ture of this compound seems well substantiated, since its preparation has been reported in the literature by three different routes (from x,y,z-tribromoquinoline by nitric acid oxidation,[10] from 5-bromoquinolinic acid by decarboxylation,[11] and from 5-aminonicotinic acid[12]). The yield of 5-bromonicotinic acid was 45%.

Anal. Calcd. for $C_6H_4BrNO_2$: C, 35.7; H, 2.00. Found: C, 35.9; H, 2.04.

The acid was then converted to the methyl ester by the usual method employing thionyl chloride and methanol. The ester was crystallized from methanol–water and consisted of colorless crystals, m. p. 93–95°. Chromatographing a small sample in benzene over activated alumina raised the m. p. to 99–100° (lit. 98–99[8]).

A small sample (1 g.) of each of the amines was then oxidized by refluxing in 40 ml. of concentrated nitric acid for twelve hours and the mixture worked up as before. The product in each case was identified as 5-bromonicotinic acid by mixed m. p. of the acid with the authentic sample and mixed m. p. of the methyl ester with the authentic sample.

3-Bromo-6-methoxy-8-(5-isopropylaminopentylamino)-quinoline Hydrobromide.—The coupling was accomplished using equimolecular (0.03 mole) quantities of 3-bromo-6-methoxy-8-aminoquinoline and 5-isopropylamino-1-bromopentane hydrobromide, and a one-mole excess of sodium acetate. This mixture was heated at steam-bath temperature for three days. At the end of this time 25 to 50 ml. of a methanol–water mixture was added, and the mixture was refluxed a day longer. When the mixture was removed from the steam-bath, a black oil settled to the bottom of the flask. Without allowing the flask to cool, the supernatant liquid was poured into a beaker. The black oil in the flask was taken up in benzene, decolorized with charcoal and cooled to yield the monohydrobromide of the drug. As the supernatant liquid cooled, crystals settled out, which generally consisted of a mixture of hydrobromide and the aminoquinoline. If the supernatant liquid was not separated from the black oil, it was not possible to separate the coupling product from starting amine. The hydrobromide as it was obtained from the first crystallization was quite pure and each crystallization (methanol–benzene solution) decreased the yield immensely. The best yield that could be obtained was 55% based on the amine used in the reaction. Usually, half the quantity of amine used in the reaction is recovered.

Anal. Calcd. for $C_{18}H_{26}BrN_3O\cdot HBr$: N, 9.11; C, 46.8; H, 5.86. Found: N, 8.62; C, 46.6; H, 5.67.

3-Bromo-6-chloro-8-(5-isopropylamino-1-pentylamino)-quinoline Hydrobromide.—This compound was prepared in a similar manner to its 6-methoxy analog.

Anal. Calcd. for $C_{17}H_{23}BrClN_3\cdot HBr$: N, 9.02. Found: N, 8.72.

(10) O. Srpek, *Monatsh.*, **10**, 710 (1889).
(11) A. Claus and F. Collischon, *Ber.*, **19**, 2763 (1886).
(12) R. Graf, *J. prakt. Chem.*, **138**, 244 (1933).

Summary

1. 2,2,3-Tribromopropanal has been found to react with *o*-nitro-*p*-substituted-anilines to produce the 3-bromoquinolines in good yields. Two of these nitroquinolines have been reduced to the amines and coupled with side chains to produce compounds of possible antimalarial activity.

2. *o*-Nitroaniline itself in this reaction produced little of the expected compound, 3-bromo-8-nitroquinoline, and large amounts of 6-bromo- and 3,6-dibromo-8-nitroquinoline.

3. A survey of numerous attempted direct halogenations of 6-methoxy-8-nitroquinoline is presented.

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[CONTRIBUTION FROM THE EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Derivatives of 4-Amino-4'-ethylaminodiphenyl Sulfone, 4-Nitro-4'-ethylaminodiphenyl Sulfone and N^1-Ethylsulfanilamide

