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EPHEDRINE SYNTHESIS I: THE PREPARATION OF PROPIOPHENONE DIETHYL ACETAL AND OF 1-PHENYL-1-ETHOXY-PROPENE-1.¹

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Ephedrine, the chief alkaloid in the Chinese drug Ma Huang, was discovered by Nagai (1) in 1887. Its constitution was shown by Späth and Göhring (2) to be represented by the formula: $C_6H_5 \cdot CHOH \cdot CH(NHCH_3) \cdot CH_3$. Since this contains two asymmetric carbon atoms, four optically active forms may exist, together with racemic or other mixtures of these four. The two active forms in which the hydroxyl and methylamino groups are adjacent were believed to represent *l*- and *d*-ephedrine: the two in which these groups are on opposite sides of the axis, to represent *l*- and *d*-pseudoephedrine (3).

Both ephedrine and pseudoephedrine have been synthesized by various procedures, but the exact relationship existing between them seems still a matter of some doubt (4). The present investigation is an attempt to throw additional light upon this question.

EXPERIMENTAL.

Propiophenone Diethyl Acetal.—The method employed follows that of Claisen (5) in which one mole of ketone in 3 moles of alcohol is treated with 1.1 mole of ethyl orthoformate in the presence of a catalyst (6, 7). Into an Erlenmeyer flask were put 72 Gm. of propiophenone, 88 Gm. of ethyl orthoformate, 84 Gm. of absolute alcohol and 0.3 cc. of 36% hydrochloric acid. The temperature increased about ten degrees, and after several hours there developed a beautiful cerise color which gradually faded into yellow. At the end of 24 hours the product was neutralized with alcoholic KOH and the ethyl formate, alcohol and excess orthoformic ester were removed by distillation. The acetal was fractionated under reduced pressure with yields, in successive operations, of 97.9%, 96.2%, 96.5% and 97.6% of the theoretical.

The product was a colorless, mobile liquid with a faint aromatic odor. A cryoscopic determination of the molecular weight in benzene showed 207.45. (Calculated for $C_6H_5 \cdot C(OC_2H_5)_2 \cdot C_2H_5$ was 208.2.) Its boiling point under varying pressure was: (6 mm. = 93-96°), (8 mm. = 99-100°), (10 mm. = 100-101°), (14 mm. = 108-110°), (23 mm. = 119°) and (760 mm. = 226-228°). When boiled at atmospheric pressure, there was a slight decomposition into the monoethyl derivative. The refractive index was $d_{25} = 1.4767$. The specific gravity $25^\circ/4^\circ$ was 0.94476.

1-Phenyl-1-Ethoxy-Propene-1.—When propiophenone diethyl acetal was boiled for some time under atmospheric pressure, it was partially decomposed into the monoethyl derivative and ethyl alcohol. In order to carry this decomposition to completion, some agent must be introduced as an alcohol acceptor (8). Acetyl chloride serves very well in this capacity, but since one by-product resulting is hydrochloric acid, which would effect complete hydrolysis of the acetal, this must be neutralized as formed. Pyridine functions admirably for this purpose.

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To a mixture of 25 Gm. of propiophenone diethyl acetal with 10 Gm. of pyridine, 10 Gm. of acetyl chloride was slowly added with stirring, the mixture being chilled with ice and salt. The odor of pyridine disappeared, the contents of the flask becoming a pasty white mass. After standing fifteen minutes, a slight excess of pyridine was added, and the reaction was allowed to stand over night. Ether was then added and the flask contents were filtered, washing the precipitated pyridine hydrochloride with ether. The filtrate was distilled, removing in order the ether, ethyl acetate and pyridine. The liquid remaining in the flask was distilled under reduced pressure, practically all passing over at 105° under 19 mm. pressure. The yields on two successive runs were 83.6% and 92.8% of the theoretical.

The product was a colorless aromatic liquid, immiscible with water, and readily hydrolyzed by acids, yielding the original ketone. It developed a pale yellow color when boiled for some time at atmospheric pressure. It instantly decolorized a solution of bromine in carbon tetrachloride. A determination of its molecular weight by the freezing-point method in benzene gave a value of 161. (Calculated for $C_9H_9C(O \cdot C_2H_5):CH \cdot CH_3$ was 162.) The boiling point under varying pressure was: (12 mm. = 95–96°), (16 mm. = 100–101°), (19 mm. = 105°) and (760 mm. = 220–221° corr.). At 25° the refractive index lay between 1.5207 and 1.5210, and the specific gravity at 25°/4° was 0.95441.

In attempting to convert this compound into racemic ephedrine, some difficulties were encountered which have not as yet been overcome, but the investigation is to be continued.

SUMMARY.

1. In attempting to synthesize ephedrine by a new method, a new compound was produced, propiophenone diethyl acetal, the physical constants of which were determined.
2. This acetal was converted into an unsaturated compound, also new in the literature, 1-phenyl-1-ethoxy-propene-1, the physical constants of which were also ascertained.
3. Work will be continued on converting this unsaturated compound into ephedrine.

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SCHEELLE SESQUICENTENNIAL.

German apothecaries held a Scheele memorial meeting in cooperation with the Society for the History of Pharmacy, in Stralsund, May 17th. Carl Wilhelm Scheele was born in Stralsund, December 1742; he died in Köping, May 1786. Swedish apothecaries participated in the memorial meeting; the addresses of the occasion included one on Scheele—the man, and another as the scientist. Scheele was employed for a number of years in the Apotek which he acquired in 1776, and here he died ten years later. Observation, experimentation and sacrificing devotion gained for him surpassing eminence.