similar results. The absence of considerable dimer in this experiment is attributed to the lower reaction temperature, and the slow rate of dimerization compared to emulsion polymerization.

The softening points for (a) and (b) were 240–245°. The initial clear temperature of (c) (procedure developed by Mr. D. W. Caird, New Product Development Laboratory, Pittsfield) was determined by compacting the polymer into a $1/8''$ cube, which is placed on a Fisher–Johns m.p. block. The upper cover glass supported a glass tube (held vertical in a bearing) which supported a 500-g. weight. The polymer was finally heated at 1° per minute, and the clear temperature defined as the temperature at which a translucent spot appeared at the center. This determination was reproducible to ±2°. The initial clear temperature of (c) was 237°. The initial clear temperature of Kel-F, NST-300, was 226°.

The polymer was soluble in aromatic solvents. Transparent films were cast from toluene solution, and they were about as brittle as polystyrene. The intrinsic viscosity of a toluene solution at 20.0° was 1.0 using concentrations in the range of 0.1–0.2 g. of polymer per 100 ml. This intrinsic viscosity probably corresponds to a mol. wt. in the range of 100,000 to 500,000.[23]

(23) A. Weissberger, Ed., "Physical Methods of Organic Chemistry," Vol. I, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1949, p. 351.

Strips of polymer were heat aged at 150–153°, 175–180° and 200–205° for 30 days in circulating air-ovens. The polymer had not discolored, fused, or become more brittle. Heat aging of polymer-powder under nitrogen at 225–230° for 33 days resulted in a weight loss of 0.7%, and some cross-linking, as evidenced by incomplete solubility of the polymer in excess toluene.

The electrical tests were run on a 5-mil sheet and the results are given below. The exact value of the AC dielectric strength could not be measured in the step-by-step test because of arcing around the edge of the samples, but it was greater than 1000 volts per mil.

The emulsion polymerization of β,β-difluorostyrene was carried out following the procedure described above. The emulsifier, per cent. conversion and softening points were: (a) Ivory soap, 3.5%, 207–211°; (b) Aerosol OT, 2.8%, 208–213°; *n*-dodecylamine hydrochloride, 7.3%, 220–225°. No decomposition was noted in these softening point determinations.

Acknowledgment.—The author is indebted to Dr. E. W. Balis, Mr. L. B. Bronk and Mrs. M. Lennig for the microanalyses, to Mr. E. M. Hadsell for the Podbielniak distillation, and to Mr. S. I. Reynolds for the electrical measurements.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE]

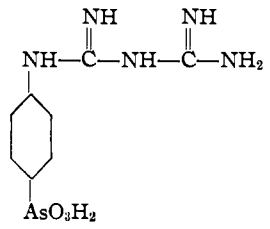
Some Derivatives and Analogs of 4-Biguanidophenylarsonic Acid[1]

BY ROBERT L. MCGEACHIN

RECEIVED SEPTEMBER 19, 1952

2-(4-Arsonophenylguanidino)-4,6-dimethylpyrimidine has been prepared from 4-biguanidophenylarsonic acid by condensation with pentanedione-2,4 and was found to have trypanocidal activity. 4-Biguanidobenzoic acid was prepared and also condensed with pentanedione-2,4 to give 2-(4-carboxyphenylguanidino)-4,6-dimethylpyridine, which proved to be highly toxic to rats.

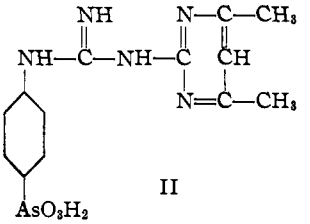
In the studies of preparation of protozoacidal organic arsenicals, 4-biguanidophenylarsonic acid



I

(I), previously reported by both Banks[2] and Sato,[3] was prepared by condensation of *p*-arsanilic acid and dicyandiamide. A modification of Sato's method was used since, in our hands, it gave more satisfactory results than those reported previously. Related compounds have been reported by Roy and Guha,[4] Bogert and Stickler[5] and Sweet, *et al.*[6]

Reports[7] that pentanedione-2,4 condenses with guanidines to give dimethylpyrimidines led us to attempt the condensation of I with pentanedione-2,4. Interest in this reaction was initially aroused by the report of Curd and Rose[8] who found that some of the pyrimidylguanidino compounds formed in the reaction of biguanides with ethyl acetoacetate had therapeutic value as antimalarials. It was also noted that the dimethylpyrimidino group expected from this reaction would be the same as that found in sulfamethazine. Condensation of I with pentanedione-2,4 in alkaline medium gave 2-(4-arsonophenylguanidino)-4,6-dimethylpyrimidine (II).



