pyridazinone[14] (VII) and a mixture of authentic VII melted at 138–140°. The analytical data of "A" was as follows:

Anal. Calcd. for $C_4H_3ON_2Cl$: C, 36.80; H, 2.30; N, 21.4. Found: C, 36.90; H, 2.41; N, 21.26.

The above mother liquor gave after cooling on ice, clusters "B," m.p. 115–116°. Products "B" and (3) were identified as equimolar mixtures of 3,6-dichloropyridazine (VI) and compound VII. The infrared spectrum of a prepared equimolar mixture of compounds VI and VII was similar to "B" and (3) and a mixture of "B" and (3) melted at 115–116° after recrystallization from carbon tetrachloride.

Anal. Calcd. for (an equimolar mixture of VI and VII) $C_8H_5ON_4Cl_3/2$: N, 20.0; mol. wt. 139.7. Found: N, 19.95; mol. wt. 145 (Rast).

Subjecting mixtures "B" or (3) to heating *in vacuo* caused sublimation of compound VI and gave pure VII as the residue.

Anal. Calcd. for $C_4H_3ON_2Cl$ (VII): C, 36.8; H, 2.30; Cl, 27.21. Found: C, 36.95; H, 2.53; Cl, 27.22.

Product (4) on sublimation *in vacuo* gave pure VI, m.p. 69°, lit. value,[8] m.p. 68–69°, and no appreciable residue remained.

1-(3'-Chloro-6'-pyridazyl)-3-chloro-6-pyridazone (IV). A 7 g. sample of the crude reaction product resulting from the reaction of maleic hydrazide and phosphorus oxychloride was sublimed for 28 hr. at 70–80°. The residue was boiled with about 500 ml. of cyclohexane and after cooling, 1 g. of compound IV, m.p. 151–152° was obtained. This material gave no depression in a mixed melting point determination with authentic IV[9] and had a similar infrared spectrum.

Conversion of compound III to compound IV. In a 50-ml. flask fitted with an efficient condenser were placed 0.182 g. (0.88 mmole) of III and 15 ml. of phosphorus oxychloride. The mixture was refluxed 5.5 hr., filtered, and the filtrate concentrated *in vacuo* until 2 ml. of liquid remained. Addition of crushed ice, followed by sufficient concd. ammonium hydroxide to basify the solution, cooling on ice overnight, and filtering gave 0.12 g. (57% yield) of slightly tan product, m.p. 150–153°. Recrystallization from cyclohexane gave a m.p. 151–152°. A mixed melting point determination with authentic IV gave no depression.

(14) This material has previously been reported, but was obtained with a half mole of water of hydration,[7] m.p. 138–140°.

α,α'-Dichlorosuccinic anhydride[15] (X). A three necked 1000-ml. flask was equipped with a coarse sintered glass gas dispersion tube and a condenser. Into this flask were placed 50 g. of maleic anhydride and 500 ml. of carbon tetrachloride. The mixture was heated to reflux and irradiated with an ultraviolet light while chlorine was introduced for about 14 hr. Upon cooling, light gray crystals deposited and evaporation of the solvent *in vacuo* gave additional material. Several recrystallizations from benzene gave a m.p. 91–92° which was raised to m.p. 95–97° (lit. value[15] m.p. 95°) after recrystallization from carbon tetrachloride.

It was found necessary to purify the crude reaction product immediately, since it discolorized readily on standing. The purified product (X) was converted very rapidly to the acid on standing in air and had to be kept dry.

Reaction of α,α,-dichlorosuccinic anhydride with hydrazine hydrate. To a mixture of 10 g. (0.059 mole) of α,α'-dichlorosuccinic anhydride and 100 ml. of acetic acid was added in 3 min. 3 g. (0.06 mole) of hydrazine hydrate with stirring. Refluxing for 1 hr., cooling, and filtering gave 4.4 g. of crystals, m.p. 225–240° dec. Concentrating the filtrate to 10 ml. gave an additional 2.5 g. of material, m.p. 256–257° dec. and evaporation to dryness afforded 3 g. of a dark residue. These solids were partially soluble in boiling ethanol. The residue was identified as hydrazine dihydrochloride, by a mixed melting point determination with an authentic sample which gave no depression, and by comparison of the infrared spectra which were identical.

