thesia after a one-minute application of the solution to the cornea of the rabbit.

From the table it may be seen that the compounds are comparatively much more effective on the cornea than on the exposed nerves. The isobutyl homolog of the series of mono-urethans, which is approximately twice as effective on the cornea as cocaine, has a much lower apparent toxicity, the minimum fatal dose for white mice, injected subcutaneously, being 1500 mg. per kilo.

Both the study of the production of anesthesia and that of the toxicity are complicated, more especially in the di-urethan series, by the tendency of the higher homologs to precipitate proteins. A further study of this feature, together with a more complete pharmacological report, will be published elsewhere.

Since these urethans show such promising local anesthetic properties, the author proposes to extend this field through the preparation of other urethan combinations of the dialkylaminopropanediols and the urethans of other amino alcohols.

Summary

The mono- and di-phenylurethans of a number of dialkylaminopropanediols have been prepared and have been shown to have interesting local anesthetic properties.

Di-*n*-butylaminopropanediol has been prepared for the first time.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING, COLUMBIA UNIVERSITY]

METHYL ISOPROPYL THIOINDIGOID DYES FROM PARA-CYMENE. I. DYES FROM AMINOCYMENE[1]

BY A. W. HIXSON AND W. J. CAUWENBERG

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Introduction

The number of known sulfur-containing indigoid dyes is very great[2] and their commercial importance is steadily increasing, as shown by the introduction of new colors of this series into the industry. These dyes are of particular interest due to the great effect of substitution on the color. Whereas the derivatives of indigo do not differ greatly in color, those of thioindigo cover almost the entire range of the spectrum. A survey of the literature showed that practically all of the simple benzene derivatives

[1] This communication is an abstract of a portion of a thesis submitted by W. J. Cauwenberg in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, to the Faculty of Pure Science of Columbia University.

[2] Truttwin, "Enzyklopadie der Kupenfarbstoffe," Springer, Berlin, 1920.

have been converted into thioindigo dyes but that no derivative containing an isopropyl group has been used. It was thought that *p*-cymene, which is produced in large quantities as a by-product in the sulfite paper industry, could be used as a starting material for the production of methyl isopropyl thioindigo dyes.

The simplest thioindigo was first prepared by Friedländer[3] by the application of the Badische modification of the Heumann synthesis for indigo to thiosalicylic acid. Condensation with chloro-acetic acid gives the desired grouping, namely, *o*-carboxyphenylthioglycolic acid. In the preparation of highly substituted derivatives, anilines containing the desired groups are usually employed. The ortho sulfur atom is introduced through a sulfonic acid group or by the Hofmann reaction. The amino group is then converted to the carboxyl by the Sandmeyer reaction and hydrolysis.

A very important industrial method for the production of *o*-aminophenylthioglycolic acids has been introduced by Herz.[4] Aromatic amines with an unsubstituted ortho position are condensed with sulfur chloride and the condensation product is caused to react with chloro-acetic acid. The resulting product is the desired substituted *o*-aminophenylthioglycolic acid. The amine is converted by the Sandmeyer reaction to the nitrile, which is then hydrolyzed and condensed to the thionaphthene. These compounds are employed to prepare a large number of sulfur-containing indigoid dyes. They may be oxidized to give thioindigos or condensed with isatin through the alpha or beta oxygen to give Thioindigo Scarlet or Ciba Violet derivatives and with acenaphthenequinone to give substituted Ciba Scarlets.

This paper presents the preparation of methyl isopropyl thioindigoid dyes from aminocymene by the sulfur chloride condensation method. 4-Methyl-6-chloro-7-isopropyl-3-hydroxythionaphthene produced by this method was condensed with isatin and acenaphthenequinone. The relative fastness properties are reported using the commercial dye made from *o*-toluidine as a standard. Spectrum analyses are also reported and the effect of the isopropyl group is a shift of nine millimicrons in the direction of the longer wave lengths.

The method followed in the synthesis of these dyes may be represented as indicated in the Flow Sheet.

