

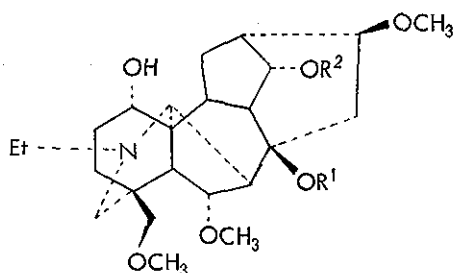
## NEOPELLINE. A PARTIAL SYNTHESIS OF 8-ACETYL-14-BENZOYLNEOLINE

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A synthesis of 8-acetyl-14-benzoylneoline has been effected in five steps from the known alkaloid, delphisine. On the basis of the reported data for "neopelline", the suggested structure of 8-acetyl-14-benzoylneoline is in error and the existence of "neopelline" in nature is doubtful.

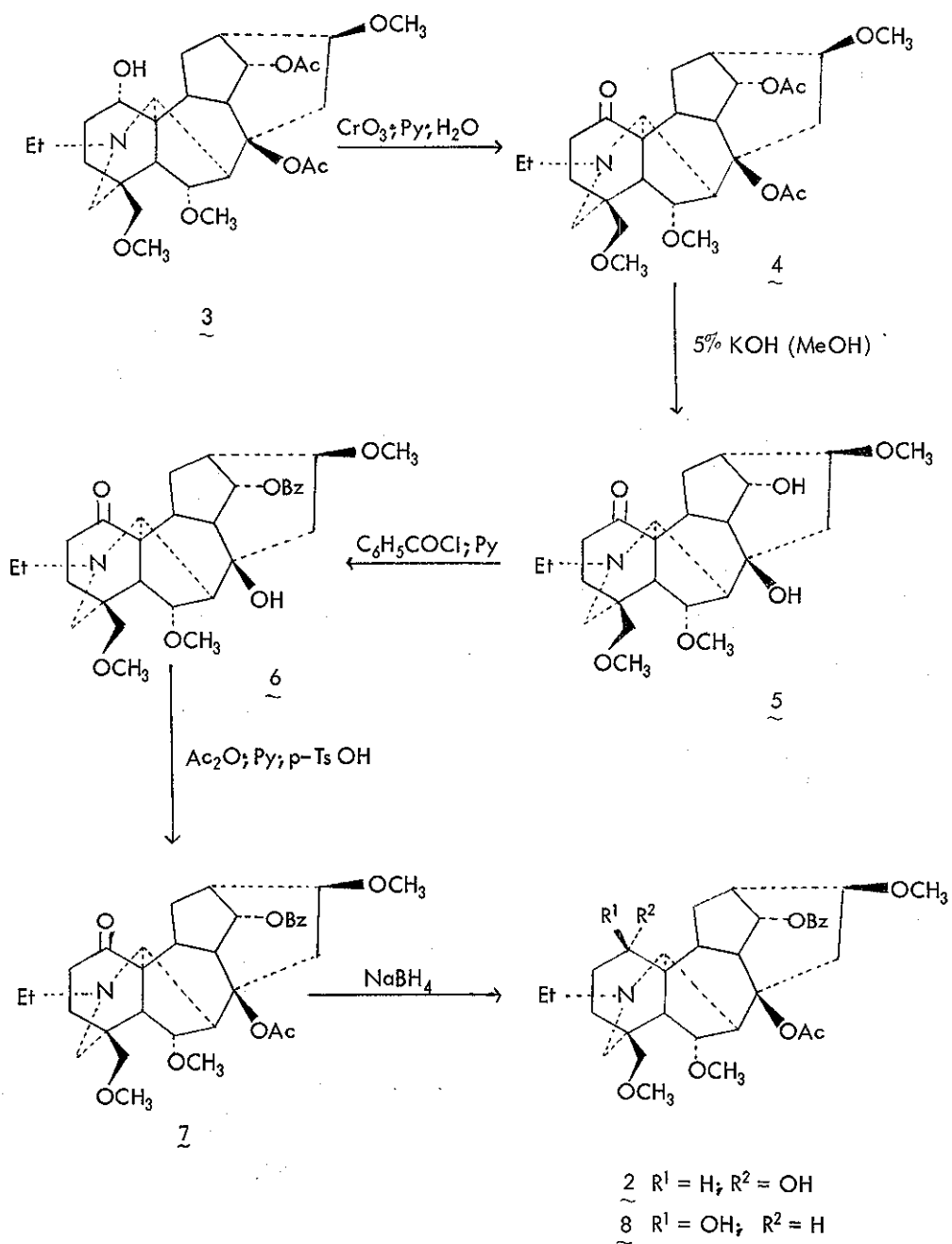
"Neopelline", an amorphous (?) diterpenoid alkaloid, was reported as an impurity in crude aconitine from Aconitum napellus by Schulze and Berger<sup>1</sup> in 1924. They reported a mp of about 80° for "neopelline", assigned the molecular formula as C<sub>32</sub>H<sub>45</sub>NO<sub>8</sub> and reported the preparation of a few salts. Alkaline hydrolysis of "neopelline" afforded the alkamine neoline, benzoic acid, and acetic acid. In 1937, Freudenberg and Rogers<sup>3</sup> failed to isolate "neopelline" from crude aconitine from A. napellus following the procedure of Schulze and Berger. However, they isolated nepelline and neoline from the fraction which was supposed to have afforded "neopelline". Since neoline was isolated from an extract which had been made basic with 0.1 N NaOH solution, these authors suggested that neoline was possibly an artifact formed as a hydrolysis product of "neopelline". The structure of neoline (1) was determined by Wiesner and co-workers<sup>4</sup> and has recently been confirmed in our laboratory.<sup>5</sup> No further work appears to have been done on "neopelline", but the correct molecular formula for neoline, C<sub>24</sub>H<sub>39</sub>NO<sub>6</sub>, requires the molecular formula of "neopelline" to be revised to C<sub>33</sub>H<sub>45</sub>NO<sub>8</sub>. The available data is insufficient for any firm structural conclusion. However, the alkaline hydrolysis products would require "neopelline" to be a monoacetyl-monobenzoyl neoline. Of the six possible monoacetyl-monobenzoyl neoline structures, the ones with an acetyl or a benzoyl group at C-1 are