BY ERNEST L. JACKSON*

4-Amino-4'-β-hydroxyethylaminodiphenyl sulfone[1] (I) possesses interesting pharmacologic and chemotherapeutic properties.[2] The first preparations of this compound by the reduction of 4-nitro-4'-β-hydroxyethylaminodiphenyl sulfone (II) regularly yielded crystals melting at 143.5–144.5°, but later a second crystalline form (Table I) melting at 130.5–131.5° usually was obtained. The dimorphic forms are distinguishable by the X-ray diffraction patterns (Fig. 1), which also demonstrate their homogeneity. The procedure[1] previously employed for the preparation of II by hydroxyethylation of 4-amino-4'-nitrodiphenyl sulfone has been improved by neutralization of the hydrobromic acid produced in the reaction and other modifications. Since compound I is only slightly soluble in water (74 mg. per 100 cc. of solution at 37°), it usually is administered orally in chemotherapeutic experiments. Phosphorylation affords its crystalline phosphoric ester (III), the sodium salt of which is readily soluble in water. This ester is prepared conveniently and in high yield by the reaction of a mixture of orthophosphoric acid and phosphorus pentoxide with I at 100°. It was obtained also by the reduction of compound IV, the phosphoric ester of II, with ammonium sulfide or ferrous sulfate. The preparation of IV by phosphorylation of II with a mixture of orthophosphoric acid and phosphorus pentoxide proved to be a superior method to preparation by way of the reaction of phosphoryl chloride with II at 100°, because in the latter reaction a considerable proportion of the material was converted into 4-nitro-4'-β-chloroethylaminodiphenyl sulfone (V). In dry pyridine solution at room temperature phosphoryl chloride showed no appreciable reaction with II. The reaction of hot 48% hydrobromic acid with I yields crystalline

* Harvard University Ph.D. 1924.

(1) Jackson, THIS JOURNAL, **70**, 680 (1948).
(2) Smith, Jackson, Junge and Bhattacharya, *Am. Rev. Tuberc.*, **60**, 62 (1949).

TABLE I

DERIVATIVES OF DIPHENYL SULFONE R—C$_6$H$_4$—SO$_2$—C$_6$H$_4$—NHCH$_2$CH$_2$—R′

No.	R	R′	M. p., °C. (uncor.)	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
I	$-NH_2$	$-OH$	130.5–131.5	$C_{14}H_{16}N_2O_3S$	57.51	5.52	9.58	10.97	57.81	5.31	9.23	11.02
II	$-NO_2$	$-OH$	.....	.....	...	..	..	...	...	..	..	...
III	$-NH_2$	$-OPO(OH)_2$	136–137[a]	$C_{14}H_{17}N_2O_6PS$[b]	...	..	7.53	8.61	...	..	7.16	8.70
IV	$-NO_2$	$-OPO(OH)_2$	189–190	$C_{14}H_{15}N_2O_8PS$[c]	...	..	6.96	7.97	...	..	6.51	8.11
V	$-NO_2$	$-Cl$	196–197	$C_{14}H_{13}ClN_2O_4S$[d]	49.34	3.84	8.22	9.41	49.79	3.91	7.99	9.18
VI	$-NH_2$	$-Br$	153–154	$C_{14}H_{15}BrN_2O_2S$[e]	47.33	4.26	7.89	9.02	47.64	4.38	7.80	8.97
VII	$-NO_2$	$-OC_2H_5$	149–150	$C_{16}H_{18}N_2O_5S$	54.84	5.18	8.00	...	55.11	5.14	8.18	...
VIII	$-NH_2$	$-OC_2H_5$	125–126	$C_{16}H_{20}N_2O_3S$	59.97	6.29	8.75	10.01	60.03	6.34	8.57	9.88

[a] Dihydrate. Calcd. for $C_{14}H_{17}N_2O_6PS\cdot 2H_2O$: H_2O, 8.8; N, 6.86; P, 7.59; 2.45 cc. of 0.1 *N* sodium hydroxide solution per 50 mg. Found: H_2O (dried at 100° *in vacuo*), 9.2; N, 6.84; P, 7.20; 2.47 cc. of 0.1 *N* sodium hydroxide (phenol phthalein). [b] P, calcd. 8.32; found, 7.83 (colorimetric). [c] P, calcd. 7.70; found, 7.65 (colorimetric). Calcd.: 2.40 cc. of 0.1 *N* sodium hydroxide solution per 50 mg. Found: 2.51 cc. (phenolphthalein). [d] Cl, calcd. 10.41; found, 10.64. [e] Br, calcd. 22.50; found, 22.32.

4-amino-4′-β-bromoethylaminodiphenyl sulfone (VI).