On cooling, the filtrate gave 4.0 g. (50%) 4-chloromaleic hydrazide, m.p. 263° dec., lit. value,[16] 254° dec., after recrystallization from ethanol.

Anal. Calcd. for $C_4H_3O_2N_2Cl$: C, 32.8; H, 2.04; N, 19.13; neut. equiv. 146.5. Found: C, 33.12; H, 2.28; N, 19.36; neut. equiv. 147.

Acknowledgment. The authors are grateful to the Purdue Research Foundation for financial support of this investigation.

LAFAYETTE, IND.

(15) A. Michael and G. Tissot, *J. prakt. Chem.*, **46**, 392 (1892).

(16) Yu. A. Baskakov and N. N. Melnikov, *J. Gen. Chem. U.S.S.R.*, **24**, 1205 (1954).

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

Syntheses in the 1,2,4-Benzotriazine Series

JAMES JIU AND GEORGE P. MUELLER

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A series of 3-substituted-1,2,4-benzotriazine-1-oxides together with a few of the 3-substituted-1,2,4-benzotriazines have been synthesized for pharmacological evaluation.

The variety of structural modifications possible in substituted 1,2,4-benzotriazines and their kinship to existing chemotherapeutic agents prompted us to explore further derivatives for biological activity. Earlier work in this field, though limited, is well documented[1] and more recently claims for the utility of 1,2,4-benzotriazines have been registered;[2,3] as yet no member of this series has found widespread use.

A group of 1,2,4-benzotriazine-1-oxides together with a few of the corresponding 1,2,4-benzotriazines has been prepared by the general synthetic scheme I–VI.

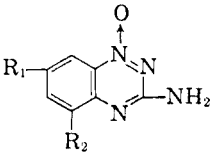
(1) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 44.

(2) B. H. Shoemaker and C. M. Loane, U. S. Patent **2,160,293** (May 30, 1939).

(3) F. J. Wolf and K. Pfister III, U. S. Patents **2,489,351** to **2,489,359** (November 29, 1949), and *J. Am. Chem. Soc.*, **76**, 3551, 4611 (1954).

TABLE I

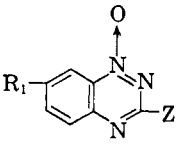
3-AMINO-1,2,4-BENZOTRIAZINE-1-OXIDES

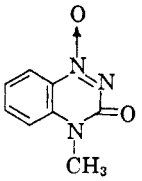


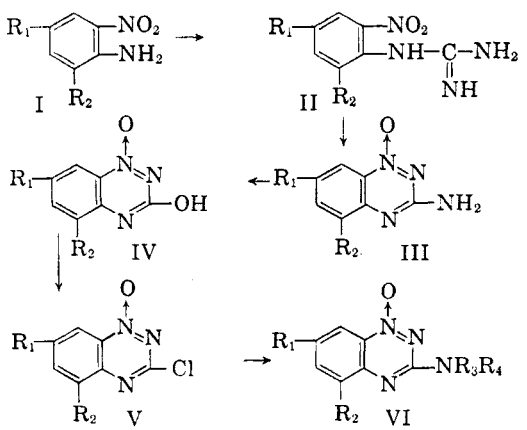
				Analyses, %[b]					
				Calcd.			Found		
R_1	R_2	M.P.[a]	Formula	C	H	N	C	H	N
Me	Me	251–253	$C_9H_{10}N_4O$	56.83	5.30	29.46	56.92	5.29	29.18
C_6H_5	H	303–305	$C_{13}H_{10}N_4O$	65.53	4.23	23.52	65.46	4.23	23.25
EtO	H	276–278	$C_9H_{10}N_4O_2$	52.42	4.89	27.17	52.61	4.97	26.77
MeO	H	278–281[c]	$C_8H_8N_4O_2$	50.00	4.19	29.16	49.99	4.19	29.05
Cl	H	>300[d]	$C_7H_5ClN_4O$	42.76	2.56	28.50	43.01	2.41	28.60

