The 4-cc. sample possessed a yellow color and a strong pine-like odor. The following constants were found: $d_{15^\circ}^{20^\circ}$ 0.8877; $n_D^{20^\circ}$ 1.4931; A. V. 0.48; E. V. 26.13; E. V. after acetylation 160.91; boiling point (micro-method) about 200° C. Tests for nitrogen and sulfur were negative.

The odor and the approximate boiling point (200° C.) were suggestive of borneol. Calculating ester values obtained in terms of $C_{10}H_{18}O$, 9.15% combined and 42.28% free alcohol were found.

SUMMARY.

The physical and chemical constants of the following volatile oils have been reported on: Oil of *Pycnothymus rigidus*, Oil of *Solidago rigida*, Oil of *Erigeron canadensis*, Oil of *Heterotheca subaxillaris*. As far as quantities permitted, the principal constituents have been identified.

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CHEMOTHERAPEUTIC STUDIES IN THE AZOBENZENE SULFONCHLORAMIDE SERIES. II. META AND PARA DERIVATIVES.*,[1]

BY SEYMOUR STERN AND ABRAHAM TAUB.[2]

In 1916 Dakin and co-workers (1), (2) investigated the mode of action of the alkali hypochlorites and concluded that their antiseptic action was due to their interaction with proteins and other amino compounds, resulting in the formation of substances containing chlorine linked to nitrogen. In their attempts to find related substances having greater practical utility, they investigated many compounds containing the chloramine group, =N—Cl. Their studies indicated that all substances containing this group showed some germicidal activity, that slight changes in this activity resulted from nuclear substitution of aromatic chloramines by halogen,

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* Presented before the Scientific Section, A. PH. A., Atlanta meeting, 1939.

[1] Abstracted in part from the dissertation submitted by Dr. Stern to the Graduate Faculty of Columbia University, College of Pharmacy, in partial fulfilment of the requirements for the degree of Doctor of Pharmacy.

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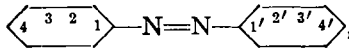
alkyl or nitro groups, and that dicyclic chloramines act similarly to the monocyclic derivatives.

Included among the substances they investigated were some of the N-halogen sulfonamide compounds, first reported by Kastle and co-workers (3), (4) in 1895, and extensively studied by Chattaway (5) in 1905. Of these, Dakin, Cohen and Kenyon (6) selected sodium-*p*-toluenesulfonchloramide because of its non-corrosive and non-protein precipitating properties, its stability in the solid form, its ready solubility in water, its effective germicidal action and its low manufacturing cost.

In 1922, Clutterbuck and Cohen (7), in their attempts to synthesize new N-chlorsulfonamides, found that not all sulfonamides reacted with alkali hypochlorites to form N-halogen derivatives; such compound formation was restricted to the aromatic sulfonamides. Furthermore, the presence of nuclear substituents such as halogen, alkyl, methoxy or nitro groups did not affect the formation of N-halogen sulfonamides; but the interspersion of alkyl side chains of more than two carbon atoms between the nucleus and the sulfonamide group did prevent N-halogen substitution.

In the present research a departure has been made from the nuclear type of compound studied by these previous investigators. Interest has been centered upon dicyclic N-chlorsulfonamides in which nuclear connection is obtained through a nitrogen to nitrogen linkage. Inspection of the azobenzene nucleus  , shows that with regard to position isomerism, three sodium aryl sulfonchloramides and twelve disodium aryl di(sulfonchloramides) are possible. The sodium salts were selected because of their solubility in water.

It is believed that the results of bacteriological tests on the compounds of these series may permit an extension of Dakin's theses, (*a*) that the presence in the molecule of more than one N—Cl group does not confer any marked increase in germicidal power, and (*b*) that the germicidal action of many of the chloramines is mole for mole greater than that of sodium hypochlorite. The results should also add to our present knowledge of the effect of position isomerism upon bacteriological activity.

A survey of the literature shows that only the mono para-isomer has been synthesized, although no study has been made of its chemotherapeutic properties. The present paper is confined to the meta and para derivatives in both the azobenzene mono and di(sulfonchloramide) series.

EXPERIMENTAL.

