

(VII), have been prepared and converted by the action of alkali into 2-methoxy-1-naphthoic acid.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE BAKER LABORATORY OF CHEMISTRY OF CORNELL UNIVERSITY]

MONOARYLGUANIDINES. III. BENZOTHIAZOLEGUANIDINE^{1,2}

BY G. B. L. SMITH, C. W. MASON AND R. H. CARROLL

RECEIVED JULY 22, 1931

PUBLISHED NOVEMBER 5, 1931

Introduction

In a previous communication it has been shown that benzoxazoleguanidine is formed from dicyandiamide and *o*-aminophenol through a process of deammonation. The present paper describes an application of this nitrile property of dicyandiamide in the preparation of benzothiazoleguanidine from *o*-aminothiophenol.

This investigation was undertaken in order that certain pharmacological properties of benzothiazoleguanidine might be studied and compared with those of the oxy and imide analogs and of other guanidine derivatives,³ and its properties as an accelerator of vulcanization of rubber might be examined.⁴

Properties of Benzothiazoleguanidine

Benzothiazoleguanidine is a white crystalline solid whose aqueous solution is a weak base which forms salts with the common acids. It differs from benzimidazoleguanidine⁵ and benzoxazoleguanidine^{1b} in that an anhydrous as well as a hydrated base is formed. The anhydrous crystals are obtained as plates when a hot saturated solution of the base is chilled and the crystals immediately separated from the mother liquor, or when either variety is crystallized from 95% ethanol. The crystals of the monohydrate separate as prismatic needles when the hot solution is slowly cooled

¹ For earlier articles of this series see (a) Smith, *THIS JOURNAL*, 51, 476 (1929); (b) Smith, Kane and Mason, *ibid.*, 51, 2522 (1929).

² The substances described were prepared by Mr. Carroll and a part of this paper is constructed from the thesis submitted by Mr. Carroll in partial fulfilment of the requirements for the degree of Bachelor of Science in Chemistry at the Polytechnic Institute of Brooklyn in June, 1930. This paper was presented at the eighty-second meeting of the American Chemical Society before the Division of Organic Chemistry at Buffalo, N. Y., August 31 to September 4, 1931.

³ Bischoff, Sahyun and Long, *J. Biol. Chem.*, 81, 325 (1929); Bischoff and Long, *J. Pharm. and Exptl. Therap.*, 41, 127 (1931).

⁴ Smith and Weiss, *Ind. Eng. Chem.*, 20, 298 (1928); an extension of this study is projected.

⁵ (a) Ziegelbauer, *Monatsh.*, 17, 653 (1896); (b) Pellizzari, *Gazz. chim. ital.*, I, 51, 89, 140 (1921); see *C. A.*, 15, 3076, 3078 (1921).

and if the plates are allowed to remain in contact with the mother liquor they soon become hydrated. This hydration takes place quite rapidly at room temperature and without at first altering the macroscopic appearance of the crystals other than rendering them opaque. Indeed it was at first thought that both forms were hydrated.

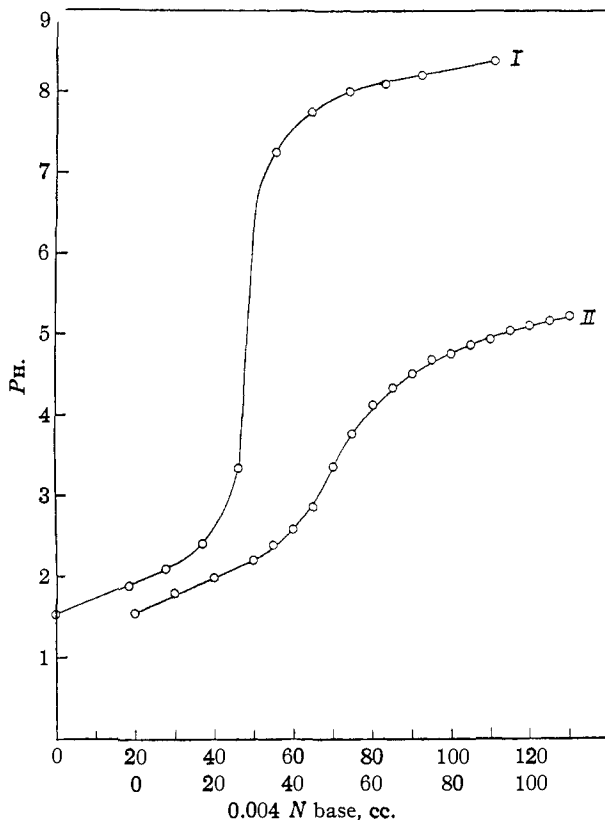
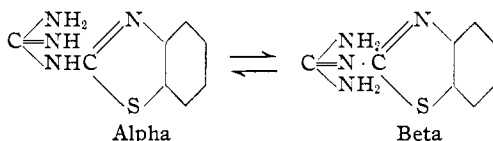


