for microscopical examination (Fig. 1). *Refractive indices* (determined by the immersion method in organic oily liquids): $n_\alpha = 1.674$; $n_\beta = 1.733$; $n_\gamma = >1.733$; all ± 0.002. n_α and n_β were most often obtained. *In parallel polarized light (crossed nicols)*, the birefringence was strong. Many fragments did not extinguish sharply with crossed nicols. *In convergent polarized light (crossed nicols)*, biaxial figures were common, especially showing fragments perpendicular to the acute bisectrix with positive optical character and relatively small axial angle.

The prismatic rods, when examined in ordinary light under the microscope, showed narrow colorless elongated prisms which broke up readily into angular fragments (Fig. 3). *Refractive indices* (determined by the immersion method in organic oily liquids): $n_\alpha = 1.605$; $n_\beta = 1.733$; $n_\gamma = >1.733$; all ± 0.002. n_α and n_β were most often obtained, many of the elongated forms showing n_α crosswise, which was also readily observed on angular fragments. *In parallel polarized light (crossed nicols)*, the birefringence was strong. Extinction on the elongated prisms was parallel. *In convergent polarized light (crossed nicols)*, partial biaxial figures were frequently found, especially fragments perpendicular or inclined to an optic axis.

We wish to thank the laboratories of the American Medical Association which, through the courtesy of Dr. Leech, first brought to our attention their observation that sulfathiazole exhibited two melting points. At that time, they were of the opinion that this was due to solvent of crystallization. However, in a later communication to us, they have confirmed our observations, and agree that it is a case of dimorphism.

Summary

The new drug, sulfathiazole (2-sulfanilamidothiazole), exists in dimorphic forms. Data have been presented giving methods of preparation, melting points, optical properties, and photomicrographs.

WASHINGTON, D. C. RECEIVED OCTOBER 10, 1940

[CONTRIBUTION FROM THE SYPHILIS DIVISION OF THE DEPARTMENT OF MEDICINE, JOHNS HOPKINS MEDICAL SCHOOL, AND THE UNITED STATES PUBLIC HEALTH SERVICE]

The Preparation of Phenylarsenoxides. IV. Disubstituted Compounds

BY G. O. DOAK, H. G. STEINMAN AND HARRY EAGLE

In continuation of our studies on the relation between the chemical structure of organic arsenicals and their treponemicidal activity (*T. pallidum*), a series of disubstituted phenylarsine oxides has been prepared. The majority of the corresponding arsonic acids have been described in the older literature.

The catalytic method of Stevinson and Hamilton[1] employing Raney catalyst, has been used in preparing arsonoanilines from the corresponding nitro compounds, with yields varying between 50 and 75%. 2-Nitro-, and 2-nitro-3-hydroxyphenylarsonic acids were not reduced to amines using Raney catalyst. Unidentified amorphous products were obtained from the reduction mixture. The addition of platinic chloride or fresh Raney catalyst did not complete the reaction.

The preparation of 3,4-dihydroxyphenylarsonic acid has been reported by the oxidation of 4-arsonophenol with potassium persulfate,[2] but subsequent investigation by Balaban[3] and in this Laboratory has not confirmed this synthesis. However, we were able to prepare 3,4-dihydroxyphenyldichloroarsine by an adaptation of a method for the preparation of catechol.[4]

While Barber has stated that the reaction between sulfites and halogenated nitroarsonic acids does not proceed normally,[5] we have prepared disodium 3-nitro-4-sulfophenylarsonate by this method. The synthesis is simpler than that employed by Barber for the free acid.[6]

Experimental Part

Table I lists the new compounds prepared. All but one of the arsine oxides (*cf.* footnote *i*, Table I) were obtained by sulfur dioxide reduction of the corresponding arsonic acids. When amino-substituted arsonic acids were reduced, best results were obtained by working in concentrated hydrochloric acid solution, from which the amine hydrochloride dichloroarsines precipitated in crystalline form. Where preliminary experiments indicated that the arsine oxides were unstable in alkaline solution, no attempt was made to isolate them, since the dichloroarsines proved satisfactory for pharmacological investigation. The phenylarsine oxides and arsonous acids were obtained as amorphous powders which showed no definite melting point.