1. Azobenzene-m-Sulfonamide, m-$C_6H_5N{=}NC_6H_4SO_2NH_2$.—Eleven grams of *m*-aminobenzenesulfonamide (prepared by the general methods of Biderman (8), and Hybbeneth (9), and modified by Stern (10) to produce better yields) were dissolved in 46 cc. of glacial acetic acid at 80° C., and a solution of 6.8 Gm. of nitrosobenzene in 40 cc. of glacial acetic acid was added. After continued heating at 80–90° C. for two hours, the dark-brown mixture was allowed to cool and poured upon 1 Kg. of chipped ice. The greenish black precipitate was collected, washed with water, dissolved in 640 cc. of 0.1*N* sodium hydroxide, and refluxed for one hour in the presence of activated charcoal. After filtering, the hot filtrate was acidified with 0.5*N* hydrochloric acid. The precipitate which formed was collected, washed free of chlorides and dried. The yield of 12 Gm. of impure crystals was crystallized from 110 cc. of hot methyl alcohol (80%) and air dried. Yield 8.1 Gm. of black crystals, m. p. 168–169° C., soluble in ethyl alcohol, methanol, acetone, pyridine, hot alkali; insoluble in water, benzene, ether, ethyl acetate or hydrochloric acid.

Kjeldahl: 0.2002 Gm. substance required 23.70 cc. 0.1*N* HCl.
Calculated for $C_{12}H_{11}N_3O_2S$; N, 16.09%. Found: N, 16.16%.

As the aromatic primary amine employed for the condensation with nitrosobenzene contained a sulfonamide group, it might be expected that this group may also have reacted in a condensation to yield a compound of the formula m-C_6H_5—N=N—SO_2—C_6H_4—NH_2. Such a compound should be soluble in hydrochloric acid and insoluble in alkali due to the free amino group. Actually the compound obtained after recrystallization was a homogeneous product entirely soluble in dilute sodium hydroxide and insoluble in dilute acid, this being characteristic of a compound containing a sulfonamide group.

2. *Sodium Azobenzene-m-Sulfonchloramide, m-C_6H_5—N=N—C_6H_4—$SO_2NaNCl.2H_2O$.*—To a well-stirred mixture of 5.2 Gm. of azobenzene-m-sulfonamide and 50 cc. of water, 82.8 cc. of sodium hypochlorite solution, containing 0.02699 Gm. of NaOCl per cc. and 2% free NaOH was added during 45 minutes, the temperature of the solution rising from 21.5° to 23° C. The insoluble black powder gradually dissolved forming a brown solution and light-brown crystals appeared. Upon heating to 75–80° C. a clear wine-red solution resulted. It was rapidly cooled and stirring was continued for another hour, the crystals forming on the walls of the flask being occasionally washed down with water until the volume measured 250 cc. The crystals were collected, washed with water and air dried, yielding 5.3 Gm. Purification was effected by dissolving the crude compound in 240 cc. of water at 90° C. containing 3.24 Gm. sodium hydroxide, 4.3 Gm. of sodium chloride and 24 cc. of the hypochlorite solution. After filtering, cooling and stirring, amorphous material deposited. After collection, it was found that three washings of the material with water were sufficient to remove chlorides. The p_H of the final wash water remained within the range 7–9 to Hydrion paper. Drying yielded a yellowish orange amorphous powder, which was insoluble in benzene, carbon tetrachloride and anhydrous ether. It dissolved in hot water, hot absolute alcohol, pyridine and acetone.

Calculated for $C_{12}H_9N_3O_2SNaCl.2H_2O$; H_2O, 10.2%. Cl, 10.04%. Na, 6.52%. Found: H_2O, 9.49%; Cl, 9.60%; Na, 6.61%.

3. *Sodium Azobenzene-p-Sulfonchloramide.*—Following the method of Gray, *et al.* (11), azobenzene-p-sulfonyl chloride was prepared and converted to the corresponding sulfonamide. After purification the latter melted at 228–229° C. This was then transformed to the sodium sulfonchloramide by the method of Chrzaszczewska and Dobrowolski (12).

