increased, and that more and more of the entering nitro group took up a position meta to the hydroxyl. However, a maximum value of about 0.8 was reached for the meta–ortho ratio. This change in directive power is ascribed to the salt-forming property of the oxygen atom of *p*-cresol. The predominating tendency toward ortho substitution, even when a large excess of acid is present, probably arises from the fact that the oxonium salt is in part un-ionized.

In the case of *p*-cresyl carbonate, increase in the amount of sulfuric acid likewise increased the meta–ortho ratio. It is assumed that here also oxonium salt formation is responsible for the change.

These changes in orientation are entirely analogous to the modification in the orientation of amino and substituted amino groups by the addition of sulfuric acid.

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The Preparation of Some Structurally Related Monoguanidines

BY CHARLES E. BRAUN

Introduction

In a study of the relationship between guanidine structure and hypoglycemic activity it became necessary to prepare the following series of structurally related monoguanidines: α-phenylguanidine sulfate, benzylguanidine sulfate, phenylaminoguanidine hydrochloride, *p*-aminophenylguanidine sulfate, *n*-hexylguanidine sulfate, cyclohexylguanidine hydrochloride, *o*-tolylguanidine hydrochloride, *m*-tolylguanidine sulfate, *p*-tolylguanidine hydrochloride, α-methyl α-phenylguanidine hydrochloride and β-phenylethylguanidine sulfate. The first four were prepared as described by previous investigators.[1]

The detailed syntheses of the latter seven are recorded here for the benefit of those interested in the field. While the nitrate salts of *o*-tolylguanidine and *p*-tolylguanidine have been described,[2] no record of their hydrochlorides could be found.

Since the compounds were synthesized for the purpose of studying their physiological reactions, special emphasis was placed upon purity, and no attempts were made to produce maximum yields. The hydrochloride and sulfate salts were selected to obtain greater water solubility than might be expected with the free bases or the nitrate salts. The results of the physiological investigation of these compounds, which is in progress, will be reported separately.

(1) Smith, THIS JOURNAL, **51**, 476 (1929); Davis and Elderfield, *ibid.*, **54**, 1499 (1932); Pellizzari, *Gazz. chim. ital.*, **21**, 330 (1891); Braun, THIS JOURNAL, **54**, 1511 (1932).

(2) Meister, Lucius and Bruning, German Patent 172,979; Kampf, *Ber.*, **37**, 1683 (1904).

Experimental

***n*-Hexylguanidine Sulfate.**—*n*-Hexylamine was prepared by the reduction of *n*-capronitrile (Eastman practical) with sodium and absolute alcohol—m. p. hydrochloride salt, 219°.

14.5 g. (0.143 mole) of *n*-hexylamine and 21.0 g. (0.151 mole) of S-methyl isothiourea sulfate in 60 cc. of water were heated under reflux at 100° for five hours. The crystals obtained upon cooling the reaction solution were filtered off, washed with dry ether and air dried. The crude salt, when dry, was treated with boiling absolute alcohol, boneblacked (norite), and filtered hot. To the cold alcoholic solution was added sufficient ether to cause permanent turbidity. Upon standing in an ice chest crystals of the sulfate deposited. These were filtered off, washed with dry ether and dried at 100° *in vacuo*. After three recrystallizations from absolute alcohol a *n*-hexylguanidine sulfate was obtained which melted at 210–212°.

The purified salt was white, crystalline, easily soluble in cold water and hot absolute alcohol, but insoluble in anhydrous ether. The final yield (purified salt) was 5.0 g. or 18.2%.

Anal. Calcd. for $C_7H_{17}N_3 \cdot 0.5H_2SO_4$: S, 8.34. Found: S, 8.37 (as $BaSO_4$).

Cyclohexylguanidine Hydrochloride.—Cyclohexylamine hydrochloride was prepared by passing dry hydrogen chloride into a cold solution of cyclohexylamine (Eastman) in anhydrous ether—m. p. cyclohexylamine hydrochloride, 204–205°.