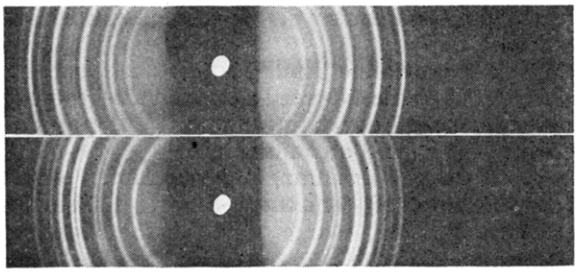
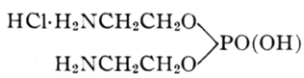


Fig. 1.—X-Ray diffraction patterns of the dimorphic forms (upper, m.p. 130.5–131.5°; lower, m.p. 143.5–144.5°) of 4-amino-4′-β-hydroxyethylaminodiphenyl sulfone.

N-*p*-Sulfanilylphenylglycine[1] has been isolated[2] from the urine of a cat receiving I. This oxidation of I suggested tests on the chemotherapeutic activity and stability *in vivo* of the ethoxy derivative (VIII). Compound VIII was prepared by the reduction of the corresponding nitro compound (VII), which resulted from the reaction of 1-bromo-2-ethoxyethane with 4-amino-4′-nitrodiphenyl sulfone. The ethoxy derivative (VIII) is more soluble in aqueous solution of crystalline human serum albumin[3] than in water. The solubilities[4] per 100 cc. of solution at 37° are 10 mg. in water and 17.5 mg. in 3% albumin solution, the *p*H of the latter solution being 5.1.

The sulfanilamide derivatives, sodium di-β-N^4-acetylsulfanilylaminoethylphosphate (X) and di-β-sulfanilylaminoethylphosphoric acid dihydrochloride (XI), are related to the diaminodiphenyl sulfone derivatives with respect to the type of substituent in the amido group. The crystalline monohydrochloride of di-β-aminoethylphosphoric acid (IX), m. p. 250°, resulted from the reaction, under specified conditions, of phosphoryl chloride with 2-aminoethanol in carbon tetrachloride medium. Outhouse[5] employed the same reactants in aqueous solution for the preparation of monoaminoethylphosphoric acid, which has been isolated from tumors[5] and also from the intestines of pigs and rabbits.[6] In accordance with formula IX, nitrogen analyses of di-β-aminoethylphosphoric acid by the Kjeldahl method and the Van Slyke nitrous acid procedure for the determination of primary amino groups yielded concordant results. Compound IX reacts readily with N-acetylsulfanilyl chloride in aqueous acetone solution to yield di-β-N^4-acetylsulfanilylaminoethylphosphoric acid, which was isolated as the crystalline trihydrate of its sodium salt (X). Deacetylation of X by reaction with 19% hydrochloric acid at 100° during one hour produced crystalline XI in high yield. This result demonstrates the resistance of the phosphoric ester linkage to acid hydrolysis. The ester (X) was not hydrolyzed during two hours at 37.5° and *p*H 5.0 by human prostatic phosphatase (activity on sodium β-glycerophosphate, 4500 units[7] per 100 g.), nor by cow's milk phosphatase (activity on sodium β-glycerophosphate, 150 units per 100 cc.) at *p*H 9.0 in the presence of 0.1 molar magnesium chloride, as indicated by the negative Fiske–SubbaRow test for phosphate ion. Failure to hydrolyze the ester may be due to the specificity[8] of action of these enzymes for monoesters.



IX

Sulfanilylamino-β-bromoethane (XIII) in pure

(3) The albumin was developed, from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

(4) *Cf.* Goldstein, *J. Pharmacol. Exp. Therap.*, (II) **95**, 102 (1949); Heymann and Fieser, *ibid.*, **94**, 102 (1948); Davis, *J. Clin. Invest.*, **22**, 753 (1943).

(5) Outhouse, *Biochem. J.*, **30**, 197 (1936); **31**, 1460 (1937); Plimmer and Burch, *ibid.*, **31**, 398 (1937); Christensen, *J. Biol. Chem.*, **135**, 399 (1940).

(6) Colowick and Cori, *Proc. Soc. Exp. Biol. Med.*, **40**, 586 (1939).

(7) Shinowara, Jones and Reinhart, *J. Biol. Chem.*, **142**, 921 (1942).