Experimental Part

Preparation of Materials.—The cymene used for this work was prepared by steam distillation of the spruce turpentine after two hours aeration at room temperature in the presence of aqueous caustic. At first the distillate was colorless and contained 37% of oil by volume. The distillation was continued until the oil had a slight yellow color and the rate had fallen to 17% oil. The average yield was 67.5%. A distillation test

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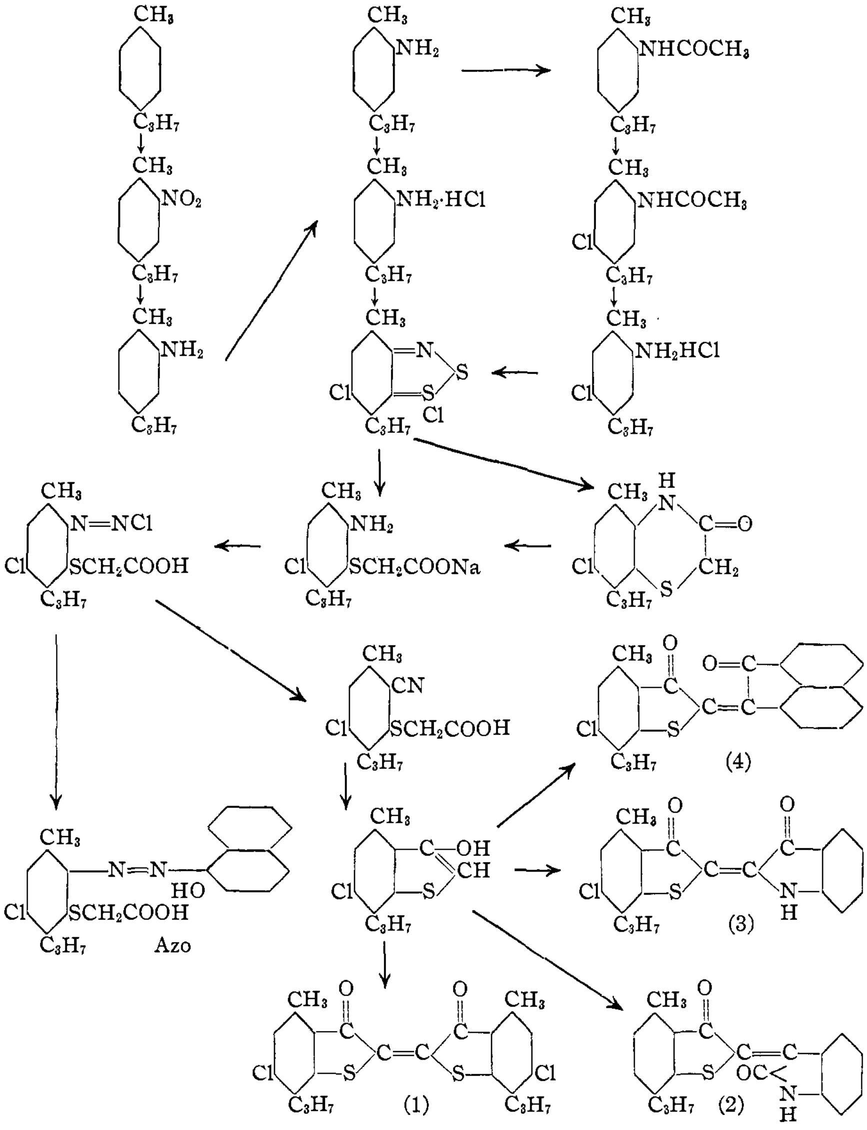
[3] Friedländer, *Ber.*, **39**, 1060 (1906).

[4] Herz, German Patent 360,690.



FLOW SHEET

showed that 80% of the oil distilled between 173.8–177.5°. The oil was not further purified for nitration.

