[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Investigations in the Retene Field. IV. The Synthesis of 6-Thioretenol and of Certain Related and Derived Compounds[1]

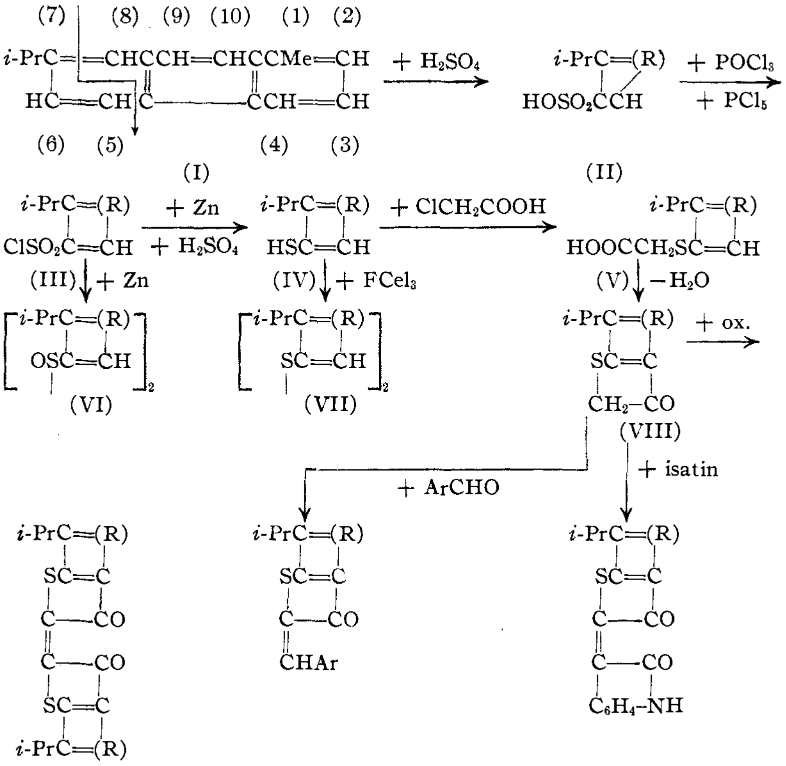
BY TORSTEN HASSELSTROM AND MARSTON TAYLOR BOGERT

In a previous article,[2] we recorded the fact that acetylretene can be condensed with aldehydes to chalcones, some of which possess tinctorial properties.

The present paper records some preliminary experiments carried out for the purpose of opening a path to a successful synthesis of thio-indigoids from retene (I).

The initial material was the B-retene sulfonic acid of Komppa and Wahlforss[3] and, in the Flow Sheet beyond, this acid is formulated according to the conclusions of Fieser and Young.[3b]

It was converted first into its sulfonchloride (III), by the action of a mixture of phosphorus oxy and pentachlorides, which yielded the thioretenol (IV) when reduced by zinc and hydrochloric acid or the disulfoxide (VI) when digested with zinc dust in benzene solution. The thioretenol was characterized by the preparation of its benzoyl derivative, and by oxidation with ferric chloride to its disulfide (VII). Condensed with chloroacetic acid, it gave the retylthioglycolic acid (V).



FLOW SHEET.—For economy of space, that portion of the retene formula (I) to the right of the arrow is indicated in the subsequent formulas by (R).

When this thioglycolic acid was subjected to the action of chlorosulfonic acid, there resulted a very unstable thioindoxyl (VIII) and a disulfonic acid of the corresponding thioindigo (IX). This recalls the observation of Heymann[4] that indigo disulfo acid is formed when fuming sulfuric acid acts upon phenylglycine.

In alkaline solution, the thioindoxyl (VIII) oxidized almost immediately to an amorphous dark solid which resisted purification and hence could not be identified as the thioindigo (IX).

Like thioindoxyl itself,[5] the retene thioindoxyl (VIII) condensed readily with isatin, and with various aldehydes, to dark amorphous solids, which we were unable to purify, but which exhibited tinctorial properties. In the case of isatin, the product was probably the impure analog (XI) of Thioindigo Scarlet R;[6] and, where the aldehydes were used, the impure thioindogenides (X).

The micro-analysis of these retene derivatives was carried out by Dr. Donald Price, and proved to be difficult and troublesome. Our experience in this respect is not unique, for Bamberger and

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[1] Presented in abstract before the Division of Dye Chemistry, at the Washington Meeting of the American Chemical Society, March 29, 1933.