II

The condensation seems to involve only the terminal amidino group of the biguanido side-chain, two molecules of water being eliminated in the course of the reaction. One molecule of water is formed from the hydrogen of the imino group plus a hydroxyl from the enol form of pentanedione-2,4 and the other from the two hydrogens of the amino group plus the ketonic oxygen in the pentanedione-2,4. II is readily soluble in dilute alkali and mod-

(1) This work was aided by a grant to the University of Louisville from the Kentucky State Medical Research Commission.

(2) C. K. Banks, J. Controulis and W. F. Holcomb, THIS JOURNAL, **68**, 2102 (1946).

(3) M. Sato, *J. Pharm. Soc. Japan*, **69**, 303 (1949).

(4) A. C. Roy and P. C. Guha, *J. Sci. Ind. Research (India)*, **9B**, 242 (1950).

(5) M. T. Bogert and W. T. Stickler, *Science*, **100**, 526 (1944).

(6) L. A. Sweet, *et al.*, THIS JOURNAL, **69**, 2258 (1947).

(7) Private communication from the Carbide and Carbon Chemicals Company.

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

erately so in dilute acid but in strong hydrochloric acid only sparingly soluble. Attempted condensation of I with ethyl acetoacetate and diethyl malonate to give 2-(4-arsonophenylguanidino)-4-hydroxy-6-methylpyrimidine and 2-(4-arsonophenylguanidino)-4,6-dihydroxypyrimidine were unsuccessful under a variety of conditions.

Condensation of I with formaldehyde was carried out in hopes of forming a pyrimidine ring by reaction of three molecules of formaldehyde with the terminal amidino group. However, apparently only one molecule of formaldehyde reacted under the conditions used.

4,4'-Bis-(biguanido)-arsenobenzene was prepared by the reduction of I using hypophosphorous acid. The hydrochloride of this compound was insoluble in water, however, so that it was unsuitable for therapeutic trials.

I was ineffective against *Trypanosoma equiperdum* in rats in dosages as high as 500 mg./kg. Toxicity trials[9] indicate that the LD_{50} intravenously in rats is 1500 mg./kg. Rats will tolerate more than 4 g./kg. orally and more than 2 g./kg. given subcutaneously. Saturated solutions have no effect within ten minutes on *Trichomonas foetus*.[10]

II was trypanocidal in rats at dosages of 500 mg./kg. given intraperitoneally. However, the LD_{50} was found to be 1000 mg./kg. giving a low therapeutic index. Moreover, at dosages of 750 mg./kg. a considerable number of the rats that did not die showed paralysis of the hind legs.

In order to see if the pyrimidylguanidino side-chain in II had contributed any of the compound's trypanocidal activity, it seemed desirable to synthesize and test an arsenic-free analog. 4-Biguanidobenzoic acid (III) was prepared by condensation of dicyandiamide with *p*-aminobenzoic acid under conditions similar to those used in the preparation of I. From III, 2-(4-carboxyphenylguanidino)-4,6-dimethylpyrimidine (IV) was prepared by condensation with pentanedione-2,4 in alkaline medium. Unfortunately, the compound was so toxic that the trypanocidal action in rats could not be determined. Dosages of IV as low as 200 mg./kg. intraperitoneally were fatal to rats within one hour. Symptoms of tremors, fits and foaming at the mouth appeared, usually within 15 minutes, growing progressively worse till death ensued. III was not trypanocidal in dosages up to 500 mg./kg. but was non-toxic at these levels.

Because of the recent interest in compounds with nitrogen-containing side-chains as antitubercular drugs, it is planned to have III tested against tuberculosis in the near future.

Experimental

4-Biguanidophenylarsonic Acid (I).—This compound was prepared by a modification of Sato's method. Sato reports a melting point of 260° for I but we have failed to confirm this. In repeated trials, this compound showed no signs of melting at 260° and was still solid at 300° although some darkening was evident at 280°; yield 45% of theoretical.

Anal.[11] Calcd. for $C_8H_{12}AsN_5O_3$: As, 24.87; N, 23.26. Found: As, 24.77; N, 23.09.

2-(4-Arsonophenylguanidino)-4,6-dimethylpyrimidine (II).—Ten grams of I was dissolved in a solution of 2.5 g. of sodium hydroxide in 75 ml. of water, 10 ml. of pentanedione-2,4 added and the mixture agitated till homogeneous. The mixture was allowed to stand for 48 hours at room temperature. Concentrated hydrochloric acid was added slowly, with agitation, till a *p*H of 6 was reached, and the mixture cooled overnight in a refrigerator. It was found that stopping at a *p*H of 6 in the neutralization procedure was a critical point. If acid were added to a *p*H of 3–4, the product as isolated was consistently low in arsenic probably because of contamination with the hydrochloride.

