The products were identified by mixed melting points with independently synthesized authentic samples: 3,3′-dinitroazoxybenzene, m.p. 142–144° [12]; 4,4′-dinitroazoxybenzene, m.p. 190–193° [13]; 3,3′-diiodoazoxybenzene, m.p. 110–113° [14]; 4,4′-diiodoazoxybenzene, m.p. 198–200°.[15] 2,2′-diiodoazoxybenzene, m.p. 140–142°, is a new compound.

Anal. Calcd. for $C_{12}H_8N_2OI_2$: N, 6.23. Found: N, 6.26, 6.13.

This compound was obtained only by electrochemical methods. All attempts at independent syntheses failed.

The synthesis of the authentic samples was carried out according to the references given above.

Infrared spectra were obtained with a double beam Perkin-Elmer Spectrometer Model 21. (Potassium bromide technique)—The absorption maxima are given in Table III.

Acknowledgment. The author wishes to thank Dr. S. Senderoff of Parma Research Laboratory, Union Carbide Corp., for helpful suggestions and discussions.

PARMA 30, OHIO

(12) H. Hofer and F. Jacob, *Ber.*, **41**, 3195 (1908).
(13) E. Bamberger and R. Hubner, *Ber.*, **35**, 3808 (1903).
(14) S. Gabriel, *Ber.*, **9**, 1409 (1876).
(15) H. Klenzer and R. Pitschke, *Ber.*, **18**, 2552 (1885).

[CONTRIBUTION FROM THE HUGH LORD LABORATORY, LORD MANUFACTURING CO.]

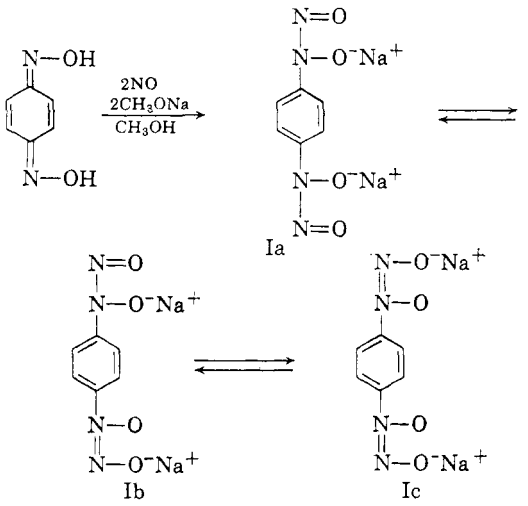
A New Reaction of Oximes and Nitric Oxide

MORRIS J. DANZIG,[1] ROCK F. MARTEL, AND SALVATORE R. RICCITIELLO

Received September 19, 1960

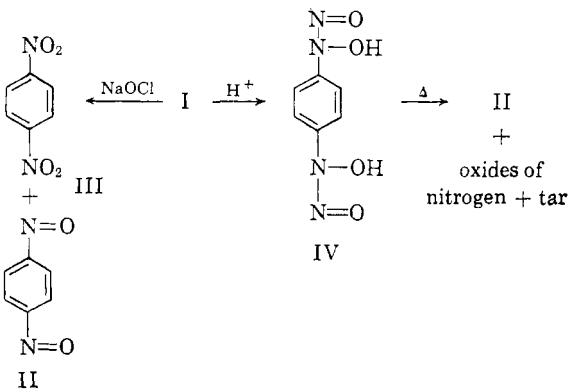
It was found that oxygen-free nitric oxide reacts with certain salts of quinone dioximes to form salts of di-*N* nitrosoaryldihydroxylamines, and with aldoximes to give *syn*-1-oximino-1-*N*-nitrosohydroxylamino types of compounds.

The preparation of *N*-nitroso compounds has usually been limited to the nitrosation reaction. In a recent communication we reported that when a methanolic solution of disodium-*p*-benzoquinone dioxime was treated with oxygen-free nitric oxide, two moles of the gas were absorbed to produce disodium - *N*,*N*′ - dinitroso - *p* - phenylenedihydroxylamine.[2] Structures Ia, b, c represent the tautomeric forms possible. Organic, as well as inorganic, salts may be prepared by an appropriate substitution of the proper base. Transition and heavy metals may be precipitated by using techniques analogous to that for Cupferron (ammonium-*N*-nitrosophenylhydroxylamine).