[2] Bogert and Hasselstrom, THIS JOURNAL, **53**, 3462 (1931).

[3] (a) Komppa and Wahlforss, *ibid.*, **52**, 5009 (1930); (b) Fieser and Young, *ibid.*, **53**, 4120 (1931); (c) Komppa and Fogelberg, *ibid.*, **54**, 2900 (1932).

[4] Heymann, *Ber.*, **24**, 1476 (1891).

[5] (a) Auwers and Arndt, *Ber.*, **42**, 537 (1909); (b) Friedländer, *Monatsh.*, **30**, 347 (1910); (c) Nödtling and Steuer, *Ber.*, **43**, 3515 (1910); (d) Pummerer, *ibid.*, **44**, 346 (1911); (e) Pummerer and Brass, *ibid.*, **44**, 1651 (1911); (f) Friedländer and Kielbasinski, *ibid.*, **44**, 3103 (1911); (g) Fries and Ehlers, *ibid.*, **56**, 1308 (1923); etc.

[6] Bezdzik and Friedländer, *Monatsh.*, **29**, 376 (1908).

Hooker[7] also report similar obstacles in their work in the retene field.

Acknowledgment.—Our thanks are due to Mr. Frank L. Fogarty, Vice-President of the Wood Chemical Products Co., Jacksonville, Fla., for a generous supply of crude retene.

Experimental

6-Retenesulfonic acid was obtained as described by Komppa and Wahlforss[3a] and by Fieser and Young,[3b] except that the sulfonation was conducted at 190° and was complete in two minutes. The yield of the colorless crystalline dry potassium salt from 50 g. of retene was 52 g. By the action of a mixture of phosphorus oxy and pentachlorides upon this salt, following the method of Komppa and Wahlforss, the 6-retenesulfonchloride (III) was secured in pale yellowish needles (from benzene), m. p. 146–147.5° (corr.); yield, 17 g. from 25 g. of potassium sulfonate. Komppa and Wahlforss gave the melting point of this sulfonchloride as 146.5–148°.

6-Thioretenol (6-Retylmercaptan) (IV).—To a mixture of 400 g. of ice and 140 g. of concentrated sulfuric acid, cooled to 0°, there was added 40 g. of the crude sulfonchloride (III), followed by 80 g. of zinc dust in small portions, while the mixture was kept at −3 to 0° and vigorously stirred for an hour. It was then boiled for seven hours, cooled, the precipitate filtered out, extracted with ether, the ether extract dried and the solvent evaporated. The crude thioretenol remained as a pale yellowish oil; yield, 32 g.

This product oxidized rapidly in the air on standing and gradually separated crystals which, when recrystallized first from ethyl alcohol and then from benzene, formed colorless scales, m. p. 226.5–227.5° (corr.), and this melting point was not altered when these crystals were mixed with crystals of the disulfide (VII) prepared as described beyond.

Benzoyl Derivative.—To a mixture of 20 cc. of pyridine and 10 g. of benzoyl chloride, there was added 2 g. of the thioretenol at room temperature and, after standing overnight, the whole was extracted with ether, the ether extract washed with dilute hydrochloric acid, with water, and finally with dilute sodium carbonate solution. Evaporation of the ether left a brownish solid, which was dissolved in hot alcohol. As this solution cooled, the benzoyl derivative separated in small nearly colorless flakes; yield, 1.5 g. Recrystallized from alcohol, it melted at 115.5–116.5° (corr.).

Anal. Calcd. for $C_{25}H_{22}OS$: C, 81.08; H, 5.95. Found: C, 80.75; H, 5.87.

6-Retyl Disulfide (VII).—To a solution of 1.5 g. of crude thioretenol in 100 cc. of alcohol, there was added 45 g. of finely pulverized ferric chloride. The mixture was shaken for an hour, poured into water, the solid material filtered out and crystallized, first from alcohol and then from benzene, giving colorless scales, m. p. 226.5–227.5° (corr.); yield, 1 g.

Anal. Calcd. for $C_{36}H_{34}S_2$: C, 81.5; H, 6.4. Found: C, 81.76; H, 6.95.

