74 g. (0.55 mole) of 1,1-difluoro-2,2-dichloroethylene (Genetron 1112, General Chemical Division) was heated in a sealed glass tube at 130° for 24 hr. The tube was cooled with Dry Ice, opened, and the light-yellow oil distilled through a 10-cm. Vigreux column. The yield of crude adduct was 66 g. (61%), b.p. 91–98° (2.5–3.0 mm). Redistillation through a 20-cm. Vigreux column gave 56 g. (52%) of product, b.p. 84–86° (1.5 mm.).

Anal. Calcd. for $C_{11}H_{10}F_2Cl_2$: C, 52.50; H, 3.98; Cl, 28.30. Found: C, 52.58; H, 4.01; Cl, 28.20.

[CONTRIBUTED FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

L(+)-2,3-Butanedithiol: Synthesis and Application to the Resolution of Racemic Carbonyl Compounds[1]

BY E. J. COREY AND RAJAT B. MITRA

RECEIVED APRIL 2, 1962

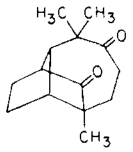
A four-step synthesis of L(+)-2,3-butanedithiol from D(−)-2,3-butanediol is reported. The applicability of the dithiol as an agent for resolution is illustrated by the preparation of dextro- and levo-forms of flavan-4-one and flavan.

The method previously described for the total synthesis of *d,l*-longifolene[2] in principle can be modified in a number of ways to allow the preparation of pure enantiomers. Of the numerous possibilities which were considered, one appeared to be by far the most attractive even though it had not previously been utilized and would require extensive preliminary study before application to the longifolene problem. This paper reports some details of this preliminary investigation which demonstrate the new technique.

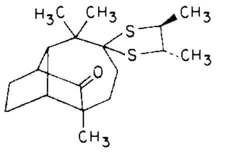
The tricyclic diketone I represented a particularly attractive intermediate for resolution in the longifolene synthesis, and, since the carbonyl group of the four carbon bridge must be reduced to a methylene group in the last stages of the process *via* a thioketal, it appeared advantageous to combine resolution and reduction, using a thioketal from an optically active 1,2-dithiol. 2,3-Butanedithiol seemed attractive as the dual-purpose reagent because of its probable accessibility.

The possibility of separating the diastereomeric thioketals II by vapor phase chromatography as well as by more conventional crystallization techniques provided further incentive.[3]

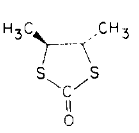
The synthesis of optically active L(+)-2,3-butanedithiol from the readily available (by fermentation[4]) D(−)-2,3-butanediol was carried out by the sequence:



I



II



III

D(−)-diol → D(+)-ditoluenesulfonate (*p*-toluenesulfonyl chloride–pyridine, 94% yield) → L(+)-dithiocyanate (potassium thiocyanate–dimethyl sulfoxide, 74% yield) → L(−)-2,3-*cyclo*-dithiocarbonate (hydriodic acid-phosphorus, 41% yield) → L(+)-dithiol (lithium aluminum hydride, 92% yield). Thiocyanate ion was chosen for the introduction of sulfur over the other possible sulfur nucleophiles because of the expectation that the introduction of the second sulfur substituent would be a critical step stereochemically. The possibility of internal nucleophilic displacement (participation of sulfur) at the stage of the 2-S-monosubstituted-3-toluenesulfonate, which would lead to racemic product, imposes the requirement that the sulfur substituent in this intermediate be a relatively poor nucleophile. On the basis of this consideration, thiocyanate ion seemed the most satisfactory nucleophile for the stereospecific introduction of sulfur with inversion of configuration at C_2 and C_3 in the butane chain. In fact, the reaction of thiocyanate ion with the bis-toluenesulfonate affords bis-thiocyanate of about 80% optical purity which indicates that even in the case of thiocyanate racemization occurs to an appreciable degree and hence that the choice of sulfur nucleophile is indeed critical. The limited amount of racemization encountered in the replacement process is only a minor disadvantage since the next intermediate in the synthetic sequence, L(−)-2,3-cyclo-dithiocarbonate (III), is a solid which can easily be recrystallized to a state of optical purity. Because III is crystalline, stable and easily converted to the optically active dithiol, we have found it convenient to accumulate this intermediate for subsequent conversion to 2,3-butanedithiol as needed.[5]

