine); the products derived by addition to 1,1-dinitroethene are potassium ethyl 2-carbethoxy-4,4-dinitrobutyrate (I), 2-guanidino-1,1-dinitroethane (VI), 1,1-dinitro-2-piperidinoethane (VII) and trimethylammonium N-(2-nitroethyl-2-nitronate) (VIII). Exchange reactions of VIII with guanidine and with piperidine yield VI and VII. Reactions of piperidine with either 1-bromo-1,1-dinitroethane or 1-chloro-1,1-dinitroethane and of sodium diethyl malonate with 1-bromo-1,1-dinitroethane result in reductive attack on halogen with displacement of the 1,1-dinitroethane anion.

1,1,1-Trinitroethane undergoes two general reactions with bases: (1) attack of the base on one of the nitro groups (equation 1) resulting in displacement of the 1,1-dinitroethane anion[4a]; this reaction involves reduction of 1,1,1-trinitroethane and results in transfer of a (positive) nitro group[4b] to the attacking base, and (2) reaction of the base with a β-hydrogen resulting in elimination of nitrous acid and formation of 1,1-dinitroethene as an (unisolated) intermediate

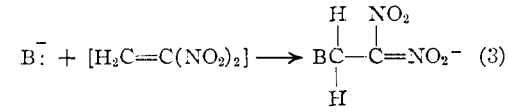


(1)

Subsequent Michael addition of the base to 1,1-dinitroethene yields a β-substituted anion of 1,1-dinitroethane (equations 2 and 3).[4c,d] Thus reac-



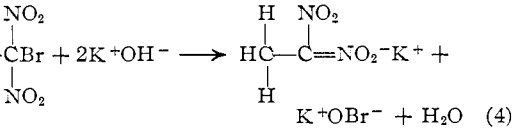
(2)



(3)

tions of 1,1,1-trinitroethane with aqueous potassium hydroxide[4a] or with hydroxylamine in potassium methoxide[4d] result in formation of potassium 1,1-dinitroethane in excellent yields (equation 1), whereas 1,1,1-trinitroethane reacts with potassium ethoxide[4c] or ethanolic potassium hydroxide,[4a] potassium methoxide[4c] and ethanolic potassium cyanide[4d] to give potassium salts of ethyl 2,2-dinitroethyl ether (~ 80%), methyl 2,2-dinitroethyl ether (~ 80%) and 3,3-dinitropropionitrile (80%), respectively.

The reactions of 1-bromo-1,1-dinitroethane with aqueous or alcoholic potassium hydroxide[5a] (equation 4), aqueous potassium carbonate,[5a] hydrazine and potassium hydroxide[5b] and potassium iodide[5c] also have been investigated and are found to involve reductive attack on (positive) bromine and formation of potassium 1,1-dinitroethane. No evidence has been obtained for processes of the elimination–addition type involving formation of 1-bromo-1-nitroethene or 1,1-dinitroethene as reaction intermediates.



(4)

As a result of the facts that: (1) there are, as yet, at least two uncorrelated reactions of bases

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(2) (a) Deceased, September 3, 1955. (b) Taken in part from a dissertation submitted by L. Zeldin to the Graduate School of The Ohio State University in partial fulfillment of the requirements for the Ph.D. degree, June, 1951.

(3) To whom inquiries with respect to this research should be made.

(4) (a) A. Hantzsch and A. Rinckenberger, *Ber.*, **32**, 628 (1899). (b) This reaction is presumed to involve attack of the base on the positive nitrogen atom of a nitro group. An alternate possibility, though less attractive, involves displacement attack on oxygen of a nitro group to give the corresponding nitrito derivative. These two possible processes can not be differentiated from the results of present investigations. (c) J. Meisenheimer, *Ber.*, **36**, 434 (1903). (d) J. Meisenheimer and M. Schwarz, *ibid.*, **39**, 2543 (1906).

(5) (a) E. ter Meer, *Ann.*, **181**, 1 (1876); (b) E. L. Hirst and A. K. Macbeth, *J. Chem. Soc.*, **121**, 2169 (1922); (c) K. Klager, *Anal. Chem.*, **23**, 534 (1951).