Upon acidic decomposition there were obtained oxides of nitrogen, *p*-dinitrosobenzene (II) and some resinous materials. The formation of tar is in keeping with the similar decomposition of Cupferron.[3]

The acid form of IV was prepared by careful acidification of I; and upon mild heating, II and tars were obtained. Oxidation of I with sodium hypochlorite also affords II and some *p*-dinitrobenzene (III). When an excess of oxidant was used, only III was obtained. Extension of this reaction to other quinone dioximes and salts with different metals are listed in Table I; in all cases analogous products were obtained.



Methylation of *N*-nitrosophenylhydroxylamine salts produces two isomers[4,5] designated as α and β.

(1) Present address: American Viscose Corp., Research and Development Division, Marcus Hook, Pa.
(2) M. J. Danzig, R. F. Martel, and S. R. Riccitiello, *J. Org. Chem.*, **25**, 1071 (1960).
(3) E. Bamberger, *Ber.*, **27**, 1554 (1894).
(4) R. Behrend and E. Konig, *Ann.*, **263**, 218 (1891).
(5) R. Lindez, *Ann.*, **275**, 133 (1893).

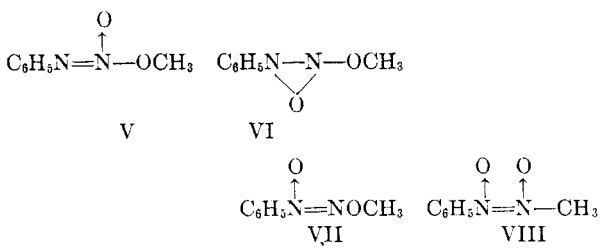
TABLE I

Quinone Dioxime	Salt	Solvent	Pressure, P.S.I.	Temp.	Formula
p-Benzo-	Na	CH_3OH	Atm. to 100	Room	$C_6H_4N_4Na_2O_4$
	Pb[a]	CH_3OH		Room	$C_6H_4N_4O_4Pb$
	Zn[a]	CH_3OH		Room	$C_6H_4N_4O_4Zn$
	Piperazino	CH_3OH	60	Room	$C_{10}H_{16}N_6O_4$
	Dipiperadine	CH_3OH	60	Room	$C_{16}H_{23}N_6O_4$
o-Benzo-	Ag[a]	CH_3OH	60	Room	$C_6H_4Ag_2N_4O_4$
9,10-Anthra-	Na	CH_3OH	60	Room	$C_{14}H_8N_4Na_2O_4$
9,10-Phenanthra-	Na	CH_3OH	60	Room	$C_{14}H_8N_4Na_2O_4$
Thymol-	Ag[a]	CH_3OH	60	Room	$C_{10}H_{12}Ag_2N_4O_4$
Aldoxime					
n-Butyrald-	Na	*n*-Heptane	Atm. to 60	Room	$C_4H_8N_3NaO_3$
Isobutyrald-	Na	*n*-Heptane	60	Room	$C_4H_8N_3NaO_3$
Benzald-	Na	*n*-Heptane	60	Room	$C_7H_6N_3NaO_3$
2-Thiophenald	Na	*n*-Heptane	60	70°	$C_5H_4N_3NaO_3S$
Cinnamald-	Na	*n*-Heptane	60	55°	$C_9H_7N_3NaO_3$
p-Chlorobenzald-	Na	*n*-Heptane	60	65°	$C_7H_5ClN_3NaO_3$

$$C_6H_5N(N{=}O)(O{-}Ag) \xrightarrow{CH_3I} C_6H_5N(N{=}O)(OCH_3) + C_6H_5N_2O_2CH_3 + AgI$$

β α

The β-isomer gives the characteristic Liebermann test, and is identical with the product obtained by the nitrosation of phenyl hydroxylamine-*O*-methyl ether. The α-isomer has been the subject of much speculation[4-8] and the structures V, VI, VII, VIII have been postulated from this isomer. Recently George *et al.*[8] have postulated VIII for this isomer, based upon its reaction with Grignard reagent. A choice between structures VII and VIII cannot be undertaken at the present, but it is worthy of note that VIII would be the structure drawn for a nitroso dimer, which in this case would be a mixed dimer.