Fig. 1.—I, Hydrochloric acid and ammonium hydroxide; II, hydrochloric acid and benzothiazoleguanidine.

The prismatic crystals (monohydrate) may be dehydrated by standing in a desiccator over phosphoric anhydride at room temperature for several days. They lose all their water of crystallization when heated to 105° for one hour but further heating does not result in further loss of weight. These dehydrated crystals or the anhydrous plates may be heated to fusion without any loss in weight. The fused material may be dissolved in water and either the anhydrous or hydrated crystals may be obtained from this solution.

A third crystalline modification has been identified microscopically in a supercooled melt of the base. This suggests that both α and β forms exist

as solid phases and the transition temperature is at or near the melting point. The replacement of oxygen with sulfur in the benzazole ring should have the effect of decreasing the electronegative character of this group^{1b} and accordingly it was thought that a triacetyl derivative might be formed. However, we have been able to prepare only a diacetyl derivative. It is possible that both compounds have the β or symmetrical formula in solution and in that case we would expect to form only the diacetyl derivative. However, it is more likely that benzothiazoleguanidine in aqueous solution is an equilibrium mixture of the two tautomeric forms, thus



as postulated in the case of dicyandiamide.^{1b}

The salts of benzothiazoleguanidine and strong acids hydrolyze in aqueous solution and can be titrated with alkali using phenolphthalein as indicator. The potentiometric titration (Fig. 1) in which the equivalent of 50 cc. of *N*/250 hydrochloric acid is titrated with a *N*/250 solution of benzothiazoleguanidine using the familiar hydrogen electrode shows that the substance is a very weak base.⁶ This finding has been confirmed using the antimony electrode.

Experimental

Materials.—The zinc salt of *o*-aminothiophenol was prepared by reducing *o*-dinitrodiphenyl disulfide with zinc in a solution of glacial acetic acid.⁷ *o*-Dinitrodiphenyl disulfide⁸ was obtained by the interaction of sodium disulfide and *o*-chloronitrobenzene⁹ in a solution of 95% alcohol.

Benzothiazoleguanidine Hydrochloride.—About 25 g. of zinc *o*-aminothiophenol and 13 g. of dicyandiamide¹⁰ were dissolved in 100 cc. of 95% alcohol and 50 cc. of concd. hydrochloric acid, and heated under a reflux for approximately one and one-half hours. On cooling a white crystalline solid separated which was filtered, washed with alcohol and then water, and dried at 105°; product obtained, 18 g.

Benzothiazoleguanidine (Dehydrated Base).—Sixteen grams of benzothiazoleguanidine hydrochloride was dissolved in the least amount of hot water and a 20% solution of sodium hydroxide was added until a pink color was produced with phenolphthalein. The precipitated base was recrystallized four times from aqueous solution, filtered and dried at 105°.

Benzothiazoleguanidine, Monohydrate (Prismatic or Needle) Form.—Four grams

⁶ D. C. Hopkins, "Thesis" for Master of Science in Chemistry, Polytechnic Institute of Brooklyn, June, 1930.

⁷ Bogert and Snell, THIS JOURNAL, 46, 1309 (1924); see also Teppema and Sebrell, *ibid.*, 49, 1748 (1927).

⁸ Wohlfahrt, *J. prakt. Chem.*, [2] 66, 553 (1902); Blanksma, *Rec. trav. chim.*, 20, 121 (1901). *o*-Diaminodiphenyl disulfide is described in German Patent 120,504.

⁹ Obtained from the Eastman Kodak Co., m. p. 31°.

