The observed abnormal course of the nitrosation of acylated 1,2-diaminoethenes with formation of highly reactive addition products to the double bond which on subsequent alcoholysis or hydrolysis yield the corresponding alkoxy derivatives or glycols is apparently caused by the two electron-releasing groups symmetrically positioned to the thereby activated double bond. Similar reactions have already been observed by Ruggli *et al.* in the case of I[3] and with 3,4-diphenylimidazolinone-2.[5] The well-known oxidation of uric acid to uric acid glycol may also belong to this kind of reaction.[6]

EXPERIMENTAL[7]

Starting materials. The *1,2-di(benzoylamino)ethene* (I) was obtained according to Ruggli[3] in a 77% yield, m.p. 212–213°, while *1,2-di(carbethoxyamino)ethene* (II) was prepared similarly from imidazole (5 g.) and ethyl chloroformate (50 g.) at 0°. The crude product of 14.4 g. (96.5%) was recrystallized from ligroin or aqueous alcohol to yield colorless crystals, m.p. 139–141°.

Anal. Calcd. for $C_8H_{14}N_2O_4$: C, 47.51; H, 6.97; N, 13.85. Found: C, 47.48; H, 6.90; N, 13.89.

II is soluble in concd. hydrochloric acid but after several minutes at room temperature the color of the solution changes to a greenish black due to decomposition.

To 2 g. of II in 60 ml. of absolute alcohol 20 mg. of $PdCl_2$ was added and the mixture hydrogenated at room temperature. The calculated amount of hydrogen was consumed in 44 min. The Pd was filtered off and after evaporation of the alcohol *in vacuo* 1.7 g. (85%) of 1,2-di(carbethoxyamino) ethane, m.p. 114°, was obtained. The mixed melting point with an authentic sample prepared from ethylenediamine and ethyl chloroformate[8] showed no depression.

1,2-Diethoxy-1,2-di(benzoylamino)ethane (IIIa). To a suspension of I (2 g.) in 50 ml. of absolute alcohol isoamyl nitrite (1.8 g.) was added and dry hydrogen chloride bubbled through the reaction mixture at 0°. A blue green coloration developed immediately and within 2 hr. all material went into solution. Water was added to the now colorless, ice-cooled reaction mixture whereupon 1.3 g. (49%) of crude IIIa, m.p. 169–173°, separated. After one recrystallization from ethanol the melting point rose to 240–242°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.78; N, 7.85. Found: C, 67.27; H, 6.78; N, 7.89.

1,2-Diethoxy-1,2-di(carbethoxyamino)ethane (IIIb) was obtained analogously from II (3 g.) and isoamyl nitrite (3.5 g.). Also in this case an immediate deep blue coloration was observed which changed soon to dark green, whereupon crystallization of IIIb started. After 20 min. 1.6 g. (37%) of colorless needles, m.p. 148°, were obtained. After one recrystallization from water IIIb melted at 151–152°.

Anal. Calcd. for $C_{12}H_{24}N_2O_6$: C, 49.30; H, 8.27; N, 9.58. Found: C, 49.18; H, 8.29; N, 9.69.

With an excess of ethyl nitrite instead of isoamyl nitrite the reaction yielded IIIb in a 69% yield. With isopropyl alcohol and isoamyl nitrite II yielded 57% of *1,2-diisopropoxy-1,2-di(carbethoxyamino)ethane* (IV), colorless needles from aqueous isopropyl alcohol, m.p. 159–161°.

Anal. Calcd. for $C_{14}H_{28}N_2O_6$: C, 52.48; H, 8.81; N, 8.74. Found: C, 52.81; H, 8.49; N, 8.74.

The reaction of II (1 g.) with isoamyl nitrite (1 g.) and hydrogen chloride in ethylene glycol (30 ml.) yielded analogously *2,3-di(carbethoxyamino)-1,4-dioxane* (V) (1.1 g., 85%), colorless needles after recrystallization from ethanol, m.p. 190–191°.

Anal. Calcd. for $C_{10}H_{18}N_2O_6$: C, 45.79; H, 6.91; N, 10.67. Found: C, 45.80; H, 6.75; N, 10.76.

1,2-dihydroxy-1,2-di(benzoylamino)ethane (VI). A solution (1.1 g.) of sodium nitrite in 10 ml. of water was added dropwise at 0° to a suspension of I (2 g.) in 100 ml. of concd. HCl. Each drop caused immediately a blue coloration which faded quickly to yellow. After stirring for 1 hr., 1 g. of unchanged starting material was filtered off. Addition of water to the filtrate yielded a crystalline precipitation of VI (0.8 g., 70%), m.p. 168–177°. Repeated recrystallization from alcohol separated this material into approximately equal amounts of a more soluble fraction, m.p. 162–164° and into a soluble fraction, m.p. 180–182°. The lower melting product was identical with the product obtained by Ruggli.[3] The higher melting isomer gave the following analytical data:

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.55; H, 4.98; N, 9.53.