3,4-Dihydroxyphenylarsine Oxide.—Diazotized 3-amino-4-hydroxyphenylarsonic acid was added dropwise to

(1) Stevinson and Hamilton, THIS JOURNAL, **57**, 1298 (1935).
(2) German Patent 271,892.
(3) Balaban, *J. Chem. Soc.*, 1088 (1929).
(4) Cumming, Hopper and Wheeler, "Systematic Organic Chemistry," Constable and Co., London, 1937, p. 206.
(5) Barber, *J. Chem. Soc.*, 2047 (1930).
(6) Barber, *ibid.*, 2556 (1931).

TABLE I

DISUBSTITUTED PHENYLARSONIC ACIDS, DICHLOROARSINES AND ARSINE OXIDES

Compound	Yield, %	Formula	As analyses, % Calcd.	Found
Phenylarsonic acid				
2,6-Dimethyl-	30	$C_8H_{11}O_3As$	32.6	33.0
3-Nitro-4-(β-hydroxyethyl)-	84	$C_8H_{10}O_6NAs$	25.7	25.6
3-Amino-4-chloro-	52	$C_6H_7O_3NClAs$	29.8	29.6
Disodium 3-nitro-4-sulfo-[a]	54	$C_6H_4O_8NSAsNa_2$	20.2	20.2
Phenyldichloroarsine				
3,4-Diamino- dihydrochloride[b]	49	$C_6H_9N_2Cl_4As\cdot 3H_2O$	19.7	19.7
3,4-Dihydroxy-	20	$C_6H_5O_2Cl_2As\cdot 2H_2O$	25.8	25.7
3-Hydroxy-4-amino- hydrochloride[c]	55	$C_6H_7ONCl_3As\cdot 2H_2O$	22.9	22.9
3-Hydroxy-2-amino- hydrochloride[d]	77	$C_6H_7ONCl_3As\cdot 3H_2O$	21.7	21.6
Phenylarsine oxide				
2,6-Dimethyl-	60	C_8H_9OAs	38.2	38.1
3-Nitro-4-methoxy-	94	$C_7H_6O_4NAs$	30.8	30.9
3-Amino-4-methoxy-	45	$C_7H_8O_2NAs$	35.2	35.4
3-Nitro-4-carboxy-	31	$C_7H_4O_5NAs$	29.2	29.2
3-Amino-4-carboxy-[e]	85	$C_7H_6O_3NAs$	33.0	32.7
3-Amino-4-carbamido-[f]	90	$C_7H_7O_2N_2As$	33.2	32.9
3-Amino-4-chloro-[g]	88	$C_6H_5ONClAs$	34.5	34.3
3-Chloro-4-hydroxy-	30	$C_6H_4O_2ClAs$	34.3	34.5
3-Amino-4-(β-hydroxyethyl)-[h]	31	$C_8H_{10}O_2NAs$	33.0	32.3
3,4-Diacetamido-	45	$C_{10}H_{11}O_3N_2As$	26.6	26.6
2-Hydroxy-5-amino-	84	$C_6H_6O_2NAs$	37.7	38.0
2-Hydroxy-3-amino-[h]	78	$C_6H_6O_2NAs$	37.7	37.9
3-Hydroxy-5-amino-[h]	21	$C_6H_6O_2NAs\cdot 3H_2O$	29.6	29.7
3,4-Dihydroxy-	10	$C_6H_5O_3As\cdot H_2O$	34.3	34.5
Phenylarsonous acid, —As(OH)$_2$				
Sodium 3-nitro-4-sulfo-	44	$C_6H_5O_7NSAsNa$	22.5	22.3
3-Nitro-4-chloro-	80	$C_6H_5O_4NClAs$	28.2	28.5
3,4-Dicarbomethoxy-	74	$C_{18}H_{11}O_6As$	24.8	24.5
3,4-Dicarbamido-[i]	73	$C_8H_9O_4N_2As$	27.6	27.6
6-Arsonosobenzimidazalone	71	$C_7H_7O_3N_2As$	31.0	30.8

