A Convenient Synthesis of Pelletierine (2-Piperidylpropanone)

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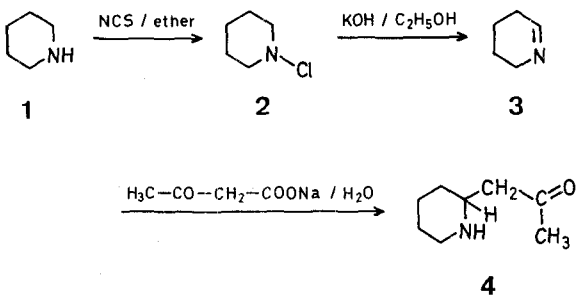
The alkaloid pelletierine (**4**)[1] was first isolated from the bark of the pomegranate tree (*Punica granatum* L.)[2]. Later it was shown to be a biosynthetic precursor of alkaloids in a variety of plant families (e.g. Lycopodium and Lythraceae)[3]. Pelletierine is also of great value in the synthesis of the Lythraceae alkaloids. Every successful synthesis of members of this class of alkaloids has utilized **4** as the starting material[4].

There are available several procedures for the preparation of **4**. However, these require the use of either relatively expensive reagents and catalysts or difficultly accessible materials. Commonly, a metallopicoline is acylated and the pyridine ring reduced[5]. The best of these procedures requires four distinct steps and produces **4** in about 40% yield[5c].

Other routes to **4** utilize the condensation of piperideine (**3**) and a keto acid[6]. Although this condensation gives moderate yields of **4**, the lack of an efficient synthesis of **3** has not made this an attractive method of preparing **4**. Piperideine (**3**) is generally prepared from *N*-chloropiperidine (**2**) and isolated as a crystalline trimer. There are three known forms of this trimer of which, one, the alpha form, is readily reversible to **3**[7]. It is difficult to obtain α-tripiperideine reproducibly.

In order to avoid this difficulty, we have adopted Rapoport's procedure for the preparation of an ethanol-ether solution of **3**[8]. This solution of **3** may be added directly to a sodium acetoacetate solution. The resulting condensation yields pelletierine (**4**) after decarboxylation. This method results in 40–50% yields of **4** in three steps without the isolation of any intermediates.



1 2 3 4

This procedure provides a rapid, simple, and inexpensive route to the valuable intermediate pelletierine. The method should also be applicable to the syntheses of homologs of **4**.

Preparation of Pelletierine (4; 2-Piperidylpropanone):
To a rapidly stirred suspension of *N*-chlorosuccinimide (23.6 g, 0.18 mol) in ether (500 ml) was added piperidine (**1**; 8.6 g, 0.10 mol). After one hour the mixture was filtered and the filtrate washed twice with water (200 ml) and once with aqueous sodium chloride (100 ml) and dried ($MgSO_4$). This ether solution of *N*-chloropiperidine (**2**) was concentrated to 75 ml and added dropwise over a period of 1 h to a stirred solution of potassium hydroxide (5.62 g, 0.10 mol) in absolute ethanol (50 ml). During the addition, the ethanol solution was maintained at 5° by cooling with an ice bath. Following the addition, the mixture was stirred at room temperature for 14 h (shorter times may be utilized) and then filtered. The filtrate, containing piperideine (**3**), was added to an aqueous solution of sodium acetoacetate prepared by heating an aqueous solution of ethyl acetoacetate (13.0 g, 0.10 mol) and sodium hydroxide (6.0 g, 0.15 mol) in water (200 ml) at 50° for 4 h. This mixture was refluxed for 4 h. After cooling, the ether and much of the ethanol were removed by concentration in vacuo. The resulting aqueous solution was extracted three times with dichloromethane (200 ml), the combined extracts dried (Na_2SO_4), and concentrated to give 13.6 g of a reddish-brown oil. Vacuum distillation afforded pelletierine (**4**); yield: 5.92 g (42%); b.p. 54°/3 torr (Lit.[9]: b.p. 86°/10 torr).

I.R. (film): $\nu = 2932, 2855, 1713\ cm^{-1}$.

^1H-N.M.R. ($CDCl_3$): $\delta = 0.7–1.9$ (m, 6H), 2.15 (s, 3H), 2.53 (broad d, 2H), 2.5–3.3 ppm (m, 4H).

Picrate: m.p. 147.5° (Lit.[9]: m.p. 147–148°).

The authors gratefully acknowledge support of this work by a Cottrell Research Grant from the Research Corporation and by a Public Health Service Grant (NS 12007).

Received: July 27, 1976

[1] 2-Piperidylpropanone (**4**) is known as pelletierine and isopelletierine. Pelletierine is the preferred name (See ref. 3).

[2] L. Marion, *The Alkaloids*, Vol I., R. Manske, H. Holmes, Eds., Academic Press, New York, 1950, p. 176.

[3] J. Brackman, R. Gupta, D. MacLean, I. Spenser, *Can. J. Chem.* **50**, 2591 (1972) and references therein.

[4] B. Loev, I. Lantos, H. Van Hoeven, *Tetrahedron Lett.* **1974**, 1101.
J. Wróbel, W. Golebiewski, *Bull. Acad. Pol. Sci.* **23**, 601 (1975).
M. Hanaoka, N. Ogawa, Y. Arata, *Chem. Pharm. Bull. (Tokyo)* **23**, 2140 (1975); and the references therein.

[5a] J. Wibaut, C. Kloppenburg, M. Beets, *Recl. Trav. Chim.* **63**, 134 (1944).

[5b] J. Büchi, F. Kracher, G. Schmidt, *Helv. Chim. Acta* **45**, 729 (1962).

[5c] M. Hanaoka, N. Ogawa, Y. Arata, *Yakugaku Zasshi* **94**, 531 (1974).

[6] E. Anet, G. Hughes, E. Ritchie, *Nature* **164**, 501 (1949).
C. Schöpf, F. Braum, K. Burkhardt, G. Dummer, H. Müller, *Justus Liebigs Ann. Chem.* **626**, 123 (1959).
J. Weisse, H. De. Klonia, B. Visser, *Recl. Trav. Chim.* **83**, 1265 (1964).
M. El-Olemy, A. Schwarting, W. Kelleher, *Lloydia* **29**, 58 (1966).

[7] C. Schöpf, H. Arm, H. Krimm, *Chem. Ber.* **84**, 690 (1951).

[8] D. Bender, L. Bjeldanes, D. Knapp, H. Rapoport, *J. Org. Chem.* **40**, 1264 (1975).

[9] J. Meisenheimer, E. Mahler, *Justus Liebigs Ann. Chem.* **462**, 301 (1928).