Ten grams (0.074 mole) of cyclohexylamine hydrochloride and 4.5 g. (0.107 mole) of cyanamide (Eastman) in 50 cc. of absolute alcohol were heated under reflux at 100° for six hours. The solution was reduced to about half its volume under atmospheric pressure, after which, upon cooling, a crystalline compound deposited. The latter was filtered off, washed with ether and dried. The crude material (10.4 g.) melted over a wide range, 158–194°. The entire batch of this crude was extracted twice with boiling acetone, washed with ether, and dried at 100° *in vacuo*. The hydrochloride after recrystallization from boiling absolute alcohol melted at 224–226°.

The purified cyclohexylguanidine hydrochloride was white, crystalline, readily soluble in cold water and in hot alcohol, but insoluble in ether and in boiling acetone. The yield (purified salt) was 8.4 g. or 64.0%.

Anal. Calcd. for $C_7H_{16}N_3Cl$: Cl, 19.96. Found: Cl, 19.92 (as AgCl).

***o*-Tolylguanidine Hydrochloride.**—*o*-Toluidine hydrochloride was prepared by passing dry hydrogen chloride into a solution of *o*-toluidine (Eastman practical) in anhydrous benzene—m. p. crude *o*-toluidine hydrochloride, 205–206°.

Forty-five grams (0.314 mole) of *o*-toluidine hydrochloride (m. p. 205–206°) and 18.0 g. (0.430 mole) of cyanamide (Eastman) in 100 cc. of absolute alcohol were heated under reflux at 100° for six hours. When the solution was concentrated to about one-third its volume the concentrate, a viscous sirup, set to an almost solid mass under vigorous agitation. The solid was filtered off, washed with a small volume of anhydrous ether, and dried at room temperature *in vacuo*. The crude material (24.5 g.) was dissolved in 450 cc. of boiling acetone, boneblacked and the solution filtered hot. The hydrochloride was precipitated in crystalline condition from the cold acetone solution by slow addition of ether. After filtration and washing with ether, it was dried at 78° *in vacuo*. A second acetone–ether purification produced an analytically pure compound which melted at 133–135°.

The purified *o*-tolylguanidine hydrochloride was white, crystalline, soluble in cold water and hot acetone, but insoluble in ether. The yield (purified salt) was 18.4 g. or 31.6%.

Anal. Calcd. for $C_8H_{12}N_3Cl$: Cl, 19.11. Found: Cl, 19.00 (as AgCl).

m-**Tolylguanidine Sulfate.**—Ten grams (0.10 mole) of *m*-toluidine (Eastman practical) and 9 g. (0.065 mole) of S-methyl isothiourea sulfate suspended in a mixture of 10 cc. of alcohol and 10 cc. of water were heated under reflux at 100° for about thirty hours. A yellowish solid which had formed after cooling was filtered off, ground under a mixture of alcohol and ether and dried at room temperature under vacuum. The alcohol–ether extraction removed practically all of the color and left a crude sulfate (5.0 g.) which melted at 210–212°. The crude material was dissolved in a large volume of hot 95% alcohol, boneblacked and filtered hot. The addition of ether to the cooled alcoholic solution precipitated the sulfate as a white, crystalline powder, easily soluble in cold water but insoluble in ether. The pure compound melted at 215–217°. The yield (purified salt) was 4.0 g. or 31.1%, calculated on 0.065 mole of *m*-toluidine.

Anal. Calcd. for $C_8H_{11}N_3 \cdot 0.5H_2SO_4$: S, 8.09. Found: S, 8.13 (as $BaSO_4$).

p-**Tolylguanidine Hydrochloride.**—Forty-two grams (0.29 mole) of *p*-toluidine hydrochloride (m. p. 243°) and 18 g. (0.43 mole) of cyanamide (Eastman) in 43 cc. of absolute alcohol were heated under reflux at 100° for six hours. When the solution was concentrated to about one-half its volume, the concentrate, after cooling, set to an almost solid mass of crystals. These were filtered off, ground under cold acetone, refiltered, washed with cold acetone and ether, and dried at room temperature *in vacuo*. The crude material (17 g.) was white and melted at 133–135°.