(8) *Cf.* Smith, *J. Pharmacol. Exp. Therap.*, **51**, 217 (1934); Green and Colowick, *Ann. Rev. Biochem.*, **13**, 155 (1944).

condition melts at 90–91° (uncor.). Crystals of the pure compound, during storage at room temperature for five years, changed to crystals melting at 183–186°. This change apparently is due to a reaction involving the primary amino group and bromine atom of the molecule, since crystals of N⁴-acetylsulfanilylamino-β-bromoethane (XII) were stable under similar conditions. Melting points of 69–70° and 78–80° have been recorded[9] for compound XIII, the first value having been reported by Dewing, *et al.*,[10] for an obviously impure specimen.

Acknowledgments.—Indebtedness is expressed to Mr. W. C. Alford, Mrs. Margaret M. Ledyard and Mrs. Evelyn G. Peake for microanalyses, to Dr. Y. T. Chang for Bratton–Marshall analyses of solutions of compound VIII, to Miss Dorothy Hastings and Mr. William C. White, of the Physical Biology Laboratory of this Institute, for X-ray diffraction patterns, to Dr. B. B. Westfall, of the National Cancer Institute, for phosphatase hydrolysis tests and to Dr. Max Tishler, of Merck & Co., Inc., for a supply of 4-amino-4′-nitrodiphenyl sulfone.

Experimental

Dimorphic Forms of 4-Amino-4′-β-hydroxyethylaminodiphenyl Sulfone (I).—Reduction of 50 g. of recrystallized II with the use of 3475 cc. of 95% ethanol, 124 cc. of 38% hydrochloric acid and 150 g. of 40-mesh, degreased iron filings as previously described[1] produced I in 75% yield. After purification by recrystallization first from ethanol and then from methanol as slightly yellow colored plates or rod-shaped prisms, the crystals melted at 130.5–131.5°. Repeated recrystallization from these solvents and from a mixture of acetone and petroleum ether did not change the melting point. The crystals frequently could be converted into the crystalline form melting at 144° by seeding a filtered solution of the low-melting form in ethanol or methanol with the high-melting crystals. When the low-melting crystals were fused in a capillary tube, the melt crystallized upon cooling and then melted at 144°. The X-ray diffraction patterns of the two forms are shown in Fig. 1.

The crystals melting at 131° showed a solubility in water of 74 mg. per 100 cc. of solution at 37 ± 0.5°. The solution was prepared by vigorous stirring of a suspension of excess pure crystals of the compound in water at 55° for eight hours and then at 37° for three hours. The resulting mixture was kept stoppered in a 37°-oven, with occasional shaking, until determinations at an interval of eight days yielded concordant results: 10 cc. of the solution, filtered at 37°, deposited upon evaporation of the solvent 0.0074 g. of the compound dried at 100° *in vacuo*.

Preparation of 4-Nitro-4′-β-hydroxyethylaminodiphenyl Sulfone (II).—To a hot solution of 150 g. of 4-amino-4′-nitrodiphenyl sulfone in 750 cc. of cellosolve (2-ethoxyethanol) were added in succession 90 cc. of water, 69 g. of 2-bromoethanol and 45 g. of powdered calcium carbonate. The mixture was kept on the steam-bath under a reflux condenser for eighty hours with thorough shaking twice daily; 35 g. of 2-bromoethanol was added and the heating continued for an additional eighty hours. After the mixture had been kept at room temperature until crystallization was complete, the crystals and excess calcium carbonate were filtered off, washed first with cold cellosolve and finally with a little 95% ethanol. This first crop usually constituted about 80% of the total yield of II. The solvent was removed from the filtrate by distillation *in vacuo*, some water was mixed with the residue and then evaporated *in vacuo*. The dark-brown sirup, after being mixed with 1000 cc. of water and neutralized with ammonium hydroxide, crystallized within twenty-four hours. The crystals were washed with cold water and then extracted with 300 cc. of boiling 95% ethanol. The solid, which failed to dissolve in this extraction, was recrystallized from 95% ethanol, yielding in four crops about 15 g. of nearly pure II. A small amount of II was obtained by fractional recrystallization of the crude residues. Final purification was accomplished by recrystallization of the combined fractions of II from 95% ethanol. The yield was 88.2 g. or 51%, most of which was almost pure.

