filtrate by reduced pressure evaporation. The residue was shaken thoroughly with water, and the mixture was allowed to stand overnight. The water was poured off, and the remaining solid was crystallized from alcohol. There was obtained 2.2 g. (17%) of 1-acetyl-1,3-diphenylurea, m. p. 103–105° (lit. 105°).

N-Methylbenzamide and Phenyl Isocyanate.—A mixture of 13.5 g. (0.1 mole) of N-methylbenzamide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated slowly to about 190° and maintained at that temperature for about two hours. The cooled reaction mixture solidified. Five recrystallizations from alcohol gave 2.6 g. (13%) of benzanilide, m. p. 160–162°, and no depression in melting point upon admixture with benzanilide.

N-Phenylphthalimide.—A mixture of 29.4 g. (0.2 mole) of phthalimide and 23.8 g. (0.2 mole) of phenyl isocyanate was refluxed for four hours. The cooled reaction mixture was broken up and boiled in alcohol. The alcohol was removed by filtration. The residue was dissolved in boiling acetic acid and treated with charcoal. This was followed by three recrystallizations from acetic acid. The product was a white solid, m. p. 204–206°, crystallizing in long white needles (lit. m. p. 204°). A yield of 6.2 g. (14%) was obtained.

Anal. Calcd. for $C_{14}H_9NO_2$: N, 6.28. Found: N, 6.25.

N,N'-Diphenylbenzamidine.—A mixture of 11.9 g. (0.1 mole) of phenyl isocyanate and 19.7 g. (0.1 mole) of benzanilide was heated at 200–220° for four hours. The solid obtained on cooling was recrystallized three times from absolute alcohol. The yield of white solid, m. p. 130–132°, was 12.1 g. (44%). A product melting at 140–144° was obtained after five more recrystallizations from alcohol. Kühn[2] reported a melting point of 145°.

Anal. Calcd. for $C_{19}H_{16}N_2$: N, 10.29. Found: N, 10.46.

Phenyl Isocyanate and Acetanilide at 200°.—A mixture of 13.5 g. (0.1 mole) of acetanilide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 200–210° for four hours. The product was broken up and boiled with 150 cc. of alcohol. This mixture was cooled and filtered. There was obtained 5.3 g. of a yellow solid which melted at about 350°. This product was recrystallized four times from boiling nitrobenzene. The final compound melted at 340–375° with decomposition.

Anal. Calcd. for $C_{36}H_{28}N_5O_4$: C, 72.72; H, 4.74; N, 11.77. Found: C, 72.79; H, 4.66; N, 11.85.

Phenyl Isocyanate and ε-Caprolactam at 200°.—A mixture of 11.3 g. (0.1 mole) of ε-caprolactam and 11.9 g. (0.1 mole) of phenyl isocyanate was heated at 190–210° for four hours. The cooled reaction mixture was dissolved in boiling alcohol and filtered. The cooled filtrate deposited 1.7 g. of white crystals melting at 202–205°. Charcoaling and concentrating the filtrate gave only a black non-crystallizable oil. Five recrystallizations of the solid product from alcohol gave a sample, m. p. 209–210°.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.79; H, 7.07; N, 14.12; mol. wt., 198. Found: C, 78.28, 78.65, 79.21; H, 7.30, 6.48, 7.24; N, 14.53, 14.74; mol. wt., 232.

Summary

1. Under mild conditions some nitrogen substituted amides react with phenyl isocyanate to form 1,1-disubstituted-3-phenylureas, and some do not react.

2. The products obtained under severe conditions are varied and not predictable.

INDIANAPOLIS, INDIANA RECEIVED APRIL 16, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF GEORGIA SCHOOL OF MEDICINE]

Chemotherapeutic Agents from Heterocyclic Amines. I. Amine Arsenicals[1]

BY DAVID FIELDING MARSH[2] AND ROBERT A. WOODBURY

The replacement of the amide NH_2 group of sulfanilamide by an NHR radical in which R represents a heterocyclic nucleus has led to compounds which are more potent and are useful for a greater variety of infections.[3] It seemed advisable to utilize these heterocyclic nuclei as substituents in other series of compounds characterized by chemotherapeutic activity.

