esters in *n*-butyl alcohol lead to the same series ("E") as is obtained by the ethyl condensation. The "E" series is the more stable form. Through the selection of esters, condensing agents and solvents, either series may be made at pleasure.

LINCOLN, NEBRASKA

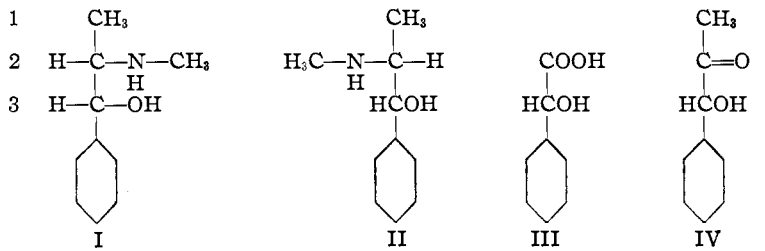
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

STUDY ON THE CONFIGURATION OF EPHEDRINE[1]

BY KARL FREUDENBERG,[2] EUGENE SCHOEFFEL AND EMIL BRAUN

RECEIVED JULY 16, 1931 PUBLISHED JANUARY 7, 1932

The configurational relationship of ephedrine and pseudoephedrine (I or II)[3] has been discussed by different investigators[4] from the viewpoint that in one of the two stereoisomers the OH group is located nearer to the $NHCH_3$ group than in the other.



I II III IV

Since the bond between carbon atoms 2 and 3 is free to rotate, the two groups can approach each other in the same way in both substances. We do not believe that any evidence with regard to the configuration can be given in this way.

The only possible way of solving the problem would be to bring the two asymmetric carbon atoms in steric correlation with substances of known configuration.

This has been carried out for carbon atom 3 in the following manner. The amide of *d*-mandelic acid (III) forms with methylmagnesium iodide the levorotatory phenylacetylcarbinol IV. This reaction was carried out with the inactive material by H. Wren,[5] whose method has been improved. The rotation of our carbinol IV is lower (about two-thirds)

[1] Steric series No. 15; preceding communication, *Ber.*, **64**, 703 (1931).

[2] Carl Schurz Memorial Professor for 1931 at the University of Wisconsin.

[3] A report on the ephedrine alkaloids is given by K. K. Chen and C. H. Kao, *J. Am. Pharm. Assocn.*, **15**, 625 (1926); *cf.* K. K. Chen and C. F. Schmidt, *Medicine*, **9**, 1 (1930).

[4] E. Schmidt, *Arch.*, **252**, 89 (1914); E. Späth and R. Göhring, *Monatsh.*, **41**, 319 (1920); H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929).

[5] Wren, *J. Chem. Soc.*, **95**, 1592 (1909).

than a levorotatory carbinol obtained by C. Neuberg[6] when sugar was fermented in presence of benzaldehyde.

By means of our synthesis the configuration of the carbinol is established although we do not claim that our substance is homogeneous. The carbinol was dissolved in an alcoholic solution of methylamine and immediately hydrogenated. From the reaction product *l*-ephedrine was isolated as the only basic substance formed. Natural *l*-ephedrine has therefore the configuration I or II. Since it can be transformed by conversion of the carbinol group into natural *d*-pseudoephedrine, this base has the opposite configuration of the carbinol group.

In preliminary experiments the synthesis was carried out with racemic mandelic acid, *d,l*-ephedrine being obtained. Experiments are in progress to establish the configuration of carbon atom 2.

Experimental Part

Fifty grams of *dl*-mandelamide or *d*-mandelamide[7] prepared from amygdalin was slowly added to a well-cooled Grignard solution of 240 g. of methyl iodide, 48 g. of magnesium and 700 g. of ether. The mixture was gently boiled for sixteen hours, decomposed with dilute sulfuric acid and extracted with ether; 40 g. of a light yellow oil was obtained which was distilled under a pressure of 15–18 mm. The fractions boiling between 110–125° (7 g.) and 125–140° (28 g.) contained the active carbinol; $[\alpha]_D$ of the active carbinol in 2% absolute alcohol solution, −108°. The same fractions gave a semicarbazone melting at 192° (from the *dl*-amide) and at 189° (from the active amide). These melting points are in agreement with observations made by C. Neuberg[6] and K. v. Auwers.[8]

Six grams of levorotatory phenylacetylcarbinol, 2 g. of palladium black and 30 cc. of a 25% alcoholic solution of methylamine were hydrogenated at pressures of 1 and of 20 atmospheres.[9] In the first case 450 cc. of hydrogen was absorbed, which is 30% of the theoretical. The yield of ephedrine is rather independent of the pressure.

