**Chloro Alkyl Esters.**—These esters were prepared in the same manner as the alkyl esters with the exception that ethylene chlorobromide or propylene chlorobromide was used in place of the alkyl halide.

**Dialkylaminoalkyl Ester Hydrochlorides.**—To a mixture of 10 g. of the chloro ester and 15 cc. of alcohol was added 10 g. of the appropriate amine. The mixture was refluxed on a steam-bath for two hours, and poured onto a mixture of cracked ice and dilute sodium hydroxide. The free base was removed and dissolved in dry ether. The hydrochlorides were formed by passing dry hydrochloric acid into the ether solution. They were purified by recrystallization from absolute alcohol or by precipitation from an alcoholic solution by the addition of dry ether. The physical properties and analytical data are in the table.

## Summary

Some alkyl and alkamine esters of *p*-fluorothiobenzoic acid were synthesized and the physical properties were determined. These compounds are rather toxic weak local anesthetics, indicating that the substitution of sulfur for an ester oxygen increases the toxicity and decreases the anesthetic efficiency of this series.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

# Diaryloxyalkane Derivatives. Diphenoxypropanesulfonamides

BY JOHN A. KING AND FREEMAN H. MCMILLAN

At the same time that a series of diphenoxyethanesulfonamides was being prepared[1] and before it was learned that these substances were trypanocidally inactive, a few of the corresponding diphenoxypropanesulfonamides were prepared. This paper reports their preparation.

$\alpha,\gamma$-Diphenoxypropane (I) was prepared by the procedure of Lohmann[2] modified according to the method of Cope[3] for diphenoxyethane. This was chlorosulfonated by a modification of the procedure of Huntress and Carten[4] to yield $\alpha,\gamma$-diphenoxypropane - 4,4′ - disulfonyl chloride (II). This, on treatment with aqueous ammonia, gave the diamide III, and on treatment with aqueous dimethylamine yielded the corresponding N,N,-N′,N′-tetramethyl amide IV.

In order to prove the structure of IV and at the same time of the disulfonyl chloride II and all products derived from it, the tetramethyl amide was synthesized by an unequivocal method. 4-Hydroxybenzenesulfondimethylamide was condensed with trimethylene bromide, in alcoholic alkaline solution, to give the same product as had been obtained from the disulfonyl chloride II and diethylamine.

Other diphenoxypropane derivatives prepared were the di-N-ethyl derivative V, from the disulfonyl chloride II and ethylamine, the diacetamido compound VI, and its sodium salt VII.

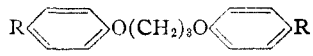
Preliminary tests carried out with these diphenoxypropane derivatives indicate that these substances are devoid of trypanocidal activity.

## Experimental Part[5,6]

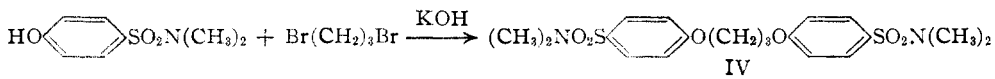
**$\alpha,\gamma$-Diphenoxypropane** (I).—A mixture of phenol (94 g. 1.00 mole), trimethylene bromide (101 g., 0.50 mole), potassium hydroxide (56 g., 1.00 mole; 66 g. of 85% C. P. base), and absolute alcohol (300 cc.) was refluxed with stirring for three hours and then poured into 3.5 liters of ice-water. The solid material (m. p. 52–54°) was recrystallized from aqueous alcohol to give 87 g. (76% yield) of product, m. p. 60–61°. Lohmann[2] reported m. p. 61°.

**$\alpha,\gamma$-Diphenoxypropane-4,4′-disulfonyl Chloride** (II).—This was prepared by the general procedure developed with $\alpha,\beta$-diphenoxyethane;[1] see the following paragraph. A small sample for analysis, after recrystallization from petroleum ether, had m. p. 121°. See Table I for analysis.