The nitration of cymene was carried out as outlined by Demonbreun and Kremers.[5] The crude nitrocymene was purified by distillation at 6 mm. and the fraction boiling between 105–127° was separated. The greater portion of this fraction boiled between 112–120°. The yield was 54.6%.

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[5] Demonbreun and Kremers, *J. Am. Pharm. Assocn.*, **12**, 296 (1923).

Aminocymene was prepared by the standard iron reduction with a yield of 88.8%. Since the amine was wanted as the hydrochloride, it was dissolved in benzene and precipitated with hydrochloric acid gas.

Condensation Product of Aminocymene and Sulfur Chloride.—Sulfur chloride (210 g.) was placed in a one-liter flask equipped with an agitator, reflux condenser and gas outlet. After cooling to 20°, 30 g. of aminocymene hydrochloride was added as fast as it could be incorporated by the agitator. The mass was stirred for three hours under these conditions and allowed to stand overnight at room temperature. The next morning it was heated to 50° and held until the evolution of hydrochloric acid had ceased. An equal volume of benzene was added and cooled to 30°. The condensation product crystallized in orange-red plates. It was separated by filtration and washed free from sulfur chloride with dry benzene. The cake was dried *in vacuo* at 50° and the yield was 38 g. or 84% of the theoretical based on $C_{10}H_{11}NS_2Cl_2$.

Since the condensation mass became very thick during the heating period and required constant attention, the amount of sulfur chloride was increased to ten parts. This increase gave a much smoother reaction but a smaller yield, 77.5%.

The compound is a bright orange-red powder which slowly changes to brown. It is hydrolyzed by water with the removal of one chlorine atom, and by alcohol, in which the hydrolysis product is soluble. It is soluble in benzene, toluene, acetic acid and other organic solvents with which it does not react. It was purified by dissolving in glacial acetic acid and precipitating with ether. The purified product gave the following analysis.

Anal. Calcd. for $C_{10}H_{11}NS_2Cl_2$: S, 22.82; Cl, 25.35; Cl/S, 1.11. Found: S, 22.08; Cl, 24.52; Cl/S, 1.11.

The material charred at 120° without melting.

The filtrate and benzene washings from the condensation was fractionated and 43% of the sulfur chloride was recovered. The total benzene recovery was 91%.

5-Chloro-2-aminocymene-3-thioglycolic Anhydride.—The sulfur chloride condensation product (16.8 g.) was added to 120 cc. of water at 10°. The suspension was well agitated for two hours, during which time the material turned to a gray precipitate with a colorless supernatant liquor. The hydrolysis product was separated by filtration and washed free of acid with cold water. The cake was suspended in 150 cc. of cold water and 25 cc. of a 40% caustic soda solution was added. A neutralized solution of 8.5 g. of chloro-acetic acid in 50 cc. of water was added and it was heated to 45°. After one-half hour at this temperature the yellow solution was filtered from solid impurities and acidified with sulfuric acid. The precipitated acid was converted to the anhydride by heating to 70°. It was filtered and washed first with water and then with dilute ammonia. The yield was 12.1 g. or 79% of the theoretical.

The material was purified by crystallization from benzene. The product was obtained as fine white crystals soluble in organic solvents, insoluble in water, dilute acids and alkalies. It melted at 159.0–159.8°.

Anal. Calcd. for $C_{12}H_{14}ONSCl$: Cl, 13.92; S, 12.57; N, 5.48. Found: Cl, 13.89; S, 12.33; N, 5.50.

The anhydride ring can be opened to the acid by heating with 40% caustic soda solution (containing an amount of caustic equal to the weight of anhydride) at 120°. The anhydride first melts and then solidifies as the sodium salt.

Allocation of the Chlorine Atom Introduced during the Sulfur Chloride Condensation.—Herz[4] states that if the amine contains an unsubstituted para position, a chlorine atom will be introduced during the sulfur chloride condensation. Analysis of the condensation product showed the presence of two chlorine atoms, one of which could not be removed by hydrolysis. The thioglycolic anhydride indicated chlorination either in the nucleus or the side chain. The anhydride ring was opened with caustic soda as previously described but the time was extended thirty minutes. The salt was dissolved in water, filtered from insoluble impurities and converted back to the anhydride. Chlorine analysis showed that the substitution was in the nucleus.

