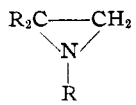
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Attempts to Prepare Optically Active Ethyleneimine Derivatives Containing an Asymmetric Nitrogen Atom

BY ROGER ADAMS AND T. L. CAIRNS[1]

The fact that many oximes exist in stable *syn-* and *anti*-forms and that the oxime of cyclohexanone-4-carboxylic acid[2] can be resolved has led to the belief that, in these compounds, the nitrogen atom probably exists in a stable tetrahedral form. The work of Meisenheimer[3] has established that many substituted hydroxylamines of the type RR'NOH cannot be resolved and the investigations of many others have failed to find an optically-active compound of the type RR'-R''N.

A factor which has been assumed to be responsible for the existence of a stable tetrahedral nitrogen atom thus resulting in stable *syn-* and *anti*-oximes is the strain of the carbon-to-nitrogen double bond. A molecule which reproduces this strain as closely as possible and, at the same time, is constituted so that the nitrogen atom is the only possible source of asymmetry in the molecule is represented by a substituted ethyleneimine of the type I.

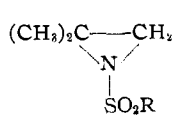


I

This report deals with the preliminary work on the synthesis of such a molecule and the determination of whether or not it may exist in optically-active forms.

It was found that the *p*-bromobenzenesulfonyl derivative of 1-amino-2-methyl-2-propanol (II) can be converted into the corresponding chloro compound (III) by means of concentrated hydrochloric acid. The chloro compound, when treated with aqueous alkali, yielded a mixture of the ethyleneimine derivative (IV) and the alcohol (II).

$(CH_3)_2COHCH_2NHSO_2R$
II
R = *p*-bromophenyl
$(CH_3)_2CClCH_2NHSO_2R$
III

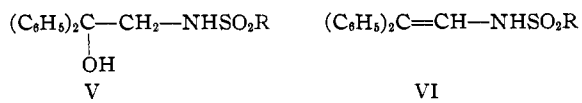


IV

Attempts were made to prepare an optically-active amide analogous to II by the use of camphorsulfonyl chloride or α-bromocamphorsulfonyl chloride. Unfortunately, these derivatives proved to be oils which could not be purified and were consequently unsuitable for further study. The corresponding diphenyl compound, aminomethyldiphenylcarbinol, also gave no crystalline α-bromocamphorsulfonamide.

A comparison of the action of aqueous alkali, under similar conditions, upon the *p*-bromobenzenesulfonyl derivative of β-chloroethylamine and the dimethyl compound (III) was studied. The former gave merely hydrolysis with the formation of 2-*p*-bromobenzenesulfonamidoethanol, whereas the latter gave essentially equivalent amounts of the alcohol (II) and the ethyleneimine derivative (IV). This result might have been anticipated from a consideration of the work of Thorpe.[4] He showed that the *gem*-dimethyl group in place of two hydrogens alters the subtended angle between the valence bonds of carbon in such a manner that the ease of formation of a three-membered ring is increased.

Attempts to convert the *p*-bromobenzenesulfonyl derivative of aminomethyldiphenylcarbinol (V) into an ethyleneimine derivative proved fruitless. The corresponding chloride could not be made by the regular procedure using thionyl chloride or hydrochloric acid. The action of thionyl chloride resulted in the formation of 1-*p*-bromobenzenesulfon-2,2-diphenylvinylamide (VI). This same compound was produced in excellent yields by the action of phosphorus pentoxide on V.



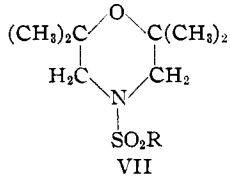
V VI

A reaction analogous to this has been reported by Krabbe[5] who found that similar products were formed by the action of certain acid chlorides or of phosphorus pentoxide on N-acyl derivatives of aminomethyldiphenylcarbinol.

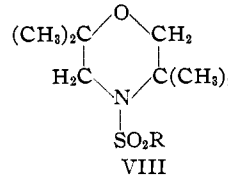
The action of phosphorus pentoxide on 1-*p*-bromobenzene-sulfonamido-2-methyl-2-propanol (II) gave neither the ethyleneimine (IV) nor the

(1) Solvay Process Company Fellow, 1938–1939.
(2) Mills and Bain, *J. Chem. Soc.*, **97**, 1866 (1910).
(3) Meisenheimer, *Ber.*, **65B**, 1799 (1932).
(4) Thorpe, "Annual Reports on the Progress of Chemistry," The Chemical Society, London, **22**, 127 (1925).
(5) Krabbe, *Ber.*, **72B**, 381 (1939).

vinylamine derivative corresponding to VI. Instead, a substance was produced which, by analysis and properties appeared to be a morpholine of structure VII or VIII.



