

L(-)-Acetone Glycerol-trityl Ether. (Compound prepared by tritylation of L(-)-acetone glycerol.)—To a cold solution of 27.8 g. of triphenylchloromethane⁷ in 90 cc. of dry pyridine was added 13.2 g. of freshly prepared L(-)-acetone glycerol ($[\alpha]_D -13.8^\circ$) and the mixture permitted to stand for two days at room temperature. The mixture was poured into 800 cc. of ice-water and stirred until most of the trityl compound had settled out. The aqueous solution was decanted and extracted once with 500 cc. of ether. This extract was used to take up the trityl compound adhering to the walls of the beaker. The solution was washed four times with 200 cc. of water and dried with anhydrous potassium carbonate. The ether solution was decanted, concentrated and the residual ether was removed in a current of air. The last traces of pyridine were removed by keeping the substance in a high vacuum over phosphorus pentoxide and sodium hydroxide; yield 34.8 g. (93.2%) of crude L(-)-acetone glycerol-trityl ether, m. p. 67–81°. The substance was purified by recrystallization from butyl ether: 34.8 g. of the trityl

ether was dissolved in 25 cc. of warm butyl ether and the solution kept overnight in an ice box. After draining off the mother liquor, the crust of crystals was broken up and the rest of the mother liquor removed by spreading the substance on a porous plate: 25.3 g. (67.8%) of analytically pure L(-)-acetone glycerol-trityl ether with a melting point of 85–86° was obtained; $[\alpha]_D^{25} -13.0^\circ$, for $c = 10.0$ in *s*-tetrachloroethane.

Summary

The conversion of D(+)-acetone glycerol into L(-)-acetone glycerol has been accomplished by means of a sequence of substitution reactions.

The transposition described offers a further example of an enantiomorphous interconversion by exchange of substituents.

TORONTO, CANADA

RECEIVED MARCH 22, 1945

[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Arsonoanilino-pyrimidines

BY RAYMOND J. ANDRES AND CLIFF S. HAMILTON

The discovery by Friedheim,¹ that 2-(4'-arsonoanilino)-4,6-diamino-*s*-triazine far exceeded trypanamide as an agent in the treatment of African trypanosomiasis, provided a new approach in the search for arsenicals effective in combatting such diseases. Banks and co-workers,² in extending the work of Friedheim to other arsonic acid derivatives of *s*-triazine, found that the *p*-arsonoanilino derivative, further substituted in the heterocyclic nucleus by an amino group, and a hydroxyl group is a very active therapeutic agent.

Since pyrimidine is closely related in structure to *s*-triazine, the present work was concerned with the synthesis of arsonoanilino derivatives of pyrimidine in which the heterocyclic nucleus was substituted by amino, hydroxyl and thioether groups.

From the mechanism proposed by Banks³ it could be predicted that a halogen on the 2, 4, or 6 carbon atom of the pyrimidine nucleus would have its known activity toward replacement by an amino group increased in the presence of hydrogen ions. Consequently, a group of 2- or 4-chloropyrimidines was selected, each member being further substituted by amino, nitro, methyl, or ethyl mercapto groups. Those chosen reacted with aminophenylarsonic acids in the presence of dilute, aqueous acid.

In the study of the action of hydrogen peroxide on 2-ethylmercapto-4-(4'-arsonoanilino)-6-methylpyrimidine, in an aqueous solution buffered by sodium bicarbonate, the sulfone was not obtained. Analysis indicated that the ethylmercapto group had been replaced by the hydroxyl

group, a hypothesis substantiated in part by the absence of sulfur from the molecule. The use of hydrochloric acid or hydrobromic acid to effect a similar replacement is reported in the literature.^{4,5} Alkaline peroxide has the advantage over previous methods in that it does not seriously affect the anilino-pyrimidine linkage.

Experimental

All melting points were corrected for exposed stem. A thermometer calibrated by the Bureau of Standards was used.

