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

Para Arsenated Mixed Ethers

BY PAUL O. BARE[1] AND CLIFF S. HAMILTON

This investigation deals with two series of arsenated mixed ethers. The parent compounds, 4-arsonophenoxyglycerol and *sym-bis*-(4-arsonophenoxy)-propanol-2 were prepared by condensing glycerol α-monochlorohydrin and *sym*-glycerol dichlorohydrin, respectively, with 4-hydroxyphenylarsonic acid.

When 4-arsonophenoxyglycerol and *sym-bis*-(4-arsonophenoxy)-propanol-2 were nitrated with nitric acid (sp. gr. 1.50) in the presence of concentrated sulfuric acid, 2-nitro-4-arsonophenoxypropylene dinitrate and *sym-bis*-(2-nitro-4-arsonophenoxy)-isopropyl nitrate were formed, respectively.

The above nitro esters were hydrolyzed readily in 2 *N* hydrochloric acid solution to their respective nitro derivatives which were reduced catalytically to the corresponding amines.

Several arsine oxides and arseno compounds were obtained from the corresponding arsonic acids by reduction with sulfurous acid in the presence of hydriodic acid and hypophosphorous acid, respectively.

Numerous attempts were made to prepare 2-hydroxy-4-arsonophenoxyglycerol from 2-amino-4-arsonophenoxyglycerol by decomposing the corresponding diazonium salt but none of these was successful.

Experimental

sym-bis-(**4-Arsonophenoxy**)-**propanol-2.**—A solution of 109 g. of 4-hydroxyphenylarsonic acid in 375 cc. of 6 *N* sodium hydroxide was cooled to 20° and 50 cc. of *sym*-glycerol dichlorohydrin was added. After refluxing for two hours the solution was cooled, made just acid to Congo red paper by the addition of 12 *N* hydrochloric acid and set in the refrigerator overnight. The arsonic acid which separated was purified by recrystallization from water.

sym-bis-(**2-Nitro-4-arsonophenoxy**)-**isopropyl Nitrate.**—*sym-bis*-(4-Arsonophenoxy)-propanol-2 (30 g.) was stirred with 90 cc. of nitric acid (sp. gr. 1.50) and 15 cc. of concentrated sulfuric acid for three hours at 0°. The product was precipitated by pouring into cold water and purified by recrystallization from water.

sym-bis-(**2-Nitro-4-arsonophenoxy**)-**propanol-2.**—A suspension of 15 g. of *sym-bis*-(2-nitro-4-arsonophenoxy)-isopropyl nitrate in 1200 cc. of 2 *N* hydrochloric acid was refluxed four hours. The ester passed into solution and was hydrolyzed to give the nitro compound which was precipitated on cooling the solution. It was purified by recrystallization from water.

sym-bis-(**2-Amino-4-arsonophenoxy**)-**propanol-2 and its Sodium Salt.**—A solution of 11.64 g. of *sym-bis*-(2-nitro-4-arsonophenoxy)-propanol-2 in 40 cc. of 2 *N* sodium hydroxide and 150 cc. of water was reduced catalytically[2,3] to the corresponding amine by the use of the Raney[4] nickel catalyst and molecular hydrogen. The catalyst was removed by filtration, the amine precipitated by adding 6 *N* hydrochloric acid until the solution was just neutral to Congo red paper and purification was effected by recrystallization from water.

A neutral solution was made by dissolving 3 g. of the pure amine and 0.61 g. of anhydrous sodium carbonate in 10 cc. of water. When this was added dropwise to 200 cc. of cold absolute ethanol while stirred mechanically the disodium salt was obtained.

4-Arsonophenoxyglycerol and its Sodium Salt.—A solution of 218 g. of 4-hydroxyphenylarsonic acid in 750 cc. of 6 *N* sodium hydroxide was cooled to 20° and 167 cc. of glycerol α-monochlorohydrin added. The solution was refluxed four hours, filtered, cooled to 20° and 200 cc. of 12 *N* hydrochloric acid added. The solution was then diluted to about two liters and heated to 90°. The barium salt of 4-arsonophenoxyglycerol was precipitated by adding hot barium hydroxide solution, the salt removed by filtration and then converted into the free acid by the use of 1 *N* sulfuric acid. The barium sulfate was filtered from the solution and the crude arsonic acid obtained by evaporating the filtrate to dryness. Purification of the acid was effected by extracting with boiling methyl cellosolve and filtering the hot solution into isopropyl ether.