unlikely, because, no known naturally occurring  $C_{19}$ -diterpenoid alkaloid contains such a moiety. Also, all the known naturally occurring esters of neoline contain an acetyl group at C-8. Therefore, the probable structure of "neopelline", as proposed earlier<sup>6</sup> on biogenetic grounds, should be 8-acetyl-14-benzoylneoline (2). To determine whether or not "neopelline" indeed has the suggested structure 2, a synthesis of 8-acetyl-14-benzoylneoline (2) from the known alkaloid delphisine (3) has been achieved following the route outlined in Scheme 1.



- 1  $R^1 = R^2 = H$   
 2  $R^1 = Ac; R^2 = Bz$

Delphisine (3) was oxidized with Cornforth's reagent ( $CrO_3$ -Py- $H_2O$ ) to give 1-ketodelphisine (4) in 93% yield. The spectral data of 4 are consistent with those published<sup>5</sup> for 1-ketodelphisine. Hydrolysis of 4 with 5% methanolic KOH solution at room temperature for 6 hr. gave 1-ketoneoline (5) in 76% yield. The physical data of the latter are consistent with the published data<sup>5</sup> for 1-ketoneoline. The latter was converted in 84% yield into the corresponding benzoate (6) [mp 128-129°C, ir: 3510, 1715, 1690, 1605, 1110, and 720  $cm^{-1}$ ;  $H^1$  nmr:  $\delta$  1.14 (triplet for  $N-CH_2-CH_3$ ),  $\delta$  3.26, 3.33, and 3.40 (three 3H singlets for three methoxyl groups), and the aromatic protons of a benzoyl group between  $\delta$  7.30 and  $\delta$  8.12] by treatment with benzoyl chloride and pyridine for 3 hr. Treatment of 6 with acetic anhydride and catalytic amounts of *p*-toluenesulfonic acid for 1 hr. on a steam bath gave 8-acetyl-14-benzoyl-1-ketoneoline (7) mp 165-66° [ir: 1725 (broad), 1690, 1605 (weak), 1120 and 720  $cm^{-1}$ ;  $H^1$  nmr:  $\delta$  1.13 (three