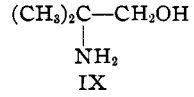
VII



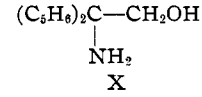
VIII

The action of sulfuric acid followed by alkali on ethanolamine has been reported to give ethyleneimine.[6] Upon treatment of 1-amino-2-methyl-2-propanol in a similar manner the reaction took a different course and β-methylallylamine was formed in good yields. Krabbe[5] found that aminomethyldiphenylcarbinol is converted by cold sulfuric acid into the corresponding vinylamine.

It is quite possible that the complications which have arisen in the formation of ethyleneimine derivatives may be avoided if the compounds IX and X are used. Under these conditions



IX



X

the possibility of dehydration to form an allylamine or a vinylamine derivative is unlikely and the synthesis of an ethyleneimine derivative should be possible.

During the preparation of this manuscript an article by Meisenheimer and Chou[7] has appeared describing attempts to prepare ethyleneimines for resolution studies. They were unsuccessful in obtaining the compounds desired, so that the possibility of resolving properly substituted ethyleneimines is still undetermined.

Experimental

2-*p*-Bromobenzenesulfonamidoethanol.—To a solution of 15 g. of ethanolamine in 150 cc. of water and 125 cc. of aqueous 10% sodium hydroxide solution, maintained at 50–70°, was added slowly 51 g. of *p*-bromobenzenesulfonyl chloride. Upon cooling the reaction mixture and acidification with hydrochloric acid an oil separated that solidified to a white crystalline solid. It was purified by recrystallization from dilute ethanol: white crystals, m. p. 93.5–95° (corr.); yield, 28 g. (59%).

Anal. Calcd. for $C_8H_{10}O_3BrNS$: C, 34.29; H, 3.57. Found: C, 34.59; H, 3.73.

2-*p*-Bromobenzenesulfonamido-1-chloroethane.—To 10 g. of 2-*p*-bromobenzenesulfonamidoethanol was added slowly 30 cc. of thionyl chloride and the mixture was then refluxed for thirty minutes. The solution was poured with rapid stirring into 300 cc. of crushed ice. The product was purified from methanol: white plates, m. p. 150–152.5° (corr.); yield, 3 g. (28%).

Anal. Calcd. for $C_8H_9O_2BrClNS$: C, 32.17; H, 3.01. Found: C, 32.12; H, 3.03.

When 3 g. of this product was shaken for fifteen minutes and then warmed on the steam cone for two hours with 200 cc. of water and 20 cc. of 10% aqueous potassium hydroxide hydrolysis took place. After filtration the filtrate, while still hot, was acidified with hydrochloric acid. White crystals of 2-*p*-bromobenzenesulfonamidoethanol separated.

1-*p*-Bromobenzenesulfonamido-2-methyl-2-propanol.—To a solution of 17.8 g. of 1-amino-2-methyl-2-propanol in 125 cc. of 10% aqueous sodium hydroxide, maintained at 50–80°, was added slowly 51 g. of *p*-bromobenzenesulfonyl chloride. The mixture was then cooled and acidified with dilute hydrochloric acid. After filtering and drying, the product was dissolved in 250–300 cc. of benzene and the solution distilled until a volume of 75–80 cc. remained. White crystals separated which were recrystallized from benzene, m. p. 96.5–98° (corr.); yield, 40 g. (96%).

Anal. Calcd. for $C_{10}H_{14}O_3BrNS$: C, 38.96; H, 4.58; N, 4.54. Found: C, 38.96; H, 4.50; N, 4.79.

When 6 g. of this product was heated under reflux for twenty minutes with 10 cc. of constant-boiling hydrobromic acid, a black oil separated. Steam distillation removed a small amount of a water-insoluble oil which was not identified. The residual solution in the distillation flask, after cooling, gave 4.5 g. (97%) of *p*-bromobenzenesulfonamide.