[a] Calcd.: S, 8.6; Na, 12.4. Found: S, 9.1; Na, 12.4. [b] Diamond shaped platelets. Calcd.: for ionizable Cl, 18.7; H_2O, 14.2. Found: Cl, 18.2; loss at 100°, 15. [c] Needles, m. p. 144–145° (cor.). Calcd.: N, 4.3. Found: N, 4.0. [d] Needles, m. p. 136–137° (cor.). Calcd.: N, 4.1. Found: N, 4.2. [e] Aqueous solutions show a blue fluorescence similar to that of the arsonic acid. [f] Calcd.: N, 12.4. Found: N, 12.6. [g] Calcd.: N, 6.4. Found: N, 6.4. [h] Yields based on the nitroarsonic acids. [i] The preceding ester was treated with concentrated ammonia at −10°. After 10 days at −25° the amide began to separate as a white amorphous powder. Calcd.: N, 10.3. Found: N, 10.2.

a boiling aqueous 10% copper sulfate solution. The mixture was then cooled in an ice-bath, filtered, and strongly acidified with hydrochloric acid. Potassium iodide was added and sulfur dioxide passed into the solution for six hours. Following filtration the mixture was extracted with ether, dried, and the solvent removed. The thick, sirupy dichloroarsine which remained was triturated with cold sulfurous acid. An amorphous solid precipitated which was washed with cold sulfurous acid and dried in a vacuum desiccator under nitrogen. The resulting arsine oxide colored rapidly in alkaline solution and gave a deep green color with ferric chloride which changed to a black precipitate on standing.

Sodium Salt of 3-Nitro-4-sulfophenylarsonic Acid.—An alkaline (phenolphthalein) solution of 3-nitro-4-chlorophenylarsonic acid and sodium sulfite containing a trace of copper acetate was concentrated until the boiling point was 106–110°, then refluxed for one hour. The solution was diluted to 400 cc., treated with charcoal, made barely acid to litmus and poured into alcohol. Disodium 3-nitro-4-sulfophenylarsonate precipitated.

2,6-Dimethyl- and 3-Nitro-4-(β-hydroxyethyl)-phenylarsonic Acids.—The former compound was prepared from the corresponding xylidene by the Bart reaction. It crystallized as needles, melting at 207–208° (cor.). Attempts to prepare the corresponding arsonoisophthalic acid by permanganate oxidation split arsenic from the ring. For the preparation of 3-nitro-4-(β-hydroxyethyl)-phenylarsonic acid, 4-(β-hydroxyethyl)-phenylarsonic acid was acetylated, then nitrated. Following hydrolysis the arsonic acid was isolated through the magnesium salt. It melted at 119–120° (cor.).

Summary

The preparation of a series of disubstituted phenyldichloroarsines and phenylarsine oxides is described.

BALTIMORE, MARYLAND
WASHINGTON, D. C.

RECEIVED OCTOBER 4, 1940

[CONTRIBUTION NO. 408[1] FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Alkylation of Biphenyl Using Alkyl Sulfates in Friedel–Crafts Syntheses

BY JACK EPELBERG AND ALEXANDER LOWY

The purpose of this investigation has been to extend the use of dimethyl sulfate and diethyl sulfate as alkylating agents in typical Friedel–Crafts syntheses to biphenyl. Alkyl sulfates have distinct advantages as alkylating agents over the lower alkyl halides and olefins in that they eliminate the necessity for pressure apparatus or very high stirring speeds. The higher boiling points of the alkyl sulfates are also advantageous in that they permit a higher reaction temperature.

The Friedel–Crafts reaction needs no discussion here since it is covered admirably by several comprehensive reviews.[2–5]

Kane and Lowy[6] have shown that satisfactory yields of monoalkylated benzenes can be obtained by condensing dimethyl, diethyl, diisopropyl and dibutyl sulfate with benzene in the presence of aluminum chloride.