When the higher melting isomer was sublimed in a vacuum benzamide, m.p. 132–133°, was obtained besides polyglyoxal. An attempted hydrolysis of VI with 40% aqueous KOH yielded benzoic acid as the only isolable product.

1-Carbethoxy-4,5-diethoxyimidazolidinone-2 (VIII). When the reaction of II (3 g.) and isoamyl nitrite (3.5 g.) in absolute ethanol with hydrogen chloride was carried on for 2 hr., the originally formed crystals went again into solution. To remove the excess of hydrochloric acid, potassium carbonate was added and then the solvent removed *in vacuo*. The residue was extracted with boiling ethanol from which 1.1 g. (30%) of VIII crystallized on cooling. M.p. 200–202°.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: C, 48.78; H, 7.36; N, 11.37. Found: C, 49.02. H, 7.43; N, 11.03.

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Benzo-1,2,3-triazines

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Recent work has demonstrated that amino-chlorobenzo-1,2,4-triazines possess remarkable pharmacological properties.[2] It seemed, therefore, of interest to investigate some representatives of the benzo-1,2,3-triazine series.

Benzo-1,2,3-triazines substituted in the 4-position are generally obtained by the diazotization of *o*-aminobenzoic acid derivatives. The desired 4-aminobenzo-1,2,3-triazine (I) and 4-hydrazino-benzo-1,2,3-triazine (II), however, were not accessible by this route, since *o*-aminobenzamidine and *o*-aminobenzamidrazone could not be prepared from *o*-aminobenzonitrile. The reluctance of *o*-

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

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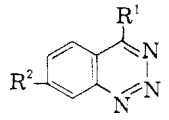
aminobenzonitrile to addition at the C≡N bond has already been observed by Pinner.[3] Compounds I and II could be obtained from the easily accessible 4-thiomethylbenzo-1,2,3-triazine[4] (III) by reaction with ammonia resp. hydrazine at room temperature, while 7-chloro-4-mercaptobenzo-1,2,3-triazine (IV) reacted with hydrazine to 7-chloro-4-hydrazinobenzo-1,2,3-triazine (V). The 4-hydroxylamino-7-chlorobenzo-1,2,3-triazine (VIII) and the 4-hydroxylamino-7-methoxybenzo-1,2,3-triazine (X) were prepared by diazotization of the corresponding substituted *o*-aminobenzamidoximes. By-products in this reaction were the 7-chloro-4-hydroxybenzo-1,2,3-triazine (IX) and the 7-methoxy-4-hydroxybenzo-1,2,3-triazine (XI).

The attempted reduction of VIII with sodium borohydride in methanol led to 2-amino-4-chlorobenzonitrile (XII) in a quantitative yield. This result was somewhat surprising since reduction of 4-hydroxybenzo-1,2,3-triazine with zinc dust and ammonium hydroxide yielded indazolone.[5] It was then found that the conversion of VIII to XII is achieved by mild alkalies as sodium carbonate or sodium bicarbonate alone. The reduction of VIII to XII is, therefore, an intramolecular process, presumably preceded by ring cleavage of VIII to the *o*-diazonium hydroxide of the benzamidoxime. A somewhat similar cleavage of condensed pyrimidine derivatives was recently reported by Taylor.[6]



	R^1	R^2
I	NH_2	H
II	$NH{\cdot}NH_2$	H
III	SCH_3	H
IV	SH	Cl
V	$NH{\cdot}NH_2$	Cl
VIII	NHOH	Cl
IX	OH	Cl
X	NHOH	OCH_3
XI	OH	OCH_3

Several of the above described benzotriazines were tested pharmacologically, but none of them showed any outstanding action, X being the best with an adrenergic blocking action similar to apresoline, but only 1/30 as active.[7]

EXPERIMENTAL[8]

4-Aminobenzo-1,2,3-triazine (I). Anhydrous ammonia was bubbled for 6 hr. into the alcoholic solution of III (1.9 g.) with ice-cooling. After 4 days at room temperature 930 mg., m.p. 278–279° (dec.) crystallized from the alcoholic solution. The crude material (60%) was recrystallized from alcohol or glacial acetic acid, melting at 284–285°.

Anal. Calcd. for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.41; H, 3.96; N, 38.00.