Action of Phosphorus Pentoxide upon 1-*p*-Bromobenzenesulfonamido-2-methyl-2-propanol, VII or VIII.—A solution of 5 g. of 1-*p*-bromobenzenesulfonyl-2-methyl-2-propanol in 100 cc. of dry benzene was refluxed for an hour with 20 g. of phosphorus pentoxide. The benzene was decanted and then steam distilled. The residual aqueous suspension was made up to a volume of 200 cc., boiled and filtered. A pale yellow solid (2.2 g.) was obtained which on crystallization from methanol gave white needles, m. p. 145–147° (corr.).

Anal. Calcd. for $C_{14}H_{20}O_3BrNS$: C, 46.4; H, 5.54; N, 3.87; S, 8.85. Found: C, 46.92; H, 5.53; N, 4.09; S, 8.95.

The filtrate from this product gave, on cooling, *p*-bromobenzenesulfonamide.

In attempting to prepare 1-*p*-bromobenzenesulfonamido-2-methyl-2-chloropropane from the alcohol by means of thionyl chloride, there was always obtained a small amount of the morpholine derivative as a by-product.

1-*p*-Bromobenzenesulfonamido-2-methyl-2-chloropropane.—A mixture of 24 g. of 1-*p*-bromobenzenesulfonamido-2-methyl-2-propanol was heated with 150 cc. of concentrated hydrochloric acid under reflux for ten minutes. Solution took place with simultaneous separation of a white solid. After dilution with one liter of water, the suspension was cooled and the product filtered and air-dried. It was purified by recrystallization from petroleum ether (b. p. 60–110°): white leaflets, m. p. 123–128° (corr.); yield, 21 g. (71%).

(6) Wenker, THIS JOURNAL, **57**, 2328 (1935).

(7) Meisenheimer and Chou, *Ann.*, **539**, 70 (1939).

Anal. Calcd. for $C_{10}H_{13}O_2BrClNS$: C, 36.70; H, 3.98. Found: C, 36.99; H, 3.97.

1-*p*-Bromobenzenesulfon-2,2-dimethylethyleneimide.—A mixture of 80 cc. of 10% aqueous sodium hydroxide and 18 g. of 1-*p*-bromobenzenesulfonamido-2-methyl-2-chloropropane was shaken vigorously for one hour. It was then warmed on the steam-cone for fifteen minutes during which time the solid present melted and collected as a yellow oil. On cooling, it resolidified and was purified from a mixture of petroleum ether (b. p. 40–60°) and chloroform: white cubic crystals, m. p. 79.5–81.5° (corr.); yield, 7.5 g. (46%).

Anal. Calcd. for $C_{10}H_{12}O_2BrNS$: C, 41.37; H, 4.13; mol. wt., 290. Found: C, 41.50; H, 4.06; mol. wt. (b. p. $CHCl_3$), 274.

This product is insoluble in aqueous alkali, does not react with a chloroform solution of bromine or with aqueous potassium permanganate in the cold.

The filtrate from the preparation of this compound gave, upon acidification, 6 g. of 1-*p*-bromobenzenesulfonamido-2-methyl-2-propanol.

If the chloro compound was refluxed with alcoholic potash instead of aqueous, a yellow oil was obtained, insoluble in aqueous alkali, the constitution of which was not determined. In addition hydrolysis of the chloro compound to the alcohol took place.

β-Methylallylamine.[6]—A solution of 40 cc. of concentrated sulfuric acid in 100 cc. of water, cooled to below 10°, was poured into a cold solution of 70 g. of 1-amino-2-methyl-2-propanol in 100 cc. of water. The mixture was distilled at 30 mm. pressure until the temperature of the solution reached 120°; the distillation was continued at 5 mm. at a temperature of 145° for one hour. A brown viscous liquid remained. After cooling 400 cc. of aqueous 40% sodium hydroxide was added and the mixture distilled rapidly until the distillate became milky. The distillate was dried over solid sodium hydroxide and then distilled through a fractionating column. There was thus obtained 33 g. of β-methylallylamine; b. p., after fractionation, 76.7–77.7° at 746 mm.; $n^{20}D$ 1.4312.

Anal. Calcd. for C_4H_9N: N, 19.76. Found: N, 19.45.

β-Methylallylamine Hydrochloride.—This was prepared in dry ether and purified from a mixture of absolute ethanol and acetone; m. p. 190–191° (corr.).

Anal. Calcd. for $C_4H_{10}NCl$: N, 13.02. Found: N, 12.91.