Materials Used

2-Amino-4-chloro-6-methylpyrimidine was prepared according to the method of Gabriel and Colman.⁶ For the preparation of **2-amino-4,6-dichloropyrimidine** the method of Büttner⁷ was used. **2-Ethylmercapto-4-chloro-6-methylpyrimidine** was synthesized according to the directions of Johns,⁸ while Roblin, *et al.*,⁹ were followed in the preparation of **2-chloro-5-nitropyrimidine**. *p*-Arsanilic acid was purified by twice recrystallizing the technical grade from dilute alcohol. The directions of Stevinson and Hamilton¹⁰ were followed for the reduction of *m*-nitrophenylarsonic acid to *m*-arsanilic acid. Parke, Davis and Company kindly furnished the two aminohydroxyphenylarsonic acids and **2-amino-4-chloropyrimidine**.

General Procedure.—One equivalent of the aminophenylarsonic acid was dissolved in boiling water containing 0.1 to 1.2 equivalents of hydrochloric acid, 50 ml. of water or a water-organic solvent mixture being present for each gram of arsonic acid. To the boiling solution was added 1.2 to 2.0 equivalents of the chloropyrimidine. The mixture was refluxed until a qualitative test with "R" acid showed the absence of the primary amino group. The hot solution was then made neutral to congo red paper and the product filtered off hot. Purification was effected by

(1) Friedheim, *Schweiz. Med. Wochschr.*, **5**, 116 (1941).
 (2) Banks, Grubisil, Tillitson and Controulis, *THIS JOURNAL*, **66**, 1771 (1944).
 (3) Banks, *ibid.*, **66**, 1127, 1131 (1944).

(4) Wheeler and Jamieson, *Am. Chem. J.*, **32**, 342 (1904).
 (5) Chi and Kao, *THIS JOURNAL*, **58**, 772 (1936).
 (6) Gabriel and Colman, *Ber.*, **32**, 2921 (1899).
 (7) Büttner, *ibid.*, **36**, 2227 (1903).
 (8) Johns, *Am. Chem. J.*, **40**, 348 (1908).
 (9) Roblin, Winnek and English, *THIS JOURNAL*, **64**, 567 (1942).
 (10) Stevinson and Hamilton, *ibid.*, **57**, 1298 (1935).

TABLE I
 TABLE OF COMPOUNDS

	Pyrimidine	Solvent	Yield, %	M. p., °C.	Formula	Analyses, %			
						As ^d		N ^e	
						Calcd.	Found	Calcd.	Found
1	2-Amino-4(4'-arsonoanilino)-6-methyl-	H ₂ O	48	>250	C ₁₁ H ₁₀ O ₂ N ₄ As·H ₂ O	21.89	21.99	16.38	16.25
2	2-Amino-4(3'-arsonoanilino)-6-methyl-	H ₂ O	55	>250	C ₁₁ H ₁₀ O ₂ N ₄ As·H ₂ O	21.89	21.85	16.38	16.28
3	2-Amino-4(2'-hydroxy-5'-arsonoanilino)-6-methyl-	H ₂ O	52	>250	C ₁₁ H ₁₀ O ₄ N ₄ As·H ₂ O	20.91	20.90	15.64	15.74
4	2-Amino-4(3'-hydroxy-4'-arsonoanilino)-6-methyl-	H ₂ O	32	>250	C ₁₀ H ₁₀ O ₄ N ₄ As ₂ ·H ₂ O	21.45	21.50	16.05	16.12
5	2-Amino-4(4'-arsonoanilino)- ^a	Acetone 10%	61	>250	C ₁₀ H ₁₁ O ₂ N ₄ As·H ₂ O	22.83	22.88	17.07	16.87
6	2-Amino-4(3'-arsonoanilino)-	Acetone 10%	49	222-223	C ₁₀ H ₁₁ O ₂ N ₄ As·H ₂ O	22.83	22.76	17.07	17.07
7	2-Amino-4(2'-hydroxy-5'-arsonoanilino)-	Acetone 10%	46	>250	C ₁₀ H ₁₀ O ₄ N ₄ As ₂ ·H ₂ O	22.35	22.37	16.72	16.69
8	2-Amino-4(3'-hydroxy-4'-arsonoanilino)-	Acetone 10%	44	247-249	C ₁₀ H ₁₁ O ₄ N ₄ As ₂ ·2H ₂ O	20.68	20.76	15.47	15.48
9	2-Amino-4(4'-arsonoanilino)-6-chloro-	Acetone 50%	49	>250	C ₁₀ H ₁₀ O ₂ N ₄ ClAs	21.74	21.52		
10	2-Amino-4(3'-arsonoanilino)-6-chloro-	Ethanol 20%	54	183-184	C ₁₀ H ₁₀ O ₂ N ₄ ClAs	21.74	21.51		
11	2-Amino-4(2'-hydroxy-5'-arsonoanilino)-6-chloro- ^b	Acetone 50%	23	>250	C ₁₀ H ₁₀ O ₄ N ₄ Cl ₂ As ₂ ·H ₂ O	20.27	20.18	15.16	15.38
12	2-Ethylmercapto-4(4'-arsonoanilino)-6-methyl-	Acetone 20%	76	>250	C ₁₂ H ₁₆ O ₂ N ₄ SA ₂	20.29	20.42		
13	2-Ethylmercapto-4(3'-arsonoanilino)-6-methyl-	Ethanol 20%	61	249.5- 250.5	C ₁₂ H ₁₆ O ₂ N ₄ SA ₂	20.29	20.41		
14	2-Ethylmercapto-4(2'-hydroxy-5'-arsonoanilino)-6-methyl-	Ethanol 25%	59	>250	C ₁₂ H ₁₆ O ₄ N ₄ SA ₂	19.44	19.46		
15	2-Ethylmercapto-4(3'-hydroxy-4'-arsonoanilino)-6-methyl-	Ethanol 25%	44	>250	C ₁₂ H ₁₆ O ₄ N ₄ S ₂ As ₂ ·H ₂ O	19.00	18.91	11.16	11.07
16	2-(4'-Arsonoanilino)-5-nitro- ^c	H ₂ O	22	>250	C ₁₀ H ₉ O ₆ N ₄ As	22.03	21.98		