The applicability of L(+)-2,3-butanedithiol to the resolution of racemic ketones can be illustrated by the experiments in the flavan-4-one series which are shown in Fig. 1. Racemic flavan-4-one (IV) is readily and completely converted to a mixture of diastereomeric ketals which is easily separated by recrystallization; isomer VA is far less soluble than VB in benzene and the solubilities are reversed in methanol. Hydrolysis of the individual isomers VA and VB using mercuric chloride–mercuric oxide promoter in aqueous methanol afforded optically

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[1] This study was supported by the National Science Foundation, G-9999.

[2] E. J. Corey, M. Ohno, P. A. Vatakencherry and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961).

[3] For the resolution of *d,l*-camphor by vapor phase chromatography of the ketals derived from D(−)-2,3-butanediol, see J. Casanova, Jr., and E. J. Corey, *Chemistry & Industry*, 1664 (1961).

[4] A. C. Neish, *Can. J. Res.*, **23B**, 10 (1945); **25B**, 70 (1948).

[5] Two other routes to optically active 2,3-butanedithiol from the di-*p*-toluenesulfonate were investigated with unsatisfactory results: (1) *via* the diisothiuronium salt (see *Org. Syntheses*, **30**, 35 (1950)) and (2) *via* the cyclotrithiocarbonate (see A. Husemann, *Ann.*, **123**, 83 (1862)).

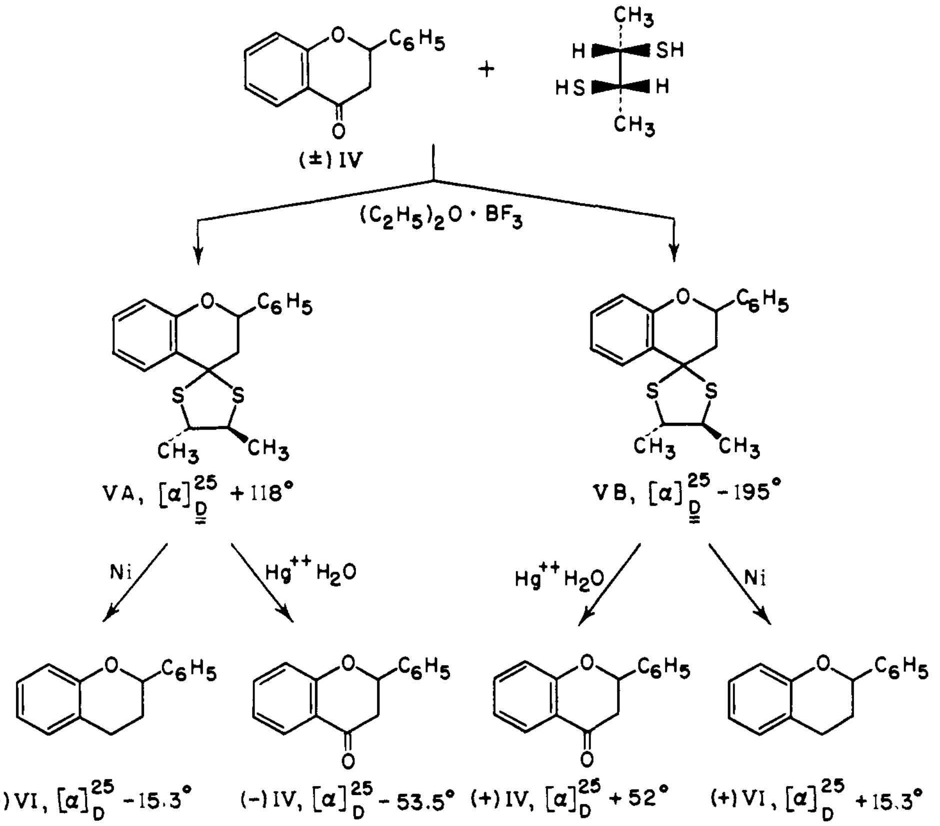

Fig. 1.

pure levo- and dextro-flavan-4-ones, respectively. Raney nickel desulfurization of VA and VB gave levo- and dextro-flavans (VI), respectively. The details of these procedures which are given in the Experimental section serve to clarify the suitability of this approach for other problems of synthesis resolution.[6] It should be noted, however, that the conditions of resolution, reduction and hydrolysis are all quite mild. The dimethylethylenethioketal grouping can also be removed reductively by the direct hydrazine–alkali treatment[7] as demonstrated by the conversion of 4-phenylcyclohexanone-dimethylethylenethioketal directly to phenylcyclohexane.

