

Anal. Calcd. for $C_{21}H_{17}O_3SN$: C, 63.77; H, 4.34. Found: C, 63.58; H, 4.33.

Summary

1,2-Phenanthrenequinone has been prepared for the first time and it has been used in securing various other phenanthrene derivatives, notably 2-hydroxy-1,4-phenanthrenequinone and sodium 1,2-phenanthrenequinone-4-sulfonate. The former compound exhibits an interesting type of hydrolytic cleavage by alkalis, observed heretofore in only one other case, while the sulfonated quinone is characterized by a remarkable stability of the sulfonic acid group, a property which appears to be connected with the spatial arrangement of the molecule.

BRYN MAWR, PENNSYLVANIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

SYNTHESIS OF EPHEDRINE AND STRUCTURALLY SIMILAR COMPOUNDS. II. THE SYNTHESIS OF SOME EPHEDRINE HOMOLOGS AND THE RESOLUTION OF EPHEDRINE

BY RICHARD H. F. MANSKE¹ AND TREAT B. JOHNSON

RECEIVED FEBRUARY 11, 1929

PUBLISHED JUNE 5, 1929

In Paper I of this series the authors described some new reactions which led to the synthesis of ephedrine. For the benefit of anyone desirous of repeating the synthesis emphasis is to be laid on the importance of using highly purified methylamine. Owing to the presence of undetermined impurities in the different preparations supplied for our research the most satisfactory results have been obtained only from Kahlbaum's hydrochloride of this base.

It was desirable to determine the generality of the reaction and to ascertain its limitations. Thus far the chief drawback has been the difficulty of preparing certain desired 1,2-diketones, although 1-phenylpropane-1,2-dione itself may be easily prepared. The troublesome cases are those in which methoxyl or hydroxyl groups are attached to the benzene nucleus. It has been found that ketonic aldehydes as well as the diketones may be used, and all primary aliphatic amines so far tried have given the expected product. In the case of aniline the product had somewhat indefinite properties, and no ephedrine-like substance was obtained from *p*-amidophenol.

Details of the synthetic products are given in the annexed table.

It is of some interest to mention that only in one or two cases was there any evidence of the presence of a second isomer, presumably related to ψ -ephedrine. An extensive search was made in the case of the N-ethyl analog of ephedrine but no isomer could be isolated.

The preparation of the *p*-ethyl derivative (see table) yielded a small

¹ Eli Lilly and Company Research Fellow, 1927-1928-1929.

TABLE I
 SUBSTITUTED EPHEDRINES

C ₆ H ₅ CH(OH)CH(R)NHC ₂ H ₅ , R =	M. p., °C. ²	Nitrogen, %		Chlorine, %	
	HCl salt	Calcd.	Found	Calcd.	Found
CH ₃	198 ³	6.50	6.32	16.45	16.61
C ₂ H ₅	226	6.10	6.24	15.45	15.53
C ₆ H ₅ CHOHCH(CH ₃)NHR, R =					
CH ₂ CH ₂ OH	166	6.05	5.94	15.32	15.50
C ₆ H ₅ CH ₂	184-185	5.05	5.09	12.78	12.83
C ₆ H ₅ CH ₂ CH ₂	207-208	4.80	4.90	12.16	12.09
ArCHOHCH(CH ₃)NHC ₂ H ₅ , Ar =					
<i>p</i> -Ethylphenyl	208	5.75	5.77	14.56	14.45
2,5-Dimethylphenyl	221	5.75	5.60	14.56	14.67
<i>p</i> -CH ₃ C ₆ H ₄ CH(OH)CH ₂ NHC ₂ H ₅	208	6.50	6.60	16.45	16.43

quantity of an isomeric base, but since the original starting material for the synthesis, *p*-ethylpropiophenone, was prepared by the Friedel-Crafts reaction, there is the possibility of some *o*-isomer being present.

Inactive ephedrine forms readily crystalline salts with many optically active acids, among which may be mentioned tartaric, *d*-camphorsulfonic and mandelic acids. No resolution could be effected with the first two and an attempt to use *d*-camphoric acid yielded a small amount of crystals which, however, contained only *dl*-ephedrine. The mandelic acids are very well suited to the purpose, the *d*-acid-*d*-base and, conversely, the *l*-acid-*l*-base, compounds being far less soluble in 95% alcohol than the other possible combinations. Three recrystallizations suffice to obtain optically pure products and the yields are good. Incidentally, the resolution of mandelic acid is very readily accomplished by means of natural *l*-ephedrine. Furthermore, the authors suggest the use of natural ψ -ephedrine to prepare *l*-tartaric acid from the racemic acid, since Späth and Göhring⁴ have shown that *dl*- ψ -ephedrine can be resolved readily by means of the active tartaric acids.

Experimental Part

The compounds described in the table were prepared and isolated as in the case of ephedrine. For the purpose of purification the hydrochlorides were dissolved in a small volume of alcohol; the solution was filtered, evaporated somewhat and treated with a small volume of acetone. Where necessary this procedure was repeated. To obtain the *N*- β -phenylethyl analog free of β -phenylethylamine, the crude mixture was conveniently recrystallized from a small volume of water, in which the ephedrine salt is sparingly soluble.

The primary amines required in the syntheses were, for the greater part,

² Melting points are corrected.

³ Hyde, Browning and Adams, THIS JOURNAL, 50, 2292 (1928), give the melting point of their product as 190-192°.