4. *Reduction of Potassium m-Nitrobenzene Sulfonate.* (*a*) *Potassium Azoxybenzene-3,3′-Disulfonate.*—In the attempt to produce potassium azobenzene-3,3′-disulfonate, the method of reduction of Mahrenholtz and Gilbert (13) was employed. To a boiling solution of 18.1 Gm. of potassium m-nitrobenzene sulfonate in 108 cc. of water was added 20.7 Gm. of potassium hydroxide in 190 cc. of water. The solution was transferred to a water-bath and five 2-Gm. portions of zinc dust were added with stirring during 1.75 hr. Heating was continued for 1.5 hr., the volatilized water being replaced. After filtering out the zinc residues a stream of carbon dioxide was passed through the cold filtrate for 1.25 hr. to precipitate the zinc compounds. Upon filtration and evaporation of the filtrate and washings, 44 Gm. of dried residue was obtained. Crystallization from 75 cc. of boiling water yielded 19.5 Gm. of air-dried salt. The lack of solubility of this salt in alcohol indicated that it was not the azo compound. Subsequent experiments by Stern (10) in which the disulfonyl chloride and disulfonamide derivatives were prepared and their melting points checked with those recorded in the literature by Brunneman (14) established the identity of the compound as potassium azoxybenzene-3,3′-disulfonate.

It was found that in order to prepare the corresponding azobenzene derivative and avoid the azoxy stage, it was necessary to carry the reduction far enough to produce a colorless reaction mixture and convert the probable hydrazo compound so produced to the azo stage by spontaneous air oxidation. This new method also has the advantage of being a rapid one.

(*b*) *Potassium Azobenzene-3,3′-Disulfonate.*—Thirty-six grams of potassium m-nitrobenzene sulfonate was dissolved in 400 cc. of hot water and 41.4 Gm. of potassium hydroxide in 54 cc. of water was added, the resulting orange solution being heated to 102° C. Under mechanical stirring, nine 4-Gm. portions of zinc dust were added in 15-minute intervals during two hours, the temperature being kept above 90° C. and constant volume being maintained by frequent additions of water. The progress of the reduction was followed by spotting the reaction mixture on filter

paper at fifteen-minute intervals just before each new addition of zinc. The color changed from orange to colorless after the ninth addition of zinc dust. After filtering off the zinc residues, the filtrate began to oxidize in contact with the air. Under mechanical stirring for 3 hr. at 80–90° C. the color reached a maximum and the reaction was considered complete. The solution was boiled, carbon dioxide passed in for two hours, the precipitated zinc compounds filtered out and the filtrate concentrated to 225 cc. The deposited crystals were collected, washed with cold water and dehydrated at 150° C. for 2.5 hr. An addition crop of crystals was obtained by concentrating the mother liquor to 115 cc. Yield 30 Gm. Subsequent experiments in which these crystals were converted to the disulfonyl chloride and the disulfonamide, whose melting points agree well with those recorded in the literature by Mahrenholtz and Gilbert (13), and Limpricht (15), prove that these crystals are potassium azobenzene-3,3′-disulfonate. The method of synthesis precludes the possibility of the formation of positional isomers.

5. Disodium Azobenzene-3,3′-di(Sulfonchloramide), ($ClNaSO_2—C_6H_4N=)_2.4H_2O$.—To a well-stirred mixture of 6.8 Gm. of azobenzene-3,3′-disulfonamide (13), (15) and 50 cc. of water, 100.5 cc. of sodium hypochlorite solution, containing 0.04443 Gm. of NaOCl per cc. and 5% free NaOH, was added during 45 minutes. After 23 cc. of the solution was added the suspended crystals formed a clear orange-brown solution, but after 40 cc. was added a buff-colored powder began to separate. After stirring for one hour the insoluble material was collected, washed twice with 5-cc. portions of water and dried, yielding 9.1 Gm. This was purified by dissolving in a hot solution containing 4.8 Gm. of sodium hydroxide, 4.8 Gm. of sodium chloride, 310 cc. of water and 50 cc. of sodium hypochlorite solution. After filtering, 150 cc. of saturated salt solution was added, the mixture cooled and the amorphous material which separated was collected and washed twice with water. The p_H range of the washings was 7–9. The air-dried powder is insoluble in absolute alcohol, carbon tetrachloride, benzene, dry ether and acetone. It is soluble in hot water and slightly in hot pyridine.

