[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Some Derivatives of Malondialdehyde

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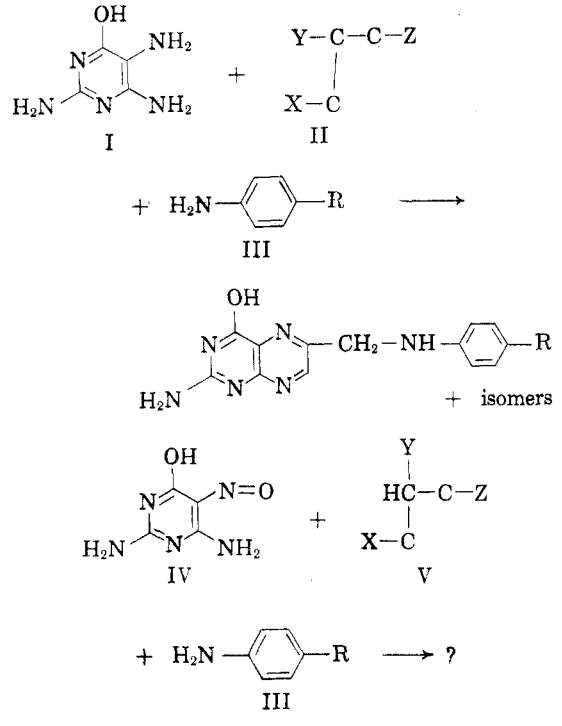
Sodium nitromalondialdehyde (NMA), prepared by several methods, has been condensed with *p*-aminobenzoic acid (PABA) and its methyl ester. The further condensation of these products, and of NMA, with certain pyrimidines in order to give pteridines, has been investigated. Some similar reactions with malondialdehyde tetramethyl acetal (MTA) have also been studied. Infrared data from some of the compounds are reported.

Pteroylglutamic acid has been synthesized in a number of laboratories.[3] Many of these syntheses are based on the simultaneous condensation of the triaminopyrimidine (I), a three-carbon intermediate (II) with a reactive group (X, Y, Z, *e.g.*, halogen, ketone, hydroxyl) at each carbon atom (as in e.g., dibromopropionaldehyde, reductone, etc.), and *p*-aminobenzoylglutamic acid (III). As each reactive group may theoretically condense with any of the amino groups, many different reactions, leading to the formation of various isomers, are possible; this usually leads to considerable difficulties in the purification of the product. It is only recently that a synthesis has been reported[31] in which intermediates of high purity were isolated.

It seemed worthwhile to investigate the condensation of a 4-amino-5-nitrosopyrimidine (IV), with a suitable three-carbon intermediate (V) and III, to see if by this means the formation of isomers could be avoided. That this type of reaction is feasible has subsequently been shown by Timmis and his coworkers[4]; however, all their products were 6,7-disubstituted pteridines, most of them polynuclear compounds.



It was decided to investigate malondialdehyde derivatives as intermediates in the proposed reaction. Nitromalondialdehyde (NMA) may be prepared in somewhat variable yield (about 35%)[5] from mucobromic acid, which is tedious to prepare.[6] We have found that it may be prepared from two commercially available compounds, β-bromo-α-chloro-β-formylacrylic acid (in 26% yield) and from mucochloric acid (in 13% yield). NMA condenses with PABA to give *p*-(*2-formyl-2-nitroethylideneamino*)*benzoic acid* (VI) and a small quantity of the di-condensation product, *p*-[3-(*p'-carboxyphenyl-*)*imino-2-nitropropylideneamino*]*benzoic acid* (VII). Similarly, with PABA methyl ester, NMA