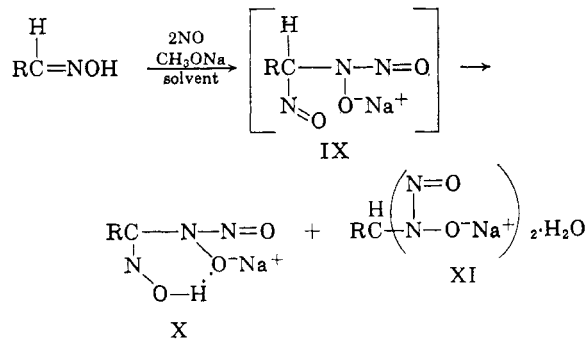


$C_6H_5N{=}N(\rightarrow O){-}OCH_3$ (V) $\quad C_6H_5N(O){-}N{-}OCH_3$ (VI)

$C_6H_5N(\rightarrow O){=}NOCH_3$ (VII) $\quad C_6H_5N(\rightarrow O){=}N(\rightarrow O){-}CH_3$ (VIII)

The adjacent positive charges on the nitrogen atoms of VIII were explained by a resonance hybrid.[8] The product obtained by methylation of the silver salt of I has a high melting point, and gives a negative Liebermann test. We therefore feel that our dimethyl ether is the difunctional analog of VII or VIII. At the present we are attempting the synthesis of the other isomers based on I.

In a similar manner, the salts of aldoximes add nitric oxide to form *syn*-1-oximino-1-*N*-nitrosohydroxylamine compounds (X). A solution of sodium *n*-butyraldoxime in methanol gave X (R= $CH_3CH_2CH_2$) in a 26% yield and 20.9% of what we designate as disodio-1,1-di-*N*-nitrosohydroxylaminobutane hydrate (XI). When the nitroso intermediate IX rearranges to form the *syn*-oxime the oximino hydrogen atom is bonded to the oxygen and is too weak an acid to form a salt for further reaction. If the rearrangement is *anti*, a disodium salt can be formed and a secondary reaction can proceed.



$$RC(H){=}NOH \xrightarrow[\text{solvent}]{2NO,\ CH_3ONa} \left[RC(H)(N{=}O){-}N(O^-Na^+){=}O\right] \rightarrow$$

IX

$$RC(N{=}O)(H){-}N(O^-Na^+){-}N{=}O + RC(N{=}O)(H){-}N{-}O^-Na^+ \cdot 2H_2O$$

X XI

The infrared spectrum of X shows chelated absorption at 2340 cm.$^{-1}$ while XI shows a hydroxyl absorption at 3500–3300 cm.$^{-1}$ The remainder of the spectrum is similar. By suspending the preformed salt of the aldoxime in hexane, X was obtained in an 88% yield with no XI. Although the absorption of nitric oxide was slower in nonpolar solvents, the reaction was more specific. Other aldoximes so treated are listed in Table I.

(6) A. Hantzsch, *Ber.*, **31**, 177 (1898).
(7) E. Bamberger and T. Ekecrantz, *Ber.*, **29**, 2412 (1896).
(8) M. V. George, R. W. Kierstead, and G. F. Wright, *Can. J. Chem.*, **37**, 679 (1959).