Thioketals were also prepared from L(+)-2,3-butanedithiol and (±)-camphor, (±)-norcamphor and (±)-menthone; however, in each case the product was liquid and not susceptible to separation by recrystallization. The derivative from (+)-camphor is also a liquid at room temperature. Nor could the diastereomeric thioketals be separated by vapor phase chromatography in these cases either on fluorosilicone (Dow Corning FS1265), silicone rubber or 1,2,3-tricyanoethoxypropane columns. From these facts two limitations on the usefulness of the dithiol resolving agent are clear: (1) the derivatives are in some instances of lower melting point than the ketones and may not be solids at room temperature and (2) the mixtures of diastereomeric dithioketals do not appear to be readily separable by vapor phase chromatography. Thus, the method would seem most applicable to ketones of higher molecular weight (on the order of 200 or above) with melting point well above room temperature.

Experimental[8]

D(+)-2,3-Butanediol Di-*p*-toluenesulfonate.—D(−)-2,3-Butanediol $[\alpha]^{25}_{D}$ −12.91°, neat, 1 dm. (21 ml., 22 g., 0.2445 mole) was added gradually to a stirred mixture of 100 g. (0.525 mole) of technical grade *p*-toluenesulfonyl chloride in 100 ml. (1.24 moles) of dry pyridine, cooled in an ice–water-bath. After about 20 min. the mixture set to a semi-solid mass and was allowed to stand overnight at room temperature. Excess of crushed ice–water was then added, the flask stoppered and shaken vigorously to prevent lump formation. Gradually, a fine crystalline suspension separated. The mixture was treated with ice-water, stirred mechanically for 2 hours and then poured with rapid stirring into a mixture of 70 ml. of concentrated hydrochloric acid and excess of crushed ice. The resulting slurry was filtered, washed thoroughly with water and dried to give 91.0 g. (93.5%) of product, m.p. 62–64°, $[\alpha]^{25}_{D}$ + 37.2° (*c* 2.105 in $CHCl_3$) (lit.[9] m.p. 65.1-65.5°, $[\alpha]^{25}_{D}$ +37.2° in $CHCl_3$). This material was satisfactory for the subsequent step.

L(+)-2,3-Dithiocyanobutane.—The ditosylate, 15 g., was added to a solution of 50 g. of potassium thiocyanate in 80 ml. dimethyl sulfoxide and the reaction mixture was stirred under nitrogen for 48 hours at 70–75° bath temperature and assayed by infrared analysis. After 8 hours only partial reaction had occurred, but after 48 hours all the tosylate had

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(6) A subsequent paper will describe the formation and separation of the longifolene intermediates II derived from *d,l*-I and L(+)-2,3-butanedithiol.

(7) V. Georgian, R. Harrison and N. Gubisch, *J. Am. Chem. Soc.*, **81**, 5834 (1959).

(8) All melting points are uncorrected. The infrared spectra were taken on a Perkin–Elmer Infracord machine. The vapor-phase chromatography was done with an F & M model 300 gas chromatograph. Microanalyses were done by the Scandinavian Microanalytical Laboratory.

(9) H. J. Lucas, F. W. Mitchell and H. K. Garner, *J. Am. Chem. Soc.*, **72**, 2138 (1950).

disappeared. The reaction mixture was poured into cold water, diluted to 600 ml. and extracted repeatedly with 3:1 pentane–methylene chloride. The organic extract was filtered to remove some insoluble yellow material, washed with water, dried and concentrated to give a crude yellow oil, 4.75 g. (74%), $[\alpha]^{25}_{\rm D}$ +76.8° (*c* 2.64 in $CHCl_3$).[10]

A small sample was distilled at 110–114° (bath) (0.2 mm.) to give an almost colorless liquid, $[\alpha]^{25}_{\rm D}$ +79.0° (*c* 2.775 in $CHCl_3$).