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(3) (a) Waller, Hutchings, Mowat, Stockstad, Boothe, Angier, Semb, SubbaRow, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 19 (1948); (b) Hultquist, Kuh, Cosulich, Fahrenbach, Northey, Seeger, Sickles, Smith, Angier, Boothe, Hutchings, Mowat, Semb, Stockstad, SubbaRow, and Waller, *J. Am. Chem. Soc.*, **70**, 23 (1948); (c) Angier, Stockstad, Mowat, Hutchings, Boothe, Waller, Semb, SubbaRow, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 25 (1948); (d) Boothe, Waller, Stockstad, Hutchings, Mowat, Angier, Semb, SubbaRow, Couslich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 27 (1948); (e) Karrer and Schwyzer, *Helv. Chim. Acta*, **31**, 777 (1948); (f) Weygand, Wacher, and Schmied-Kowarzik, *Chem. Ber.*, **82**, 25 (1949); (g) Weygand and Schmied-Kowarzik, *Chem. Ber.*, **82**, 333 (1949); (h) King and Spensley, *J. Chem. Soc.*, 144 (1952); (i) Forrest and Walker, *J. Chem. Soc.*, 2002 (1949); (j) Tschesche, Korte, and Peterson, *Chem. Ber.*, **84**, 579 (1951); (k) Weisblat, Magerlein, Hanze, Myers, and Rolfson, *J. Am. Chem. Soc.*, **75**, 3625 (1953); (l) Sletzinger, Reinhold, Grier, Beachem, and Tishler, *J. Am. Chem. Soc.*, **77**, 6365 (1955).

(4) (a) Felton and Timmis, *J. Chem. Soc.*, 2881 (1954); (b) Spickett and Timmis, *J. Chem. Soc.*, 2887 (1954); (c) Osdene and Timmis, *J. Chem. Soc.*, 2214 (1955).

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

(6) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, **27**, 60 (1947).

gives *methyl* p-(2-*formyl*-2-*nitroethylideneamino*)*benzoate* (VIII).

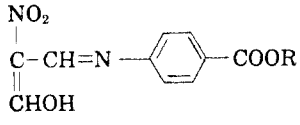
The condensation of NMA, VI, and VIII with a number of pyrimidines (see Table I) was investigated.

TABLE I
PYRIMIDINE SUBSTITUENTS

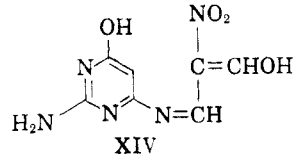
Compound	2	4	5	6	Reference
IV	NH_2	NH_2	NO	OH	7
X	CH_3S	NH_2	NO	OH	7
XI	NH_2	NH_2	NO	OC_2H_5	7
XII	NH_2	NH_2		OH	7
XIII	NH_2	NH_2	Br	OH	7

No condensation products could be isolated in a pure state from the reactions of NMA, VI, or VIII with the pyrimidines IV, X, or XI. The reactions with IV had to be carried out in aqueous alkali; with X and XI, which were used because of their greater solubility, acetic acid or sodium in ethylene glycol were used as media.

NMA condenses with (XII) to give 2-*amino*-6-*hydroxy*-4-(2′-*nitro*-2′-*formylethylideneaminopyrimidine* (XIV), isolated as the sodium salt. Acidification gave a colorless, highly insoluble solid. An attempted nitrosation led to the isolation of the free form of XIV. The condensation of VI with XII unexpectedly also gave XIV as the product. No reaction took place with XIII under the same conditions, the sodium salt of XIII being recovered.



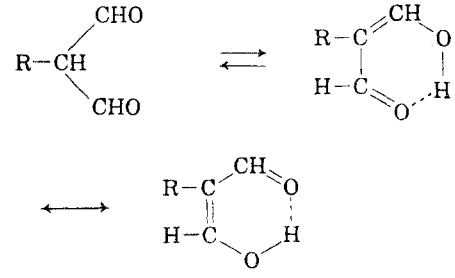
VI R = H
VIII R = CH_3



XIV

The reactivity and structure of malondialdehyde derivatives has received some attention. Most of these compounds do not very readily form dicondensation products, such as dianils or pyrimidines. Thus phenylmalondialdehyde (XV), and the closely related phenylmalononitrile and α-formylphenylacetonitrile, do not condense with guanidine.[8] XV gives only a monoanil[9] whereas the methyl ether of XV readily gives a dianil and reacts with guanidine to form a pyrimidine.[10] On the basis of these results, it has been suggested[9] that XV should be considered as hydroxymethylene phenylacetaldehyde.