TABLE I (*Continued*)

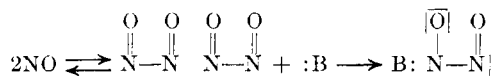
Quinone Dioxime	Carbon[b,c] Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Metal Calcd.	Metal Found	Yield, %
p-Benzo-	29.76	29.57	1.66	1.74	23.14	22.88	19.4	19.36	98
							51.3	51.1	
							24.92	25.01	
	42.30	42.30	5.60	5.65	29.6	29.5			94
	52.30	52.36	7.66	7.63	22.4	22.91			93
o-Benzo-							52.91	53.3	57
9,10-Anthra-							13.50	13.03	94
9,10-Phenanthra-							13.50	13.46	96
Thymol-							45.99	46.10	94
Aldoxime									
n-Butyrald-	28.4	28.37	4.73	4.51	24.90	24.40			88
Isobutyrald-	28.41	27.34	4.76	4.62	24.90	24.9			77
Benzald-	41.4	41.35	2.95	3.07	20.7	20.1	11.38	11.03	91
2-Thiophenald	28.70	28.32	1.93	2.38	20.09	19.99	10.99	10.56	91
Cinnamald-					18.3	17.75	10.04	10.11	91
p-Chlorobenzald-	35.37	35.16	2.12	1.98	17.68	16.72	9.67	9.88	75

[a] Prepared from Na salt. [b] Difficulty was encountered in obtaining accurate analysis because of the explosive character and light sensitivity of some of these compounds. [c] Microanalysis by Galbraith Laboratories, Knoxville, Tennessee.

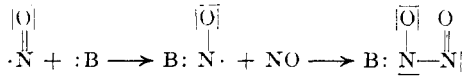
Hydrolysis of X (R=$CH_3CH_2CH_2$) by sodium hydroxide gave starting material and butyric acid. On acidic decomposition, oxides of nitrogen were liberated, butyraldoxime and butyric acid were isolated. Similar acidic decomposition of XI (R=$CH_3CH_2CH_2$) also afforded butyric acid.

Attempts to determine the course of reaction based on the usual free radical or nitrosyl moiety were not rational. The original reaction in the absence of base was unsuccessful, as was the reaction on benzaldoxime *O*-methyl ether. Nitric oxide, also, does not add to a carbon double bond, and will not initiate polymerization but has been known to trap radicals. This in conjunction with the fact that the reactions are more rapid in polar solvent indicated an ionic type of reaction involving nitric oxide.

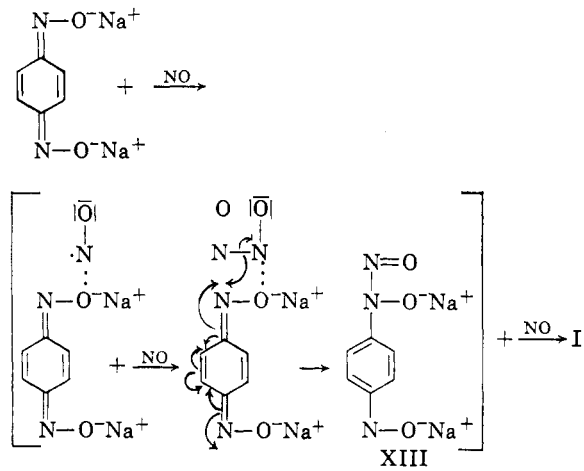
Recently the Lewis acid nature of nitric oxide, based upon the reaction of nitric oxide with secondary amines and reactions with alkaline sulfite ion, was proposed.[9,10] Drago postulated a general mechanism of and subsequently kinetic data showed



the following route of reaction.[11]



The reactions described here are of basic salts of oximes and nitric oxide, and not nitric oxide dimer since the dimer exists only at low temperatures. The initiating step would then be an ionic attack by nitric oxide followed by a rapid addition of nitric oxide *via* the odd electron, and rearrangement to a stable aromatic structure XIII. The final product I is obtained by trapping the resultant intermediate by NO. Similar reaction paths for the formation

