was then calculated from this titer, the equivalent weight and the normality of the standard alkali. Four- to fivefold variations in the sample weights did not change the value obtained for the percentage of 5-substituted aminotetrazole in the equilibrium mixture. This seems to indicate that the equilibrium is not appreciably shifted during freezing of the melt. Every effort was made to avoid disturbing the sample during the heating period. If the melt solidified or if the sample isomerized without melting, the results were not included.

Isomerizations in ethylene glycol were effected by adding an accurately weighed sample of the tetrazole (0.2–0.9 g.) to 10 ml. of ethylene glycol in a 25-ml. flask with an air condenser. The flask was immersed for 15 minutes in a silicone oil-bath preheated to 200–202°; the solution reached the boiling point of ethylene glycol (192–194°) in about 5 minutes. The flask was then removed and rapidly plunged into an ice–water-bath to freeze the equilibrium. The samples were titrated as before and the titer corrected for the slight acidity of the ethylene glycol.

An attempt also was made to study the isomerization in tetrahydronaphthalene at 200°. Three tetrazoles, differing widely in their extent of isomerization, all showed 26–28% acid form in the equilibrium mixture. In contrast to the normal behavior experienced in ethylene glycol solution, these solutions became very darkly colored. The reason for this peculiar result has not been determined.

Approximately 0.011 *N* solutions of 5-substituted aminotetrazoles in 50% aqueous ethanol were titrated potentiometrically with standard alkali at 27°. The *p*H at the half-neutralization point was taken as the pK_a.

1-(4-Anisyl)-2-aminoguanidine Hydroiodide.—This compound was made in essentially quantitative yield by the hydrazinolysis of S-methyl-4-anisylisothiourea hydroiodide in absolute ethanol. After recrystallization from absolute ethanol, it melted at 150–151°.

Anal. Calcd. for $C_8H_{14}N_4OI$: C, 31.08; H, 4.56. Found: C, 31.22; H, 4.23.

1-(2-Tolyl)-2-aminoguanidine hydroiodide was prepared by a method similar to that just described; m.p. 153–154° after recrystallization from absolute ethanol–diethyl ether.

Anal. Calcd. for $C_8H_{14}N_4I$: C, 32.78; H, 4.81. Found: C, 33.01; H, 4.50.

Benzal 1-(2,4-Xylyl)-2-aminoguanidine picrate was prepared by reaction of equivalent quantities of benzaldehyde and 1-(2,4-xylyl)-2-aminoguanidine hydroiodide in hot aqueous alcohol solution and adding an equivalent quantity of ammonium picrate; m.p. 190–192° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{22}H_{21}O_7N_7$: C, 53.33; H, 4.27. Found: C, 53.93; H, 4.28.

Acknowledgment.—The authors are indebted to Mr. LeMoyne Plischke, who performed many of the isomerizations, and to Dr. William Urry, University of Chicago, and Dr. Robert W. Van Dolah of this Laboratory for their interest and helpful suggestions.

CHINA LAKE, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Monomer Synthesis.[1] Triazines. The Reaction of Phenylbiguanide with Ethyl Oxalate and Ethyl Formate

BY C. G. OVERBERGER AND SEYMOUR L. SHAPIRO[2]

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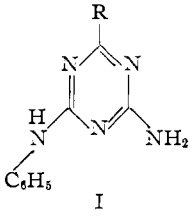
The reaction of phenylbiguanide with formic acid, formamide, dimethylformamide and ethyl formate has been investigated and shown to give I (R = H), the use of ethyl formate being the preferred procedure. Reaction of phenylbiguanide with ethyl oxalate gave a compound of inconclusive structure $C_{10}H_9N_5O_2$ which readily was converted to triazine derivatives, I (R = COOH) and its hydrates, $COOCH_3$, $COOC_2H_5$, COO-*n*-C_3H_7, $CONH-NH_2$. Reactions of I (R = $COOCH_3$ and $COOC_2H_5$) are also described. Decarboxylation of I (R = COOH) to give I (R = H) was effected thermally and with acids. The reaction of chloral with phenylbiguanide was also investigated. A complex reaction mixture was obtained from which I (R = H) and the formic acid salt of phenylbiguanide were characterized.