In a review,[11] Eistert mentions that bromomalondialdehyde (XVI) and reductone[12] (XVII) also give only monoanils, and these compounds all give enol ethers with diazomethane. He considers that the *cis*-enol form is stabilized by a chelate ring (see Figure 1) which can still be formed in the monoanil, but not in the dianil. (It is interesting to note that chloromalondialdehyde condenses with N-methylaniline to give a colorless product; all the other anils mentioned are yellow. No tautomerism, chelation, or conjugation with the benzene ring is possible in this compound.)



XV R = C_6H_5
XVI R = Br
XVII R = OH
XVIII R = NO_2

Fig. 1

NMA (XVIII), which, like the above malondialdehyde derivatives has an electron-withdrawing group on the central carbon atom, may be slightly more reactive; it gives a dianil with aniline, though only a monoanil with aniline hydrochloride.[13] Urea gives principally a mono-ureide, but guanidine, in the presence of piperidine, reacts to give a pyrimidine.[14] As has been shown, it gives mono- and di-condensation products with PABA. Nevertheless, it is clear that the first condensation takes place much more readily than the second, and that the second may not take place if the other reactant does not contain a sufficiently basic amino group. Consequently an attempt was made to methylate

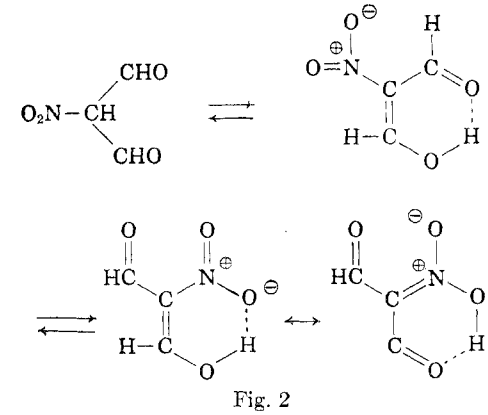


Fig. 2

(7) Ulbricht and Price, *J. Org. Chem.*, **21**, 567 (1956).
(8) Russell and Hitchings, *J. Am. Chem. Soc.*, **74**, 3443 (1952).
(9) Rupe and Knup, *Helv. Chim. Acta*, **10**, 299 (1927).
(10) Rupe and Knup, *Helv. Chim. Acta*, **30**, 846 (1927).
(11) Eistert, *Arkiv. Kemi.*, **2**, 129 (1950).
(12) Reductone also gives a monocondensation product with PABA (Euler and Hasselquist, *Rec. trav. chim.*, **69**, 402 (1950)).
(13) Hill and Torrey, *Am. Chem. J.*, **22**, 89 (1899).
(14) Hale and Brill, *J. Am. Chem. Soc.*, **34**, 82 (1912).

XVIII with diazomethane, since the enol ether should be more reactive; but no product could be isolated. This may be because in NMA (and in a monocondensation derivative) tautomerism and chelation is also possible with the nitro group (see Figure 2) to give a nitronic acid.

Malondialdehyde tetramethyl acetal (MTA) condenses with PABA to give *p-(2-formylethylideneamino)benzoic acid* (XIX); difficulties in purification were probably due to the simultaneous formation of the di-condensation product, though this was not isolated (some higher-melting material, however, was obtained). With tosyl-PABA,[3k] which should only give a mono-condensation product, no reaction occurred. With the pyrimidine X in 90% formic acid, MTA reacted to give a product insoluble even in concentrated aqueous alkali.