Gough and King[4] showed the trypanocidal activity of *p*-arsenosobenzamide, and Eagle, Doak, Steinman and Hogan[5] have exhaustively investigated simple derivatives and homologs of this compound and have indicated their favorable treponemicidal activity.

The present communication reports the preparation of *p*-arsenosobenzamidoheterocycles by the reaction of *p*-dichloroarsylbenzoyl chloride with the required amine in benzene followed by hydrolysis of the *p*-arsenosobenzamidoheterocycles.

Experimental Part

Preparation of Amides.—The amine (0.2 mole), recrystallized from benzene before use, was dissolved in 250–600 ml. of warm benzene in an erlenmeyer flask and 12 ml. of freshly distilled *p*-dichloroarsylbenzoyl chloride[6] was added with shaking. The mixture was refluxed for twenty minutes to an hour and the supernatant liquid decanted into a beaker. The material which adhered to the flask was dissolved in warm 95% ethanol. On cooling, the desired *p*-arsenosobenzamide separated and was removed by filtration. Partial evaporation of the filtrate yielded some *p*-arsenosobenzoic acid. The by-product amine hydrochloride can be obtained by complete evaporation of the filtrate. The yields of amide were 35–45%, based on the amount of amine used. By recrystallizing the residual material from absolute methanol instead of 95% ethanol it was possible to prepare the dichloroarsylbenzamides. The decanted benzene contained some of the corresponding dichloroarsylbenzamide along with some unreacted amine. The products are white amorphous powders that are tinged slightly yellow or pink if

(1) Presented on the program of the Medicinal Division at the American Chemical Society meeting, New York, September 11, 1944.

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(3) Fosbinder and Walton, THIS JOURNAL, **61**, 2032 (1939); and Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940).

(4) Gough and King, *J. Chem. Soc.*, 669 (1930).

(5) (a) Doak, Eagle and Steinman, THIS JOURNAL, **62**, 3012 (1940); (b) Steinman, Doak and Eagle, *ibid.*, **66**, 192 (1944); and (c) Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **81**, 142 (1944).

(6) Prepared by the method of Lewis and Cheetham, THIS JOURNAL, **43**, 2117 (1921), from *p*-carboxyphenylarsonic acid which was synthesized either by their method or from *p*-cyanophenylarsonic acid prepared by the method of Linsker and Bogert, *ibid.*, **65**, 932 (1943).

not absolutely pure. The compounds are not water soluble to any appreciable extent but are readily soluble in methanol, ethanol and chloroform. None of these compounds has a definite melting point, but they begin to decompose above 220° and decomposition is complete at 300°.

TABLE I

ARSENOSO COMPOUNDS DERIVED FROM HETEROCYCLIC AMINES

R-*p*-Arsenosobenzamido-Compound	As analysis, % Calcd.	Found	N analysis, % Calcd.	Found	MTD[a] mouse
2-R-Thiazole[b]	25.45	25.2	9.55	9.4	7.5
2-R-4-Methylthiazole	24.3	24.1	9.11	9.1	3.5
2-R-Thiazoline[c]	25.3	25.0	9.48	9.3	30.0
2-R-Pyridine[d]	26.0	26.1	9.74	9.8	2.0
2-R-Pyrimidine[e]	25.9	25.8	14.56	14.4[f]	30.0
2-R-4-Methylpyrimidine[e]	24.7	24.9	13.9	13.7[f]	3.5
2-R-4,6-Dimethylpyrimidine[e]	23.6	23.6	13.3	13.0[f]	3.5
R-*p*-Dichloroarsylbenzamido-					
2-R-Thiazole	21.45	21.4	8.0	7.9	..
2-R-Thiazoline[g]	21.3	21.3	7.8	7.8	..