The monosodium salt was obtained by dissolving 11.68 g. of the pure arsonic acid and 2.12 g. of anhydrous sodium carbonate in 25 cc. of water and adding this solution dropwise to 300 cc. of 95% ethanol which was cooled and stirred mechanically.

2 - Nitro - 4 - arsonophenoxypropylene Dinitrate.—4-Arsonophenoxyglycerol (30 g.) was stirred with 90 cc. of nitric acid (sp. gr. 1.50) and 15 cc. of concentrated sulfuric acid for three hours at 10°. The product was precipitated by pouring into cold water and purified by recrystallization from water.

2-Nitro-4-arsonophenoxyglycerol and its Sodium Salt.—2-Nitro-4-arsonophenoxypropylene dinitrate (50 g.) was hydrolyzed by refluxing two hours with 200 cc. of 2 *N* hydrochloric acid. The solution was made neutral to Congo red paper with 6 *N* sodium hydroxide and concentrated until salt began to crystallize on the surface. Upon cooling the nitro compound separated as an oil which was dissolved in boiling methyl cellosolve and filtered into synthetic methanol from which the product separated as a light yellow powder.

(1) Parke, Davis and Company Fellow.

(2) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).

(3) Stevinson and Hamilton, *ibid.*, **57**, 1600 (1935).

(4) Covert and Adkins, *ibid.*, **54**, 4116 (1932).

TABLE I

	Name	Crystal form	Yield, %	M. p., °C.	Formula	As analyses, % Calcd.	Found
1	*sym-bis*-(4-Arsonophenoxy)-propanol-2	Colorless plates	30	>270	$C_{15}H_{18}O_9As_2$	30.49	30.52
2	*sym-bis*-(2-Nitro-4-arsonophenoxy)-isopropyl nitrate	Yellow rosets	92	Effervesces at 218	$C_{15}H_{15}O_{18}N_3As_2$	23.94	24.08
3	*sym-bis*-(2-Nitro-4-arsonophenoxy)-propanol-2	Yellow needles	96	Effervesces at 260	$C_{15}H_{16}O_{13}N_2As_2$	25.76	25.78
4	*sym-bis*-(2-Amino-4-arsonophenoxy)-propanol-2	White needles	74	Effervesces at 186	$C_{15}H_{20}O_9N_2As_2$	28.72	28.59
5	Sodium salt of 4	White granules	90	...	$C_{15}H_{18}O_9N_2As_2Na_2$	26.48	26.41
6	4-Hydroxyphenylarsonic acid	Pink rhomboids	85–90	177–178	$C_6H_7O_4As$	34.38	34.33
7	4-Arsonophenoxyglycerol	White powder	55–60	>250	$C_9H_{13}O_6As$	25.67	25.71
8	Sodium salt of 7	Tiny white granules	90	...	$C_9H_{12}O_6AsNa$	23.88	24.02
9	4-β,γ-Dihydroxy-*n*-propoxyphenylarsenious oxide	Tiny white granules	82	122–123	$C_9H_{11}O_4As$	29.05	28.98
10	4,4′-*bis*-(β,γ-Dihydroxypropoxy)-arsenobenzene	Orange powder	90	164–165	$C_{18}H_{22}O_6As_2$	30.98	30.94
11	2-Nitro-4-arsonophenoxypropylene dinitrate	Yellow plates	75–80	132–133	$C_9H_{10}O_{12}N_3As$	17.55	17.54
12	Tetranitrate of 4,4′-*bis*-(β,γ-dihydroxy-propoxy)-3,3′-dinitroarsenobenzene	Light tan powder	80	98–99	$C_{18}H_{16}O_{18}N_6As_2$	19.88	19.79
13	2-Nitro-4-arsonophenoxyglycerol	Yellow powder	63–68	>250	$C_9H_{12}O_8NAs$	22.24	22.12
14	Sodium salt of 13	Yellow granules	95	...	$C_9H_{11}O_8NAsNa$	20.88	20.74
15	3-Nitro-4-β,γ-dihydroxy-*n*-propoxyphenyl-arsenious oxide	Yellow powder	71	167–168	$C_9H_{10}O_6NAs$	24.74	24.90
16	4,4′-*bis*-(β,γ-Dihydroxypropoxy)-3,3′-dinitro-arsenobenzene	Yellow powder	85	197–198	$C_{18}H_{20}O_{10}N_2As_2$	26.12	26.13
17	2-Amino-4-arsonophenoxyglycerol	Very light gray powder	60	194–196 (dec.)	$C_9H_{14}O_6NAs$	24.41	24.18
18	Sodium salt of 17	Very light gray granules	70–75	...	$C_9H_{13}O_6NAsNa$	22.78	22.62
19	3-Amino-4-β,γ-dihydroxy-*n*-propoxyphenyl-arsenious oxide	White powder	20	>250	$C_9H_{12}O_4NAs$	27.39	27.16
20	4,4′-*bis*-(β,γ-Dihydroxypropoxy)-3,3′-diamino-arsenobenzene	Yellow powder	85	170–173 (dec.)	$C_{18}H_{24}O_6N_2As_2$	29.16	28.98