¹⁰ Purchased from the American Cyanamid Company.

of anhydrous base was dissolved in 950 cc. of hot water. The beaker was insulated by wrapping with asbestos, allowed to cool slowly and to stand for forty-eight hours. The recrystallized base was then separated by filtration, dried between filter papers, finally on an unglazed porcelain plate and analyzed for water and nitrogen.

Benzothiazoleguanidine, Anhydrous (Plate) Form.—Two grams of anhydrous base was dissolved in 400 cc. of hot water and cooled rapidly in an ice-bath. The plate crystals which separated were filtered immediately, pressed between filter papers, dried on a porcelain plate and analyzed for water, sulfur, and nitrogen.

Benzothiazoleguanidine Salts.—One and one-half gram samples of anhydrous base were dissolved in the least amount of hot water and then treated with a slight excess of the respective acid. The salts prepared were all sparingly soluble in water and crystallized when the solutions were cooled.

Diacetylbenzothiazoleguanidine.—Three grams of the base was dissolved in 10 cc. of 95% alcohol, 25 g. of acetic anhydride added, and the mixture was heated under a reflux for ninety minutes. It was then poured into 300 cc. of cold water and allowed to stand overnight. The white solid was filtered, washed several times with water, and dried in a desiccator over anhydrous calcium chloride. The analytical and other data for the bases, salts and diacetyl derivative are given in the accompanying table.

TABLE I
ANALYTICAL AND OTHER DATA OF BENZOTHAZOLEGUANIDINE

Compound	M. p., °C.	Calcd.	Analyses, %			Soly. at 20° G./100 g. of H ₂ O	Solubility non- aqueous solvents
			Found	Found	Found		
Base (dried at 105° after four recrystallizations)	175-176	C	49.95	49.82	49.74	0.0696	Insol. CS ₂ ; sl. sol. in Bz; sol. Et ₂ O; v. sol. in EtOH and acetone
		H	4.11	4.24	4.36		
		S	16.68	16.56	16.41		
		N	29.15	29.39	29.17		
Base (plate form)	175-176	H ₂ O	0.00	0.00	0.00
		S	16.68	17.10	17.42		
		N	29.15	29.56	29.97		
Base monohydrate (prismatic form)	175-176	H ₂ O	8.57	8.29	8.45
		N	26.70	26.66	26.72
Sulfate	294-295	S	19.89	19.85	19.93	0.0160	Insol. acetone; sl. sol. in Bz, CS ₂ , Et ₂ O; sol. EtOH
Hydrochloride	239-241	HCl	15.95	15.72	15.79	2.3080	Sl. sol. acetone, Bz; sol. CS ₂ , EtOH, Et ₂ O
Nitrate	236-239	N	27.46	27.36	27.22	0.0631	Sl. sol. Et ₂ O, Bz; sol. CS ₂ , EtOH, acetone
Picrate	280-289	N	23.28	23.41	23.46	0.0030	Sl. sol. EtOH, ace- tone, Et ₂ O, Bz; sol. CS ₂
Diacetyl derivative		S	11.60	11.85	11.78		

Microscopical Studies

Benzothiazoleguanidine.—As prepared on a microscope slide from a dilute solution of the hydrochloride, by means of sodium hydroxide, a very granular precipitate is first obtained, apparently as droplets of the "supercooled" base. These change, by

solution, into two forms of crystals: (a), lath-shaped needles and prisms, single and in radiating clusters, and (b), mossy rosettes of fine leaflets and larger single leaflets.

On recrystallizing the base from hot aqueous solution by cooling, a bulky mass of irregular flakes separates. On digestion at room temperature for twelve hours or more, these flakes are replaced by needles and fine prisms. The prismatic crystals when dry alter slowly at room temperature to pseudomorphs which consist of very fine grains and, therefore, appear practically opaque. This alteration is progressive through the crystals, and is accelerated by warming the dry material.

When the prismatic crystals, or their pseudomorphic alteration product, are warmed for a few minutes in contact with water and allowed to cool, they become studded with small tabular crystals which grow to a fair size on further digestion and finally replace the prismatic pseudomorphs completely. These crystals also form free in the solution. If the alteration product of the prismatic crystals is dissolved in water nearly boiling, and the solution cooled fairly rapidly, thin plates and curving leaflets separate. Digestion of the pseudomorphs at room temperature for twenty-four hours gives no evidence of grain growth in the fine particles of the alteration product.