[a] Maximal tolerated dose for intraperitoneal injection in twenty gram mice, expressed as the number of milligrams/kilogram, and determined by Dr. H. J. Robinson, Merck Institute for Therapeutic Research, Rahway, N. J. [b] 2-Aminothiazole was generously supplied by Dr. D. F. Robertson, Merck & Co., Rahway, N. J. [c] 2-Aminothiazoline was generously supplied by Dr. George W. Raiziss, Dermatological Research Laboratories, Philadelphia, Pa. [d] Previously synthesized by Doak, *et al.*, ref. 5a. [e] 2-Aminopyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine were generously supplied by Dr. Jackson P. English, American Cyanamid Co., Stamford, Conn., and Dr. E. H. Northey, Calco Chemical Division of the American Cyanamid Co., Bound Brook, N. J. [f] The customary difficulties in determining the nitrogen content of pyrimidines was experienced. The values represent the average of the two highest determinations. The other nitrogen determinations and the arsenic determinations are the average of three or more determinations. [g] The dichloroarsylbenzamide compounds of pyridine, 4-methylthiazole and the pyrimidines were not isolated.

Pharmacological Activity.—We are grateful to Dr. H. J. Robinson of the Merck Institute for Therapeutic Research for carrying out preliminary tests on these compounds. Our own preliminary studies against *T. equiperdum* infections in mice have not proved encouraging. Dr. Robinson found that although the compounds are highly active *in vitro* against *T. equiperdum* and *Dirofilaria immitis*, their high toxicity *in vivo* for the host makes their use undesirable. The results with the 2-*p*-arsenosobenzamidopyridine agree with those of Eagle, *et al.*,[5c] who reported the MTD for mice as 2.3 mg./kg. and although the compound possessed a high treponemicidal activity it had a low chemotherapeutic index.

Summary

The *p*-arsenosobenzoyl derivatives of 2-aminothiazole, 2-aminothiazoline, 2-aminopyridine, 2-amino-4-methylthiazole, 2-aminopyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4,6-dimethylpyrimidine were synthesized. The *p*-dichloroarsylbenzoyl derivatives of 2-aminothiazol- and 2-aminothiazoline have been prepared.

Preliminary pharmacological tests with these compounds have not indicated favorable chemotherapeutic activity.

AUGUSTA, GA. RECEIVED JUNE 16, 1949

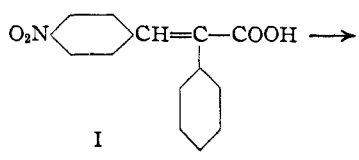
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Three Aminodiiodophenyl-phenylpropionic Acids

BY T. R. LEWIS, MARGARET G. PRATT, E. D. HOMILLER, B. F. TULLAR AND S. ARCHER

Several years ago a program was initiated in this Laboratory the goal of which was the discovery of a superior radiopaque to be used in clinical cholecystography. As a part of this study, three isomeric aminodiiodophenylphenylpropionic acids were prepared for pharmacological evaluation. The synthesis of these acids is the subject of the present report.

A common structural feature which is shared by the cholecystographic agents examined clinically up to now is the diiodohydroxyphenyl group. It has been suggested that the presence of the hydroxyl in a gall-bladder contrast medium is necessary for visualization of this organ.[1] The utility of our compounds has been determined by Hoppe[2] who has found that the amino may replace the hydroxyl group without impairing the usefulness of the drug.[3] It is our belief that the sole function of these radicals is to facilitate the introduction of the iodine atoms into the benzene ring. The diiodo acid, III, was prepared according to the equations



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(1) Epstein, Natelson and Kramer, *J. Am. Roentgenol.*, **56**, 202 (1946).

(2) Hoppe and Archer, *Federation Proc.*, **8**, 303 (1949).

(3) Other work in this Laboratory has demonstrated that neither the amino nor hydroxyl group is essential for good visualization.