If the above substitution theory is correct, then *p*-chloro-aminocymene should give the same condensation product and anhydride. This procedure was thought to be the best method of attack for the solution of this problem. The *p*-chloro-aminocymene was prepared by the method reported by Wheeler and Giles[6] and converted to the thioglycolic anhydride. The anhydrides obtained from aminocymene and *p*-chloro-aminocymene were identical, as shown by analyses, melting point and mixed melting point. The position of the chlorine atom is therefore established, being assigned to the 5-position or para to the amino group.

TABLE I

SUMMARY OF THE ANALYSES OF THE ANHYDRIDES

	Cl	S	N	M. p., °C.
Calcd.	13.92	12.57	5.48	......
Aminocymene	13.89	12.33	5.50	159.0–159.8
Chloro-aminocymene	13.90	12.50	..	159.8
Mixed	...	...	..	159.8

Diazotization of 5-Chloro-2-aminocymene-3-thioglycolic Acid.—A solution of the sodium salt which was obtained from an experiment similar to the one described under the preparation of the anhydride was filtered and to the clear solution, which contained 0.045 mole, was added 3.45 g. of sodium nitrite dissolved in 20 cc. of water. This solution was added through a dropping funnel to 50 cc. of water, 50 g. of ice and 15 cc. of hydrochloric acid. The temperature was held at 10° by means of an external ice-bath. The diazo solution was filtered and diluted to 500 cc.

Efficiency.—A β-naphthol solution containing 0.00139 mole as the sodium salt was titrated with the above diazo solution. Twenty-one cubic centimeters of the diazo solution was required, which gives an efficiency of 73.4%.

Azo Dye.—Two hundred and fifty cubic centimeters of the diazo solution after neutralization was added to a cold solution of 2.5 g. of β-naphthol in 100 cc. of water plus enough caustic soda to give a clear solution. The dye formed immediately and was coagulated with acetic acid. It was separated by filtration, washed and dried. The yield was 7.0 g. or 99.4% of the theoretical. The crude dye was crystallized from acetic acid and the pure compound was obtained as long red needles with a metallic reflex.

Anal. Calcd. for $C_{22}H_{21}O_3N_2SCl$: Cl, 8.27; S, 7.48. Found: Cl, 8.28; S, 7.50.

Preparation of 2-Cyano-5-chlorocymene-3-thioglycolic Acid and 4-Methyl-6-chloro-7-isopropyl-3-hydroxythionaphthene.—The conversion of the aminophenylthioglycolic acid to the cyano derivative may be applied to the sodium salt obtained either from the anhydride or from the chloro-acetic acid condensation. The reaction is very sensitive to sulfite, sulfide and hydroxyl ions. The sulfite and sulfide ions were

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[6] Wheeler and Giles, THIS JOURNAL, **44**, 2605 (1922).

removed by salting out the sodium salt with sodium chloride at 10° and washing the cake with cold saturated brine. The hydroxyl-ion concentration was adjusted by the addition of dilute acetic acid.

A solution (1.5 liters) containing 0.31 mole of the sodium salt prepared from 0.392 mole of the sulfur chloride condensation product was cooled to 10° and saturated with sodium chloride. The precipitated salt was filtered and washed with cold saturated brine. The washed product was dissolved in warm water and diluted to 765 g. Twenty-five grams of this solution was acidified and converted to the anhydride, which was weighed. It was 10% by weight. The remainder of the solution (740 g. or 0.29 mole) was diazotized by the method previously described. The neutral diazo solution was added to the cyanide and adjusted to *P*H 6.1 using chlor phenol red as indicator. The reaction mass was heated to 50° and held for thirty minutes. The stirring was stopped and the material allowed to stand overnight at room temperature. The clear supernatant liquor was acidified with hydrochloric acid. The cuprous cyanide and nitrile were separated and the nitrile was extracted with dilute sodium carbonate. The carefully neutralized solution was separated from the precipitated tar and after saturating with sodium chloride the sodium salt of the nitrile separated as long white needles. It was purified by recrystallization from water and converted to the free acid. The nitrile separated as a light tan-colored oil.