The hydrochloride was prepared by dissolving I in a mixture of 2*N* hydrochloric acid–methanol and evaporation *in vacuo*, m.p. 160–163° (dec.).

4-Hydrazinobenzo-1,2,3-triazine (II). To III (2 g.) in 30 ml. of alcohol 0.6 g. of hydrazine hydrate was added. An immediate evolution of methylmercaptan was observed. After standing overnight 1 g. (55%) was obtained which was recrystallized from ethanol, melting at 191–192° (dec.).

Anal. Calcd. for $C_7H_7N_5$: N, 43.45. Found: N, 43.79.

7-Chloro-4-mercaptobenzo-1,2,3-triazine (IV). To a solution of 2-amino-4-chlorobenzonitrile[9] (4.5 g.) in 25 ml. of pyridine triethylamine (3 g.) was added and H_2S passed into the reaction mixture for 4 hr. at room temperature. The mixture was then poured into 200 ml. of water whereupon a dark oil separated which became solid on shaking. The crude 2-amino-4-chlorobenzothioamide thus obtained was recrystallized from water to yield 4.3 g. (78%), m.p. 150–151°.

Anal. Calcd. for $C_7H_7ClSN_2$: N, 15.00; S, 17.17. Found: N, 14.87; S, 17.08.

To dilute HCl cooled to 0° 2 g. of 2-amino-4-chlorobenzothioamide was added followed by the dropwise addition of $NaNO_2$ (0.8 g.) in water. The colorless crystals changed gradually to a yellow amorphous material. Crystallization of the crude material from alcohol yielded 1.4 g. (67%) of IV, melting at 215–217° (dec.).

Anal. Calcd. for $C_7H_4ClSN_3$: C, 42.53; H, 1.53; N, 21.26. Found: C, 43.08; H, 1.52; N, 21.29.

4-Hydrazino-7-chlorobenzo-1,2,3-triazine (V). Hydrazine hydrate (0.4 g.) was added to IV (1 g.) in alcohol. An immediate evolution of H_2S was observed. After refluxing for 3 hr. the precipitated colorless needles were collected on a filter. The product was recrystallized from dioxane to yield 0.8 g. (80%), m.p. 195–198° (dec.).

Anal. Calcd. for $C_7H_6ClN_5$: N, 35.80: Found: N, 35.66.

2-Amino-4-chlorobenzamidoxime (VII). To 2-amino-4-chlorobenzonitrile (8 g.) in 150 ml. of absolute alcohol hydroxylamine hydrochloride (3.7 g.) and sodium (2.4 g.) was added and the mixture refluxed for 20 hr., diluted with water, and extracted with ether. Evaporation of the dried solvent yielded 8.5 g. (86%), melting at 127–128° after recrystallization from alcohol–water.

Anal. Calcd. for $C_7H_8ClN_3O$: C, 45.29; H, 4.34; N, 22.63. Found: C, 45.31 H, 4.26; N, 22.62.

4-Hydroxylamino-7-chlorobenzo-1,2,3-triazine, hydrate (VIII). To the ice-cooled solution of 10.5 g. of the preceding product in dilute hydrochloric acid, sodium nitrite (3.9 g.) in water was added dropwise. Every drop caused precipitation of the bright yellow benzo-1,2,3-triazine derivative. After filtering off and washing with water VIII was recrystallized from aqueous alcohol whereby 7.6 g. (70%) of bright yellow needles of VIII, m.p. 205–206° (dec.) was obtained in form of the hydrate.

Anal. Calcd. for $C_7H_5ClN_4O{\cdot}H_2O$: C, 39.12; H, 3.28; N, 26.17; Cl, 16.51. Found: C, 39.57; H, 3.55; N, 26.12; Cl, 16.44.

A small amount of crystals precipitating from the mother liquors were identified as *7-chloro-4-hydroxybenzo-1,2,3-triazine* (IX) by mixed melting point with an authentic sample prepared as follows:

2-Amino-4-chlorobenzamide[10] was prepared in a quantitative yield by heating 2-amino-4-chlorobenzonitrile with 85% sulfuric acid for 90 min. on a steam bath, m.p. 185–186° (lit. 181°). To 2-amino-4-chlorobenzamide (2.4 g.) in dilute hydrochloric acid, sodium nitrite (1 g.) in water was added.

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After standing overnight in an icebox 2.2 g. (86%) of colorless needles separated from the reaction mixture which after recrystallization from alcohol melted at 219–220° (dec.).

Anal. Calcd. for $C_7H_4ClN_3O$: C, 46.24; H, 2.22; N, 23.13. Found: C, 46.22; H, 2.38; H, 23.16.

