ethylene bromide. This is what might be expected on the law of chances if it is assumed that the system contains highly polarized or ionized molecules and the energy content of the three compounds is approximately the same.

An attempt was made to test the reversibility of the reaction and to arrive at the equilibrium point from the other direction. Ethylene chlorobromide and aluminum chloride were mixed and allowed to stand under the same conditions as in the previous experiment. On fractionating the same three fractions were obtained and the weights were approximately in the same ratio, which indicates that the reaction is easily reversible and should be represented by the equation: $2C_2H_4ClBr \rightleftharpoons C_2H_4Cl_2 + C_2H_4Br_2$. The reaction mixtures darken in color as the reaction progresses and a small amount of hydrogen halide is evolved. Very little tar is formed, however, and this by-reaction is evidently very superficial in nature when the experiment is conducted at room temperature. To make sure that no exchange of halogen occurred between aluminum chloride and ethylene bromide, an experiment was tried in which ethylene chloride was omitted. The ethylene bromide was unchanged. Plans are being made to study these reactions more accurately; both equilibrium and velocity measurements will be attempted.

I wish to take this opportunity to thank Professor Frank O. Rice of Johns Hopkins University for his helpful advice in carrying out this work, and the Department of Chemistry at Johns Hopkins University for so kindly allowing me the privileges of the laboratory during the spring term of 1927–1928.

Summary

A mechanism for the Friedel-Crafts reaction has been suggested.

The hypothesis predicts that metathetical reactions will occur between certain types of aliphatic halogen compounds in the presence of aluminum chloride. Experimental evidence is given that such reactions do occur, and some of them have been studied.

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SYNTHESIS OF EPHEDRINE AND STRUCTURALLY SIMILAR COMPOUNDS. I. A NEW SYNTHESIS OF EPHEDRINE

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RECEIVED OCTOBER 15, 1928 PUBLISHED FEBRUARY 5, 1929

Although the constitution of ephedrine (III) is no longer in doubt, interest in this base has been renewed by the pharmacological work of K. K. Chen.[2] Since it seemed not improbable that other bases analogously constituted might possess more desirable or at least interesting physiological properties,[3] the authors entered this field with a view to the improvement of known methods of synthesis or to the discovery of new ones.

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[1] Holder of the Eli Lilly Company Research Fellowship in Organic Chemistry, 1927–1928.

[2] Chen and Kao, *J. Am. Pharm. Assocn.*, **8**, 625a (1926). Bibliography is given in this paper.

[3] Hyde, Browning and Adams, THIS JOURNAL, **50**, 2297 (1928).

It was observed that a solution of 1-phenyl-1,2-propanedione,[4] C_6H_5-$COCOCH_3$, in petroleum ether reacts exothermally with dried gaseous methylamine to form a colorless crystalline compound with the elimination of water. This substance is unstable and gradually decomposes to an indefinite mixture. Treatment with acids regenerates the two components and titration shows that approximately one molecule of amine is combined with one of the diketone. Aside from purely speculative formulas for this compound only two (I and II) need be mentioned, and of these the former may at once be disposed of on purely theoretical grounds.

$C_6H_5C{=}(NCH_3)COCH_3$ I $\quad$ $C_6H_5COC{=}(NCH_3)CH_3$ II $\quad$ $C_6H_5CH(OH)CH(NCH_3)CH_3$ III

The considerable affinity demand of the phenyl group[5] leaves the α-carbon relatively saturated so that any negative ions (CN, HSO_3, etc.) have a tendency to attach themselves to the β-carbon in preference. Furthermore the effect of the carbonyl groups is reciprocal (the ketone group of ethyl pyruvate is more reactive than those of acetone, ethyl acetoacetate, or ethyl levulinate),[6,7] that is, each enhances the additive capacity of the other. Finally, methylbenzyl ketone reacts readily with bisulfites, whereas ethylbenzyl ketone does not, and the former is more reactive than acetone,[7] so that the phenyl group enhances the additive capacity of the β-carbon, an effect in accord with the Flürscheim's theory of alternate affinity demand.[5]

Sufficient experimental proof of the correctness of Formula (II) is found in the fact that catalytic reduction leads to ephedrine (III), that is, the carbonyl group is reduced to a secondary alcohol and the imino double bond (—C=N—) is reduced at the same time.