With biphenyl the reaction may be summarized by the equation

$$3(RO)_2SO_2 + 6C_{12}H_{10} + 2AlCl_3 \longrightarrow 6C_{12}H_9R + 6HCl + Al_2(SO_4)_3$$

It was desirable to determine the position of the entering alkyl groups and in order to accomplish this, an oxidation of each alkylated product was carried out and a study of the oxidation products made. The oxidation products isolated indicated that the monoalkylated products consisted of a mixture of meta and para isomers with the meta predominating. The dialkylated products consisted of a mixture of various isomeric dialkyl biphenyls.

Experimental

The apparatus employed for the alkylations was the usual one-liter three-necked flask, into one neck of which extended a dropping funnel and thermometer. The central neck was fitted with a mercury seal and a motor-driven glass stirrer. The third neck was connected to a modified Hopkins-type reflux condenser. This condenser could be cooled by water, or it could be packed with solid carbon dioxide. This latter procedure was employed when dimethyl sulfate was the reactant. Fractionations were conducted with a twelve-plate column packed with helices.[7,8] By means of a constant pressure regulator the pressure could be maintained constant throughout the fractionation. A reflux ratio of 1:12 to 1:15 was used.

The aluminum chloride used throughout was of 99.5% purity. The biphenyl was recrystallized from hot alcohol (m. p. 70°). The alkyl sulfates were purified by vacuum distillation before use.

Diethyl Sulfate.—A large series of experiments was conducted in which the general conditions affecting the yield such as reaction time, temperature, solvent, rate of addition and proportions of reagents have been studied. With diethyl sulfate as the alkylating agent these experiments showed that low temperatures and longer reaction time favored high yields. The best yield resulted with a ratio of diethyl sulfate to biphenyl to aluminum chloride of $1\frac{1}{2}:1:1\frac{1}{8}$. This experiment is described here.

Biphenyl (308 g., 2 moles) was stirred with *o*-dichlorobenzene (680 cc.). When the biphenyl had gone into solution, aluminum chloride (300 g., 2.25 moles) was added. The reaction mixture was cooled on an ice-bath (5–8°). Diethyl sulfate (462 g., 3 moles) was then added dropwise during four and one-half hours. At the end of ten hours the ice-bath was removed and the reaction allowed to proceed at 24° for a period of four hours, making a total reaction time of fourteen hours. Throughout this time there was a rapid evolution of hydrogen chloride. The reaction product was poured over cracked ice acidified with 200 cc. of hydrochloric acid and allowed to hydrolyze overnight. The top oily layer was decanted, the remainder extracted with benzene. The benzene was distilled and the remaining oil combined with the first portion. The oil was first washed with aqueous sodium carbonate, water and then dried over anhydrous calcium chloride. The *o*-dichlorobenzene was first removed by vacuum distillation, and the distillation continued until the excess unreacted biphenyl

(1) Abstracted from a thesis presented by Jack Epelberg to the Graduate School in partial fulfillment of the requirements for the Ph.D. degree. Presented at the Detroit meeting of the A. C. S. Sept., 1940.

(2) G. Krãnzlein, "Aluminiumchlorid in der organischen Chemie," Verlag Chemie G. m. b. H., Berlin, revised edition, 1932.

(3) N. O. Calloway, *Chem. Rev.*, **17**, 327 (1935).

(4) P. H. Groggins, "Unit Processes in Organic Synthesis," McGraw-Hill Book Co., Inc., New York, N. Y., second edition, 1938.

(5) D. V. Nightingale, *Chem. Rev.*, **25**, 329 (1939).

(6) H. L. Kane and A. Lowy, THIS JOURNAL, **58**, 2605 (1936).

(7) F. C. Whitmore and A. R. Lux, *ibid.*, **54**, 3451 (1932).

(8) C. D. Wilson, G. T. Parker and K. C. Laughlin, *ibid.*, **55**, 2795 (1933).