Anal. Calcd. for $C_{13}H_{14}O_2NSCl$: S, 11.30. Found: S, 11.76.

The tar which precipitated during the evolution of the nitrogen and contained the greatest portion of the nitrile was isomerized at 80° with dilute caustic soda and transferred to a mechanically agitated apparatus to which was connected a reflux condenser and oil separator. It was refluxed with a 25% sulfuric acid solution and the thionaphthene distilled as a colorless oil which assumed a red color due to atmospheric oxidation. The rate was about 5 g. in eight hours. The yield was 19.5 g. or 39.8% of the theoretical on the diazo salt.

The thionaphthene is a colorless oil heavier than water, in which it is insoluble. It is soluble in organic solvents and caustic soda, with which it forms a sodium salt. It cannot be distilled at atmospheric pressure without decomposition but distils readily at 10 mm. The fraction boiling between 191–193° at 10 mm. was separated for analysis.

Anal. Calcd. for $C_{12}H_{13}OSCl$: S, 13.30. Found: S, 13.31.

An interesting observation was made on this oil. When sealed in glass tubes at atmospheric and 10 mm. pressure and exposed to sunlight the red color of the oil at reduced pressure was discharged in five to seven minutes and after standing in the dark for twelve hours returned to its former intensity. The action of sunlight on vat dyes is generally considered to be a reduction of the dye to the leuco compound. In an atmosphere deficient in oxygen the color of this oil was discharged due to the reduction of the dissolved dye to the colorless leuco.

Dyes from 4-Methyl-6-chloro-7-isopropyl-3-hydroxythionaphthene

4,4-Dimethyl-6,6-dichloro-7,7-di-isopropyl-2,2-*bis*-thionaphthene Indigo. 1.[7]—Thionaphthene was dissolved in ten parts of 5% caustic soda solution and heated to 60°.[8] One-half part of sulfur was added and the heating continued until the dye was completely precipitated. It was separated by filtration, washed and dried. The yield was quantitative.

The dye was purified for analysis by crystallization from xylene, from which it was obtained as fine red crystals. It is sparingly soluble in high-boiling organic solvents.

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[7] The numbers after the names of the dyes refer to the flow sheet.

[8] Fierz, "Kunstliche Organische Farbstoffe," Springer, Berlin, **1926**, p. 461.

Anal. Calcd. for $C_{24}H_{22}O_2S_2Cl_2$: S, 13.42; Cl, 14.88. Found: S, 13.35; Cl, 14.71.

4-Methyl-6-chloro-7-isopropyl-2-thionaphthene-3-indol Indigo. 2.—Thionaphthene (1.76 g.) and isatin (1 g.) were dissolved in 30 cc. of acetic acid[9] and heated to 90°. The catalyst (two drops of hydrochloric acid) was added and held at 90° for thirty minutes. The dye, which separated in fine red crystals, was filtered and recrystallized from xylene. The yield was 1.7 g. or 63%.

Anal. Calcd. for $C_{20}H_{16}NO_2SCl$: S, 8.67; Cl, 9.61. Found: S, 8.65; Cl, 9.41.

4-Methyl-6-chloro-7-isopropyl-2-thionaphthene-2-indol Indigo. 3.—Isatin (1.35 g.) was dissolved in 50 cc. of benzene with 1.9 g. of phosphorus pentachloride to form isatin chloride,[10] which was added to 1.76 g. of thionaphthene dissolved in 200 cc. of benzene at 50°. The violet dye which formed immediately was separated and recrystallized from xylene. The yield was 2.4 g. or 89%.

