Communications TO THE EDITOR

The Synthesis of Racemic Allococaïne and Racemic Allopseudococaïne

Sir:

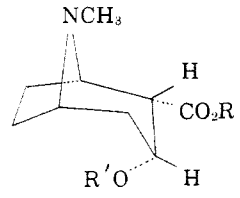
Willstätter and his collaborators demonstrated that cocaïne, one of the classical topics of alkaloid chemistry, is a 2-carbomethoxy-3-benzoxytropane and that the latter should exist as four stereoisomeric racemic (and eight optically active) modifications.[1,2,3] It appears that, of these, only racemic 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.

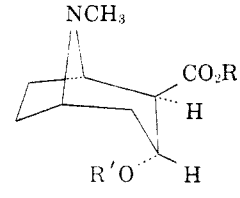
Inasmuch as the two ecgonine methyl esters already known both have the β-configuration of the C_3-OH,[6,7] the new isomers (I and V) must both have the α-configuration. In its reaction with methyl iodide, V resembles ecgonine methyl ester and I pseudoecgonine methyl ester.[8] For reasons given earlier,[7] 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