Calculated for $C_{12}H_8N_4O_4S_2Na_2Cl_2.4H_2O$: H_2O, 13.8%; Cl, 13.5%; Na, 8.8%. Found: H_2O, 13.05%; Cl, 13.23%; Na, 8.55%.

6. Disodium Azobenzene-4,4′-di(Sulfonchloramide), ($ClNaSO_2—C_6H_4N=)_2.4H_2O$.—Into a flask containing 50 cc. of water and 6.8 Gm. of azobenzene-4,4′-disulfonamide, prepared by the method of Stern and Linnell (16), 82.8 cc. of sodium hypochlorite solution, containing 0.05398 Gm. of NaOCl per cc. and 4% free NaOH, was added while stirring during 45 minutes. A red solution formed upon heating to 65° C. and the insoluble impurties were filtered out. After chilling and stirring for one hour, the filtrate and washings, which measured 150 cc., was saturated with 53.8 Gm. of sodium chloride. The orange-red material which separated was collected, washed with 25 cc. of water and dried, yielding 9.0 Gm. It was purified by dissolving in 102 cc. of water at 80° C. containing 3.6 Gm. sodium hydroxide and 48 cc. of the hypochlorite solution. After filtration, 450 cc. of saturated salt solution was added, the mixture heated to 80° C. and 30 Gm. of sodium chloride added. Chilling to 25° C. caused the separation of the disodium azobenzene-4,4′-di(sulfonchloramide). After collection and washing with five 10-cc. portions of water, the material was air dried. It is an orange powder, insoluble in carbon tetrachloride, benzene, ether and acetone. It is slightly soluble in hot absolute alcohol or pyridine, and very soluble in water.

Results of preliminary bacteriological tests carried out at room temperature against *Staphylococcus aureus* indicate the following order of activity:

Compound.	5-Minute Exposure to Antiseptic.	2-Hour Exposure to Antiseptic.
Chloramine-T	1.0	1
Sodium azobenzene-*m*-sulfonchloramide	0.15	10
Sodium azobenzene-*p*-sulfonchloramide	10.0	100
Disodium azobenzene-3,3′-di(sulfonchloramide)	0.1	10
Disodium azobenzene-4,4′-di(sulfonchloramide)	0.1	10

Results by the agar cup-plate method indicate that the meta and para monosulfonchloramides are slightly less penetrating than chloramine-T, and the two di(sulfonchloramides) are equal to chloramine T.

SUMMARY.

1. Details have been given for the synthesis of potassium azoxybenzene-3,3'-disulfonate, and a rapid method has been presented for the preparation of the corresponding azo derivative, whereby the azoxy stage is avoided.

2. A new intermediate, azobenzene-*m*-sulfonamide, has been synthesized.

3. Three new compounds of the azobenzene sulfonchloramide series have been synthesized.

4. Preliminary bacteriological results show that all the compounds of this series show bactericidal activity and compare favorably with chloramine-T.

The authors are indebted to Professor Fanchon Hart for conducting the bacteriological tests.

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SALTS OF ISOPROPANOLAMINE.

I. TRIISOPROPANOLAMINE.*

BY GEORGE W. FIERO.[1]

Isopropanolamines are now manufactured in quantities and at prices which would make them available for pharmaceutical and cosmetic preparations. Triethanolamine salts have been used as emulsifying agents in such preparations. It appears that isopropanolamines would have similar properties to triethanolamine.

Triisopropanolamine is a white solid, readily soluble in water and possessing a peculiar, disagreeable odor. It has the following physical properties:[2]

Molecular Weight	191.78	Color	<60 on Pt-Co scale
Specific Gravity	1.0196	Vapor Pressure at 20°	Below 0.1 mm.
Melting Point	45° C.	Boiling Point	144° at 5 mm.

* Presented before the Scientific Section, A. PH. A., Atlanta meeting, 1939.

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[2] The writer is indebted to Carbide and Carbon Chemicals Corp. for these data.