Communications TO THE EDITOR

The Synthesis of Racemic Allococaïne and Racemic Allopseudococaïne

Sir:

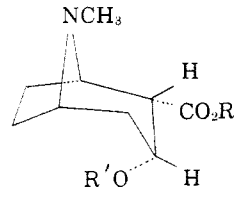
Willstätter and his collaborators demonstrated that cocaïne, one of the classical topics of alkaloid chemistry, is a 2-carbomethoxy-3-benzoxytropane and that the latter should exist as four stereoisomeric racemic (and eight optically active) modifications.[1,2,3] It appears that, of these, only racemic cocaïne[4] and racemic pseudococaïne have been synthesized[2,3,4] and that only the former has been resolved.[4] I wish to report that the other two possible racemic cocaïnes have recently been synthesized in this laboratory.

Hydrogenated in aqueous acetic acid with Adams' catalyst, racemic 2-carbomethoxytropinone[4,5] furnishes in about 80% yield a third racemic ecgonine methyl ester (I) [*Anal.* Calc'd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6. Found: C, 60.4; H, 8.8], m.p. 81.5–83.5°, which on benzoylation affords a third racemic cocaïne (II) [*Anal.* Calc'd for $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0. Found: C, 67.3; H, 6.9], m.p. 82–84°. Hydrolysis of I gives a mixture of two racemic ecgonines, one of which melts at 242° (III) [*Anal.* Calc'd for $C_9H_{15}NO_3$: C, 58.4; H, 7.8. Found: C, 58.1; H, 8.0] (hydrochloride, m.p. 213°) and the other at 237° (IV). Esterification of the former compound results in the fourth racemic ecgonine methyl ester (V) [*Anal.* Calc'd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6. Found: C, 60.0; H, 8.6], m.p. 80°, which on benzoylation gives the fourth racemic cocaïne (VI) [*Anal.* Calc'd for $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0. Found: C, 67.5; H, 6.7], m.p. 98°. The latter ecgonine (IV) gives a hydrochloride [*Anal.* Calc'd for $C_9H_{16}ClNO_3$: C, 48.8; H, 7.3. Found: C, 49.0; H, 7.2] melting at 231–233° (dec.) and hence appears to be identical with Willstätter's 'drittes racemisches Ekgonin.'[4] The *picrates* of I, II, V, and VI melt at 204°, 179°, 136°, and 162°, respectively.

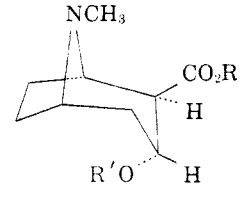
Inasmuch as the two ecgonine methyl esters already known both have the β-configuration of the C_3-OH,[6,7] the new isomers (I and V) must both have the α-configuration. In its reaction with methyl iodide, V resembles ecgonine methyl ester and I pseudoecgonine methyl ester.[8] For reasons given earlier,[7] this indicates that V has the β-configuration of the 2-carbomethoxy group. Accordingly, it is tentatively concluded that II is allococaïne and VI allopseudococaïne.[7]

2,4-Dicarbomethoxytropinone, prepared by Robinson's biological method[9] (binoxalate, m.p. 148°), is saponifiable to racemic 2-carbomethoxytropinone.[4,5] Preliminary experiments indicate that *d*-pseudoecgonine methyl ester can feasibly be oxidized with chromic-sulfuric acid in acetone to the optically active form of this β-keto ester. Hence it appears that all the cocaïnes, optically active as well as racemic, are obtainable and their relative and absolute configurations ascertainable.[10]

I hope to give soon a detailed account of the preparation, properties, stereochemistry, resolution, and pharmacological properties of certain of the foregoing and related compounds.



I R = CH_3, R′ = H
II R = CH_3, R′ = C_6H_5CO
IV R = R′ = H



V R = CH_3, R′ = H
VI R = CH_3, R′ = C_6H_5CO
III R = R′ = H

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(1) Willstätter and Müller, *Ber.*, **31**, 2655 (1898).
(2) Willstätter and Bode, *Ann.*, **326**, 42 (1903).
(3) Willstätter and Bommer, *Ann.*, **422**, 15 (1921).
(4) Willstätter, Wolfes, and Mäder, *Ann.*, **434**, 111 (1923).
(5) Preobrashenski, Schtschukina, and Lapina, *Ber.*, **69**, 1615 (1936).
(6) Fodor and Kovács, *J. Chem. Soc.*, 724 (1952).
(7) Findlay, *J. Am. Chem. Soc.*, **75**, 1033 (1953); **76**, 2855 (1954).
(8) *Cf.*, reference 4, pp. 127–128.
(9) *Cf.*, Robinson, *J. Chem. Soc.*, **111**, 762 (1917); see also Schöpf and Lehmann, *Ann.*, **518**, 1 (1935).
(10) *Cf.*, Hardeggar and Ott, *Helv. Chim. Acta*, **38**, 312 (1955).