TABLE II

3-OXYGENATED-1,2,4-BENZOTRIAZINE-1-OXIDES



				Analyses, %[b]					
				Calcd.			Found		
R_1	Z	M.P.,[a]	Formula	C	H	N	C	H	N
H	OH	244–246[e]	$C_7H_5N_3O_2$	51.53	3.09	25.76	51.31	3.12	25.90
MeO	OH	244–246	$C_8H_7N_3O_3$	49.74	3.66	21.75	49.32	3.49	21.64
Cl	OH	259–262[f]	$C_7H_4ClN_3O_2$	42.55	2.04	21.27	42.75	2.07	21.55
H	OEt	111–113	$C_9H_9N_3O_2$	56.54	4.74	21.98	56.78	4.82	22.10
H	OBu	52.5–53.5	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.17	60.47	6.45	18.96
		237–241	$C_8H_7N_3O_2$	54.23	3.99	23.72	54.59	4.15	23.89



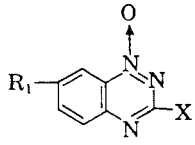
The substituted *o*-nitroanilines (I) were condensed with cyanamide or monosodium cyanamide under acid conditions, yielding *o*-nitrophenylguanidines (II), which were cyclized directly to the 3-amino-1,2,4-benzotriazine-1-oxides (III) (Table I), in alkali.[3–5] Diazotization converted the latter to 3-hydroxy-1,2,4-benzotriazine-1-oxides (IV) (Table II), and these on treatment with phosphorous oxyhalides[3,6] yielded 3-chloro- or 3-bromo-1,2,4-benzotriazine-1-oxides (V) (Table III). A mixture of the 3-hydroxy- and 3-chloro-1,2,4-benzotriazine-1-oxides was also obtained by diazotization, as recorded,[5] in the presence of a mixture of potassium ferrocyanide and potassium ferricyanide.

Condensation of the 3-chloro-1,2,4-benzotriazine-1-oxides with selected amines yielded the appropriately 3-substituted amino-1,2,4-benzotriazine-1-oxides (VI) (Table IV).

(4) F. Arndt, *Ber.*, 46, 3522 (1913).
(5) F. Arndt and B. Rosenau, *Ber.*, 50, 1248 (1917).
(6) R. F. Robbins and K. Schofield, *J. Chem. Soc.*, 3186 (1957).

TABLE III

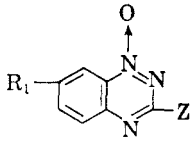
3-HALOGENATED-1,2,4-BENZOTRIAZINE-1-OXIDES



				Analyses, %[b]					
				Calcd.			Found		
R_1	X	M.P.[a]	Formula	C	H	N	C	H	N
H	Cl	117–119[g]	$C_7H_4ClN_3O$	46.30	2.22	23.14	46.36	1.92	22.93
Cl	Cl	157–158.5[h]	$C_7H_3Cl_2N_3O$	38.92	1.40	19.45	39.02	1.67	18.93
MeO	Cl	188.5–190.5	$C_8H_6ClN_3O_2$	45.41	2.86	19.86	45.48	2.77	19.78
H	Br	154–156	$C_7H_4BrN_3O$	37.19	1.78	18.59	37.48	1.86	18.44