Anal. Calcd. for $C_6H_8N_2S_2$ (172.27): C, 41.86; H, 4.68. Found: C, 42.01; H, 4.85.

L(−)-4,5-Dimethyl-1,3-dithiolane-2-one (III).—A mixture of the foregoing crude dithiocyanate (4.45 g., $[\alpha]^{25}_{\rm D}$ + 76.8°), 30 ml. of 47% hydriodic acid and 1 g. of red phosphorus was heated to reflux at bath temperature 150° for 4 days. The mixture was cooled, diluted to 100 ml. with water and extracted with methylene chloride. The extract was filtered to remove phosphorus, washed with a saturated salt solution, dried and evaporated to give 2.185 g. (57%) of a slightly oily solid at room temperature, $[\alpha]^{25}_{\rm D}$ −147° (*c* 0.785 in $CHCl_3$).

One recrystallization from petroleum ether gave 1.50 g. (41%) of crystalline dithiocarbonate, m.p. 48–50°, $[\alpha]^{25}_{\rm D}$ −182.5° (*c* 1.04 in $CHCl_3$).

Two more recrystallizations from ether–petroleum ether gave the analytical specimen as shining colorless plates, m.p. 51–51.5°, $[\alpha]^{25}_{\rm D}$ −184.8° (*c* 0.450 in $CHCl_3$). The infrared spectrum showed strong bands at 6.02, 11.4 and 11.6 μ and a medium-intensity doublet at 5.7 and 5.8 μ (presumably overtones of the 11.4 and 11.6 μ bands).

Anal. Calcd. for $C_5H_8OS_2$ (148.24): C, 40.54; H, 5.44. Found: C, 40.75; H, 5.50.

It is noteworthy that ethylene dithiocarbonate has been reported[11] to have a single peak at 1638 cm.$^{-1}$ (6.1 μ), whereas, according to Angell,[12] ethylene carbonate exhibits a doublet of equal and strong intensity at 1774 and 1800 cm.$^{-1}$ in the liquid phase. This has been ascribed to an interaction of the C=O stretching frequency (around 1800 cm.$^{-1}$) with the first overtone (at 1780 cm.$^{-1}$) of the "skeletal breathing" vibration at 890 cm.$^{-1}$. In solution in CCl_4 and CS_4, the C=O stretching is shifted to 1825 and 1830 cm.$^{-1}$, and the 1780 cm.$^{-1}$ band is of only medium intensity; whereas, in the vapor phase, (C=O stretching at 1870 cm.$^{-1}$) there is no interaction at all and the 1780 cm.$^{-1}$ band is of very low intensity.

L(+)-2,3-Butanedithiol.—A solution of 9.0 g. of the dithiocarbonate (m.p. 49–51°, $[\alpha]^{25}_{\rm D}$ −185° in $CHCl_3$) in 50 ml. of dry ether was added dropwise to a cooled mixture of 6 g. of lithium aluminum hydride in 150 ml. of dry ether. The mixture was maintained at reflux for 4 hours, cooled, treated dropwise with water and acidified with hydrochloric acid. The ether layer was separated and the aqueous acid layer was thoroughly extracted with ether and the combined ethereal solution was washed with saturated salt solution, dried and distilled under vacuum to give the dithiol, 6.8 g. (92%), as a colorless liquid, b.p. 95° (80 mm.), $[\alpha]^{25}_{\rm D}$ + 14.2° (*c* 20.42 in $CHCl_3$), $\alpha^{25}_{\rm D}$ (neat +11.46° (1 dm. tube).

Anal. Calcd. for $C_4H_{10}S_2$: C, 39.34; H, 8.25. Found: C, 39.37; H, 8.29.