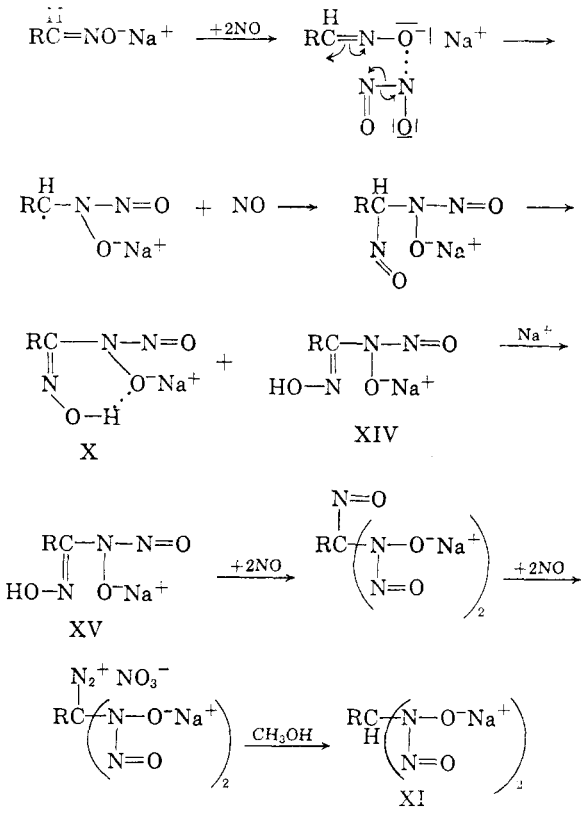


XIII

of I may be drawn involving simultaneous attack at both oximino groups, or initial attack on the oximino nitrogen.

A similar route may be drawn for the reaction of aldoximes. The yields of X and XI using methanol as a solvent were poor, and the proposed competing reactions indicate this. After formation of XIV the new oxime may obtain its sodium ion from any other sodium salt of an oxime, and the first step may be repeated. When the new nitroso adduct XIV is formed, the well known diazotization of a C nitroso compound may take place,[12] followed by decomposition of the diazo compound by solvent. The

(9) R. S. Drago and F. E. Paulik, *J. Am. Chem. Soc.*, **82**, 96 (1960).
(10) R. S. Drago, *J. Am. Chem. Soc.*, **79**, 2049 (1957).
(11) R. S. Drago, private communication.
(12)(a) A. N. Nesmezanov and S. T. Iaffe, *J. Gen. Chem., U.S.S.R.*, **11**, 392 (1941). (b) L. G. Donaruma and D. S. Carmody, *J. Org. Chem.*, **22**, 635 (1957). (c) E. Bamberger, *Ber.*, **51**, 634 (1918). (d) E. Bamberger, *Ber.*, **30**, 508 (1897).



reaction of XV with nitric oxide would be similar to the reaction of ketoximes with nitric oxide. We have found that the salts of ketoximes do react with nitric oxide, but the materials we have obtained were unstable, and no identifiable product was isolated.

EXPERIMENTAL

Apparatus. This reaction may be carried out in any type of stirred stainless steel pressure vessel of a Paar low pressure hydrogenator modified with a stainless steel tank and gauge. All tubing and valves are stainless steel. The nitric oxide was Matheson 99+% pure and was passed through a stainless steel Kuentzel bomb 1 ft. long 2 in. I.D. packed with sodium hydroxide. Care must be taken that gas inlet and exit ports do not become clogged.

Procedure with the Paar shaker system. The solution of base in methanol was prepared and placed in a reaction bottle. To this was added an equivalent amount of the oxime, the contents were cooled in solid carbon dioxide and placed in the Paar apparatus. Oxygen was removed by evacuating with a pump and flushing three times with oil-pumped oxygen-free nitrogen and finally evacuated. The shaker was started and nitric oxide was admitted to the reaction vessel; when adsorption of gas was complete, the nitric oxide was removed by flushing with nitrogen and evacuating by a water aspirator. The product was isolated by filtration, washed, and dried.

In cases where nonpolar solvents were used the salt of the aldoxime was preformed and suspended in solvent.

Procedure with autoclave. To a solution of a base and solvent was added an equivalent amount of oxime. The solution was cooled and placed in the bomb and capped. The oxygen was removed by evacuation and sweeping with oil-pumped oxygen-free nitrogen and the bomb was finally evacuated. Stirring was started and nitric oxide was continuously added until absorption was complete. The nitric oxide was removed as previously described, and the product, isolated by filtration, was washed and dried.