TABLE IV

3-SUBSTITUTED AMINO-1,2,4-BENZOTRIAZINE-1-OXIDES



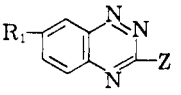
			Analyses, %[b]					
			Calcd.			Found		
R_1 = H, Z	M.P.[a]	Formula	C	H	N	C	H	N
Morpholino	174–176	$C_{11}H_{12}N_4O_2$	56.88	5.21	24.13	56.42	5.38	24.19
Piperidino	108–110	$C_{12}H_{14}N_4O$	62.59	6.13	24.33	62.75	5.96	23.97
Hexamethyleneimino	121–122.5	$C_{13}H_{16}N_4O$	63.91	6.60	22.94	64.40	6.77	23.38
3-Ketopiperazino	254–257	$C_{11}H_{11}N_5O_2$	53.87	4.52	28.56	53.62	4.53	28.23
Isoquinolino	125–126.5	$C_{16}H_{14}N_4O$	69.05	5.07	20.13	68.80	5.29	19.93
β-Phenylethylamino	193–195	$C_{15}H_{14}N_4O$	67.65	5.30	21.04	67.74	5.34	20.64
β-Dimethylaminoethylamino	128.5–131	$C_{11}H_{15}N_5O$	56.63	6.48	30.03	56.94	6.48	30.05
β-Diethylaminoethylamino	77.5–80	$C_{13}H_{19}N_5O$	59.75	7.33	26.80	59.93	7.22	26.59
β-Morpholinoethylamino	170.5–173	$C_{13}H_{17}N_5O_2$	56.71	6.23	25.44	56.66	6.35	25.49
γ-Di-*n*-butylaminopropylamino	77–78.5	$C_{18}H_{29}N_5O$	65.22	8.82	21.13	64.97	8.72	21.57
γ-Morpholinopropylamino	143–144.5	$C_{14}H_{19}N_5O_2$	58.11	6.62	24.21	57.95	6.38	23.97
Thiosemicarbazido	253–255 (dec.)	$C_8H_8N_6OS$	40.67	3.41	35.57	40.50	3.24	35.32
β-Hydroxyethylamino	114–116	$C_9H_{10}N_4O_2$	52.42	4.89	27.17	52.42	4.79	26.93
β-Hydroxy-β-methylpropylamino	159–160	$C_{11}H_{14}N_4O_2$	56.40	6.02	23.92	56.48	6.00	24.26
(α,α-Bishydroxymethyl-ene)ethylamino	127–128	$C_{11}H_{14}N_4O_3$	52.79	5.64	22.39	53.04	5.66	22.67
Methylglucamino	135–137	$C_{14}H_{20}N_4O_6$	49.40	5.92	16.46	49.27	5.99	15.93
Furfurylamino	172–178	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13	59.55	4.38	22.96
Hydrazino	207.5–209	$C_7H_7N_5O$	47.45	3.99	39.53	47.46	3.92	39.02
α-Methylhydrazino	134–135	$C_8H_9N_5O$	50.25	4.74	36.63	50.69	5.11	37.21
R_1 = Cl								
Methylphenylamino[i]	158.5–160	$C_{14}H_{11}ClN_4O$	58.64	3.87	19.54	58.37	3.78	19.61
β-Dimethylaminoethylamino	157–161	$C_{11}H_{14}ClN_5O$	49.35	5.27	26.16	49.67	5.50	26.37

Direct *O*-alkylation of 3-hydroxy-1,2,4-benzotriazine-1-oxide was not feasible as shown by attempts to methylate in the usual way with methyl iodide; the product proved to be 4-methyl-3-keto-3-4-dihydro-1,2,4-benzotriazine-1-oxide.[7] The 3-alkoxy derivatives were obtained in other ways; for example, the attempted displacement in 3-chloro-1,2,-4-benzotriazine-1-oxide with sodium cyanide and ethanol led to formation of 3-ethoxy-1,2,4-benzotriazine-1-oxide (VIII) R = C_2H_5; also with potassium fluoride, or potassium glutamate, and *n*-butanol the reaction yielded 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide (VIII) R = C_4H_9. Similar displacement where

(7) L. Ergener, *Rev. fac. sci. univ. Istanbul*, 15*A*, No. 2, 91 (1950); *Chem. Abstr.*, 44, 10718 (1950).

TABLE V

3-SUBSTITUTED AMINO-1,2,4-BENZOTRIAZINES

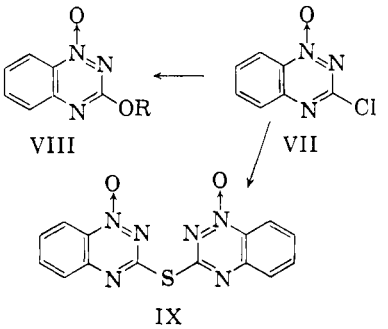


R_1 = H	M.P.[a]	Formula	Analyses, %[b] Calcd. C	H	N	Found C	H	N
3 Ketopiperazino	237–239.5	$C_{11}H_{11}N_5O$	57.63	4.84	30.55	57.95	4.93	30.73
β-Dimethylaminoethylamino	98–100	$C_{11}H_{15}N_5$	60.80	6.96	32.24	60.82	6.83	32.00
Hydrazino	173–175	$C_7H_7N_5$	52.16	4.38	43.46	52.14	4.51	44.06
α-methylhydrazino	85–89	$C_8H_9N_5$			39.98			40.44