β-Methylallylamine Picrate.—The picrate formed in ethanol solution and purified from dilute ethanol had a melting point of 202–206° (corr.).

Anal. Calcd. for $C_{10}H_{12}O_7N_4$: N, 18.66. Found: N, 18.48.

N-(β-Methylallyl)-*p*-bromobenzenesulfonamide.—This product was prepared from β-methylallylamine and *p*-bromobenzenesulfonyl chloride and formed white crystals from a mixture of petroleum ether (b. p. 40–60°) and chloroform; m. p. 74–76° (corr.).

Anal. Calcd. for $C_{10}H_{12}O_2BrNS$: C, 41.37; H, 4.13; N, 4.82. Found: C, 41.46; H, 4.13; N, 4.96.

N-Phenyl-N'-(β-methylallyl) Thiourea.—This product was prepared from phenyl isothiocyanate and β-methylallylamine and purified from dilute ethanol; white crystals, m. p. 78–79° (corr.).

Anal. Calcd. for $C_{11}H_{14}N_2S$: N, 13.59. Found: N, 13.34.

N-(β-Methylallyl)-phthalimide.—A mixture of 28 g. of potassium phthalimide and 18 g. of β-methylallyl chloride was heated in a sealed tube at 150° for three hours. The reaction product was transferred to a flask by treatment with benzene, and the benzene and excess β-methylallyl chloride were removed by steam distillation. The brown solid which remained behind was purified by crystallization from methanol with norite; white crystals, m. p. 88.5–90° (corr.).

Anal. Calcd. for $C_{12}H_{11}O_2N$: N, 6.96. Found: N, 6.90.

This product was hydrolyzed to β-methylallylamine as follows. A solution of 4 g. of N-(β-methylallyl)-phthalimide in 15 cc. of ethanol was allowed to stand for twenty-four hours with 2.5 g. of 40% aqueous solution of hydrazine hydrate. The solution was then acidified with hydrochloric acid and concentrated to a small volume. The precipitate of phthalyl hydrazide was filtered and the filtrate made basic with aqueous sodium hydroxide. Upon distillation β-methylallylamine was obtained. The product from the action of sulfuric acid upon 1-amino-2-methyl-2-propanol proved to be identical with it.

1-*p*-Bromobenzenesulfonamido-2,2-diphenyl-2-ethanol.—A solution of 9 g. of *p*-bromobenzenesulfonyl chloride in 75 cc. of boiling benzene was added slowly to a hot solution of 8 g. of aminomethyldiphenylcarbinol[8] in 75 cc. of benzene and 5 cc. of pyridine. The mixture was allowed to stand at room temperature for twelve hours, then 2.2 g. of potassium hydroxide in about 50 cc. of water was added. The benzene and most of the pyridine was removed by steam distillation and the pale yellow residue purified from dilute methanol: white crystals, m. p. 151–153° (corr.); yield, 16 g. (quantitative).

Anal. Calcd. for $C_{20}H_{18}O_3BrNS$: C, 55.55; H, 4.17. Found: C, 55.65; H, 4.16.

1-*p*-Bromobenzenesulfon-2,2-diphenylvinylamide.—A mixture of 50 cc. of thionyl chloride and 5 g. of 1-*p*-bromobenzenesulfonamido-2,2-diphenyl-2-ethanol was refluxed for thirty minutes. The solution was then poured into 400 cc. of ice. The 4.5 g. of brown gummy material was dissolved in acetone and precipitated with water after which it was extracted with petroleum ether (b. p. 60–110°). The petroleum ether insoluble residue was crystallized from dilute acetone; white plates, m. p. 197–198°.

Anal. Calcd. for $C_{20}H_{16}O_2BrNS$: C, 57.97; H, 3.87; S, 7.73; Br, 19.34. Found: C, 58.08; H, 3.93; S, 7.59; Br, 19.04.

The product also could be obtained by refluxing for thirty minutes 2 g. of 1-*p*-bromobenzenesulfonamido-2,2-diphenyl-2-ethanol in 200 cc. of benzene with 10 g. of phosphorus pentoxide.

The product was soluble in hot aqueous alkali.

By heating for one hour a mixture of 1 g. of this compound with 5 g. of chromic anhydride in 30 cc. of glacial acetic acid and then pouring into ice water, benzophenone

(8) Paal and Weidenkaff, *Ber.*, **38**, 1686 (1905).

was obtained. 1-*p*-Bromobenzenesulfon-2,2-diphenylvinylamide dissolved in chloroform reacted rapidly with a chloroform solution of bromine with the evolution of hydrogen bromide.