Properties of the Different Forms of Benzothiazoleguanidine.—Recrystallized by cooling a hot aqueous solution as thin flakes and plates, sometimes curving or skeletal but more commonly rectangular in outline, appear (I). All views exhibit parallel extinction and the material is biaxial, which places it in the orthorhombic system. $2E$ is about 100° , with extreme dispersion of the optic axes, $r < v$. The acute bisectrix is perpendicular to the plane of the plates, with the axial plane usually parallel to their longer direction. The sign of double refraction is positive. Refractive indices (± 0.005): $\alpha = 1.700$; $\beta = 1.740$; (exhibited only by edgewise views of plates) $\gamma = 1.8 +$ (est.).

The crystals developed by warming the altered prisms (pseudomorphs) in water and allowing to cool are closely similar to the above plates, except that they are more or less equidimensional grains or tablets (I). Some show truncated ends, with terminal angles of about 92° . Their small size and compact clustering hinder observations of their optical properties, but as far as can be ascertained the refractive indices are the same as those of the larger plates.

Digestion of the plate crystals in water at room temperature for twelve hours or more yields thin prismatic crystals (II), six- or eight-sided and usually with pinacoidal end faces. All side views of the prisms exhibit parallel extinction, and they probably belong to the orthorhombic or to the monoclinic system. The refractive indices (± 0.005) are α (vibrations \parallel to elongation of prisms) 1.525 , $\beta = 1.745$, $\gamma = 1.8$ (est.). The sign of double refraction indicated by these refractive indices is negative.

The two forms of crystals resulting from the precipitation of the base by alkali appear to be identical with the plates and prisms described above. The needle-like crystals possess the same refractive indices as the latter. The plates slowly change to prisms on standing in water.

Crystallization of the plates from alcohol yields elongated plates and tabular crystals, having truncated ends and terminal angles of about 92° , together with the optical properties of the original plates (I). On moistening the prismatic crystals (II) with alcohol, fine-grained crystals are formed, evidently as a result of dehydration, in aggregates which are pseudomorphs of the prisms, and separately. Some of these, of fair size, are tabular in habit or even prismatic, with terminal angles of 92° and the optical properties of the original plates.

On fusion, the material solidifies in spherulites and dense radiating and laminary masses, with marked undercooling possible and more or less permanently suspended freezing. If the cooling is gradual, crystals develop in fair-sized grains having uniform orientation throughout. Extinction is parallel to the direction of the crystal growth,

which is also the direction of vibration of the slower component. The plane of the optic axes is transverse of this direction, but the acute bisectrix is markedly inclined and only one optic axis is observable. $2E$ is about 50° with $r < v$ and double refraction positive. This points to the crystals of this modification (III) being in the monoclinic system. The refractive indices are: $\alpha = ca\ 1.5$, $\beta = 1.60$, $\gamma = 1.72$.

A different solid phase may separate if the freezing has been very slow. This modification is apparently the more stable at room temperature, and well-defined crystals of it gradually extend through the preparation in the manner typical of solid transformations. The growth of these crystals is markedly accelerated by the presence of a solvent such as alcohol (just as the transformation from monoclinic to rhombic sulfur is hastened by contact with carbon disulfide). It is difficult to ascertain whether enantiotropy or monotropy exists, on account of the slowness of the change in the absence of a solvent, but if the transformation is actually a reversible one the transition temperature must lie very near the melting point.

The stable modification exhibits distinctive crystal habit as it grows through the solid metastable phase, with tabular form and terminal angles of about 92° . Extinction is parallel for all views, with the axial plane parallel to the elongation of the crystals and the acute bisectrix perpendicular to their principal plane. $2E$ is about 100° , with very marked dispersion $r < v$, and positive double refraction. The refractive indices as determined on fragments are $\alpha = 1.70$, $\beta = 1.74$, $\gamma =$ about 1.8 (est.). The properties of this modification correspond to those of I.

On the basis of the above properties, it appears that the anhydrous modification of benzothiazoleguanidine which crystallizes in plate-like crystals (I) is formed from hot aqueous or alcoholic solution of either modification, or from a very slowly cooled melt, and that the hydrated prismatic form (II) is formed only by digestion of I in water at room temperature or by slow precipitation of the base by alkali. II when dry is altered slowly at room temperature, more rapidly on heating, to a pseudomorphic aggregate which may be the anhydrous base.