[a] Melting points taken on a Fischer-Johns block, uncorrected. [b] The authors express their appreciation to Dr. R. T. Dillon and his staff of the Analytical Department of the G. D. Searle and Co. for the analytical data presented here. [c] Lit. m.p. 258–259°, see ref. 3. [d] Lit. m.p. 302° (dec.), see ref. 3. [e] Lit. m.p. 219°, see ref. 4. [f] Lit. m.p. 230–231°, see ref. 3. [g] Lit. m.p. 117–118°, see ref. 6. [h] Lit. m.p. 153–154°, see ref. 3. [i] Obtained as a by-product in the preparation of 3,7-dichloro-1,2,4-benzotriazine-1-oxide using phosphorus oxychloride and dimethylaniline. This was probably formed from traces of monomethylaniline present in the reaction medium.

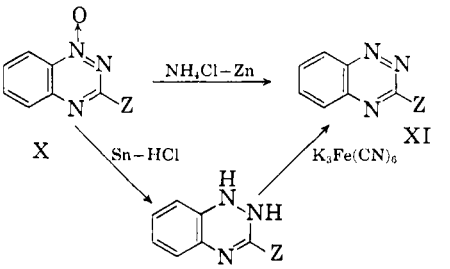
solvolysis preponderates was recently reported to occur in the purines.[8]

3 - Mercapto - 1,2,4 - benzotriazine - 1 - oxide has been prepared from *o*-nitrophenylthiourea[5] but our attempts to do so starting either with 3-hydroxy-1,2,4-benzotriazine-1-oxide and phosphorus pentasulfide, or with the 3-chloro-1,2,4-benzotriazine-1-oxide and sodium hydrosulfide were unsuccessful. Turning to the thiuronium-complex reaction[9–11] we found that treatment of the chloro compound with thiourea in absolute alcohol formed the sulfide (IX).



VIII VII IX

The 1,2,4-benzotriazines (XI) were prepared either by direct treatment of the 1-oxides (X) with zinc dust and ammonium chloride in water,[3] or by reduction



X XI

with tin and hydrochloric acid[4] to give first the 3 - substituted -1,2 - dihydro - 1,2,4 - benzotriazines (XII) which were readily oxidized by potassium ferricyanide to the 3-substituted-1,2,4-benzotriazines (XI) (Table V).

EXPERIMENTAL

Preparation of the 3-amino-1,2,4-benzotriazine-1-oxides. Method A. 3-Amino-1,2,4-benzotriazine-1-oxide. A mixture of 5.00 g. of *o*-nitroaniline and 10.95 g. of monosodium cyanamide in a large beaker was heated gently on a hot plate until the nitroaniline melted. The cooled solid was then mixed well, and then 25 ml. of concentrated hydrochloric acid was added all at once. Immediately a very vigorous reaction ensued, which subsided in a few minutes. The reaction mixture was allowed to cool slowly to room temperature; then 25 ml. of water was added followed by 20 g. of sodium hydroxide. After the vigorous reaction subsided, the mixture was heated on a steam bath for 30 min. On cooling, crystals formed, which were collected and washed well with water. (This material may be used in this form for subsequent reactions.) Recrystallization from ethanol gave 3-amino-1,2,4-benzotriazine-1-oxide, yield 2.60 g., m.p. 285.5–288°.

Method B. 3-Amino-1,2,4-benzotriazine-1-oxide. A mixture of 10 g. of *o*-nitroaniline and 10 g. of cyanamide was fused by heating on a steam bath. To the cooled mixture was added 25 ml. of concentrated hydrochloric acid. The reaction mixture was swirled and heated gently on a steam bath until all solids were liquefied. After allowing to cool to room temperatures, 25 ml. of water and 20 g. of sodium hydroxide were added to the reaction mixture. The reaction mixture was heated on a steam bath for 30 min., and then diluted with water. The solid, 8.30 g., was collected by filtration

(8) As an example, L. Goldman, J. W. Marsico, and M. J. Weiss, at the 133rd American Chemical Society Meeting at San Francisco, April 13, 1958, obtained a 6-methoxy β-purine on treating the 6-chloro-β-purine with di*iso*-propylamine in refluxing methanol.