After evaporation of the alcohol and methylamine under reduced pressure a sirupy mass was obtained which was taken up in 2 cc. of warm alcohol and 10 cc. of a dry ethereal solution of hydrochloric acid added. A dark brown oil separated which began to crystallize after washing twice with 10 cc. of absolute ether. The crystalline mass was then washed with 2 cc. of dry chloroform, the white crystals filtered, dissolved in 2 cc. of absolute alcohol and recrystallized by careful addition of absolute ether. The chloroform filtrate was made alkaline, extracted with ether for seventy-two hours, the ether extract acidified with dry hydrochloric acid, and the brown oil separating out was treated as above, yielding a second somewhat impure crystallization product which may contain a stereoisomer. The crystals of the first portion (0.8 g.) melted at 218° with decomposition; $[\alpha]_D^{20}$ in absolute alcohol, $-0.32° \times 6/1 \times 0.060$ g. = $-32°$ (± 2).

Anal. Subs., 5.1 mg.: 0.330 cc. N (740 mm., 20°). Calcd.: N, 6.97. Found: N, 7.11.

A sample of natural *d*-ephedrine hydrochloride decomposed at 215–216° (a mix-

[6] Neuberg, *Biochem. Z.*, **128**, 613 (1922).

[7] K. Freudenberg and L. Markert, *Ber.*, **58**, 1753 (1925).

[8] Auwers, *Biochem. Z.*, **192**, 227 (1928).

[9] Feulgen, *Ber.*, **54**, 360 (1921); F. Knoop, *Z. physiol.*, **148**, 290 (1925).

ture at 213°) and had an $[\alpha]_D^{20}$ −33° (E. Späth and R. Göhring[10] indicate −34.5° in water and a decomposition point of 217–218°).

From *dl*-mandelic amide, *dl*-ephedrine was obtained. The hydrochloride melted with decomposition at 183° (E. Späth and R. Göhring[10] indicate a decomposition point of 188–189.5).

Anal. Subs., 5.050 mg.: 0.295 cc. N (740 mm. 20°). Calcd.: N, 6.97. Found: N, 6.72.

The salt was dissolved in absolute alcohol and dry barium hydroxide added. When the barium-free filtrate was mixed with petroleum ether, the free base began to crystallize out; m. p. 74.5°. Späth and Göhring indicate 73–74°.

Anal. Subs., 2.4 mg.: 0.183 cc. N (740 mm. 20°). Calcd.: N, 8.48. Found: N, 8.38.

Summary

l-Ephedrine has been synthesized from *d*-mandelic acid and the the configuration at the carbinol group shown.

MADISON, WISCONSIN, AND HEIDELBERG, GERMANY

[A CONTRIBUTION FROM THE CHEMICAL LABORATORIES, UNIVERSITY OF MISSOURI]

SOME REACTIONS OF DI-HALOGEN BARBITURIC ACIDS

BY DOROTHY NIGHTINGALE AND ARTHUR EDWARD SCHAEFER

RECEIVED JULY 16, 1931 PUBLISHED JANUARY 7, 1932

The 5,5-di-halogen barbituric acids have been known since 1864, but there is relatively little in the literature concerning their reactions. Baeyer[1] observed that there was a difference in the reactivity of the two halogens in 5,5-dibromobarbituric acid and states that one bromine is more readily replaced than the other. Trzcinski[2] reports the reaction of dibromobarbituric acid with thiourea and with potassium or ammonium thiocyanate. Whiteley[3] prepared the hydrazone of 1,3-diphenylalloxan from 5,5-dibromo-1,3-diphenylbarbituric acid and phenylhydrazine. Biltz and Hamburger[4] developed a method for the preparation of monobromobarbituric acid from the dibromobarbituric acid and ammonia.

These facts suggested the possibilities of reactions of various classes of nitrogen compounds, such as amines, carbazides, acid amides, etc., not only with the dibromobarbituric acid but also with the corresponding dichloro derivative.

Since one molecule of thiourea or one molecule of phenylhydrazine reacts with the dibromobarbituric acid with the elimination of two molecules of hydrogen bromide, it was expected that primary amines would

[10] Späth and Göhring, *Monatsh.*, **41**, 319 (1920).

[1] Baeyer, *Ann.*, **130**, 33 (1864).

[2] Trzcinski, *Ber.*, **16**, 1057 (1883).

[3] Whiteley, *J. Chem. Soc.*, **91**, 1334 (1907).

[4] Biltz and Hamburger, *Ber.*, **49**, 635 (1916).