The preparation of triazine derivatives of type I (R = H, COOH) was required in order to aid in the proof of structure of several intermediates useful in the synthesis of vinyl triazines. Reaction of esters with biguanide to give triazines has been explored in some detail.[3] Compound I (R = H) recently has been reported by several investigators[4] prepared by the reaction of phenylbiguanide and formic acid. We have repeated this synthesis and in addition synthesized I (R = H) using ethyl formate, formamide and dimethylformamide. N-Phenylformoguanamine (I, R = H) forms readily in 67% yield with ethyl formate at room temperature in methanol whereas the procedure of Papini using formic acid required reflux temperatures and a longer time for cyclization to obtain a similar yield. A discrepancy in the melting point of the picrate of I (R = H) with the previously reported value[4a] was noted. A side product in the ethyl formate reaction was the phenylbiguanide salt of formic acid confirmed by independent synthesis of the salt, the formic acid probably arising from hydrolysis of the ester upon liberation of water on aromatization to the triazine. The oxalate, hydrochloride, picrate and phenylurea derivatives of I (R = H) were prepared and characterized. A crystalline well defined monobromide also was obtained and proved to be the *p*-bromophenyl derivative, identical with a known sample prepared from *p*-bromophenylbiguanide and ethyl formate. A recent patent[5] has reported the *p*-bromo derivative al-



I

(1) This is the sixth in a series of papers concerned with the preparation of vinyl monomers. For the fifth paper, see C. G. Overberger, C. Frazier, J. Mandelman and H. F. Smith, THIS JOURNAL, **75**, 3326 (1953).

(2) This paper comprises a portion of a thesis presented by Seymour L. Shapiro in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(3) J. T. Thurston, U. S. Patent 2,461,943 (1949) and similar patents

(4) (a) P. Papini and A. Folena, *Gazz. chim. ital.*, **80**, 837 (1950); (b) O. Clauder and G. Bulcsu, *Magyar Kém Folyoirat*, **57**, 68 (1951).

(5) Richter, Gedeon, Vegyesseti Gyar Rt. (Hungarian Corp.), Brit. Patent 676,024 (July 23, 1952); *C. A.*, **47**, 3887 (1953).

though a discrepancy is noted in the melting point. A monoacetyl derivative also was prepared and although its structure was not determined it is most likely attached to the primary amino group.

When equimolar quantities of ethyl oxalate and phenylbiguanide were mixed in methanol at 10°, a yellow precipitate immediately formed and the product was isolated in quantitative yield; for convenience the product will be referred to as compound II.

If the reaction was allowed to proceed at room temperatures, significant quantities of I (R = $COOCH_3$) were formed (see Experimental section). At 23° after 6 days the reaction product was exclusively I (R = $COOCH_3$). The structure of II based on its elementary analysis, its infrared absorption spectrum, its limited stability and its subsequent reactions may be either a six-membered bicyclic bridged carbonyl derivative, a seven-membered ring or one of several five-membered ring structures. The evidence, however, is not sufficient to justify a conclusion on this point. II on heating in a dry state evolved carbon monoxide as shown by a hemoglobin test.[6]

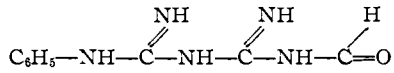
It was impossible to obtain direct derivatives of II due to its instability.

Prolonged boiling of II with methanol, ethanol or propanol in each instance gave the pure corresponding triazinoic ester I (R = COOR). The reaction time was shortened by using catalytic amounts of sulfuric acid. The ease of reaction with the alcohols follows qualitatively Hine's order of their acidity.[7] When II reacted with 20% ethanolic oxalic acid, I (R = $COOC_2H_5$) was obtained. When II reacted with 37% oxalic acid in ethanol hydrolysis and decarboxylation occurred and the oxalic acid salt of I (R = H) was obtained. The aromatization and decarboxylation to I (R = H) was also observed when II was treated with formic acid or with ethanolic hydrochloric acid. Reaction of II with water gave a series of hydrates of I (R = COOH). At 80°, the dihydrate was obtained. At 100°, the monohydrate was formed and on prolonged boiling with water, I (R = COOH) without water of crystallization is obtained.