It is interesting to note that only a very small proportion of ψ-ephedrine accompanies the main product, *dl*-ephedrine. The method of Eberhardt[8] yields a considerable amount of the ψ-form and that of Späth and Göhring[9] yielded the ψ-form almost exclusively. To offer an explanation for this observation the authors assume that there is a repulsion between the N- and the ketonic O-atoms, their mean positions in space being on opposite sides of the carbon chain, so that the reduced product also tends to have the HO- and CH_3NH-groups distant from each other, a postulate already

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[4] This diketone was prepared by the action of NO_2 on propiophenone. The details will form the subject of a future communication. See also a paper by Gilman and Johnson, THIS JOURNAL, **50**, 3341 (1928).

[5] Flürscheim, *J. Chem. Soc.*, **95**, 718 (1909); **97**, 87 (1910).

[6] Lapworth, *ibid.*, **83**, 997 (1903).

[7] The result of a systematic investigation carried out at the University of Manchester in England and to be published shortly in the *Journal of the Chemical Society;* first paper, Lapworth and Manske, *J. Chem. Soc.*, **1928**, 2533.

[8] Eberhardt, *Arch. Pharm.*, **258**, 97 (1920).

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

advanced on other grounds for ephedrine. Conversely, it has been proposed that these groups are specially adjacent in ψ-ephedrine.[10]

Experimental Part

dl-**Ephedrine.**—A mixture of 50 cc. of absolute ethyl alcohol, 7.4 g. of methylphenyl diketone ($^1/_{20}$ mole) and an alcoholic solution of methylamine containing 1.6 g. ($^1/_{20}$ mole) was reduced catalytically with hydrogen in the presence of 0.1 g. of platinum oxide.[11] In some experiments there was a long induction period and then the yield was low. This behavior could be obviated by reducing the catalyst first and then adding the reactants. When reduction no longer proceeded, the catalyst was removed by filtration and about half the alcohol removed under reduced pressure. By this means any excess of methylamine was removed. The solution was made just acid with alcoholic hydrogen chloride and evaporated to dryness. The solid hydrochloride was washed with cold acetone and dried. The yield was 2.5–4.0 g. A small amount of ψ-ephedrine hydrochloride could be extracted from this by means of hot chloroform and by working up a number of extractions sufficient was obtained for definite identification (m. p. 164°; free base, m. p. 118°).[9,11] The *dl*-ephedrine hydrochloride was purified by recrystallizing once from alcohol–acetone and melted at 189°.[9]

Anal. Calcd. for $C_{10}H_{15}ON \cdot HCl$: N, 6.95; Cl, 17.60. Found: N, 6.98; Cl, 17.70.

The free base was recrystallized from chloroform–petroleum ether and melted at 75°.[12]

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.71; H, 9.09; N, 8.49. Found: C, 72.43; H, 9.01; N, 8.20.

Summary

1. A new reaction has been discovered whereby it is possible to synthesize the alkaloid ephedrine.

2. This reaction consists in taking advantage of the differential additive capacity of the two ketonic groups in alkylaryl *o*-diketones.

3. 1-Phenyl-1,2-propanedione condenses with one molecule of methylamine and the condensation product on reduction yields *dl*-ephedrine.

4. Several homologs of ephedrine have been synthesized by this method and their description will form the subject of an early communication.

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[10] Henry, "The Plant Alkaloids," Blakiston Sons, **1924**.

[11] Adams and Shriner, This Journal, **45,** 2171 (1923).

[12] Melting points are corrected.