If the above-mentioned oil was dissolved in 25 cc. of water, made neutral to litmus by the addition of sodium carbonate and the resulting solution added dropwise to 400 cc. of 95% ethanol which was cooled and stirred mechanically, the monosodium salt of 2-nitro-4-arsonophenoxyglycerol was obtained.

2-Amino-4-arsonophenoxyglycerol and its Sodium Salt.—A solution of 3.37 g. of pure 2-nitro-4-arsonophenoxyglycerol in 2 cc. of water and 35 cc. of 95% ethanol was reduced catalytically to the amine. The catalyst was removed by filtration and the filtrate added very slowly to 350 cc. of dry ether which was cooled and stirred mechanically. The amine separated as an almost white solid with no definite crystalline form.

By reducing catalytically 7.18 g. of the monosodium salt of 2-nitro-4-arsonophenoxyglycerol in 20 cc. of water, filtering and adding the filtrate dropwise to 500 cc. of absolute ethanol which was cooled and stirred mechanically, the monosodium salt of 2-amino-4-arsonophenoxyglycerol was obtained.

4-β,γ-Dihydroxy-*n*-propoxyphenylarsenious Oxide and 3-Nitro-4-β,γ-dihydroxy-*n*-propoxyphenylarsenious Oxide.—These arsenious oxides were prepared from their corresponding arsonic acids by reduction with sulfurous acid, employing hydriodic acid as a catalyst. Purification was effected by recrystallization from water.

3-Amino-4-β,γ-dihydroxy-*n*-propoxyphenylarsenious Oxide.—2-Amino-4-arsonophenoxyglycerol was reduced to its oxide in hydrochloric acid solution with sulfurous acid using hydriodic acid as a catalyst. It was necessary to salt out the oxide by using sodium chloride and it was purified by boiling the dried oxide with water to remove the adsorbed sodium chloride.

4,4′-*bis*-(β,γ-Dihydroxypropoxy)-arsenobenzene, 4,4′-*bis*-(β,γ-Dihydroxypropoxy)-3,3′-dinitro-arsenobenzene and 4,4′-*bis*-(β,γ-Dihydroxypropoxy)-3,3′-diaminoarsenobenzene.—These arseno compounds were prepared by reduction of the corresponding arsonic acids with 25% hypophosphorous acid solutions, the first two at 95° and the third at room temperature.

Tetranitrate of 4,4′-*bis*-(β,γ-Dihydroxypropoxy)-3,3′-dinitroarsenobenzene.—A solution of 3 g. of 2-nitro-4-arsonophenoxypropylene dinitrate in 15 cc. of acetone and 10 cc. of water was refluxed over a water-bath for one hour with 10 cc. of a 50% solution of hypophosphorous acid. The arseno compound was precipitated by pouring the solution into cold water.

Summary

1. 4-Hydroxyphenylarsonic acid was condensed with *sym*-glycerol dichlorohydrin and glycerol α-monochlorohydrin to form *sym-bis*-(4-arsonophenoxy)-propanol-2 and 4-arsonophenoxyglycerol.

2. Nitration of *sym-bis*-(4-arsonophenoxy)-propanol-2 and 4-arsonophenoxyglycerol with a mixture of nitric acid (sp. gr. 1.50) and concentrated sulfuric acid gave the respective nitro esters.

3. Hydrolysis of the nitro esters in 2 *N* hydrochloric acid yielded the corresponding nitro compounds.

4. Catalytic reduction of the nitro compounds resulted in the formation of *sym-bis*-(2-amino-4-arsonophenoxy)-propanol-2 and 2-amino-4-arsonophenoxyglycerol.

5. 4,4′-*bis*-(β,γ-Dihydroxypropoxy)-arsenobenzene, 4,4′-*bis*-(β,γ-dihydroxypropoxy)-3,3′-dinitro-arsenobenzene, 4,4′-*bis*-(β,γ-dihydroxypropoxy)-3,3′-diaminoarsenobenzene, and the

tetranitrate of 4,4′-*bis*-(β,γ-dihydroxypropoxy)-3,3′-dinitroarsenobenzene were prepared from the corresponding arsonic acids by reduction with hypophosphorous acid.