(9) R. K. Robins, L. B. Holum, and F. W. Furcht, *J. Org. Chem.*, **21**, 833 (1956).

(10) J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 2052 (1956).

(11) C. L. Arcus and P. A. Hallgarten, *J. Chem. Soc.*, 2987 (1956).

and washed well with water. Recrystallization from ethanol gave 3-amino-1,2,4-benzotriazine-1-oxide, m.p. 284–287°C.

3-Hydroxy-1,2,4-benzotriazine-1-oxide. A solution of 130 g. of 3-amino-1,2,4-benzotriazine-1-oxide in 1400 ml. of water and 510 ml. concentrated sulfuric acid was cooled to 0°. Over a period of 2.5 hr. a solution of 254 g. of sodium nitrite in 350 ml. of water was added dropwise. During the addition an ice-bath was used to maintain a 0° temperature. The reaction mixture was stirred at room temperatures for 39.5 hr., filtered, and the product washed well with water; yield 120.9 g. This product melting at 241–244°, was satisfactory for use in further reactions. Recrystallization from methanol gave 3-hydroxy-1,2,4-benzotriazine-1-oxide, m.p. 244–246°.

3-Chloro-1,2,4-benzotriazine-1-oxide. A solution of 170 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide in 1350 ml. of phosphorus oxychloride was heated at reflux for 2 hr. The reaction mixture was distilled to dryness *in vacuo*, and the residue was poured over cracked ice. The mixture was diluted with water and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue was taken up in hexane and allowed to crystallize to give 3-chloro-1,2,4-benzotriazine-1-oxide, m.p. 115–117°; yield 106.1 g.

Preparation of both 3-hydroxy- and 3-chloro-1,2,4-benzotriazine-1-oxide. A stirred suspension consisting of 10 g. of 3-amino-1,2,4-benzotriazine-1-oxide, 6 g. of potassium ferrocyanide, 6 g. of potassium ferricyanide, 200 ml. concentrated hydrochloric acid, and 300 ml. of water was cooled to 4°. To the cooled mixture was added over a period of 2 min. a solution of 6 g. of sodium nitrite in 20 ml. of water. The mixture was stirred at 4° for an additional 30 min., then at 25° for 30 min. The precipitate was filtered. The filtrate on neutralization with sodium carbonate yielded 0.75 g. of starting material.

The precipitate was slurried with water and twice with ethyl ether. The combined ethyl ether extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* left a white residue which was taken up in hexane and allowed to crystallize, giving 1.64 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, m.p. 114–116°. Recrystallization from aqueous methanol gave the pure compound, m.p. 117–119°.

The ether-extracted aqueous mixture was filtered, and the greenish precipitate dissolved in 50 ml. of 10% potassium hydroxide. The basic solution was filtered and the filtrate acidified with diluted hydrochloric acid. The 3-hydroxy-1,2,4-benzotriazine-1-oxide was collected by filtration and recrystallized from methanol, m.p. 244–247°; yield 1.55 g.

3-Bromo-1,2,4-benzotriazine-1-oxide. To 4.00 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide was added 35 ml. of phosphorus oxybromide. The mixture was heated to reflux for 10 min. and then allowed to cool to room temperatures for 15 min. The cooled solution was then poured over cracked ice and water. The heterogeneous mixture was extracted with chloroform. The combined chloroform extracts were washed with water, filtered through a sintered-glass funnel to remove any tarry material, then dried over sodium sulfate. The solvent was distilled *in vacuo* and the residue taken up in methanol and allowed to crystallize to give 2.82 g. of 3-bromo-1,2,4-benzotriazine-1-oxide, m.p. 154–156°.

3-(β-Dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide. A solution of 1.50 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 5 ml. of β-dimethylaminoethylamine in 130 ml. of 1-butanol was allowed to stand at room temperatures for 16 hr., then heated to reflux for 1.5 hr. The solvent was distilled under reduced pressure and the resulting residue taken up in chloroform and washed with water. After drying with sodium sulfate and evaporating the solvent *in vacuo*, the residue was crystallized from hexane to give 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide, m.p. 128.5–131°C.; yield 1.36 g.