^a Preparation of this compound by Banks indicated only by disappearance of the primary aromatic amino group. ^b Hydrochloride crystallized from water. ^c Free arsonic acid crystallized from water. ^d Arsenic analyses were performed by the method of Cislak and Hamilton.¹¹ ^e Selenium was used as a catalyst in the analyses for nitrogen.

dissolving the arsonic acid in either dilute hydrochloric acid or dilute sodium bicarbonate solution and reprecipitating the product at the boiling point by neutralizing the solution to congo red paper with ammonium hydroxide or acetic acid. In a few cases the product or its hydrochloride crystallized from water.

When an alcohol-water or acetone-water solution was used as a solvent for the reactants, the reaction mixture was made alkaline to litmus with sodium bicarbonate, evaporated to a small volume to remove the organic solvent, diluted with water to the original volume, and purified in the manner given in the previous paragraph.

A number of the arsonic acids were isolated as hydrates and identified by analyses for arsenic and nitrogen. Attempts to obtain the anhydrous arsonic acids resulted in a partial dehydration of the arsonic acid group.

2-Hydroxy-4-(4'-arsonoanilino)-6-methylpyrimidine.—Two grams of 2-ethylmercapto-4-(4'-arsonoanilino)-6-methylpyrimidine was suspended in 20 ml. of water, 10 ml. of 27.5% hydrogen peroxide was added, and sodium bicarbonate was dissolved in the suspension until a clear solution was formed. The mixture was warmed on the steam-bath for thirty minutes, cooled, and made acid to congo red paper with acetic acid. The crude arsonic

acid was dissolved in dilute ammonium hydroxide and precipitated as light tan crystals by adding acetic acid until the solution tested acid to congo red paper; yield, 1 g. (57%); m. p. >250°.

Anal. Calcd. for C₁₁H₁₂O₄N₄As: As, 23.04. Found: As, 22.76.

2-Hydroxy-4-(3'-arsonoanilino)-6-methylpyrimidine.—The preparation of the meta isomer was effected in the same manner as the para compound. The yield of light tan crystals which melted at >250° was 0.8 g. (46%).

Anal. Calcd. for C₁₁H₁₂O₄N₄As: As, 23.04. Found: As, 22.73.

Summary

1. Several 2- and 4-chloropyrimidines were condensed in dilute acid with amino and amino-hydroxyphenylarsonic acids.

2. Ten per cent. hydrogen peroxide in the presence of sodium bicarbonate caused the ethylmercapto group attached to the pyrimidine ring to be replaced by the hydroxyl group.

(11) Cislak and Hamilton, *THIS JOURNAL*, **52**, 638 (1930).