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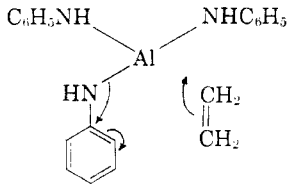
The *ortho*-Alkylation of Aromatic Amines

Sir:

The nuclear alkylation of aromatic amines in the past has not been regarded as a practical reaction because of complications arising from the characteristics of the amino group. We wish to report a new reaction by which primary and secondary aromatic amines are alkylated with olefins exclusively in the *ortho* positions. The reaction is of interest both from a theoretical viewpoint and also in that it provides a direct route to

a series of compounds previously available only through multi-step syntheses. The reaction is effected through the use of aluminum anilide type catalysts, and a cyclic mechanism, I, is presumed to be involved, the details of which will be discussed in a forthcoming paper.



I

The following general alkylation procedure was used. The catalyst was prepared by heating the amine with aluminum turnings until hydrogen evolution had ceased. Concentrations of 3.5 to 7 mole-percent of the aluminum anilide were employed. In an experiment using the latter concentration, aniline was alkylated with ethylene at 600–800 p.s.i. and 330° over a seven-hour period in a steel autoclave. The product was hydrolyzed, the aluminum hydroxide removed by filtration, and the material fractionated to yield aniline (0.4%), 2-ethylaniline (1.2%), 2,6-diethylaniline (89%), and some higher-boiling materials. The 2,6-diethylaniline (b.p. 235–236°, n_D^{20} 1.5461; *Anal.* Calc'd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.9; H, 10.0; N, 9.8) was identified by diazotization to the corresponding phenol, which was found to be identical with an authentic sample of 2,6-diethylphenol on the basis of infrared spectrum and mixture melting point.[1]

The alkylation of aniline with higher olefins proved to be sluggish and a small yield of the branched mono-alkylaniline was the only product from each reaction. Alkylation with propylene gave 2-isopropylaniline (b.p. 217–218°, n_D^{20} 1.5483; hydrochloride, m.p. 182–185°; picrate, m.p. 159–161°),[2] and isobutylene yielded 2-*tert*-butylaniline (b.p. 227–228°, n_D^{20} 1.5450; acetyl derivative, m.p. 161.5–162.5°).[3]

The N-alkylanilines were found to alkylate at considerably lower temperatures than aniline; however, only one alkyl group could be introduced. Thus N-ethylaniline was alkylated with ethylene at 205° to give an 86% yield of N-ethyl-2-ethylaniline (b.p. 223°; n_D^{20} 1.5398. *Anal.* Calc'd for $C_{10}H_{15}N$: N, 9.4. Found: N, 9.6). The product was identified by comparison with an authentic sample produced by the reaction of 2-ethylaniline with ethyl iodide.

The alkylation of N-alkylanilines with higher olefins proceeded readily with olefins of the propylene type ($RCH{=}CH_2$).

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(1) All melting points and boiling points are uncorrected.

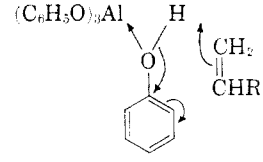
(2) Brown, Bayer, and Blessing, *Ber.*, **57**, 3997 (1924) report the hydrochloride of 2-isopropylaniline to melt at 182° and the picrate to melt at 160°.

(3) Brown and Nelson, *J. Am. Chem. Soc.*, **75**, 24 (1953) report a refractive index of n_D^{20} 1.5453 for 2-*tert*-butylaniline, and Craig, *J. Am. Chem. Soc.*, **57**, 195 (1935) has prepared 2-*tert*-butylacetanilide, m.p. 159–161°.

The *ortho*-Alkylation of Phenols

Sir:

We wish to report a novel alkylation by which 2-alkyl- and 2,6-dialkylphenols may be produced with little or no alkylation occurring at the 4-position. The reaction is that of a phenol with an olefin in the presence of a catalytic amount of the corresponding aluminum phenoxide. The reaction would appear to be analogous to the *ortho*-alkylation of aromatic amines concurrently being reported by these Laboratories; however, it appears that there may be a fundamental difference in the mechanisms. Thus whereas ethylene is more reactive than substituted olefins in the aromatic amine alkylation, the reverse order of reactivity is observed in the phenol alkylation. Details of a cyclic concerted carbonium ion type mechanism, I, will be presented in a forthcoming paper.



I

The reactions were carried out by treating the phenol containing 3–4 mole percent of its aluminum phenoxide with the desired olefin in a steel autoclave. The catalyst was washed from the product with dilute hydrochloric acid and the compounds were isolated by fractional distillation.

Ethylene reacted with phenol at 320° and 600–800 p.s.i. over a ten-hour period to give 24% of 2-ethylphenol (b.p. 201–202°, n_D^{20} 1.5372; 2-ethylphenoxyacetic acid derivative, m.p. 138–140°)[1,2] and 8% of 2,6-diethylphenol (m.p. 37–38°, b.p. 219°).[3]

(1) All melting points and boiling points are uncorrected.

(2) Steinkoff and Hopner, *J. prakt. Chem.*, [2], **113**, 140 (1926) report 2-ethylphenoxyacetic acid to melt at 140–141°.

(3) von Auwers and Wittig, *Ber.*, **57**, 1275 (1924) prepared 2,6-diethylphenol, m.p. 37.5–38°.