In cases where inert solvents were used the salts of the aldoximes were preformed and suspended in solvent.

Decomposition of I. To 5 ml. of concd. hydrochloric acid was added 1.2 g. of I, and the resulting mixture was warmed gently. Oxides of nitrogen were evolved. When reaction ceased the yellow solid was filtered, washed, and dried. The yield of *p*-dinitrosobenzene was 0.50 g. (73%). The infrared spectrum was identical to that of an authentic sample.

Oxidation of I. To a stirred solution of 0.50 g. of I in 25 ml. water was slowly added 3 ml. of 5.5% sodium hypochlorite. A yellow precipitate formed and the solution turned yellow. Stirring was continued for 15 min., and 1.90 g. (67.5 %) of *p*-dinitrosobenzene was isolated by filtration. The infrared spectrum was identical with that of an authentic sample.

The filtrate was treated with 7 additional ml. of sodium hypochlorite stirred for 15 min. A yellow precipitate of 0.090 g. of *p*-dinitrobenzene was isolated. The infrared spectrum, melting point and mixed melting point were identical with that of an authentic sample. Further oxidation of the *p*-dinitrosobenzene with sodium hypochlorite yielded *p*-dinitrosobenzene.

Dimethyl ether of I. A solution of 12.1 g. of I in 700 ml. of distilled water was prepared and filtered. To the solution was added with stirring 34 g. of silver nitrate in 100 ml. of water. The precipitate was filtered, washed with distilled water and methanol to yield 15.85 g. of silver salt. The dried salt was suspended in 100 ml. of methanol and 14.2 g. of methyl iodide was added. The flask was sealed and stirred for 24 hr., an additional 12 g. of methyl iodide was added, and stirring was continued for 9 days. The salts were filtered, washed with methanol, evaporated to one-half volume, cooled, and filtered. The crude dimethyl ether (1.8 g.) was washed with ether and recrystallized four times from ethanol to yield 150 mg. (1.2%) of product, m.p. 208–211°.

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.49; H, 4.35; N, 24.83.

Acidic decomposition of X ($R = CH_3CH_2CH_2$). To 5 ml. of concd. hydrochloric acid was slowly added 3.0 g. of X. A vigorous reaction ensued with the liberation of oxides of nitrogen. When the reaction ceased, the solution was neutralized to *p*H 8 with sodium hydroxide, extracted with ether, and dried. The ether was removed and 0.3 g. (19.4%) of butyraldoxime was isolated. The infrared spectrum was identical with that of an authentic sample. The aqueous solution was acidified with hydrochloric acid, ether, washed, and dried. After removal of the solvent 0.8 g. (51.2%) of butyric acid was isolated. The infrared spectrum was identical with that of an authentic sample.

Basic decomposition of X ($R = CH_3CH_2CH_2$). To a solution of 20 ml. of 5% sodium hydroxide was added 3.0 g. of X. The mixture was warmed on a steam bath. After 2.5 hr. the solution was cooled, neutralized, and filtered. There was isolated 1.4 g. of insoluble starting material. The aqueous solution was acidified, extracted with ether, washed, and dried. Removal of the ether gave 0.6 g. (38.4%) of butyric acid, as identified by infrared spectrum.

Reaction of n-butyraldoxime with nitric oxide in methanol. To a solution of 27.0 g. (0.50 mole) of sodium methoxide in 200 ml. of methanol was added 43.5 g. (0.50 mole) of *n*-butyraldoxime. The resulting solution was allowed to react with nitric oxide as described. The reaction mixture was filtered, and washed with methanol to give 22.0 g. (26%) of *syn*-1-*N*-nitrosohydroxylaminobutane.

Anal. Calcd. for $C_4H_8N_3NAO_3$: C, 28.4; H, 4.73; N, 24.9. Found: C, 28.37; H, 4.59; N, 24.4.

An excess of ether was added to the filtrate and 25.0 g.

(20.9%) of a grey tinted hydrate of disodio-1,1-di-*N*-nitrosohydroxylaminobutane was isolated.