Reaction appeared to occur between XIX and the pyrimidine XI, using sodium acetate in ethylene glycol, but no crystalline derivative could be isolated. The work of Spickett and Timmis[4b] indicated that the solubility of the nitrosopyrimidine was an important factor, *e.g.*, IV cannot be condensed with β-naphthol, though certain more soluble pyrimidines do react. The condensation of the more soluble XI with β-naphthol, using the conditions of Spickett and Timmis, was therefore carried out, but no pteridine was isolated.

Infrared data for some of the compounds are summarized in Table II.

TABLE II

INFRARED SPECTRA FOR VARIOUS COMPOUNDS IN POTASSIUM BROMIDE DISCS[a]

VI[b]		VIII[c]		XIV[d]		IV[e]		XII[f]	
ν	% Abs.	ν	% Abs.	ν	% Abs.	ν	% Abs.	ν	% Abs.
3100–2900	40	3200	39	3550	48	3300–3000	93	3260	87
		2940	24	3470	58			3230	83
1690	58	1725	72	3360	74	1700	93	3100–3060	94
1650	69	1680	26	3160	57	1610–30	95		
1620	57	1655	78	3050	55	1500	94	1550–1670	95
1600	77	1625	67	1570–1620	95	1355	81		
1570	74	1600	76			1310	92	1460	84
1480	56	1580	74	1500–25	93	1255	91	1365	81
1430	43	1495	61	1440–60	92	1140–50	89	1280	78
1355	65	1430	53	1485	51			1245	65
1270–80	80	1310	86	1310–40	95			1175	45
1180	51	1265	90	1245	86			1135	50
1130	42	1175	58	1155	61				
		1120	40	1105	59				
		1100	59						

[a] In a Perkin-Elmer twin beam instrument. [b] *p*-(2-Formyl-2-nitroethylideneamino)benzoic acid. [c] Methyl *p*-(2-formyl-2-nitroethylideneamino)benzoate. [d] 2-Amino-6-hydroxy-4-(2′-nitro-2′-formylethylideneamino)pyrimidine. [e] 2,6-Diamino-4-hydroxy-5-nitrosopyrimidine. [f] 2,6-Diamino-4-hydroxypyrimidine.

EXPERIMENTAL[15]

Mucobromic acid.[6] An improved yield is obtained by using furoic acid recrystallized from carbon tetrachloride (charcoal), and by concentrating the mother liquors from the reaction (in a hood). Yield, after recrystallization from water, 72% (lit.,[6] 60%).

Sodium nitromalondialdehyde (NMA) (XVIII). (a) *From mucobromic acid*[5]: Yield, about 35%.

(b) *From β-bromo-α-chloro-β-formylacrylic acid:* The acid (42.4 g.) in ethanol (100 ml.) was added to a solution of sodium nitrite (55.2 g.) in water (100 ml.) with stirring, at 58–60° during 30 min. Stirring was continued for 1 hr., without external heating. The solution was reheated to 60°, and left in the refrigerator overnight. The solid (11.2 g.) was filtered and crystallized from 75% ethanol, giving 7.14 g. (26%) of XVIII. In an experiment identical except that during the additional 1 hr. stirring the temperature was maintained at 60°, the yield was reduced to 18%.

(c) *From mucochloric acid:* Mucochloric acid (33.8 g.) was added in solution, as above, in 25 min., a little external cooling being necessary to keep the temperature from rising above 60°. After stirring for a further 35 min. and cooling overnight, the solid was filtered and extracted with boiling 75% ethanol (70 ml.), which, on cooling, gave 2.83 g. of NMA. The mother liquor was used to extract the residue, giving another 0.69 g.; total yield 3.52 g. (13%). No NMA at all was obtained when the reaction was carried out using twice the concentrations above, at 50–54°; nor when the addition was carried out at 35–40°, followed by raising the temperature to 58°.