6. 4-β,γ-Dihydroxy-*n*-propoxyphenylarsenious oxide, 3-nitro-4-β,γ-dihydroxy-*n*-propoxyphenylarsenious oxide and 3-amino-4-β,γ-dihydroxy-*n*-propoxyphenylarsenious oxide were prepared from the corresponding arsonic acids by reduction with sulfurous acid employing hydriodic acid as a catalyst.

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Derivatives of Piperazine. XII. Alpha Amino Ketones Derived from N-Phenylpiperazine and Derivatives

BY BURT L. HAMPTON AND C. B. POLLARD

Four new α-amino ketones (Table I) derived from N-phenylpiperazine have been prepared with the object of studying the effects of various reducing agents on these ketones. It was hoped that secondary alcohols, similar in structure to ephedrine and related compounds, could be prepared which would possess useful physiological properties. The effect of various reducing agents on the ketones prepared will be reported in a subsequent publication.

The syntheses may be effected in two ways:

A. Since N-phenylpiperazine is a much stronger base than the products obtained, two moles of it in ether solution in the cold may be mixed with one mole of the phenacyl halide and the solution allowed to stand for several hours or overnight. A portion of the free ketone obtained separates out together with the hydrochloride of N-phenylpiperazine which may be removed by washing with water. The remainder of the product is obtained by evaporating off the ether and washing the residue with a small portion of cold alcohol. The whole is then recrystallized from alcohol. In the case of the reaction between N-phenylpiperazine and *p*-chlorophenacyl bromide alcohol was used as the solvent, the product being obtained by evaporating the alcohol to a small volume, cooling, filtering the precipitate, washing with water and then recrystallizing from alcohol.

B. The same products may be obtained by refluxing for thirty minutes in alcoholic solution one mole of the phenacyl halide and one mole of N-phenylpiperazine together with a slight excess of sodium carbonate. The alcoholic solution is evaporated to a small volume, cooled, the precipitate filtered off, washed with water and then recrystallized from alcohol. The yields are from 80 to 85%, method B giving better results.

The ketones are slightly soluble in alcohol and ether, soluble in chloroform and insoluble in water. They do not show a sharp melting point, but melt over a 2° range.

All of the ketones readily form oximes by refluxing them in alcoholic solution with molecular proportions of hydroxylamine. The oximes are not very soluble in alcohol, and are, therefore, very readily isolated. In contrast to the ketones the oximes melt over a range of 1°. The yields of the oximes are from 80 to 85%.

The hydrochlorides of the ketones are prepared

TABLE I

	Compound	M. p. (corr.), °C.	Formula	Recryst. from	N, % Found	N, % Calcd.	Cl, % Found	Cl, % Calcd.
1	N-phenyl-N′-phenacylpiperazine	106–108	$C_{18}H_{20}ON_2$	EtOH	9.96	9.99		
2	N-phenyl-N′-*p*-methylphenacylpiperazine	136–138	$C_{19}H_{22}ON_2$	EtOH	9.57	9.52		
3	N-phenyl-N′-*p*-methoxyphenacylpiperazine	145–147	$C_{19}H_{22}O_2N_2$	EtOH	9.17	9.03		
4	N-phenyl-N′-*p*-chlorophenacylpiperazine	131–133	$C_{18}H_{19}ON_2Cl$	EtOH	8.95	8.90		
5	Oxime of 1	157–158	$C_{18}H_{21}ON_3$	EtOH	14.36	14.23		
6	Oxime of 2	184–185	$C_{19}H_{23}ON_3$	BuOH	13.66	13.59		
7	Oxime of 3	182–183	$C_{19}H_{23}O_2N_3$	BuOH	12.84	12.92		
8	Oxime of 4	169–170	$C_{18}H_{20}ON_3Cl$	BuOH	12.63	12.74		
9	Monohydrochloride of 1	210–212	$C_{18}H_{21}ON_2Cl$	Abs. EtOH	8.70	8.84	11.62	11.19
10	Monohydrochloride of 2	235–237	$C_{19}H_{23}ON_2Cl$	Abs. EtOH	8.53	8.47	11.12	10.72
11	Monohydrochloride of 3	227–229	$C_{19}H_{23}O_2N_2Cl$	EtOH	8.10	8.08	10.51	10.23
12	Monohydrochloride of 4	225–227	$C_{18}H_{20}ON_2Cl_2$	EtOH	7.71	7.98	10.33	10.09