Diastereomeric Thioketals from (±)-Flavan-4-one and (+)-Butane-2,3-dithiol.—(±)-Flavan-4-one, 7 g., m.p. 77–78° (lit.[13] m.p. 76°), was added to 6.0 g. (1.56 equiv.) of L(+)-2,3-butanedithiol, $[\alpha]^{25}_{\rm D}$ + 14.2° in $CHCl_3$, and the mixture was warmed slightly to form a homogeneous solution. It was then cooled to room temperature and treated with 10 ml. of boron fluoride etherate. Gradually solid thioketal separated out. After 45 min. at room temperature the mixture was treated with excess of cold 10% sodium hydroxide solution and extracted with benzene. The benzene extract was washed with water, dried and evaporated to give 10.5 g. (quantitative) of solid thioketal mixture, m.p. 120–165°, $[\alpha]^{25}_{\rm D}$ −45° (*c* 0.69 in $CHCl_3$).

One recrystallization of the above mixture from 50 ml. of benzene gave 3.1 g., m.p. 184–190°, $[\alpha]^{25}_{\rm D}$ +70° in $CHCl_3$. Three further recrystallizations from benzene gave 1.77 g. (35%), m.p. 194–195°, $[\alpha]^{25}_{\rm D}$ +114° (*c* 1.47 in $CHCl_3$). This material was used for the subsequent hydrolysis and desulfurization. Exhaustive recrystallization of this material gave fully resolved thioketal, m.p. 195°, $[\alpha]^{25}_{\rm D}$ +118° (*c* 0.36 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{20}OS_2$: C, 69.50; H, 6.14. Found: C, 69.45; H, 6.12.

The mother liquor from the first recrystallization was concentrated and two further successive crops collected. The final mother liquors were evaporated to dryness to give material with $[\alpha]^{25}_{\rm D}$ −140° ($CHCl_3$), which after two recrystallizations from methanol gave 1.16 g. (23%), m.p. 139–140°, $[\alpha]^{25}_{\rm D}$ −192° (*c* 1.375 in $CHCl_3$). This was used for subsequent experiments. Further recrystallizations from methanol gave the pure (−)-isomer, m.p. 140–141°, $[\alpha]^{25}_{\rm D}$ −195° (*c* 0.33 in $CHCl_3$). The infrared spectrum was identical in all respects with that of the (+)-isomer.

(−)-Flavan-4-one.—A solution of 300 mg. of (+)-thioketal, m.p. 195°, $[\alpha]^{25}_{\rm D}$ + 114° in $CHCl_3$, in 125 ml. of methanol and 3 ml. of water was treated with excess of mercuric chloride and mercuric oxide and the mixture was heated to reflux on a steam-bath for 4 hours. Removal of the solvent, extraction with benzene and filtration gave after evaporation of the benzene a semi-solid residue which was thoroughly extracted with petroleum ether. The petroleum ether solution on evaporation gave 185 mg. (90%) of crude (−)-flavan-4-one, m.p. 65–70°. Recrystallization from petroleum ether furnished a pure sample as colorless needles, m.p. 77–78°, $[\alpha]^{25}_{\rm D}$ −53.5° (*c* 2.27 in $CHCl_3$).[14]

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.49; H, 5.43.

(+)-Flavan-4-one.—Prepared as described above from 132 mg. of (−)-thioketal, m.p. 139–140°, $[\alpha]^{25}_{\rm D}$ −192° in $CHCl_3$, the product was obtained as colorless needles, m.p. 76°, $[\alpha]^{25}_{\rm D}$ + 52° (*c* 0.75 in $CHCl_3$). The infrared spectrum was identical in all respects with that of the enantiomer.

(−)-Flavan.—A mixture of 300 mg. of (+)-thioketal, m.p. 195°, $[\alpha]^{25}_{\rm D}$ +114° in $CHCl_3$, and 2 g. of Raney nickel in 15 ml. of benzene was stirred at reflux temperature for 4 hours. Filtration, washing of the nickel with boiling benzene and removal of the benzene, gave 160 mg. (84%) of crude solid product. Recrystallization from methanol gave pure (−)-flavan, m.p. 60–61° (lit.[15] m.p. of the racemate, 44–45°), $[\alpha]^{25}_{\rm D}$ −15.3° (*c* 3.48 in $CHCl_3$).

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.58; H, 6.71.