N-p-Sulfanilylphenyl-β-aminoethylphosphoric Acid (III).—A mixture of 37.5 g. of 85% orthophosphoric acid and 20 g. of phosphorus pentoxide was heated on the steam-bath under a reflux condenser for one hour. It was then mixed thoroughly with 25 g. of pure low-melting I and 5 g. of phosphorus pentoxide. The thick sirup was kept for five hours at 100° under a reflux condenser with protection from atmospheric moisture. Some ice-water was mixed with the sirup, which finally was stirred with 250 cc. of water until the product had solidified. The solid was dissolved in 200 cc. of water by neutralization with ammonium hydroxide, the solution treated with Norit and the compound precipitated by addition of hydrochloric acid. The yield of thrice precipitated, air-dried III was 31 g. (89%) melting at 133–134°. Additional crude III was isolated from the mother liquors upon concentration. The analytical sample was recrystallized from water as slightly tan colored prismatic needles of the dihydrate. The air-dried dihydrate loses weight at 100° *in vacuo* to yield the anhydrous compound, which is quite hygroscopic. The compound is difficultly soluble in hot water and only slightly soluble in cold acetone, methyl ethyl ketone, methyl isobutyl ketone and methyl *p*-tolyl ketone. It showed diazotization and coupling with the Bratton–Marshall[11] reagents.

Compound III was prepared also by reduction of the corresponding nitro compound (IV) with ammonium sulfide.[12] A solution of 0.4 g. of IV in 2.5 cc. of 6 *N* ammonium hydroxide, cooled in ice-water, was saturated with hydrogen sulfide and then heated in an open test-tube on the steam-bath for one hour. Some sulfur was filtered off and washed with water. From the filtrate and washings was isolated, after concentration and acidification, 0.3 g. of slightly impure III. After purification the dihydrate melted at 136–137°. Reduction of IV in ammoniacal solution by ferrous sulfate[13] also produced III, the yield being low apparently due to the formation of a slightly soluble iron salt.

N-[p-(p-Nitrophenylsulfonyl)-phenyl]-β-aminoethylphosphoric Acid (IV).—A solution of 10 g. of II in 80 g. of phosphoryl chloride was kept at 100° under a reflux condenser for three hours. The addition of 150 cc. of petroleum ether to the cold mixture precipitated a brown sirup, which was separated and mixed cautiously with ice-water. After the suspension had been made slightly alkaline with sodium hydroxide, *ca.* 6 g. of the chloro derivative (V) was filtered off, washed with water and purified by recrystallization as yellow prisms from aqueous acetone, absolute ethanol and methanol. The alkaline filtrate and washings from the crude V were combined, neutralized by hydrochloric acid and concentrated to 100 cc. The ester (IV) was precipitated by addition of hydrochloric acid and purified by recrystallization as light-yellow needles or plates from a mixture of acetone and benzene. The crystals, after being dried overnight in an evacuated desiccator over calcium chloride, lost 3.4% in weight at 100° *in vacuo* without significant change in the melting

(9) Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p. 54.

(10) Dewing, Gray, Platt and Stephenson, *J. Chem. Soc.*, 239 (1942).

(11) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

(12) *Cf.* Robertson, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 52.

(13) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1917).

point of 189–190°. The compound is soluble in hot acetone, slightly soluble in benzene and difficultly soluble in hot water, from which it crystallizes as plates.

The reaction of 1 g. of II during eight hours with a mixture of orthophosphoric acid and phosphorus pentoxide at 100° as described under III yielded 1.2 g. of crude IV. Purified by precipitation from the filtered aqueous solution of its sodium salt and final recrystallization from water, it melted at 189–190°.

4-Amino-4′-β-bromoethylaminodiphenyl Sulfone (VI).—A solution of 30 g. of I in 120 cc. of redistilled 48% hydrobromic acid was refluxed for five hours and then concentrated until 50 cc. of distillate had been collected The solution was refluxed for five hours and again concentrated until 35 cc. of distillate had been collected. After being refluxed for an additional two hours, the solution was diluted with 150 cc. of water which precipitated a sirup that crystallized upon being stirred. The crystals were washed with cold water, then suspended in water and the mixture neutralized by ammonium hydroxide. Additional material was recovered from the filtrates after neutralization. The compound was purified by recrystallization from methanol as rod-shaped prisms, Norit being used for decolorization. It may be recrystallized also by addition of sufficient water to a solution of the crystals in 30% hydrobromic acid to produce turbidity. The yield of slightly brown crystals melting near 150° was 25.5 g. or 70%. The analytical sample was dried at 100° *in vacuo*.