6-Retyl Disulfoxide (VI).—A solution of 4 g. of the sulfonchloride (III) in 40 cc. of benzene was prepared and to it were added 5 cc. of water and 7 g. of zinc dust. After boiling this mixture for three hours under a reflux, the benzene was distilled off and the residue extracted with a dilute sodium carbonate solution. From this alkaline solution there separated, on standing, 3.2 g. of a microcrystalline precipitate. This precipitate was treated with hydrochloric acid and extracted with ether. The solid recovered from the ether extract crystallized from alcohol in small colorless needles, m. p. 142.5–143.5° (corr.), insoluble in a sodium carbonate solution.

Anal. Calcd. for $C_{36}H_{34}O_2S_2$: C, 76.6; H, 6.4. Found: C, 76.81; H, 6.30.

It had been expected that this reaction would result in the production of the sulfinic acid, but apparently the latter, if formed initially, immediately underwent the following change, $3RSO_2H \longrightarrow RSOSOR + RSO_2OH + H_2O$, a transition which has been observed before[8] in the case of unstable sulfinic acids.

6-Retylthioglycolic Acid (V).—To a solution of 10 g. of thioretenol in 250 cc. of water and 20 cc. of a 40% potassium hydroxide solution, containing also a small amount of sodium hydrosulfite to prevent oxidation and warmed to 70°, there was added sodium chloroacetate (prepared from 8.5 g. of the free acid) dissolved in a small quantity of water and the heating of the mixture was continued for an hour. It was then allowed to cool, acidified with dilute hydrochloric acid, the crystalline precipitate collected, dried at room temperature and crystallized from benzene. Colorless glistening scales were thus obtained, m. p. 138.5–139.5° (corr.), which darkened on standing in the light; yield, 12.5 g.

Anal. Calcd. for $C_{20}H_{20}O_2S$: C, 74.07; H, 6.17. Found: C, 73.7; H, 6.1.

Methyl - isopropyl - naphthothioindoxyl (Ketodihydro-6-retothiophene) (VIII).—To 20 cc. of chlorosulfonic acid cooled below 0°, 2 g. of the thioglycolic acid (V) was added in small portions during two minutes. The mixture was then poured upon ice, the precipitate extracted with ether (to free it from insoluble tarry material), the ether extract dried and the ether distilled off. The residual crude thioindoxyl (0.6 g.) was a yellow oil, not volatile with steam, which congealed to a yellow crystalline solid as it cooled, but rapidly oxidized in the air, especially in alkaline solution, to a reddish-black amorphous solid.

This thioindoxyl was insoluble in the ordinary solvents and could not be obtained analytically pure. Similar difficulties have been encountered in the rosindole[9] and the tetraindole-ethene derivatives.[10]

It condensed with isatin, and with benzaldehydes, to amorphous solids, which functioned as dyes in hydrosulfite vats, but could not be satisfactorily purified.

6-Retenethioindigo Disulfonic Acid.—The tarry material noted above which remained as an insoluble residue after the ether extraction of the crude thioindoxyl (VIII) dissolved freely in water to a deep bluish-green solution.

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(7) Bamberger and Hooker, *Ann.*, **229**, 151 (1885).

(8) (a) Pauly and Otto, *Ber.*, **10**, 2182 (1877); (b) *ibid.*, **11**, 2070 (1878); (c) Hinsberg, *ibid.*, **41**, 2836, 4294 (1908).

(9) Fischer and Wagner, *ibid.*, **20**, 815 (1887).

(10) Hasselstroem, *Ann. Acad. Sci. Fennicae*, XXX, **13**, 6 (1929).

It was precipitated by dilute hydrochloric acid, redissolved in dilute potassium hydroxide solution, reprecipitated by hydrochloric acid, washed repeatedly with dilute hydrochloric acid, dried, dissolved in alcohol (to a deep red solution) and precipitated by the addition of ether as a microcrystalline greenish-black, solid. It was somewhat hygroscopic and still impure.

Anal. Calcd. for $C_{40}H_{32}O_8S_4$: C, 62.5; H, 4.2. Found: C, 60.88; H, 4.50.