The crude product was dissolved in 90 cc. of boiling absolute alcohol, boneblacked, and filtered hot. After reducing the volume of the solution, a small amount of a white crystalline compound deposited. This was filtered off, washed with ether and dried at room temperature. The dry material weighed 1.3 g. and melted at 245–247°. Analytical data established this compound as the hydrochloride salt of *p*-tolylbiguanide.

Anal. Calcd. for $C_9H_{14}N_5Cl$: Cl, 15.57. Found: Cl, 15.68 (as AgCl).

These data are not in agreement with those of Beutel,[3] who reported that *p*-tolylbiguanide hydrochloride had the formula $C_9H_{14}N_5Cl \cdot 0.5H_2O$, and that the anhydrous salt melted at 235°, uncorrected.

The alcoholic filtrate, after removal of the *p*-tolylbiguanide salt, was concentrated at 100°. The concentrate when cool, deposited 11.7 g. of crystalline material which, when dry, melted at 130–133°. This impure hydrochloride was treated with 200 cc. of cold absolute alcohol, in which it was almost completely soluble. After filtration the solution was concentrated, cooled and treated with ether until a permanent turbidity existed. Upon standing in an ice chest the solution deposited a batch of white crystals which were filtered off, washed with ether and dried at 78° *in vacuo*. The purified *p*-tolylguanidine hydrochloride was white, crystalline, soluble in water and hot absolute alcohol but insoluble in ether. It melted at 136–137°. The yield (purified salt) was 9.5 g. or 17.4%.

Anal. Calcd. for $C_8H_{12}N_3Cl$: Cl, 19.11. Found: Cl, 19.06 (as AgCl).

α-**Methyl-**α-**Phenylguanidine Hydrochloride.**—Methylaniline hydrochloride was prepared by passing dry hydrogen chloride into a cold solution of methylaniline (Eastman, b. p. 81–82° (14 mm.)) in benzene.

48.5 g. (0.34 mole) of methylaniline hydrochloride (m. p. 121°) and 17 g. (0.41 mole) of cyanamide (Eastman) in 30 cc. of absolute alcohol were heated under reflux at 100° for ten hours. After cooling, the solution deposited a large quantity of white crystals which were filtered off, washed with ether and dried at room temperature *in vacuo*. The crude hydrochloride weighed 43.8 g. and melted at 206–208°.

Purification was effected by dissolving the salt in boiling absolute alcohol, boneblacking, filtering hot and adding sufficient ether to the cold filtrate to produce perma-

(3) Beutel, *Ann.*, **310**, 344 (1900).

nent turbidity. After the alcohol–ether solution had stood in an ice chest, the purified hydrochloride crystallized out, was filtered off, washed with ether and dried at 100° *in vacuo*. The pure α-methyl α-phenylguanidine hydrochloride was white, crystalline, soluble in cold water and hot alcohol but insoluble in ether. It melted at 217–218°. The yield (pure salt) was 22.3 g. or 35.3%.

Anal. Calcd. for $C_8H_{12}N_3Cl$: Cl, 19.11. Found: Cl, 19.03 (as AgCl).

β-Phenylethylguanidine Sulfate.—Twenty grams (0.165 mole) of β-phenylethylamine (b. p. 76.5–78° (8 mm.)) and 20 g. (0.144 mole) of S-methylisothiourea sulfate in 250 cc. of water were heated at 100° for four hours. After evaporation of most of the water a crystalline material deposited, which was filtered off, washed with small volumes of acetone and ether and air dried. The crude material melted rather abnormally. It softened at 80°, appeared to evolve a gas between 95–105°, and then solidified. The second solid melted without decomposition at 170–172°. These observations suggested that possibly the original solid was a hydrate which lost its water of crystallization at 95–105°, leaving an anhydrous compound which melted at 170–172°. The original and final substances gave positive sulfate reactions.

Recrystallization from boiling absolute alcohol produced large glistening crystals, soluble in cold water and giving a positive sulfate reaction. The material from absolute alcohol softened at 60–65°, appeared to evolve a gas at 95° and then solidified. The second solid melted without decomposition at 168–173°. A second recrystallization from absolute alcohol produced identical results. The crystalline compound was air dried, and its sulfur content determined in order to prove or disprove the idea that the compound, crystallized from alcohol, is β-phenylethylguanidine sulfate with alcohol of crystallization. The analytical data established this point.