Summary

1. An investigation has been undertaken to determine whether ethyleneimine derivatives of the type $R_2C\underset{\llcorner\_\_\_\_\_\lrcorner}{—CH_2—}NR$ can be resolved.

2. Preliminary experiments have indicated that the *p*-bromobenzenesulfonyl derivatives of 1-amino-2-methyl-2-propanol can be converted to the chloride and then to the corresponding ethyleneimine. The replacement of the *p*-bromobenzenesulfonyl group with an optically active sulfonyl group has not yet been successful, since the compounds produced were oils and could not be purified. Corresponding treatment of the *p*-bromobenzenesulfonyl derivative of ethanolamine did not result in the formation of an ethyleneimine.

3. The *p*-bromobenzenesulfonyl derivative of aminomethyldiphenylcarbinol upon treatment with phosphorus pentoxide or thionyl chloride gave 1-*p*-bromobenzenesulfon-2,2-diphenylvinylamide. Similar treatment of 1-*p*-bromobenzenesulfonamido-2-methyl-2-propanol gave what appeared to be a morpholine derivative.

4. Action of sulfuric acid on 1-amino-2-methyl-2-propanol gave β-methylallylamine.

URBANA, ILLINOIS RECEIVED JULY 10, 1939

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

The Isolation of α-Spinasterol from Alfalfa

BY ERHARD FERNHOLZ AND MILDRED L. MOORE

In the course of experiments directed toward the isolation of vitamin K from alfalfa, small amounts of a crystalline sterol were obtained regularly. After a number of recrystallizations it melted at 168°. It was characterized as a sterol by the formation of a digitonide, and by positive Liebermann, Salkowski, and Tortelli-Jaffé reactions. The properties of this sterol suggested to us the possibility that it might be identical with α-spinasterol[1] which was first isolated from spinach,[1] and also has been found in senega root.[2] There is little doubt that the sterol isolated by Dam[3] from alfalfa under similar circumstances and called by him medicagosterol II is in fact α-spinasterol.

The constants observed by us, by Dam, and the latest values for α-spinasterol as recorded by Larsen and Heyl[4] are given in Table I.

TABLE I

	Fernholz and Moore alfalfa sterol		Dam, *et al.* medicagosterol II		Larsen and Heyl α-spinasterol	
	M. p., °C.	$[\alpha]_D$	M. p., °C.	$[\alpha]_D$	M. p., °C.	$[\alpha]_{5461}$
Sterol	168	±0	164	−2.4	172.5	−3.7
Acetate	183	−5	173	...	187	−5.8
m-Dinitrobenzoate	195	±0	195	...	...	...

(1) M. C. Hart and F. W. Heyl, *J. Biol. Chem.*, **95**, 311 (1932).
(2) J. C. E. Simpson, *J. Chem. Soc.*, 730 (1937).
(3) H. Dam, *et al.*, *Helv. Chim. Acta*, **22**, 313 (1939).
(4) Larsen and Heyl, THIS JOURNAL, **56**, 2663 (1934).

The data agree well enough if one takes into consideration the difficulties of obtaining the sterol in pure form. The melting point reported for α-spinasterol has gone up steadily in successive publications.

Further evidence for the identity of our sterol with α-spinasterol was obtained by studying its catalytic hydrogenation. Our sterol also took up only one mole of hydrogen using Adams catalyst. The compound obtained was still unsaturated and the melting point and rotation of the dihydrosterol and its acetate agreed well with those reported for α-spinasterol and its acetate. Titrations with perbenzoic acid were carried out, and it was found that 3 atoms of oxygen were consumed by the sterol itself and 2 atoms by the hydrogenated sterol. In the literature, on the other hand, it has been reported[4] that 2 or 1 atom, respectively, is used up. We are unable to explain this difference, but have obtained the same result with authentic α-spinasterol,[5] while stigmasterol under the same conditions consumed a little less oxygen than is calculated for two double bonds. It is not rare, however, that sterols use more perbenzoic acid than the number of double bonds would indicate. A pertinent example is dihydro-

(5) We are greatly indebted to Dr. C. Donald Larsen, University of Rochester, for samples of α-spinasterol and its acetate. Mixed melting points with the corresponding derivatives of our sterol did not show a depression.