6-Retenethioindigo (IX).—When 1 g. of the crude thioindoxyl (VIII) was suspended in 100 cc. of a 5% sodium hydroxide solution, it oxidized almost immediately to the thionindigo. The mixture was boiled for ten minutes, cooled, the amorphous greenish-black precipitate removed and dried at room temperature. It was insoluble in the usual neutral organic solvents or in dilute mineral acids. In chloroform, glacial acetic acid or nitrobenzene, it dissolved slightly to a reddish solution, from which it was reprecipitated as a reddish-black amorphous solid by the addition of alcohol. Its purification was exceedingly troublesome. It was dissolved in a large volume of chloroform, precipitated by the addition of alcohol, washed on the filter with dilute hydrochloric acid, water, alcohol, and finally ether. This procedure was repeated thrice, and the product was then ashless when burned, but still very impure.

It dissolved with difficulty in an alkaline sodium hydrosulfite solution to a brownish vat which dyed cotton a bluish-green.

6-Retothiophene-3-indole-indigo (XI).—A solution of 0.6 g. of the crude thioindoxyl (VIII), 0.5 g. of isatin and 20 cc. of boiling glacial acetic acid, was allowed to cool to room temperature. Ten drops of concentrated hydrochloric acid were added and the mixture was heated for a few minutes. Addition of water precipitated the dye completely. It was filtered out, washed with water, then with alcohol and dried, when it appeared as a dark red amorphous powder, which could not be crystallized from any of the solvents tried.

Like analogous compounds in the simple indigo series,[9,10] it retained the solvent very tenaciously, and at higher temperatures (120° and above) evolved acetic acid vigorously. In alkaline sodium hydrosulfite, it formed a yellowish vat which dyed cotton reddish shades.

Thioindogenides (X) were prepared from the crude thioindoxyl and various aldehydes, essentially as described above for the isatin condensation product (XI), and proved equally difficult of purification. They were dark amorphous solids, which formed yellowish vats with alkaline hydrosulfite solution and dyed cotton the following shades: benzaldehyde, yellow; *p*-hydroxybenzaldehyde, orange; and *p*-dimethylaminobenzaldehyde, reddish.

Summary

6-(or B-)Retenesulfonic acid has been converted into its sulfonchloride, the corresponding thioretenol, retyl disulfoxide, disulfide, thioglycolic acid, thioindoxyl, and certain derivatives of these, some of which possess tinctorial properties.

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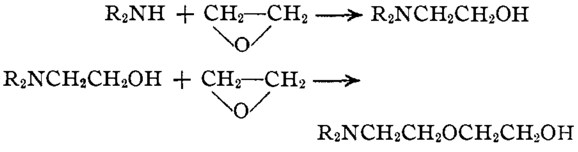
The Local Anesthetic Action of Dialkylaminoethoxyethyl *p*-Aminobenzoates

BY LEONE A. RUBERG AND R. L. SHRINER

The structural variations which have been made in compounds of the novocaine type (formula I) have had for their purpose the securing of a molecule which would possess low toxicity, high anesthetizing power, and no irritation. A study of local anesthetic action of *p*-aminobenzoates of the type of formula II showed that introduction of the ether linkage in the side chain conferred on the molecule the ability to cause surface anesthesia as well as injection anesthesia.[1] It was also established that the compound where $n = 1$ possessed pharmacological properties superior to those of compounds where $n = 0$, 2, 3 or 4. The present work had for its purpose the preparation of compounds of structure III which contain only one ether linkage, but in which the R groups were varied from methyl to butyl in order to determine how the alkyl groups attached to the nitrogen influenced the pharmacological action of this series of esters.

I (p) $H_2NC_6H_4COO(CH_2)_nNR_2$
II (p) $H_2NC_6H_4COO(CH_2CH_2O)_nCH_2CH_2N(C_2H_5)_2$
III (p) $H_2NC_6H_4COOCH_2CH_2OCH_2CH_2NR_2$

The requisite dialkylaminoethoxyethanols were prepared by the reaction between secondary amines and ethylene oxide. The reaction



$$R_2NH + \underset{\diagdown O \diagup}{CH_2\text{—}CH_2} \longrightarrow R_2NCH_2CH_2OH$$

$$R_2NCH_2CH_2OH + \underset{\diagdown O \diagup}{CH_2\text{—}CH_2} \longrightarrow R_2NCH_2CH_2OCH_2CH_2OH$$

requires two moles of ethylene oxide, but the products consist of a mixture of the compounds[2] re-

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(1) Horne and Shriner, *J. Pharmacol.*, **48**, 371 (1933).

(2) Horne and Shriner, THIS JOURNAL, **54**, 2925 (1932); Headlee, Collett and Lazzell, *ibid.*, **55**, 1066 (1933).