Anal. Calcd. for $(C_9H_{13}N_3 \cdot 0.5H_2SO_4) \cdot C_2H_5OH$: S, 6.19. Calcd. for $C_9H_{13}N_3 \cdot 0.5H_2SO_4$: S, 7.56. Found: S, 6.65 (as $BaSO_4$).

The remainder of the crystalline material was heated for six hours at 78° *in vacuo* and then at 100° *in vacuo* to drive off the alcohol of crystallization. The compound, after heating, lost its glistening crystalline appearance and became dull. It melted at 175–177°. Repeated recrystallizations from absolute alcohol followed by heating *in vacuo* failed to raise the melting point. The sulfur content of the compound melting at 175–177° was 7.63%, which established it as β-phenylethylguanidine sulfate. In one experiment a final melting point of 180.5–181° was observed but subsequent trials failed to confirm this. The purified sulfate was white, very soluble in water and hot absolute alcohol, only slightly soluble in acetone and insoluble in ether. The yield (purified salt m. p. 175–177°) was 12.3 g. or 40.3%, calculated on 0.144 mole of β-phenylethylamine.

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Summary

1. The methods of preparation and general properties of the following monoguanidines have been described: *n*-hexylguanidine sulfate, cyclohexylguanidine hydrochloride, *o*-tolylguanidine hydrochloride, *m*-tolyl-

guanidine sulfate, *p*-tolylguanidine hydrochloride, α-methyl α-phenylguanidine hydrochloride and β-phenylethylguanidine sulfate.

2. A corrected formula and melting point for *p*-tolylbiguanide hydrochloride have been reported.

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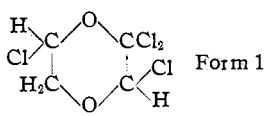
Derivatives of Dioxane

BY J. BÖESEKEN, F. TELLEGEN AND P. COHEN HENRIQUEZ

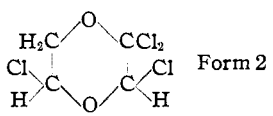
In a previous communication[1] we mentioned the first results of a research on the chlorination of 1,4-dioxane. 2,3-Dichlorodioxane, the first product of chlorination, was separated; the chlorine atoms proved to be very mobile as they are in all α-chloro ethers. With sodium ethylate we isolated the 2,3-diethoxydioxane, while with glycol the two isomeric naphthodioxanes (1,4,1′,4′-tetroxadecahydronaphthalene). These investigations were continued in different directions.

A. The Action of Chlorine on Dioxane.—Neither repeated distillation nor investigation of the products of hydrolysis of the first fraction gave any indication of the existence of monochlorodioxane. The investigation of the mechanism of the first stage of the chlorination is still being continued.

On chlorinating dichlorodioxane, it appeared that chlorine is rapidly absorbed. The first time the chlorination was continued for sixteen hours at 130–150° and the product was carefully fractionated. The first fraction, boiling below 102° (15 mm.), appeared to have a chlorine content corresponding with tetrachlorodioxane. Hydrolysis by means of boiling water produced glycolic aldehyde. Subsequent treatment with dinitrophenylhydrazine gave the dinitrophenylhydrazone of glycolic acid and the dinitrophenylosazone of glycolic aldehyde. The quantity of these precipitates was in accordance with the expectation, based on the decomposition of one of the following tetrachlorodioxanes



Form 1



Form 2

Butler and Cretcher[2] succeeded, after a chlorination of twelve hours, in the isolation of a crystalline asymmetrical and two isomeric symmetrical tetrachlorodioxanes besides the liquid asymmetrical one, just mentioned. In the higher-boiling fractions of the product obtained by the chlorination of dichlorodioxane during sixteen hours, only very little oxalic acid could

(1) *Rev. trav. chim.*, **50**, 909 (1931); *Proc. Acad. Sci.*, **34**, 631 (1931).
(2) Butler and Cretcher, THIS JOURNAL, **54**, 2987 (1932).