

# Communications TO THE EDITOR

## The Synthesis of Racemic Allococaine and Racemic Allo pseudococaine

Sir:

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

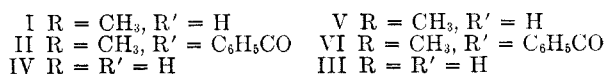
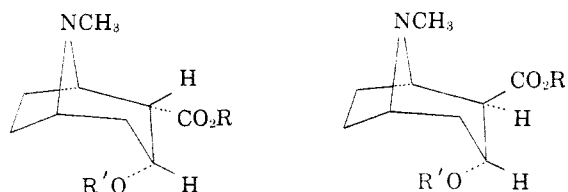
Hydrogenated in aqueous acetic acid with Adams' catalyst, racemic 2-carbomethoxytropinone<sup>4,5</sup> furnishes in about 80% yield a third racemic ecgonine methyl ester (I) [Anal. Calc'd for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>: C, 60.3; H, 8.6. Found: C, 60.4; H, 8.8], m.p. 81.5–83.5°, which on benzylation affords a third racemic cocaine (II) [Anal. Calc'd for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>: 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<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>: 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<sub>10</sub>H<sub>17</sub>NO<sub>3</sub>: C, 60.3; H, 8.6. Found: C, 60.0; H, 8.6], m.p. 80°, which on benzylation gives the fourth racemic cocaine (VI) [Anal. Calc'd for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>: 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<sub>9</sub>H<sub>16</sub>ClNO<sub>3</sub>: 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'.<sup>4</sup> 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  $\beta$ -configuration of the C<sub>3</sub>-OH,<sup>6,7</sup> the new isomers (I and V) must

both have the  $\alpha$ -configuration. In its reaction with methyl iodide, V resembles ecgonine methyl ester and I pseudococaine methyl ester.<sup>8</sup> For reasons given earlier,<sup>7</sup> this indicates that V has the  $\beta$ -configuration of the 2-carbomethoxy group. Accordingly, it is tentatively concluded that II is allococaine and VI allo pseudococaine.<sup>7</sup>

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

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.



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(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

(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).