If II or I (R = $COOCH_3$) is treated with dilute alkali, solution is effected and upon acidification a trihydrate of I (R = COOH) is obtained. The trihydrate was insoluble in water and on heating a suspension in water gave the non-hydrated compound. The dihydrate and trihydrate lose water quantitatively on drying in a vacuum to give the non-hydrated compound. The infrared spectra of the acids obtained from the dehydrated materials are essentially identical. Both the non-hydrate and the trihydrate decarboxylate[8] smoothly at their melting point to yield N-phenylformoguanamine (I, R = H).

Treatment of I (R = $COOC_2H_5$) with diethylaminoethyl alcohol and dimethylaminoethyl alcohol gave the corresponding esters. Treatment of II with hydrazine gave I (R = CO—NH—NH_2). Reaction of II in isopropyl alcohol with diethylaminoethyl alcohol resulted in only the diethylaminoethanol salt of I (R = COOH).

Since Blicke[9] had recently shown that amines could be formylated smoothly with chloral, the reaction of chloral with phenylbiguanide also was investigated. The reaction mixture is complex, however, and only 10.7% of I (R = H) could be isolated. The formic acid salt of phenylbiguanide also was isolated along with phenylbiguanide hydrochloride. Water eliminated in the aromatization step may hydrolyze the intermediate



to give formic acid. Other products were not positively identified.

I (R = CONH—NH_2) is isosteric with isonicotinic acid hydrazide,[10] which has been found to be an effective tuberculostatic agent. This compound was tested *in vitro* and shown to be inactive. The tuberculostatic inactivity of our compound may be a function of its extreme insolubility in water or a function of the amino and anilino groups attached to the triazine ring. Fox[11] has established that in isonicotinic acid derivatives of established tuberculostatic activity, introduction of *o*-amino groups yields inactive compounds.

Experimental[12]

N-Phenylformoguanamine, I (R = H). (A) Formic Acid.—A solution of 10 g. (0.0565 mole) of phenylbiguanide and 50 ml. of 85% formic acid was refluxed for 3 hours according to the general procedure of Clauder and Bulcsu. The formic acid was removed under reduced pressure and the residue triturated with 100 ml. of water and treated with 10% sodium hydroxide until the washing gave a *p*H of 9. The precipitate was removed and washed with water, 8.5 g., m.p. 228–230°. Recrystallization was effected from 200 ml. of dioxane, 7.5 g., m.p. 235–236° (70.8%) (70%, reported as hydrochloride, m.p. 258–260°).[4b]

Anal.[13] Calcd. for $C_9H_9N_5$: C, 57.74; H, 4.85. Found: C, 58.08; H, 4.99.

The picrate was prepared from a dioxane solution of I (R = H) with aqueous picric acid and was recrystallized from water to give a melting point 248–249° dec.

Anal. Calcd. for $C_{15}H_{12}N_8O_7$: C, 43.28; H, 2.91. Found: C, 43.54; H, 2.97.

Phenylurea Derivative of I (R = H).—To a solution of 2.0 g. (0.0107 mole) of I (R = H) in 60 ml. of hot dioxane was added 1.4 g. (0.0118 mole) of phenyl isocyanate. The reaction mixture was refluxed for 5 hours and allowed to stand overnight. The precipitated product was filtered off, 1.5 g. (45.9%) m.p. 235–245°; on recrystallization from dioxane the product melted at 253–254°.

Anal. Calcd. for $C_{16}H_{14}N_6O$: C, 62.73; H, 4.61. Found: C, 62.70; H, 4.81. From the filtrate there was obtained unreacted I (R = H) and diphenylurea. Other derivatives are described subsequently.