4-Hydroxylamino-7-methoxybenzo-1,2,3-triazine (X). The 2-amino-4-methoxybenzamidoxime (VI) was prepared from 2-amino-4-methoxybenzonitrile[11] in a manner quite analogous to that described above for the amidoxime (VII). The crude VI (2 g.) was dissolved without further purification in 2*N* hydrochloric acid and sodium nitrite (0.7 g.) dissolved in water was added dropwise with ice-cooling. The benzotriazine (X) which separated (1.1 g., 62.5%) was recrystallized from glacial acetic acid and dried for analysis over potassium hydroxide at 100°; m.p. 215–216 (dec.).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.15. Found: C, 49.75; H, 4.00; N, 29.23.

When the mother liquor of the diazotization of VI was kept overnight in an ice-box 0.2 g. (12.5%) of *4-hydroxy-7-methoxybenzo-1,2,3-triazine* (XI) crystallized. XI was recrystallized from water, colorless needles, m.p. 220–221° (dec.).

Anal. Calcd. for $C_8H_7N_3O_2$: N, 23.72. Found: N, 24.19.

Reduction of VIII with sodium boronhydride. A solution of $NaBH_4$ (2 g.) in methanol was added to a finely divided suspension of VIII (2 g.) in 300 ml. of methanol and refluxed for 4 hr. Addition of water precipitated 0.7 g. of 2-amino-4-chloro-benzonitrile (XII), m.p. 160–161°. XII was identified by a mixed melting point with an authentic sample.[9]

When VIII was dissolved in 2*N* NaOH, 2*N* Na_2CO_3, or dilute $NaHCO_3$ the solution became turbid after a few minutes and the nitrile XII precipitated in an almost quantitative yield.

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Morphine-*N*-Methyl-C^{14}

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Several years ago Rapoport *et al.*[1] reported the synthesis of morphine-*N*-methyl-C^{14} from codeine-*N*-methyl-C^{14} in a 22% yield. In order to increase the availability of labeled morphine for pharmacological studies, methods of preparation were investigated which would give a good yield of product in a one step synthesis from normorphine.

A consideration of the instability of morphine toward high temperatures, strong acids, and strong alkalies, of the ease with which the molecule is *O*-methylated, and of the susceptibility of the isolated carbon-carbon bond toward catalytic hydrogenation,[2] eliminated selection of many of the classical methods for *N*-methylation. Since Tarpey *et al.*[3] have shown in the case of 4-phenyl-4-carbethoxypiperidine that formaldehyde-C^{14}-formate reductive methylation occurs exclusively with incorporation of the *N*-methyl-C^{14} group into the molecule, this method was adapted to the synthesis of morphine-*N*-methyl-C^{14}.

The results of paper chromatography and infrared studies indicated that morphine is largely destroyed when refluxed for 4 hr. with half an equivalent of 37–38% formalin solution and two equivalents of formic acid. The infrared spectrum of the crude resinous reaction product obtained from refluxing normorphine with a 20% excess each of formalin and formic acid showed the presence of a significant quantity of morphine. Application of the findings of Wagner and co-workers[4] on the factors influencing the Wallach reaction greatly facilitated the final selection of reaction conditions. High temperatures for extended periods enhance decomposition of the product so the procedure employed entailed gentle reflux in absolute ethanol for a short period.

N-Methylation of normorphine proceeded smoothly in the case of nonlabeled material, but difficulty was encountered in the direct application of the procedure to commercially available paraformaldehyde-C^{14} because of varying amounts of impurities. To avoid the assay for percentage formaldehyde-C^{14} freed under the reaction conditions, the syntheses were carried out in two stages; first the reaction was executed in the usual manner assuming complete depolymerization, and second the crude product was recycled using a small quantity of unlabeled paraformaldehyde in order to convert all of the original starting material to morphine.

In the early stages of development of the reaction conditions, the crude product was always found to contain 3–5% normorphine. This impurity could be removed neither by recrystallization from a wide variety of solvents or solvent mixtures nor by precipitation of the bases from aqueous solution at any *p*H. Chromatography on neutral or basic alumina using a number of different solvents and solvent mixtures failed to effect the desired separation. Application of a solvent system which produced significantly different R_f values for morphine and normorphine on paper strips to a powdered cellulose column proved acceptable for the separation of the two alkaloids. Since losses on the cellulose column were greater than those in the recycling procedure, the latter method was adopted for the synthesis of the labeled material. The cellulose chromatography procedure is somewhat tedious in application to larger amounts of material but is reported here as a technique satisfactory for

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