(+)-Flavan.—A mixture of 300 mg. of (−)-thioketal, m.p. 139–140°, $[\alpha]^{25}_{\rm D}$ −192° ($CHCl_3$), and 2 g. of Raney nickel in 15 ml. of benzene was stirred under reflux for 4.5 hours. Working up as described in the preceding experiment gave 165 mg. (86%) of crude solid product. Recrystallization from methanol gave pure (+)-flavan, m.p. 59–61°, $[\alpha]^{25}_{\rm D}$ +15.3° (*c* 3.615 in $CHCl_3$). The infrared spectrum was identical in all respects with that of the enantiomer.

Thioketal of Cholestanone.—Cholestanone, 50 mg., was treated with 120 mg. of L(+)-2,3-butanedithiol and about 100 mg. of boron fluoride etherate at room temperature under nitrogen for 2 hours and then poured into excess of cold 10% sodium hydroxide solution, extracted with a 2:1 mixture of pentane–methylene chloride and worked up to give a semi-solid product which when triturated with methanol gave 63 mg. (100%) of crystalline product, m.p. 102.5–104.5°, $[\alpha]^{25}_{\rm D}$ +9.4° (*c* 2.1 in $CHCl_3$). This was recrystallized from methanol to give the analytical specimen, m.p. 103–104°.

Anal. Calcd. for $C_{31}H_{54}S_2$ (490.87): C, 75.84; H, 11.08. Found: C, 75.43; H, 10.90.

Thioketal of 4-Phenylcyclohexanone and Direct Wolff–Kishner Reduction.—To a solution of 52 mg. of 4-phenylcyclohexanone in 223 mg. of L(+)-2,3-butanedithiol was added about 250 mg. of boron fluoride etherate at 25°. After 2 hours at room temperature the thioketal was isolated in the usual way and obtained as a liquid. The crude thioketal, 104 mg., was treated with 1 ml. of hydrazine and 100 mg. of sodium in 3 ml. of dry ethylene glycol and the mixture

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(10) For conversion of (+)-2-butyl *p*-toluenesulfonate to (−)-2-butyl thiocyanate, with KSCN in EtOH, see J. Kenyon, H. Phillips and V. P. Pitman, *J. Chem. Soc.*, 1072 (1935).

(11) R. Mecke, R. Mecke and A. Luttringhaus, *Z. Naturforsch.*, **10B**, 367 (1955).

(12) C. L. Angell, *Trans. Faraday Soc.*, **52**, 1178 (1956).

(13) L. Reichel and K. Müller, *Ber.*, **74**B, 1741 (1941).

(14) This modification of mercuric-ion promoted thioketal hydrolysis is superior in this case to those previously described; *cf.* C. Djerassi, M. Shamma and T. Y. Kan, *J. Am. Chem. Soc.*, **80**, 4723 (1958).

(15) K. Hultzsch, *J. prakt. Chem.*, **158**, 275 (1941).

was heated at 190–195° for 12 hours. The reaction mixture was cooled, diluted with water and worked up to give 51 mg. (quantitative from phenylcyclohexanone) of phenylcyclohexane as a mobile liquid, identical with an authentic sample as shown by infrared absorption and vapor phase chromatography.

[CONTRIBUTION FROM THE BOUND BROOK LABORATORIES, AMERICAN CYANAMID CO., BOUND BROOK, N. J.]

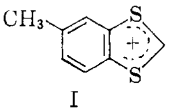
The 1,2-Dithiolium Cation. A New Pseudoaromatic System. II. Condensation of Phenyl-1,2-dithiolium Salts with Tertiary Aromatic Amines[1]

BY ERWIN KLINGSBERG AND ANN M. SCHREIBER

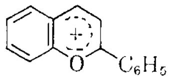
RECEIVED JANUARY 26, 1962

Phenyldithiolium salts condense with tertiary aromatic amines, giving rise to a new family of basic dyes, which may also be obtained from 1,2-dithiole-3-ones and 1,2-dithiole-3-thiones. Spectral properties are discussed.

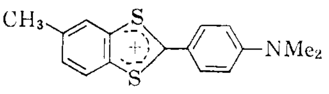
Electrophilic substitutions by pseudoaromatic cations constitute an interesting class of carbonium ion reactions, recently investigated by Wizinger and by Shriner. Thus dimethylaniline is attacked by the methylbenzo-1,3-dithiolium (I) and flavylium (II) cations to give the highly colored salts of III[2] and IV,[3a,b] respectively.