(B) Ethyl Formate.—Phenylbiguanide, 17.7 g. (0.1 mole) was dissolved in 75 ml. of methanol and 7.4 g. (0.1 mole) of ethyl formate added. The product began to precipitate in 5 minutes and a thick slurry of product was formed within one hour. The solid was removed by filtration after standing overnight and washed with water to give 12.8 g. (68.6%) of product, m.p. 235–236°. The methanol and water were removed to give a residue which was treated with acetonitrile. The insoluble residue was taken up in water and any insoluble material removed. Concentration of the water

(6) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1945, p. 113.
(7) J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952).
(8) N. H. Cantwell and E. V. Brown, *ibid.*, **74**, 5967 (1952).
(9) F. F. Blicke and C. Lu, *ibid.*, **74**, 3933 (1952).
(10) H. H. Fox, *Science*, **116**, 129 (1952).
(11) H. H. Fox, *J. Org. Chem.*, **17**, 547 (1952).
(12) Melting points are not corrected.
(13) Analyses by Drs. Weiler and Strauss, Oxford, England.

solution and recrystallization of the residue from hot acetonitrile gave 1.13 g. (5.1%) of the formic acid salt of phenylbiguanide, m.p. 178–179°. A mixed melting point with an authentic sample, m.p. 179–180°, was not depressed, mixed m.p. 179–180°.

(C) Formamide.—Phenylbiguanide, 17.7 g. (0.1 mole) was dissolved in 50 ml. of commercial formamide and the reaction mixture heated to reflux. Ammonia was evolved and after 15 minutes, the reaction mixture darkened considerably and white crystals formed on the condenser which are probably ammonium bicarbonate. The reaction mixture was refluxed for 2 hours and upon cooling, the entire mass solidified. The product was removed by filtration, 14.5 g., and was recrystallized from dioxane to give 8.5 g. (45.5%) of product, m.p. 225–233°. The picrate prepared from this product, m.p. 248–249° dec., did not depress when mixed with an authentic sample of the picrate, m.p. 248–249° dec., mixed m.p. 248–249° dec.

Dimethylformamide.—Phenylbiguanide, 17.7 g. (0.1 mole) was dissolved in 50 ml. of dimethylformamide and the reaction mixture permitted to reflux. An outlet tube from the condenser was led into a solution of picric acid. On refluxing for 4 hours, dimethylamine was evolved continuously. The reaction mixture was poured into water to give a white product which was redissolved in 100 ml. of dioxane and reprecipitated with 400 ml. of water, 7.5 g., m.p. 218–225°. Recrystallization from dioxane gave 4.5 g. (24%) m.p. 228–232°. The melting point of the picrate, m.p. 247–248° dec., did not depress when mixed with the picrate of an authentic sample, m.p. 248–249° dec., mixed m.p. 247–248° dec. (<300°).[13a]

Dimethylamine was identified by its picrate, m.p. 157–158° (160° cor.).[14]

With both formamide and dimethylformamide, purification of the product was difficult.

Bromination of I (R = H).—A solution of 25 ml. of glacial acetic acid, 2.5 g. of anhydrous sodium acetate and 1.87 g. (0.01 mole) of I (R = H) was prepared and 1.6 g. (0.01 mole) of bromine dissolved in 10 ml. of acetic acid was added. The reaction mixture was allowed to stand at room temperature for 12 hours and was then heated on the steam-bath for 3 hours, cooled and neutralized with concentrated ammonium hydroxide. From analysis, the white product obtained is a mixture of monobromo and dibromo derivative. The pure monobromo derivative was obtained by boiling 1.9 g. of the solid mixture with 300 ml. of water, removing the solid by filtration, drying in vacuum and recrystallizing from xylene, to give a product melting at 260–261° (242–243°).[5]

Anal. Calcd. for $C_9H_8BrN_5$: C, 40.62; H, 3.02; Br, 30.03. Found: C, 40.61; H, 3.28; Br, 29.95.

Reaction of *p*-Bromophenylbiguanide with Ethyl Formate.—To a solution of 2.92 g. (0.0115 mole) of *p*-bromophenylbiguanide[15] in 5 ml. of methanol and 0.4 ml. of methyl cellosolve was added 0.85 g. (0.0115 mole) of ethyl formate. The reaction mixture, which deposited a white precipitate within 5 minutes, was allowed to stand overnight. The reaction mixture was diluted with 60 ml. of water brought to reflux and the solid removed by filtration. The white product, dried over phosphorus pentoxide, weighed 1.9 g. (71.5%), m.p. 260–261°. A mixed melting point with the bromo derivative of I (above) was not depressed, m.p. 260–261°, mixed m.p. 261–262°.