p-(2-Formyl-2-nitroethylideneamino)benzoic acid (VI) *and p-(3-(p′-carboxyphenylimino)-2-nitropropylideneamino)benzoic acid* (VII). To a stirred solution of NMA (6.3 g.) in water (45 ml.) was added a solution of PABA (6.0 g.) in water (60 ml.) containing sodium hydroxide (1.9 g.) in 75 min. After standing for 5 hr., the solution was acidified with hydrochloric acid, filtered, and washed with water, and recrystallized from glacial acetic acid, giving yellow crystals of *p-(formyl-2-nitroethylideneamino)benzoic acid;* yield, 8.7 g. (82%). After further recrystallization from acetic acid it had m.p. 265°, dec.

Anal. Calcd. for $C_{10}H_8O_5N_2$: C, 50.9; H, 3.4; N, 11.8. Found: C, 51.3; H, 3.6; N, 12.0.

If the recrystallization is carried out so that not quite all the solid goes into solution, the residue may be recrystallized separately from acetic acid, giving a small variable quantity (about 300 mg.) of orange crystals of *p-(3-(p′-carboxyphenylimino)-2-nitropropylideneamino)-benzoic acid,* m.p. 329°, dec. (rapid heating after insertion at 315°).

(15) Melting points are uncorrected. Where no melting point is given, the compound either decomposes on heating, or does not melt below 300°. Analyses are by Microtech Inc., Skokie, Ill., and by Drs. Weiler and Strauss, Oxford, England.

Anal. Calcd. for $C_{17}H_{13}O_6N_3$: C, 57.4; H, 3.7; N, 11.8. Found: C, 57.0; H, 3.7; N, 12.1.

VII may also be prepared by the condensation of VI with PABA in methanol or aqueous alkali.

Methyl p-(2-formyl-2-nitroethylideneamino)benzoate (VIII). A solution of PABA methyl ester (5.1 g.) in aqueous methanol (80%, 50 ml.) containing piperidine (4 drops) was slowly added to a solution of NMA (4.7 g.) in aqueous methanol (60%, 75 ml.) with stirring, during 1.5 hr. After standing for 4 hr., the solution was concentrated under reduced pressure, during which the sodium salt of VIII crystallized. The mixture was acidified with 20 ml. of 2 *N* hydrochloric acid, filtered, and the product recrystallized from methanol. The yield of yellow crystals of *methyl p-(2-formyl-2-nitro-ethylideneamino)benzoate* was 6.26 g. (74%). It was purified by further crystallization from methanol, m.p. 186–188°.

Anal. Calcd. for $C_{11}H_{10}O_5N_2$: C, 52.8; H, 4.0; N, 11.2. Found: C, 52.7; H, 3.9; N, 11.3.

2-Amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)-pyrimidine (XIV). (a) *From NMA.* NMA (1.0 g.) and XII (1.0 g.) were heated together in water (10 ml.) for 1 hr. at 120° (oil bath). After cooling, the yellow sodium salt was filtered, giving 1.4 g. of the *sodium salt* of *2-amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)-pyrimidine.* The product was recrystallized from aqueous sodium hydroxide.

Anal. Calcd. for $C_7H_6O_4N_5Na.{}^1/_2H_2O$: C, 32.8; H, 2.7; N, 27.4; Na, 8.9. Found: C, 32.5; H, 2.6; N, 27.3; Na, 9.1.

(b) *From VI.* VI (1.0 g.) and XII (0.58 g.) in water (25 ml.) containing sodium hydroxide (0.39 g.) were refluxed for 15 min., and again after standing overnight. After cooling, 1 g. of yellow solid was collected. Recrystallization from dilute aqueous sodium hydroxide gave the pure *sodium salt* of *XIV.*

Anal. Calcd. for $C_7H_6O_4N_5Na\cdot{}^1/_2H_2O$: C, 32.8; H, 2.7; N, 27.4. Found: C, 32.6; H, 2.8; N, 27.3.