The fact that I is so slowly transformable into II, and that they appear to be capable of coexisting at ordinary temperatures point less to polymorphism than to possible tautomerism. However, allotropy does exist between I and the phase separating from the supercooled melt (III), which may be a monotropic modification.

Benzothiazoleguanidine Hydrochloride.—On crystallization from water, it forms thin prisms or needles, in radiating clusters and spherulites. All side views exhibit parallel extinction and negative elongation, with strong double refraction. The axial plane is lengthwise, with $2V$ large. The refractive indices (± 0.005) are $\alpha = 1.590$, $\beta = 1.765$, $\gamma = 1.82+$, indicating negative double refraction.

Benzothiazoleguanidine Sulfate.—Precipitated from a solution of the base by dilute sulfuric acid, it appears in the form of fine granules and small spherulites, strongly birefringent and highly refractive. Single crystals of size sufficient for further study were not obtained.

Benzothiazoleguanidine Nitrate.—Recrystallizes from water as dense bristling spherulites and fine needles, parallel extinction. For light vibrating crosswise of the needles the refractive index is about 1.53; for vibrations lengthwise, about 1.78.

Benzothiazoleguanidine Picrate.—Very fine grained; no evidence of crystalline form other than the strong double refraction exhibited by the tiny particles.

Summary

A new monoarylguanidine, benzothiazoleguanidine, has been prepared through the reaction between dicyandiamide and *o*-aminothiophenol. The base, nitrate, picrate, hydrochloride and diacetyl derivative have

been isolated and certain physical and chemical properties of these substances are described. An anhydrous crystalline base as well as a hydrated (the monohydrate) crystalline base has been prepared. A third crystalline modification of the base has been identified when the melted base is supercooled. This is believed to be a tautomeric form of benzothiazoleguanidine. The results of microscopical studies of these substances are presented.

BROOKLYN, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

STUDIES IN THE ANTHRONE SERIES.

III. THE SYNTHESIS OF 3-METHOXYPHthalALDEHYDE ACID AND A NEW SYNTHESIS OF CHRYSAZIN^{1,2}

BY CHARLES A. NAYLOR, JR., WITH JOHN H. GARDNER

RECEIVED JULY 23, 1931

PUBLISHED NOVEMBER 5, 1931

As a number of the naturally occurring anthrone and anthraquinone derivatives are related to chrysazin, 1,8-dihydroxyanthraquinone, a convenient method for the synthesis of compounds of this type would be of value for the solution of some problems regarding the structure of these substances. The most promising method of attack is the phthalaldehyde acid condensation originated by Bistrzycki and his co-workers and improved by Adams and his students,³ provided that suitable starting materials can be obtained.

First of all, it was necessary to obtain a phthalaldehyde acid substituted in the position ortho to the aldehyde group with hydroxyl or a group which could be replaced by hydroxyl. A search of the literature suggested 3-nitrophthalaldehyde acid,⁴ but some preliminary experiments on the synthesis of anthraquinone derivatives through the condensation of nitrophthalaldehyde acids with phenols led to unexpected complications.⁵ Another method of attack was suggested by the work of Bentley, Robinson and Weizmann on the oxidation of 1,5-dihydroxynaphthalene monomethyl ether.⁶ They obtained in this way 3-methoxyphthalic acid and a compound which might have been, from the method of preparation, either

¹ Previous papers in this field are (a) Steyermark with Gardner, *THIS JOURNAL*, 52, 4884 (1930); (b) *ibid.*, 52, 4887 (1930).

² Based upon a portion of a thesis submitted by Charles A. Naylor, Jr., Fellow in Chemistry, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Washington University, June, 1931.

³ Brubaker and Adams, *THIS JOURNAL*, 49, 2279 (1927), give a bibliography of the work in this field.

⁴ Wegscheider and v. Dubrav, *Monatsh.*, 24, 805 (1903).

⁵ Rolf, "Thesis," Washington University, 1930.

⁶ Bentley, Robinson and Weizmann, *J. Chem. Soc.*, 91, 104 (1907).