Acetylation of I (R = H).—The monoacetate was prepared in the usual manner,[16] m.p. 167–169°, recrystallized from acetonitrile.

Anal. Calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84. Found: C, 57.87; H, 5.05.

Reaction of Ethyl Oxalate and Phenylbiguanide.—To a solution of 53.1 g. (0.3 mole) of phenylbiguanide in 250 ml. of anhydrous methanol was added slowly with stirring 43.8 g. (0.3 mole) of ethyl oxalate. After about 2 minutes, a yellow precipitate appeared which thickened in one hour to a yellow mass. After 2.5 hours, the product was removed by filtration and washed thoroughly with methanol to give 55 g. (79.4%) of product, m.p. 209–214°. The product was recrystallized from acetonitrile, m.p. 222–225° dec.

Anal. Calcd. for $C_{10}H_9N_5O_2$: C, 51.94; H, 3.92; N, 30.3. Found: C, 52.08; H, 3.82; N, 30.0.

The filtrate and the methanol washings were allowed to evaporate to give 7.3 g. (10%), m.p. 204–205° of I (R = $COOCH_3$), the methyl ester of 3-amino-5-anilino-2,4,6-triazinoic acid.

Anal. Calcd. for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; mol. wt., 245. Found: C, 54.00; H, 4.46; mol. wt., 263 (camphor).

Reaction at 10° overnight gave 98.5% of II. Reaction at 23° for 5 hours gave 87.4% of II and 6.1% of I (R = $COOCH_3$). Reaction at 23° for 6 days in a large excess of methanol gave 62.5% of I (R = $COOCH_3$). The initial yellow precipitate slowly was converted to the white product, I (R = $COOCH_3$).

Reaction of II with Alcohols.—II is insoluble in the lower boiling alcohols in the cold. Solution was effected by reaction in the boiling alcohol to form the triazinoic acid ester and completion of the reaction could be recognized by the formation of a clear solution. To 75–100 ml. of the alcohol was added 2.31 g. (0.01 mole) of II and the solution refluxed until clear. In the catalyzed reaction, 4 drops of concentrated sulfuric acid was added before refluxing. On cooling, analytically pure products crystallized. Table I summarizes the data.

TABLE I

REACTION OF II WITH ALCOHOLS

Alcohol	Time to effect complete soln., hr.	Yield, %
Uncatalyzed		
CH_3OH[a]	1	73.5
C_2H_5OH[b]	6	92.4
n-C_3H_7OH[c]	2.5	80.5
Catalyzed		
CH_3OH	0.75	67.3[d]
C_2H_5OH	1.0	77.2
n-C_3H_7OH	0.5	77.5

[a] Recrystallized from methanol–water mixtures, m.p. 204–205°. [b] Recrystallized from acetonitrile–water mixture, m.p. 197–199°. *Anal.* Calcd. for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.0. Found: C, 55.80; H, 5.03; N, 26.8. [c] Recrystallized from *n*-propyl alcohol, m.p. 194–195°. *Anal.* Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.6. Found: C, 57.40; H, 5.55; N, 25.6. [d] Dilution of the filtrate with water gave an additional 0.32 g. (total yield 80.5%). The yields in the other reactions can also be improved this way.

Reaction of II with Water and Alkali. Preparation of Hydrates of I (R = COOH).—To a suspension of 4.5 g. (0.0195 mole) of II in 150 ml. of water was added 4.5 ml. of 6 *N* sodium hydroxide. Solution was effected and upon acidification, a thick light yellow precipitate formed. After washing the precipitate with water, it melted at 235–237° with effervescence (cloudy melt), 4.9 g. (88%).

Anal. Calcd. for $C_{10}H_{15}N_5O_5$ (trihydrate of I, R = COOH): C, 42.10; H, 5.30. Found: C, 42.20; H, 5.55.

To a suspension of 0.52 g. (0.0212 mole) of I (R = $COOCH_3$) in 25 ml. of water was added 3.7 ml. of 0.548 *N* sodium hydroxide and the reaction warmed gently to effect complete solution. Upon addition of acid, filtration and washing, a 73% yield of the trihydrate of I (R = COOH) was obtained, m.p. 235–237 with effervescence.