4-Nitro-4′-β-ethoxyethylaminodiphenyl Sulfone (VII).—To a hot solution of 18 g. of 4-amino-4′-nitrodiphenyl sulfone in 90 cc. of 2-ethoxyethanol were added 10 g. of 1-bromo-2-ethoxyethane, 10 cc. of water and 5 g. of powdered calcium carbonate. The mixture was kept at 100° under a reflux condenser for one hundred and five hours, with occasional shaking. After removal of excess calcium carbonate, the solution was concentrated *in vacuo* to a thick sirup to which some water was added and evaporated *in vacuo*. A solution of the residue in 85 cc. of hot 95% ethanol, after neutralization with ammonium hydroxide and filtration, deposited at room temperature impure crystals of VII. Preliminary purification was accomplished by extraction of the difficultly soluble crystals with six parts of hot methanol, additional VII being isolated from the soluble portion; yield 11 g. or 48%. Pure VII was obtained by recrystallization from acetone as yellow needles or rod-shaped prisms, Norit being employed when necessary.

4-Amino-4′-β-ethoxyethylaminodiphenyl Sulfone (VIII).—Reduction of 2.3 g. of VII by iron filings (7 g.) and 1.5% hydrochloric acid in ethanol solution (84 cc.) was carried out as described previously for 4-amino-4′-ethylaminodiphenyl sulfone,[1] with the exception that the time of refluxing the reaction mixture was two hours; yield 1.8 g. or 86%. The compound was purified by recrystallization from ethanol or methanol as virtually colorless plates.

Compound VIII is readily soluble in acetone; soluble in ethanol, methanol and warm benzene; and slightly soluble in diethyl ether. Its solubility in water, determined at 37 ± 0.5° as described for compound I, is 10.0 mg. per 100 cc. of solution. Analysis of the solution by the Bratton and Marshall[11] method with the use of an electrophotometer showed a solubility of 9.7 mg. For the solubility in serum albumin solution, a suspension of excess crystals of VIII in 3% solution of crystalline human serum albumin in distilled water was stirred vigorously at 37° for two and one-half hours and then kept stoppered in a 37°-oven for forty-three hours, with frequent shaking. After filtration at 37° and suitable dilution of the sample with water, the albumin was precipitated from an aliquot by trichloroacetic acid and analysis carried out according to the Bratton and Marshall technique; solubility, 17.5 mg. per 100 cc. of solution, the *p*H of the solution being 5.1. With the use of bovine albumin powder (fraction V, Armour and Co.) a comparison of the analytical procedure with a gravimetric method, which involved no precipitation of the albumin, showed agreement of the results within 10%.

Di-β-aminoethylphosphoric Acid Monohydrochloride (IX).—To a mixture of 48 g. of 2-aminoethanol and 100 cc. of dry carbon tetrachloride at 0–5° was added dropwise, with shaking, during one hour, a solution of 38 g. of phosphoryl chloride in 25 cc. of dry carbon tetrachloride, the mixture being removed from the ice-bath toward the end of the operation. After the gum, which had separated, had been mixed thoroughly with the solution, the mixture was kept at 95–100° under a reflux condenser for one hour. The gummy product was separated at room temperature from the carbon tetrachloride layer and washed thrice with cold carbon tetrachloride. The red solution of the gum in 150 cc. of water was shaken at 25° with Norit, filtered and concentrated *in vacuo* (bath, 50°) to a thick sirup, which was mixed thoroughly with 35 cc. of warm absolute ethanol. After the ethanol had been removed by distillation *in vacuo*, the sirup was taken up in 50 cc. of warm methanol. The solution, kept for several days over calcium chloride in a desiccator at room temperature, deposited crystals of IX, the amount being increased by addition of methanol at intervals. The crystals were washed free of sirup with cold methanol; yield 26 g. melting near 235°. The compound was purified by recrystallization as colorless, spear-shaped prisms from 80% methanol at 5°, the solution of the crystals in 1.3 parts of water at 50° being decolorized with carbon prior to addition of the methanol. The analytical sample was dried in an evacuated desiccator over calcium chloride; m. p. 250° (uncor.).