TABLE I



| Compound | R | % yield of pure product | M. p.,[5] °C. | Formula | Analyses, %[6] Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| I | —H | 76 | 60–61 | | | | | | | |
| II | —$SO_2Cl$ | 85 | 121 | $C_{15}H_{14}O_5S_2Cl_2$ | 42.35 | 3.32 | | 42.26 | 3.38 | |
| III | —$SO_2NH_2$ | 85 | 194.5–195 | $C_{15}H_{18}N_2O_5S_2$ | 46.63 | 4.66 | 7.25 | 46.67 | 4.72 | 7.48 |
| IV | —$SO_2N(CH_3)_2$ | ... | 191 | $C_{19}H_{26}N_2O_5S_2$ | 51.59 | 5.88 | 6.33 | 51.69 | 6.02 | 6.68 |
| V | —$SO_2NHC_2H_5$ | 69 | 143.5–144 | $C_{19}H_{28}N_2O_5S_2$ | 51.59 | 5.88 | 6.33 | 51.65 | 5.89 | 6.36 |
| VI | —$SO_2NHCOCH_3$ | 67 | 169–170 | $C_{19}H_{22}N_2O_5S_2$ | 48.51 | 4.68 | 5.97 | 48.75 | 4.68 | 5.98 |
| VII | —$SO_2N(Na)COCH_3$ | 100 | dec. | $C_{19}H_{20}N_2O_5S_2Na_2$ | Na, | 8.95 | | Na, | 9.06 | |



IV

**$\alpha,\gamma$-Diphenoxypropane-4,4′-disulfonamide** (III).—The general preparative procedure is that previously described,[1] but some modification was necessary. Varying molar proportions of chlorosulfonic acid were used to determine the optimal conditions for the reaction. The crude chloroform solution of the disulfonyl chloride was stirred with excess aqueous ammonia and the resultant disulfonamide was removed by filtration, dried and weighed. The results are given in Table II.

(1) King, THIS JOURNAL, **66**, 2076 (1944).
(2) Lohmann, *Ber.*, **24**, 2632 (1891).
(3) Cope, THIS JOURNAL, **57**, 572 (1935).
(4) Huntress and Carten, *ibid.*, **62**, 603 (1940).
(5) All melting points are uncorrected.
(6) Microanalyses by Misses P. Curran and A. Rainey.

TABLE II

| Molar proportion of Diphenoxypropane | Chlorosulfonic acid | % excess of chlorosulfonic acid | % yield of disulfonamide |
|---|---|---|---|
| 1 | 4 | 0 | 26 |
| 1 | 5 | 25 | 85 |
| 1 | 6 | 50 | 83 |
| 1 | 8.5 | 112 | 64 |

The disulfonamide, after recrystallization from an ethanol–methyl ethyl ketone mixture, was in the form of feather-like clusters, m. p. 194.5–195°[7] (see Table I for analysis). The structure of the material prepared in these Laboratories has been unequivocally proved, as will be shown in the following paragraph.

**N,N,N',N'-Tetramethyl-α,γ-diphenoxypropane-4,4'-disulfonamide (IV). A.**—A portion of the same chloroform solution of α,γ-diphenoxypropane-4,4'-disulfonyl chloride, of which part had been used to prepare the amide III, m. p. 194.5–195°, was treated with an excess of aqueous dimethylamine. The resultant solid, after two recrystallizations from ethanol, was in the form of flaky crystals, m. p. 191° (see Table I for analysis).

**B.**—A mixture of 4-hydroxybenzenesulfondimethylamide[1] (620 mg., 3.1 millimoles), potassium hydroxide (175 mg., 3.1 millimoles), and trimethylene bromide (300 mg., 1.5 millimoles) in ethanol (10 cc.) was refluxed one hour. The mixture was poured into water and the white solid formed was recrystallized once from ethanol then once from methanol; m. p. 187–189°. When this substance (m. p. 187–189°) was mixed with a sample of the same material (m. p. 191°) prepared by procedure A, the mixture melted at 188–190°.