To 250 ml. of water at 80° was added 1.0 g. (0.0043 mole) of finely powdered II. The insoluble material, 0.1 g., was removed and the filtrate on standing overnight gave the dihydrate, m.p. 222–225°, with effervescence (cloudy melt), 0.65 g. (62.8%).

Anal. Calcd. for $C_{10}H_{13}N_5O_4$: (dihydrate of I, R = COOH): C, 44.94; H, 4.90. Found: C, 45.08; H, 5.05.

To 100 ml. of boiling water was added 1.0 g. (0.0034 mole) of finely powdered II. Most of II dissolved and after removal of traces of solid, the filtrate was allowed to stand overnight, m.p. 223–225° with effervescence, 0.75 g. (69.5%).

Anal. Calcd. for $C_{10}H_{11}N_5O_3$ (monohydrate of I, R = COOH): C, 48.19; H, 4.45. Found: C, 47.83; H, 4.67.

(14) J. Mitchell and W. M. D. Bryant, THIS JOURNAL, **65**, 128 (1943).

(15) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

(16) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1948, p. 297.

Two grams (0.007 mole) of the trihydrate was suspended in 300 ml. of water and the suspension heated to reflux for 2 hours. The white solid on filtration and thorough washing with water melted at 232–233° with effervescence, 1.60 g. (98.5%).

Anal. Calcd. for $C_{10}H_9N_5O_2$ (I, R = COOH): C, 51.94; H, 3.92; N, 30.3. Found: C, 51.75; H, 4.01; N, 30.2.

If the dihydrate is heated at 80° at 20 mm. pressure in a drying pistol for 3 hours, 2 moles of water are quantitatively lost.

Anal. Calcd.: H_2O, 13.5. Found: H_2O, 13.1.

The trihydrate likewise loses water quantitatively under the above conditions.

Anal. Calcd.: H_2O, 18.9. Found: H_2O, 18.5.

Thermal Decarboxylation of I (R = COOH).—The trihydrate, 0.6 g. (0.021 mole) was heated for 5 minutes in an oil-bath maintained at 240–245°. At the end of this time, gas evolution ceased and a clear brown melt was obtained and a few needles obtained by sublimation. The melt on cooling solidified and was recrystallized from 17 ml. of dioxane, m.p. 231–233°, 0.39 g. (99%). A mixed melting point with an authentic sample of I (R = H) was not depressed.

Acid-catalyzed Decarboxylations.—To a solution of 37 g. (0.29 mole) of oxalic acid dihydrate and 100 ml. of ethanol was added 15 g. (0.065 mole) of II and the solution heated to the boiling point. Dry solid was removed by filtration and the filtrate refluxed for 6 hours. The reaction mixture was concentrated on the steam-bath to give a yellow oil. At the point where crystals began to separate, 150 ml. of water was added. On standing for several days, 13 g. (72%) of crystals was obtained, m.p. 203–207°. This product was recrystallized from isopropyl alcohol and was the oxalic acid salt of I (R = H), m.p. 212–213°.

Anal. Calcd. for $C_{11}H_{11}N_5O_4$: C, 47.65; H, 4.00. Found: C, 48.12; H, 4.29.

The aqueous solution, 4.4 g. (0.0159 mole) of the oxalate salt, on addition of base, gave 2.0 g. (67.5%) of I (R = H) after one recrystallization from dioxane. A mixed melting point with an authentic sample, m.p. 232–234°, was not depressed, mixed m.p. 232–234°.

When 8 g. (0.035 mole) of II was refluxed for 2 hours in a solution of 20 g. (0.16 mole) of oxalic acid dihydrate and 100 ml. of ethanol, on cooling 50% of I (R = $COOC_2H_5$) was obtained, the structure confirmed by mixed melting point.