3-Thiosemicarbazido-1,2,4-benzotriazine-1-oxide. A mixture of 1.00 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 1.00 g. thiosemicarbazone in 50 ml. of 1-butanol was heated to reflux for 2 hr. The reaction mixture was allowed to cool and the solid collected by filtration. The crystalline solid was recrystallized from aqueous dimethyl formamide to give 0.85 g. of 3-thiosemicarbazido-1,2,4-benzotriazine-1-oxide, m.p. 253–255° (dec.).

3-(α,α-Bishydroxymethylene)ethylamino-1,2,4-benzotriazine-1-oxide. A solution of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, 5 g. of 2-amino-2-methyl-1,3-propanediol in 125 ml. of 1-butanol was heated to reflux for 2 hr. The solvent was distilled *in vacuo*, and the residue taken up in chloroform and water. The water layer was further extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue was chromatographed on 75 g. of silica gel. Elution with ethyl acetate–benzene (7:13) gave 3-(α,α-bishydroxymethylene)ethylamino-1,2,4-benzotriazine-1-oxide, which was recrystallized from ethyl acetate, m.p. 127–128°; yield 0.37 g.

4-Methyl-3-keto-3,4-dihydro-1,2,4-benzotriazine-1-oxide. To 2 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide, 10 g. potassium carbonate and 150 ml. of methanol in a pressure bottle was added 50 ml. of methyl iodide. The pressure bottle was sealed and heated at 65–70° for 18 hr. The excess methanol was blown off with nitrogen and the residue taken up in chloroform and water. The water layer was further extracted with chloroform. The combined chloroform extracts were washed with water and dried over sodium sulfate and then evaporated to dryness *in vacuo*. The solid residue was recrystallized from methanol to give 1.22 g. of 4-methyl-3-keto-3,4-dihydro-1,2,4-benzotriazine-1-oxide, m.p. 235.5–240°.

3-Ethoxy-1,2,4-benzotriazine-1-oxide. A suspension of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 2 g. of sodium cyanide in 50 ml. of ethanol was heated at reflux for 1 hr. The solvent was evaporated under nitrogen and the residue taken up in water and chloroform. The aqueous layer was further extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was taken up in hexane and allowed to crystallize, yielding 3-ethoxy-1,2,4-benzotriazine-1-oxide, m.p. 106.5–109°. Further recrystallization from methanol gave 1.20 g., m.p. 111–113°.

Preparation of 3-n-butoxy-1,2,4-benzotriazine-1-oxide. Method A. To a solution of 1.5 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 6 g. of glutamic acid in 150 ml. of 1-butanol was added about 5 g. of potassium carbonate. The heterogeneous mixture was stirred mechanically for 2 hr. and then evaporated to dryness *in vacuo*. The residue was taken up in chloroform and water, the water layer further extracted with chloroform, and the combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization from aqueous isopropyl alcohol gave 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide, m.p. 53–54°.

Method B. A suspension of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 5 g. of potassium fluoride in 175 ml. of 1-butanol was distilled until 50 ml. of distillate was collected. A condenser was put on the reaction flask and the reaction mixture was heated at reflux for 21 hr. The solvent was distilled and the residue diluted with water and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and then evaporated to dryness. Crystallization of the residue from pentane gave 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide, m.p. 52–53°.

Bis[3-(1-oxo-1,2,4-benzotriazyl)]sulfide (IX). A mixture of 2.0 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 2.0 g. of thiourea in 125 ml. of absolute ethanol was heated to reflux for 4 hr. The solution was cooled and the solid collected and washed with a few ml. of ethanol. The solid was slurried in 100 ml. of hot ethanol, cooled, and filtered to give bis[3-(1-oxo-1,2,4-benzotriazyl)] sulfide, yield 1.20 g., m.p. 267–271.

Anal. Calcd. for $C_{14}H_8N_6OS_2$: C, 51.84; H, 2.49; N, 25.92; S, 9.89. Found: C, 51.80; H, 2.43; N, 26.35; S, 10.29.

3-Chloro-1,2,4-benzotriazine. A suspension consisting of 1.00 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, 0.40 g. of zinc dust, and 0.30 g. of ammonium chloride in 25 ml. of water was stirred mechanically for 17 hr. at room temperature. The reaction mixture was diluted with an equal volume of acetic acid and then filtered. The filtrate was extracted with hexane and the combined hexane extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from pentane yielded 0.35 g. of 3-chloro-1,2,4-benzotriazine, m.p. 96–98°.