**N,N'-Diethyl-α,γ-diphenoxypropane-4,4'-disulfonamide (V).**—α,γ-Diphenoxypropane-4,4'-disulfonyl chloride (42.5 g., 0.10 mole, crude, m. p. 116–117°) dissolved in chloroform (200 cc.) was stirred at room temperature for forty five minutes with aqueous ethylamine (100 g. of 33% solution, 0.73 mole), the chloroform was separated and the solvent was removed to leave the crude product (33.0 g.), m. p. 138–142°. After recrystallization from ethanol it weighed 30.7 g. (69% yield) and melted at 143.5–144° (see Table I for analysis).

**N,N'-Diacetyl-α,γ-diphenoxypropane-4,4'-disulfonamide (VI).**—A mixture of α,γ-diphenoxypropane-4,4'-disulfonamide (31.5 g., 0.0815 mole) and acetic anhydride (250 cc.) was refluxed one hour then poured onto ice and allowed to stand overnight. The solid product (m. p. 163–168°) was recrystallized from aqueous acetic acid to give the pure diacetyl derivative (25.6 g., 67% yield), m. p. 169–170° (see Table I for analysis).

The material crystallizes as a monohydrate and if the sample is dried in a vacuum at not over 80° it analyzes for a monohydrate.

*Anal.* Calcd. for $C_{19}H_{22}N_2O_8S_2 \cdot H_2O$: C, 46.71; H, 4.92; N, 5.73. Found: C, 46.73; H, 4.72; N, 5.92.

The diacetyl derivative VI (25.0 g., 0.0512 mole of monohydrate) was dissolved in 106 cc. of 0.962 *N* sodium hydroxide (the theoretical amount), the solution was evaporated to a thick paste and the residue was triturated with ethanol to give the white solid disodium salt VII (see Table I for analysis).

(7) A compound of m. p. 245–255° prepared in 44% yield from α,γ-diphenoxypropane with chlorosulfonic acid, and giving satisfactory analyses, was reported by Huntress and Carten.[4] In the light of results reported in the present paper, however, their product could not have been α,γ-diphenoxypropane-4,4'-disulfonamide.

## Summary

1. α,γ-Diphenoxypropane has been converted by chlorosulfonic acid followed by ammonia into the 4,4'-disulfonamide.

2. The orientation of the two chlorosulfonyl groups entering the molecule has been proved by showing that an amide prepared from the disulfonyl chloride is identical with that synthesized directly from the corresponding 4-hydroxybenzenesulfonamide and trimethylene bromide.

3. The following four other N-substituted disulfonamides were prepared: dimethyl, ethyl acetyl, and sodio-acetyl.

4. None of these compounds have trypanocidal activity.

RENSSELAER, NEW YORK RECEIVED NOVEMBER 1, 1944

# NOTES

## Mechanism of the Reaction between Hindered Allyl Esters and Grignard Reagents

BY RICHARD T. ARNOLD AND R. WINSTON LIGGETT[1]

In two previous publications from this Laboratory[2,3] it was shown that allylic esters of hindered carboxylic acids react with Grignard reagents to give hydrocarbons and halomagnesium salts according to the following equation.

$$R{-}C(=O){-}OCH_2CH{=}CH_2 + R'MgX \longrightarrow R{-}C(=O){-}OMgX + R'CH_2CH{=}CH_2$$

An experimental result obtained over a year ago has forced us to make some drastic alterations in the mechanism proposed earlier.[2] It has been found that the olefin produced when phenylmagnesium bromide is allowed to react with *n*-crotyl mesitoate is pure *n*-crotylbenzene (I) and apparently contains none of the isomeric isocrotylbenzene.

$$2,4,6\text{-}(CH_3)_3C_6H_2COCH_2CH{=}CHCH_3 + C_6H_5MgBr \longrightarrow 2,4,6\text{-}(CH_3)_3C_6H_2CO_2MgBr + \underset{\text{I}}{C_6H_5CH_2CH{=}CHCH_3}$$

This seems of especial interest since it is well known that either of the pure isomeric crotyl halides gives a mixture of isomeric hydrocarbons when treated with the Grignard reagent.

We believe that the new mechanism outlined

(1) Dupont Post Doctorate Fellow 1941–1942.

(2) Arnold, Bank and Liggett, THIS JOURNAL, **63**, 3444 (1941).

(3) Arnold and Liggett, *ibid.*, **64**, 2875 (1942).