To 30 ml. of alcoholic hydrochloric acid (32 ml. of 95% ethanol, 44 ml. of concentrated hydrochloric acid, 35 ml. of water) was added 2.31 g. (0.01 mole) of II and the solution refluxed for 10 minutes. On cooling the hydrochloride of I (R = H) 0.6 g. (26.8%) separated. This hydrochloride can be recrystallized from an ethanol–water mixture, m.p. 246–255° with dec. (245–255° dec. prepared directly from I, R = H and HCl).[4a]

Anal. Calcd. for $C_9H_{10}ClN_5$: C, 48.40; H, 4.48. Found: C, 48.47; H, 4.66.

The solution was made alkaline with dilute sodium hydroxide to give I (R = H), m.p. 232–233°, mixed melting point with I (R = H), m.p. 234–235°, mixed m.p. 232–234°.

It was qualitatively established that refluxing 1 g. of II with 5 ml. of formic acid and evaporation to dryness and recrystallization from dioxane gave I (R = H).

Transesterification. Conversion of I (R = $COOC_2H_5$) to I (R = $COOC_2H_4N(CH_3)_2$ and $COOC_2H_4N(C_2H_5)_2$).—Two grams (0.0087 mole) of I (R = $COOC_2H_5$) was treated with an excess (5 g., 0.0424 mole) of diethylaminoethyl alcohol and the solution refluxed for 2.5 hours. Dilution with water gave 1.2 g. of crude product, m.p. 145–150°, recrystallized from 60 ml. of acetonitrile, 0.90 g. (31.4%), of I (R = $COOC_2H_4N(C_2H_5)_2$), m.p. 172–173°.

Anal. Calcd. for $C_{16}H_{22}N_6O_2$: C, 58.16; H, 6.71; N, 25.4. Found: C, 58.08; H, 7.03; N, 25.1.

The dimethylaminoethyl ester, I (R = $COOC_2H_4N(CH_3)_2$) was prepared in a similar way (34.4%), m.p. 197–198°.

Anal. Calcd. for $C_{14}H_{18}N_6O_2$: C, 55.61; H, 6.00; N, 27.8. Found: C, 55.24; H, 6.01; N, 27.7.

Reaction of II with Hydrazine.—To a suspension of 2.31 g. of II (0.01 mole) in 60 ml. of ethanol, was added 0.64 g. (0.02 mole) of anhydrous hydrazine. The reaction was heated to boiling and then allowed to stand for 48 hours. The product was removed by filtration, 2.1 g., m.p. 224–233° dec., recrystallized from water m.p. 245–247°.

Anal. Calcd. for $C_{10}H_{11}N_7O$: C, 48.96; H, 4.53. Found: C, 48.84; H, 4.70.

Pyrolysis of II.—A sample of II was heated in a stream of nitrogen at 240–245° for one hour and all gases were passed through 1 *N* hydrochloric acid and then into a dilute solution of hemoglobin. The formation of the cherry red carboxyhemoglobin served as a qualitative test for carbon monoxide.[6]

Reaction of Phenylbiguanide with Chloral.—Phenylbiguanide, 17.7 g. (0.1 mole), finely powdered, was suspended in 50 ml. of chloroform and vigorously stirred during the dropwise addition of 15 g. (0.1 mole) of chloral according to the general procedure of Blicke.[10] A vigorous heat of reaction was noted and the reaction was refluxed with stirring for 2 hours and allowed to stand overnight. A white precipitate formed which was removed and washed with chloroform, 12.9 g., and then the solid was extracted with cold water. The water extract on evaporation gave 6.32 g. of product, recrystallized from acetonitrile, m.p. 178–179°, identified as the formic acid salt of phenylbiguanide.

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.4. Found: C, 48.86; H, 5.83; N, 31.4.

This product was identical with the formic acid salt of phenylbiguanide obtained by treating 0.01 mole of phenylbiguanide with formic acid in 60 ml. of acetonitrile, 2.1 g. (94.5%), m.p. 175–176°, mixed m.p. 177–178°.

Extraction of the remaining solid from the initial reaction with hot dioxane gave 2.0 g. of pure I (R = H), m.p. 230–235°, mixed m.p. 230–235°.

The residue from the dioxane extract gave 2.86 g. of impure phenylbiguanide hydrochloride, m.p. 234–237°.

Several other crystalline products were obtained but they were not identified.

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