The white precipitate formed was filtered off, washed with water and dried in air at 120° overnight; yield 9.5 g. (78%). It does not melt up to 300°. The product is somewhat hygroscopic.

Anal. Calcd. for $C_{13}H_{16}AsN_5O_3$: As, 20.54. Found: As, 20.28.

On one occasion, 5 ml. of concd. hydrochloric acid was added to 15 ml. of the reaction mixture after the reaction was complete. The thick white precipitate formed was filtered off, washed with alcohol and ether and dried overnight at 120°. Apparently it is the monohydrate hydrochloride of III. This product is very hygroscopic.

Anal. Calcd. for $C_{13}H_{19}AsClN_5O_4$: As, 17.91. Found: As, 17.56.

Reaction of I with Formaldehyde.—Two grams of I was dissolved in 5.2 ml. of 10% sodium hydroxide and 10 ml. of water. Ten ml. of 20% formalin was added and the mixture allowed to stand at room temperature for 24 hours. Concentrated hydrochloric acid was added till a *p*H of 6 was reached, giving a white precipitate. This was filtered, washed with alcohol and ether and dried in air at 120° overnight; yield 1.1 g. (52%). The compound does not melt up to 300°.

Anal. Calcd. for $C_9H_{12}AsN_5O_3$: As, 23.94. Found: As, 23.75.

4,4'-Bis-(biguanido)-arsenobenzene.—Two grams of I was suspended in 15 ml. of water and 10 ml. of 50% hypophosphorous acid added. The solution was heated just to boiling for several minutes and then allowed to stand at room temperature overnight. To the resultant clear yellow solution, 3 ml. of concd. hydrochloric acid was added, a flocculent yellow solid precipitating. This solid was centrifuged, the supernatant fluid decanted, the precipitate washed with water and recentrifuged. This procedure was repeated three times. The yellow solid was suspended in 25 ml. of water and 10% sodium hydroxide added, with vigorous agitation, till a *p*H of 9 was reached. The product was filtered off, dried *in vacuo* over calcium chloride overnight, and then in air at 110° for four hours. It was found that if the preliminary drying *in vacuo* were omitted and the product dried in air at 110° while still moist, considerable darkening occurred; yield 0.9 g. (54%) of a dark yellow solid that does not melt up to 300°.

Anal. Calcd. for $C_{16}H_{20}As_2N_{10}$: As, 29.86. Found: As, 29.48.

4-Biguanidobenzoic Acid (III).—To 13.7 g. of *p*-aminobenzoic acid dissolved in 50 ml. of water and 9 ml. of concd. hydrochloric, 20 g. of dicyandiamide was added. The mixture was heated to boiling under reflux conditions for six hours, then cooled in a refrigerator overnight. The white precipitate which formed was filtered off and the filtrate allowed to evaporate at room temperature for three days. An additional crop of crystals was obtained. The product was dried in air at 110° overnight; total yield 8.7 g. (39%), m.p. 237°.

Anal. Calcd. for $C_9H_{11}N_5O_2$: N, 31.67. Found: N, 31.35.

2-(4-Carboxyphenylguanidino)-4,6-dimethylpyrimidine (IV).—Two grams of III was dissolved in a solution of 1.2 g. of sodium hydroxide in 15 ml. of water, 2.5 ml. of pentanedione-2,4 added and the mixture agitated till homogeneous. The mixture was allowed to stand at room temperature for

(9) Data supplied by Research Laboratories, Parke, Davis and Company.

(10) Determined by Dr. B. B. Morgan, University of Wisconsin.

(11) A modification of the method of F. E. Cislak and C. S. Hamilton, THIS JOURNAL, 52, 638 (1930), was used in the arsenic analyses. Nitrogen was determined by micro-Kjeldahl procedure.

48 hours. The product was isolated in the same manner as II and purified by reprecipitating from sodium hydroxide solution with concd. hydrochloric acid; yield 0.8 g. (31%). m.p. 253°.

Anal. Calcd. for $C_{14}H_{16}N_6O_2$: N, 24.56. Found: N, 24.65.