Anal. Calcd. for $C_4H_{16}N_4Na_2O_6$: C, 20.00; H, 4.17; N, 23.3; Na, 19.17. Found: C, 19.90; H, 4.68; N, 23.9; Na, 19.16.

Acknowledgment. We are indebted to Miss Virginia Barber for infrared absorption data and Mrs. Ann Wise for the preparation of some aldoximes.

ERIE, PA.

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF U. S. VITAMIN AND PHARMACEUTICAL CORP.]

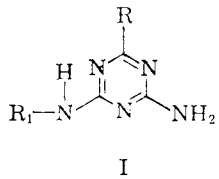
Guanamines. VIII. 6-(Substituted Phenyl)guanamines

SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, AND LOUIS FREEDMAN

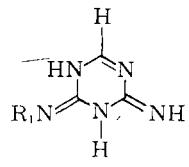
Received October 17, 1960

A series of 2-substituted amino-4-amino-6-phenyl- (and substituted phenyl)-*s*-triazines has been synthesized and the influence of structural variation on the ultraviolet absorption spectra reported.

Diuretic activity in a series of guanamines I, R = H, was ascribed to the tautomer II; whereas with homologs of I, R = alkyl, noted ineffectiveness was associated with equilibria which diminished the population of forms such as II.[1]



I

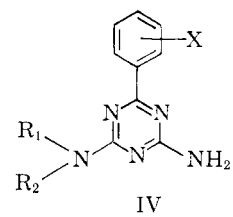


II

To challenge this concept, aryl variants of R envisioned as capable of stabilizing II were prepared (Table I), in the hope that an increase in the absolute concentration of forms such as III, rather than an unfavorable equilibrium concentration would enhance diuretic activity.[2]

Most of the compounds were prepared by condensation of the requisite acid chloride[3] with the substituted biguanide.[4] For compounds 5–12 reaction of the biguanide in methyl salicylate as a solvent, under controlled heating was the method of choice. The reduction of compound 23 to 2-amino-4-*n*-amylamino-6-*m*-aminophenyl-*s*-triazine was effected using rhodium-on-carbon.[5] On testing as a diuretic this compound was inactive while the other compounds were too insoluble for evaluation of their pharmacological properties.

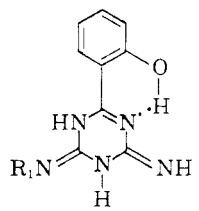
Spectral characteristics of these compounds indicate that the 6-phenyl group of IV could interact with the triazine nucleus as an unhindered biphenyl,[6] although the R_1R_2N— group can influence



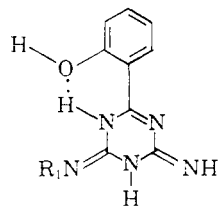
IV

X = H, *o*-OH, *o*-OCH_3, *m*-NO_2, *m*-NH_2

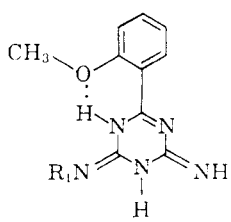
co-planarity of the 6-position substituent.[7] The role of the azomethine linkage in heteroaromatics, as imparting a pseudocarbonyl function,[8] could be



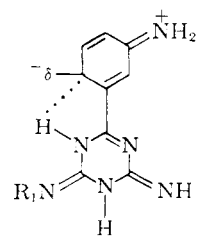
IIIa



IIIb



IIIc



IIId

(1) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957).

(2) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).

(3) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959).

(4) (a) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959) for arylbiguanides; (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959) for alkyl and aralkylbiguanides.

(5) S. L. Shapiro, K. Weinberg, T. Bazga, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5146 (1959).

(6) H. Gilman, *Org. Chemistry*, Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 172.

(7) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379 (1960).

(8) (a) S. L. Shapiro, E. Isaacs, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **26**, 68 (1961); (b) J. T. Thurston, F. C. Schaefer, J. R. Dudley, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2992 (1951); (c) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1462 (1959); (d) R. Levine and S. Raynolds, *J. Org. Chem.*, **25**, 530 (1960).