Scheme 1

proton triplet for N-CH<sub>2</sub>-CH<sub>3</sub>),  $\delta$  1.46 (3H, singlet for acetate group)<sup>6</sup>,  $\delta$  3.26, 3.42 and 3.49 (three 3H singlets for three methoxyl groups),  $\delta$  5.12 (1H, doublet of doublets for C-14 proton) and other signals in the aromatic region for the benzoate group] in 69% yield.

Reduction of 7 with sodium borohydride gave the desired product, 8-acetyl-14-benzoylneoline (2) [mp 196-97°C;  $[\alpha]^{28}_D + 9.7^\circ$  (c 0.9 ab. EtOH); ir: 3510, 1725, 1720, 1600, 1100, and 720 cm<sup>-1</sup>; <sup>1</sup>H nmr:  $\delta$  1.17 (3H, triplet for N-CH<sub>2</sub>-CH<sub>3</sub> group),  $\delta$  1.46 (3H, singlet for C-8 acetate)<sup>7</sup>,  $\delta$  3.24, 3.35 and 3.42 (three 3H singlets for three methoxyl groups),  $\delta$  5.11 (1H, doublet of doublet for proton attached to C-14) and aromatic signals between  $\delta$  7.40 and  $\delta$  8.12 for a benzoate group]] in 20% yield and its epimer, 8-acetyl-14-benzoyl-1-epi-neoline (8) [mp 172-4°C;  $[\alpha]^{28}_D + 11.4^\circ$  (c 1.7 EtOH), ir: 3500, 1720, 1610, 1120 and 720 cm<sup>-1</sup>; <sup>1</sup>H nmr:  $\delta$  1.08 (3H, triplet for N-CH<sub>2</sub>-CH<sub>3</sub>),  $\delta$  1.48 (3H, singlet for C-8 acetate),  $\delta$  3.23, 3.32 and 3.40 (three 3H singlets for C-6, C-16, and C-18 methoxyl groups),  $\delta$  5.14 (1H, doublet of doublet, for C-14  $\beta$ H) and other signals for a benzoate group] in 64% yield. The epimers 2 and 8 were separated on preparative alumina plates using hexane-ethanol (95:5) as developer. The structures of compounds 2 and 8 and other intermediates were confirmed by their carbon-13 nmr spectra.<sup>8</sup> The low yield<sup>9</sup> of the 1- $\alpha$ -OH isomer (the desired product) relative to the 1- $\beta$ -OH isomer is characteristic of the NaBH<sub>4</sub> reduction of 1-ketoneoline derivatives.<sup>5</sup>

None of the properties of the synthetic 8-acetyl-14-benzoylneoline (vide infra) matches those published and available for "neopelline". Although the lack of an authentic sample of "neopelline" prevents a direct comparison with our synthetic product, the profound difference in the physical properties of the two compounds is sufficient to suggest that they are indeed not identical. Although biogenetic considerations strongly suggest the possibility of the existence of 8-acetyl-14-benzoylneoline in nature, the occurrence of "neopelline" as a pure compound is now doubtful.

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9. Reported yields are based on the crystalline products after purification on preparative tlc plates. Melting points are corrected.

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