⁴ Späth and Göhring, Monatsch., 41, 319 (1920).

commercial preparations. Benzylamine and β -phenylethylamine were prepared by hydrolyzing the corresponding phthalimides with hydrazine hydrate.⁵

Resolution of *dl*-Ephedrine.—A mixture of 13.8 g. of *dl*-ephedrine and 7.7 g. of *d*-mandelic acid was dissolved in 30 cc. of hot 95% alcohol. On cooling the *d*-ephedrine-*d*-mandelate crystallized out. After two recrystallizations from a small volume of alcohol the product consisted of colorless, rhombic plates, melting at 170° with previous sintering at 167°. The combined mother liquor yielded a further small amount of this product. The salt as thus obtained was basified with potassium hydroxide and the base was extracted with ether. The ethereal solution was evaporated to a small volume and treated with alcoholic hydrogen chloride. The *d*-ephedrine hydrochloride as thus obtained melted at 218 to 218.5° and had $[\alpha]_D^{24} + 35.6$ in 2% aqueous solution; yield, 5.3 g.

The mother liquor from the mandelate of the *d*-base was basified and the extracted base treated with 7.7 g. of *l*-mandelic acid. The crystalline mandelate was twice recrystallized from a small volume of alcohol; m. p. 170° with previous sintering at 167°. The *l*-ephedrine hydrochloride obtained from the mandelate melted at 218 to 218.5°, alone or admixed with a purified specimen from Ma Huang, and had $[\alpha]_D^{24} - 35.5$ in 2% aqueous solution; yield, 6.7 g.

It was now possible to obtain a further amount of *d*- and then *l*-base from the mother liquor from the mandelate crystallizations by alternate treatment with *d*- and *l*-mandelic acid, respectively.

Resolution of Mandelic Acid.—Considerable quantities of mandelic acid were required in the resolution of ephedrine and as far as the authors are aware the most convenient source of *d*-mandelic acid is from the sparingly soluble cinchonine salt. This process was described almost simultaneously by McKenzie⁶ and by Rimbach.⁷ McKenzie prepared a number of salts of *d*- and *l*-mandelic acid with various alkaloids and recorded their melting points among other physical properties. Rimbach did not record melting points. Recently Ward, Chrisman and Nicholas,⁸ while in agreement with McKenzie in so far as the resolution is concerned, pointed out a discrepancy in the melting points as recorded by the latter for the quinine salts of the *d*- and *l*-acids. The present authors found for the melting point of cinchonine-*d*-mandelate 176–177°. McKenzie gives 79–80°. Probably this author interchanged a number of his figures.

Undoubtedly the simplest method of preparing *l*-mandelic acid is by resolution with *l*-ephedrine when this base is available. For this purpose 12 g. of *l*-ephedrine and 12 g. of *dl*-mandelic acid are heated together in 40 cc. of 95% alcohol. The crystals obtained on cooling are twice recrystallized from a small volume of alcohol. The optically pure mandelic acid obtained by acidification, extraction with ether and recrystallization by spontaneous evaporation of an acetone solution melted at 133.5° and had $[\alpha]_D^{20} - 156.9$ in 2% aqueous solution. The yield was 5.9 g.

Some *d*-mandelic acid was obtained from the combined mother liquor from which no more crystalline salt was obtainable. The acid after several recrystallizations from water melted at 132°.

Summary

1. A series of bases, structurally similar to ephedrine, has been prepared in order to demonstrate the generality of the reaction described in Paper I.

⁵ Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

⁶ McKenzie, *J. Chem. Soc.*, 75, 966 (1899).

⁷ Rimbach, *Ber.*, 32, 2385 (1899).

⁸ Ward, Chrisman and Nicholas, *J. Chem. Soc.*, 2186 (1928).

2. Synthetic ephedrine has been resolved into its dextro- and levorotatory antipodes, one of which is identical with the base obtained from the Chinese drug, Ma Huang.

3. The resolution was effected by means of *d*- and *l*-mandelic acid and, conversely, natural *l*-ephedrine lends itself admirably to the preparation of pure *l*-mandelic acid.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF ZION COLLEGE AND OF THE COLLEGE OF LIBERAL ARTS, NORTHWESTERN UNIVERSITY]

PHENYLISOTHIOCYANATE AND ORTHO-TOLYLISOTHIOCYANATE AS REAGENTS FOR PRIMARY AROMATIC AMINES

BY THEO. OTTERBACHER AND FRANK C. WHITMORE

RECEIVED FEBRUARY 19, 1929

PUBLISHED JUNE 5, 1929

Isothiocyanates (mustard oils) react with primary amines to form substituted thioureas suitable for purposes of identification. They are easily crystallized and have convenient melting points. The two isothiocyanates studied in the present work are readily available. They do not react readily with water or alcohol.

The reactions were carried out in alcohol solution. In some cases they took place spontaneously with the evolution of heat, while in others the mixture had to be heated to induce reaction. Since there were no by-products and since the products crystallized well, they were easily purified to constant melting points by crystallization from alcohol. The yields were almost quantitative.

Phenylhydrazine was also treated with phenylisothiocyanate. It reacted violently with two molecules of the mustard oil.

Hydrazobenzene also reacted with two molecules of mustard oil.

Experimental Part

The substituted thiocarbanilides were prepared by dissolving the calculated amounts of the amine and mustard oil in a convenient quantity of alcohol. From 10 to 50 g. of the amines were used as the thiocarbanilides were desired for another purpose. If no reaction took place in the cold, the contents of the flask were heated to boiling. After gentle boiling for a minute or two, the reaction mixture was allowed to cool. If the product did not separate, even when the wall of the tube was rubbed with a glass rod, the process was repeated until the desired effect was produced. (All of the amines will react in the cold if allowed to stand long enough.) The substituted thiocarbanilide was then filtered off and dissolved in boiling alcohol, filtered while hot and the material separating from the filtrate on