3-Hydrazino-1,2,4-benzotriazine. Treatment of 1.0 g. of 3-chloro-1,2,4-benzotriazine with 0.5 gm. of hydrazine hydrate with warming gave immediately a dark yellow solution which on standing crystallized. The solid was taken up in 35 ml. of ethanol and allowed to crystallize. The crystals were collected and recrystallized from benzene to give 3-hydrazino-1,2,4-benzotriazine, yield 0.55 g., m.p. 173–175°.

3-(β-Dimethylaminoethyl)amino-1,2,4-benzotriazine. A suspension of 1.0 g. of 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide, 0.4 g. of zinc dust, and 0.3 g. of ammonium chloride in 25 ml. of water was stirred mechanically for 17 hr. at room temperature. The reaction mixture was diluted with water and extracted with chloroform and benzene. The combined chloroform and benzene extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was taken up in hexane and allowed to crystallize giving 0.57 g. of 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine, m.p. 98–100°.

CHICAGO 80, Ill.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ST. OLAF COLLEGE]

Reactions of Diamines with Isocyanates and Isothiocyanates

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Diamines react with less than equivalent quantities of isocyanates and isothiocyanates to yield the mono- and disubstituted ethylenediamines and recovered diamine. The distribution of products is dependent on the reactivity of the reagent, on concentration, and on the solvent.

Recently it was shown[2] that acids react with diamines to give amides and recovered diamine in nearly the predicted yields based on random distribution. It was of interest to observe if the more facile reactions of diamines with isothiocyanates and isocyanates might yield similar distributions of products.

Amines react with isocyanates to give substituted ureas.[3] Similarly, reaction of diamines with equivalent amounts of isocyanates would be expected to give addition at each of the two amino groups. With less than two moles of isocyanates, the diamines should give mixtures in which the relative yields of the products would depend on the ratios of reactants.

$$H_2N(CH_2)_xNH_2 + b\ RNCO \longrightarrow \underset{(I)}{H_2N(CH_2)_xNH_2} + \underset{(II)}{RNHCONH(CH_2)_xNH_2} + \underset{(III)}{RNHCONH(CH_2)_xNHCONHR}$$

There is the possibility that II would react with a second molecule of isocyanate to give $(RNHCO)_2N(CH_2)_xNH_2$ (IV), but the decreased basicity of the substituted nitrogen in II relative to the primary amine should minimize this reaction.

In the above equation, when b is greater than O but less than 2, the recovery of I would be $\left(\frac{2-b}{2}\right)^2$, the formation of III would be $\left(\frac{b}{2}\right)^2$, and the yield of II would be $\left(b - \frac{b^2}{2}\right)$. When the reactants are present in equimolar quantities and b therefore is 1, the respective yields of I, II, and III would be 25%, 50%, and 25%.

The reaction of amines with isocyanates is known to occur very rapidly. It thus would be anticipated, as frequently was encountered, that the yield of III might be above the expected value due to a concentration effect at the instant of mixing the reactants. It is known[3] that isocyanates vary appreciably in their reactivities depending on the nature of the alkyl or aryl groups. It would be reasonable to expect that the isocyanates with the lesser reactivity would approach the statistical distribution more closely. The reactions of diamines with isothiocyanates[4] would parallel these considerations and substituted thioureas would result. The lower reactivity of the isothiocyanates would cause slower reactions and thus allow an approach to the statistical distribution.

Ideally, in each run the three products, I, II and III, would be isolated quantitatively. However, once the existence of all three products was established, it was expeditious to isolate only the disubstituted product III quantitatively and on occasion product II. The separation was accomplished due to the low solubility of the disubstituted compound in dilute acid solution in contrast to the appreciable solubility of the other products.

The data presented in Table I relate to the yields

(1) To whom requests for reprints should be addressed.

(2) C. Agre, G. Dinga, and R. Pflaum, *J. Org. Chem.*, 21, 561 (1956).

(3) J. Saunders and R. Slocombe, *Chem. Rev.*, 43, 203 (1948).

(4) D. Schroeder, *Chem. Rev.*, 55, 181 (1955).