Anal. Calcd. for $C_{20}H_{16}NO_2SCl$: S, 8.67. Found: S, 8.52.

4-Methyl-6-chloro-7-isopropyl-2-thionaphthene-acenaphthene Indigo. 4.—Thionaphthene (0.95 g.) and acenaphthenequinone (0.7 g.) were dissolved in 30 cc. of acetic acid and heated to 90°.[11] Two drops of hydrochloric acid was added and the reaction held at 90° for thirty minutes. The dye was separated and crystallized from xylene with a yield of 1 g. or 64%.

Anal. Calcd. for $C_{24}H_{17}O_2SCl$: S, 7.92. Found: S, 7.82.

Properties of Dyes

Solubility.—These dyes are insoluble in water, dilute acids and alkalies and salts with the exception of alkaline hyposulfite, with which they form the vat.

Fastness.—The relative fastness to light was determined by exposing them for seventy-two hours to an ultraviolet lamp (used less than 200 hours) at a distance of eighteen inches.

The fastness to washing was determined by applying the standard test except that the time was increased from five to ninety minutes.

TABLE II

PROPERTIES OF DYES

No.	Color in H_2SO_4	Color of vat	Color in xylene[a]	Wash test	Fastness to light	Color of crystals
FF[a]	Green	Yellow	Pink y	Exc.[a]	Exc.	Red
I	Green	Yellow	Pink y	Good	Exc.	Red
2	R violet	Colorless	Orange	Good	Fair	Orange
3	B green	Yellow	Violet	Exc.	Good	B black
4	Green	Violet	Yellow y	Good	Fair	Red
Azo	Red	......	Yellow	...	...	Red

[a] y after color in xylene denotes yellow fluorescence. FF is the commercial dye made from *o*-toluidine. Exc. for excellent.

Spectrum Analyses.—These analyses were made with a Koenig–Martens spectrophotometer using xylene as the solvent.

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[9] German Patent 205,377.

[10] Bezdzik and Friedländer, *Monatsh.*, **29**, 377 (1908).

[11] Bezdzik and Friedländer, *ibid.*, **30**, 284 (1909).

TABLE III

SPECTRUM ANALYSES OF DYES

No. of dye	FF[a]	1	2	3	4	Azo
Wave length, millimicrons	540	549	503 514	576	478 514	465 496

[a] The value given for FF (Ref. 8, p. 464) is 540.

The authors acknowledge their indebtedness to Dr. B. Kurrelmeyer, Department of Physics, Columbia University, for his helpful suggestions during the spectrum analyses of these dyes.

Summary

1. A number of new sulfur derivatives were prepared from aminocymene.
2. The position of the chlorine atom introduced into the nucleus during the sulfur chloride condensation of aminocymene hydrochloride was determined.
3. A new azo dye was prepared.
4. Four new thioindigoid dyes containing an isopropyl group were prepared.
5. Fastness tests and spectrum analyses of the dyes were made.
6. The effect of the isopropyl group was found to be a shift of nine millimicrons in the direction of the longer wave lengths.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL ENGINEERING, COLUMBIA UNIVERSITY]

METHYL ISOPROPYL THIOINDIGOID DYES FROM PARA-CYMENE. II. DYES FROM SODIUM CYMENE SULFONATE[1]

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Introduction

The original Heumann synthesis of indigo may be applied to thiophenols for the preparation of thioindigo dyes and this method is now employed in the industry on substituted thiophenols. These compounds are usually prepared by the reduction of the corresponding sulfonyl chlorides or by the action of potassium ethyl xanthate on diazotized amines. After condensing with chloro-acetic acid, the substituted phenylthioglycolic acids are internally dehydrated to the thionaphthene derivatives by chloro-sulfonic or sulfuric acids.

The application of this method to sodium cymene sulfonate would produce thioindigoid dyes which are isomeric with those prepared from amino-

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[1] This communication is an abstract of a portion of a thesis submitted by W. J. Cauwenberg in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, to the Faculty of Pure Science of Columbia University.