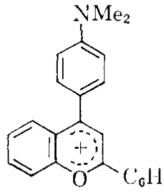
I



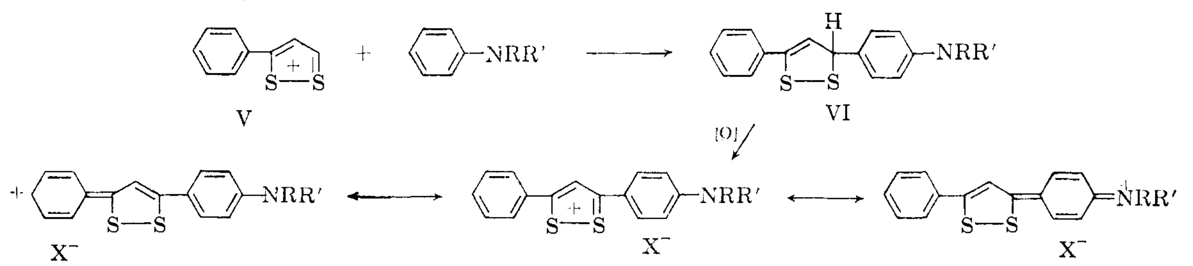
II



III



IV

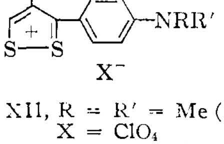


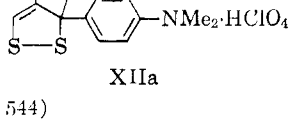
The recently discovered phenyl-1,2-dithiolium salts[4] also show electrophilic activity. Reaction occurs in a few minutes in warm ethanol with dimethylaniline or other tertiary aromatic amines, giving intense violet dyes readily isolated as perchlorates. Assignment of structure VIII and XII to these products is based on elementary analysis and the following considerations: Substitution in the phenyl ring *para* to the dimethylamino group was confirmed by the finding that N,N-dimethyl-*m*-toluidine reacted much like dimethylaniline, giving a very similar product, while N,N-dimethyl-*p*-toluidine did not react under the same conditions. As for the dithiolium ring, the natural expectation that substitution would occur at the positive 3- (or 5-) position rather than the neutral 4-position[4] is borne out by the finding that the 3- and 4-phenyldithiolium salts react under similar conditions to give products of similar character; the 4-phenyl isomer obviously cannot react at the 4-position.

Two additional syntheses of VIII provide further proof of structure and further analogies between the chemistry of the 1,2-dithiolium system and the older benzo-1,3-dithiolium (I) and flavylium (II) systems. Since flavone condenses with dimethylaniline in phosphorus oxychloride to give IV,[3a] it was of interest to demonstrate that under these conditions 5-phenyl-1,2-dithiole-3-one (XIV) gives VIII.

Secondly, Soder and Wizinger[2] recently have shown that III is obtained from the benzo-1,3-dithiole-2-thione (XV) *via* its methylsulfonium salt (XVI).

VII, R = R' = Me (λ_{max} 557)
VIIIa, X = ClO_4
b, X = I
IX, R = Me; R' = Ph (λ_{max} 550)
X = ClO_4
X, R = Me; R' = CH_2CH_2CN (λ_{max} 537)
X = ClO_4





XIIa

XII, R = R' = Me (λ_{max} 544)
X = ClO_4
XIII, R = Me; R' = CH_2CH_2CN
X = ClO_4 (λ_{max} 525)

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(1) Presented on March 27, 1962, at the 141st National Meeting of the American Chemical Society, Washington, D. C.

(2) L. Soder and R. Wizinger, *Helv. Chim. Acta*, **42**, 1779 (1959).

(3) (a) R. Wizinger and A. Luthiger, *ibid.*, **36**, 526 (1953). (b) R. L. Shriner, in "The Roger Adams Symposium," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 103.

(4) For the first paper in this series, see E. Klingsberg, *J. Am. Chem. Soc.*, **83**, 2934 (1961).