Attempted nitrosation of XIV; isolation of free XIV. To a solution of the sodium salt of XIV sodium nitrite was added, and the solution was acidified with acetic acid. A solid separated from the yellow solution, but there appeared to be no nitrosation (no change in color). The solution was heated until gas was evolved, and hydrochloric acid was then added until most of the solid dissolved. After filtration and cooling, ammonia was added to *p*H 7. The solid which separated was filtered and dried, and was *2-amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)pyrimidine.*

Anal. Calcd. for $C_7H_7O_4N_5$: C, 37.4; H, 2.9; N, 30.4. Found: C, 37.3; H, 3.1; N, 30.6.

p-(2-Formylethylideneamino)benzoic acid (XIX). To a solution of ammonium chloride (10 g.) in water (50 ml.) MTA (6.3 g.) was added. After stirring at 60° for 15 min., a solution of PABA (5.0 g.) in aqueous methanol (50%, 100 ml.) was added in 5 min. to the yellow solution, the color changing to reddish brown. Heating and stirring at 60° were continued for 25 min., and stirring at room temperature for 5 hr. The product was filtered, giving 6.2 g. of *p-(2-formylethylideneamino)-benzoic acid.* After several recrystallizations it was obtained as orange-brown crystals, m.p. 247–248°, dec.

Anal. Calcd. for $C_{10}H_9O_3N$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.3; H, 5.0; N, 7.8.

When the condensation was carried out in 50% methanol at 50°, most of the PABA was recovered unchanged. When 10% hydrochloric acid was used in place of ammonium chloride, at 60°, the yield was 7.3 g., but the product was darker and much more difficult to purify.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, DE PAUL AND PURDUE UNIVERSITIES]

Improved Method for the Synthesis of Alkyl Azides[1]

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An improved method has been devised for the preparation of alkyl azides involving the use of Carbitols as solvents for the interaction of an alkyl halide and sodium azide. The method eliminates the hazards and restrictions of sealed tubes and the formation of troublesome azeotropes. Utility of the procedure is demonstrated by the preparation of seven *n*-alkyl- and two cycloalkyl azides with yields from 64.4 to 99.6%, considerably higher than previously reported. Five new *n*-alkyl azides are described: propyl, pentyl, heptyl, octyl, and decyl azides.

Although 1-azido-2-methylbutane (one of the amyl azides) has been prepared by Levene and Rothen[3] using a sealed tube reaction, pure pentyl azide has not been hitherto prepared. Inasmuch as it was desired as an intermediate, a study of its preparation was carried out. The name 1-azido-pentane can be found in *Chemical Abstracts.*[4] An examination of the original literature[5] disclosed that the product was really a mixture of isomeric amyl azides since it was prepared from mixed amyl iodides (b.p. 140–148°) and silver azide. The boiling point given[5] for the isomeric amyl azides was 121–130°.

Pentyl azide was prepared from pentyl iodide and activated sodium azide.[6] Precaution was taken to wash the pentyl iodide with saturated sodium sulfite solution and to distil it under vacuum in the presence of deposited silver. In order to avoid the use of a sealed tube, the reaction was carried out in boiling propyl alcohol. In working up the product mixture, an effort was made to remove the propyl alcohol by diluting with water and then extracting the ether solution with saturated salt solutions. However, due to the incomplete removal of propyl alcohol, considerable difficulty was encountered in isolating the desired pentyl azide. Although the

(1) This study was supported by a grant from the Office of Naval Research.

(2) De Paul University, to whom all requests for reprints and additional information should be addressed.

(3) Levene and Rothen, *J. Biol. Chem.*, **115**, 415 (1936).

(4) *Chem. Abstrs.*, **46**, 10440 (1952).

(5) Werle and Fries, *Biochem. Z.*, **322**, 511 (1952).

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