Anal. Calcd. for $C_4H_{14}N_2O_4PCl$: C, 21.76; H, 6.40; N, 12.70; P, 14.04; Cl, 16.07. Found: C, 21.70; H, 6.70; N (Kjeldahl), 12.52; N (Van Slyke NH_2), 12.87; P, 13.76; Cl (ionizable), 15.83.

Sodium Di-β-N⁴-acetylsulfanilylaminoethylphosphate (X).—To a solution of 6 g. of IX in 30 cc. of water was added a solution of 12 g. of N-acetylsulfanilyl chloride in 40 cc. of acetone. After the addition of 10 g. of sodium bicarbonate, the mixture was shaken for thirty minutes at room temperature. The product, which crystallized promptly, was washed with cold acetone; yield 17.4 g. It was purified by recrystallization from water as clusters of fine colorless needles of the trihydrate; air-dried for analysis; m. p. 142–143° (uncor.).

Anal. Calcd. for $C_{20}H_{26}N_4O_{10}PS_2Na\cdot 3H_2O$: H_2O, 8.3; N, 8.56; P, 4.73; S, 9.80. Found: H_2O, 8.1; N, 8.39; P, 4.72; S, 9.80.

Di-β-sulfanilylaminoethylphosphoric Acid Dihydrochloride (XI).—A solution of 2 g. of X in 40 cc. of 19% hydrochloric acid was kept at 100° under a reflux condenser for one hour. The solution was cooled in ice-water until crystallization was complete, the crystals collected and air-dried; yield 1.4 g. After purification by recrystallization from 5 *N* hydrochloric acid as slightly yellow plates, the analytical sample was dried in an evacuated desiccator over sodium hydroxide; m. p. 196–197° (uncor.). The compound showed diazotization and coupling with the Bratton–Marshall reagents.

Anal. Calcd. for $C_{16}H_{23}Cl_2N_4O_8PS_2$: Cl, 12.50; N, 9.88; P, 5.46; S, 11.30. Found: Cl (ionizable), 12.41; N, 9.76; P, 5.67; S, 11.43.

Crystals of the dihydrochloride are readily soluble in cold water, from which a difficultly soluble hydrate crystallizes promptly as clusters of prismatic needles. The crystals separating from a solution of 0.1 g. of XI in 2 cc. of water at room temperature were recrystallized twice from water and dried overnight in an evacuated desiccator over calcium chloride. The chlorine-free crystals melted at 136–137° (uncor.).

Anal. Calcd. for $C_{16}H_{23}N_4O_8PS_2 + 1.5H_2O$: H_2O, 5.2; N, 10.75; P, 5.94. Found: H_2O (dried at 97° *in vacuo*), 5.1; N, 10.64; P, 5.89.

N⁴-Acetylsulfanilylamino-β-bromoethane (XII).—To a solution of 26 g. of β-bromoethylamine hydrobromide in 180 cc. of water was added 180 cc. of acetone and 29.7 g. of N-acetylsulfanilyl chloride. The solution was shaken at room temperature during the addition of 22 g. of sodium bicarbonate. After forty-five minutes at 25° the crystals were collected and washed with a little 50% acetone. Ad-

ditional XII was obtained from the filtrate to make the yield 35 g. Purified by recrystallization from aqueous acetone at 5°, it melted at 170–171° (uncor.). Jensen and Thorsteinsson[14] reported a melting point of 172–173° for the compound, prepared with the same reactants in acetone–pyridine solution.

Sulfanilylamino-β-bromoethane (XIII).—A solution of 100 g. of pure XII in a mixture of 108 cc. of 95% ethanol and 108 cc. of 38% hydrochloric acid was heated on the steam-bath under a reflux condenser for thirty minutes during which time colorless crystals, apparently the hydrochloride of XIII, separated. After being cooled to room temperature, the mixture was diluted with 160 cc. of water and neutralized with sodium bicarbonate. The crystals were washed with cold water and air-dried; yield 80 g. or 92%. For purification a solution of crude XIII in 95% ethanol at 75° was treated with Norit, filtered and left at 5° to complete crystallization as long prismatic needles; m. p. 90–91°. The analytical sample was dried in an evacuated desiccator over calcium chloride.

Anal. Calcd. for $C_8H_{11}BrN_2O_2S$: Br, 28.63; S, 11.48. Found: Br, 28.58; S, 11.70.