Acknowledgments.—The author is grateful to the American Cyanamid Company for a sample of dicyandiamide, the Carbide and Carbon Chemicals Company for a sample of pentanedione-2,4, to Dr. C. K. Banks and Mr. Robert E. Cox for helpful suggestions during the course of this research and to Dr. W. F. Cantrell for aid in the testing of the compounds reported.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

The Synthesis of the 3,9-Diazabicyclo[3.3.1]nonane Ring System[1]

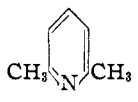
BY RODERICK A. BARNES AND HENRY M. FALES[2]

RECEIVED SEPTEMBER 12, 1952

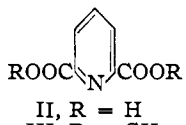
Dimethyl scopolinate has been prepared from 2,6-lutidine by oxidation to dipicolinic acid followed by esterification, catalytic reduction and methylation. The reaction of dimethyl scopolinate with benzylamine produced the bicyclic imide which was converted by lithium aluminum hydride to 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane.

The most widely used method for synthesizing bicyclic amines related to the tropane alkaloids has been the procedure developed by Robinson and co-workers.[3] The most difficult aspect of this procedure is usually the preparation of the required dialdehyde.

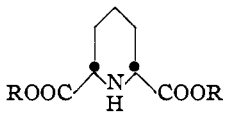
The present investigation was undertaken to see if a practical method could be worked out for converting the readily available 2,6-lutidine (I) to a bicyclic system. Several attempts were made to transform the two methyl groups into substituents which would be capable of further elaboration toward the desired bicyclic system. The only transformation which was satisfactory from the standpoint of yield was oxidation to dipicolinic acid (II).



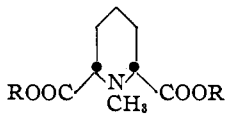
I



II, R = H
III, R = CH_3



IV, R = H
V, R = CH_3

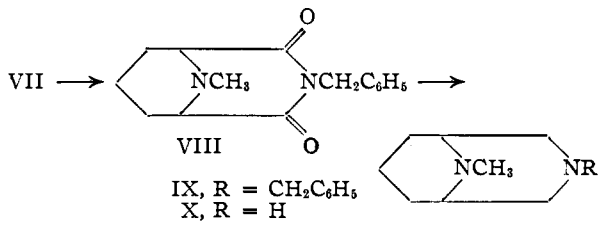


VI, R = H
VII, R = CH_3

Acid II, either as its potassium salt or its ester (III), was readily hydrogenated by Raney nickel to yield the corresponding piperidine (IV or V). In order to prove that the hydrogenation had taken place to yield the *cis* isomer, IV was converted to scopolinic acid (VI). Since VI was originally obtained by oxidation of dihydroscopoline[4] it must have the *cis* structure.

Our sample of dimethyl scopolinate (VII) formed a methiodide which differed in melting point from that previously reported.[5] This discrepancy was resolved when an attempted acyloin condensation with VII failed. The recovered ester was found to produce a methiodide which did agree with the literature value. However, saponification of the recovered ester did not yield scopolinic acid but its stereoisomer, isoscopolinic acid which is the previously unreported *trans*-acid. From this it was concluded that the alkaline conditions during the attempted acyloin condensation caused isomerization of the *cis*-ester to the *trans*-ester. It was later observed that even on standing ester VII was gradually isomerized; the tertiary nitrogen is apparently a strong enough base to cause some enolization. This accounts for the fact that the methiodide reported by Schmidt was actually a derivative of isoscopolinic acid even though it had been prepared from scopolinic acid.

When either stereoisomer of VII was heated with benzylamine the bicyclic imide (VIII) was formed in 60% yield along with small amounts of the diamide. The reduction of VIII with lithium



VIII

IX, R = $CH_2C_6H_5$
X, R = H

aluminum hydride proceeded very smoothly (86% yield) to form the oxygen-free base IX.[6] The benzyl group could be removed by hydrogenolysis in alcoholic hydrochloric acid solution to yield X which was isolated as the dihydrochloride.

It was found that IX formed only a monomethiodide and a monopicrate while X formed a dipicrate and a dihydrochloride. An examination of models of these two bases suggested that this difference between the two bases is due to steric

(1) Presented at the 122nd Meeting of the A.C.S., Atlantic City, N. J., September 15, 1952.

(2) Abstracted from a thesis presented by H. M. Fales to the Graduate Faculty for the Ph.D. degree, September, 1952.

(3) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 2485 (1932), have prepared the only previously reported example of the 3,9-diazabicyclo[3.3.1]nonane ring system; N-methylaztropinone was obtained in 7.5% yield.

(4) E. Schmidt, *Arch. Pharm.*, **247**, 79 (1909).

(5) E. Schmidt, *ibid.*, **253**, 499 (1915).

(6) A 5-mg. sample of this compound caused immediate depressor action when administered by vein to an anesthetized cat. The authors wish to thank Dr. E. Rohrmann and the Eli Lilly Company for making this test.