The crystals melting at 90–91°, after having been kept in a stoppered bottle at room temperature for five years, were observed to have changed to crystalline material melting at 183–186° which showed less solubility in acetone and in ethanol than the original crystals.

At a concentration of 20 mg. % compound XIII showed no appreciable inhibition of the growth of a human strain of tubercle bacilli in glycerol broth.[15]

(14) Jensen and Thorsteinsson, *Dansk Tids. Farm.*, **15**, 41 (1941); *C. A.*, **35**, 5110 (1941); see also ref. 10.

(15) Smith, Emmart and Westfall, *J. Pharmacol. Exp. Therap.*, **74**, 163 (1942).

Summary

4-Amino-4′-β-hydroxyethylaminodiphenyl sulfone (I) crystallizes as dimorphic forms, m. p. 130.5–131.5° and 143.5–144.5°. Crystalline N-*p*-sulfanilylphenyl-β-aminoethylphosphoric acid, prepared preferably by phosphorylation of I with a mixture of orthophosphoric acid and phosphorus pentoxide, was obtained also by reduction of the corresponding nitro compound. 4-Amino-4′-β-ethoxyethylaminodiphenyl sulfone (VIII), the corresponding nitro compound, 4-amino-4′-β-bromoethylaminodiphenyl sulfone and 4-nitro-4′-β-chloroethylaminodiphenyl sulfone have been prepared. The effect of crystalline human serum albumin on the solubility of compound VIII in water is demonstrated.

Di-β-aminoethylphosphoric acid monohydrochloride, m. p. 250°, reacts with N-acetylsulfanilyl chloride to produce di-β-N⁴-acetylsulfanilylaminoethylphosphoric acid which, upon deacetylation with hot hydrochloric acid, yields crystalline di-β-sulfanilylaminoethylphosphoric acid dihydrochloride, the ester linkage of which is resistant to hydrolysis by acids and by phosphatase. Pure sulfanilylamino-β-bromoethane melts at 90–91°.

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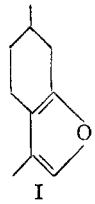
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

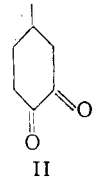
The Autoxidation of Menthofuran

BY R. B. WOODWARD* AND R. H. EASTMAN†

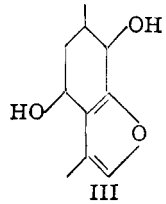
Menthofuran (I) is a terpenoid substance of unusual structure which has been isolated from *Mentha piperita*,[1] and synthesized from *d*-pulegone.[2] The furan is subject to very ready autoxidation,[3] which leads ultimately to a weakly acidic *product*, m. p. 188°. The empirical formula, as well as the constitution of the autoxidation product, have been in doubt. Treibs[2] suggested the formula $C_7H_{10}O_2$, and the structure (II), while Dewein[4] proposed the formula $C_{10}H_{14}O_3$, and the structure (III).



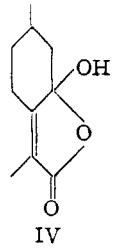
I



II



III



IV

In this communication it is shown that the autoxidation product of menthofuran has the structure (IV) In our hands, the substance, obtained either by alkali extraction of old peppermint oils, or from menthofuran, by autoxidation, by chromic acid oxidation or by oxidation with hydrogen peroxide in acetic acid, melted at 188°, had $[\alpha]^{30}D$ −61.6° (EtOH), reduced permanganate rapidly in the cold, did not react with bromine in carbon tetrachloride, and gave no color with ferric ion or with Schiff reagent. It was not soluble in aqueous sodium bicarbonate, but dissolved in, though it

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(1) Carles, *Parfumerie moderne*, **22**, 615 (1929) (*cf. Schimmel and Co. Reports*, 64 (1930)); Wienhaus, *Z. angew. Chem.*, **47**, 415 (1934); Bedoukian, THIS JOURNAL, **70**, 621 (1948); Schmidt, *Ber.*, **80**, 538 (1947).

(2) Treibs, *ibid.*, **70**, 85 (1937).

(3) In acetic acid, the autoxidation takes place with the evolution of heat and the production of a deep blue solution with a strong red fluorescence. The phenomenon has been used as a test for the presence of menthofuran in peppermint oils (*cf.* ref. 1b) ("U. S. Pharmacopoeia XI," p. 259).

(4) Dewein, Dissertation, Leipzig, 1935.