Phytochemistry, Vol. 25, No. 9, pp. 2241–2242, 1986.
Printed in Great Britain.

0031–9422/86 $3.00 + 0.00
Pergamon Journals Ltd.

(−)-*N*-FORMYLNOREPHEDRINE FROM *CATHA EDULIS*

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(*Received* 6 *January* 1986)

Key Word Index—*Catha edulis*; Celastraceae; (−)-*N*-formylnorephedrine; (−)-*N,O*-diformylnorephedrine; formylation; conformation; cisoid; transoid; NMR.

Abstract—The alkaloidal fraction of *Catha edulis* yielded upon repeated chromatography (−)-*N*-formylnorephedrine whose ^{1}H NMR and ^{13}C NMR spectra suggested the presence of cisoid (major) and transoid forms (minor). The identity of the isolated compound was established by comparison with the major product obtained by formylating (−)-norephedrine; the minor product was found to be (−)-*N,O*-diformylnorephedrine.

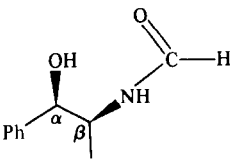
INTRODUCTION

As a part of our ongoing [1] study of the constituents of Saudi Arabian Khat (*Catha edulis* Forsk.), examination of the alkaloidal fraction revealed the presence of a crystalline compound, hitherto unreported from this source. In view of its possible contribution to the pharmacological effects of Khat, a study was undertaken to characterize it and this paper describes its isolation, structure elucidation and synthesis.

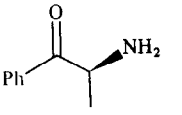
RESULTS AND DISCUSSION

The alkaloid fraction (see Experimental) of a locally grown sample of Khat provided upon repeated chromatography, then crystallization from *n*-hexane–ether, compound **1**, $C_{10}H_{13}NO_2$, mp 72–73° and $[\alpha]_D^{25}$ −45° (*c* 1.1; $CHCl_3$). Its IR spectrum suggested the presence of a formyl* group, while the ^{1}H NMR spectrum suggested the presence of two forms of the compound since double signals were observed for the methyl and benzylic protons. The proton noise decoupled ^{13}C NMR spectrum confirmed this, since all major signals showed double signals for each carbon. Of particular significance was the signal at δ49.7 (β-C) with its satellite at δ53.5, as this pattern indicated that the compound existed mostly in the cisoid conformation (as drawn). This conclusion is based on the fact that in this conformation the β-carbon interacts sterically with the carbonyl carbon resulting in a shielding effect [2, 3].

(−)-*N*-Formylnorephedrine was reported [4] as an intermediate in the synthesis of (−)-cathinone (**2**). However, in that report it was obtained as an oil with no given specific rotation, and its two conformational forms were not described. Furthermore, its method of preparation by refluxing a toluene solution of (−)-norephedrine formate could not be reproduced satisfactorily in our hands despite repeated attempts. In all cases, the conversion either did not proceed or a low yield of 10% or less, based on ^{1}H NMR analysis, was obtained. Thus, a more reliable method was needed to make the compound in order to confirm the identity of the isolated material. This was accomplished by heating (−)-norephedrine (**3**) with 99% formic acid resulting in the formation of a product identical with **1** (same spectral data, mp, mmp, sp. rot.) and the less polar **4** which were separated by column chromatography on silica gel. The diformyl derivative **4**, like **1**, exhibited ^{1}H NMR and ^{13}C NMR spectra that indicated the occurrence of two conformational forms of



1



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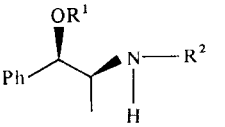

3 $R^1 = R^2 = H$
4 $R^1 = R^2 = CHO$

*Despite its amide nature, pure **1** was found to stay preferentially in acidic water when partitioned with chloroform, and mostly goes to the chloroform layer upon alkalinization.

which the cisoid form with the β-C eclipsing the carbonyl oxygen was predominant.

The presence of *N*-formyl alkaloids in plants is not uncommon and numerous examples are described in the literature [5]. What remains to be established is the contribution of **1** to the pharmacological action of Khat, and this study is now in progress.

EXPERIMENTAL

Mps: uncorr; IR: KBr; ^{1}H NMR: 100 MHz, $CDCl_3$, TMS as int. standard; ^{13}C NMR: 25.0 MHz, $CDCl_3$, TMS as int. standard. TLC was performed on silica gel plates using $CHCl_3$–MeCN (3:2) as solvent and visualization under short wavelength UV light. HPLC was performed on a Porasil column using a cyclohexane–EtOAc gradient with a UV detector set at 280 nm. The plant material was collected during April–May 1984 in Fifa, Saudi Arabia. A voucher specimen is deposited in the herbarium of the Research Center, College of Pharmacy, King Saud University.

Isolation of (−)-N-*formylnorephedrine* (**1**). The powdered leaves (1.5 kg) were alkalinized with 10% NH_3 (200 ml), then exhaustively extracted with Et_2O in a Soxhlet. The solvent was concd, then extracted with 2 M HCl (4 l.), alkalinized to pH 9 with Na_2CO_3, extracted with $CHCl_3$, and then evaporated to leave a thick residue (1.60 g). Filtration on Al_2O_3 (grade I) using $CHCl_3$ then evaporation left a green residue (1.06 g). This residue (1.0 g) was subjected to prep. HPLC using cyclohexane–EtOAc gradient as solvent. The fraction with the highest polarity (0.32 g) was filtered over a bed of SiO_2, evaporated and the residue crystallized from hexane–Et_2O to give colourless needles (0.25 g) of **1**, mp 72–73°; $[\alpha]_D^{25}$ −45° (*c* 1.1; $CHCl_3$); UV λ_{max}^{MeOH} (log ε): 252 (2.1), 258 (2.2), 264 (2.1) and 208 (3.8); IR ν_{max}^{KBr} cm^{-1}: 3350 and 3230 (OH), 1640 (amide CO); ^{1}H NMR ($CDCl_3$): δ0.94 (*d*, *J* = 6 Hz, Me) with a less intense *d* at 1.03 (*J* = 6 Hz), 4.30 (*br m*, HCN), 4.51 (*br s*, exchangeable OH), 4.78 (*d*, *J* = 2.9 Hz) with a similar minor *d* at 4.60 (CHOH), 6.63 (*br d*, exch. very slowly (NH), 7.29 (*s*, ArH) and 7.94 (*br s*) with a similar minor signal at 7.68 (HCO); ^{13}C NMR ($CDCl_3$): δ164.5 (27%) with a major signal at 161.5 (*d*, HCO), 140.8 and 140.2 (27%, C-1), 2 double intensity *d* at 128.1 and 126.0 (*o*- and *m*-C), *d* at 127.4 (*p*-C) with three minor doublets at 128.3, 127.9 and 126.5, 76.4 (29%) and 75.4 (*d*, CHOH), 53.5 (25%) and 49.7 (*d*, HCN), and 16.1 (24%), 13.7 (*q*, Me): MS *m/z*: 179 $[M]^+$ (< 1%) with the base peak at *m/z* 73. (Found: C, 67.01; H, 7.25; N, 7.77. $C_{10}H_{13}NO_2$ (179) requires: C, 67.02; H, 7.31; N, 7.82%.)

Formylation of (−)-*norephedrine* (**3**). (−)-Norephedrine (**3**, 5.0 g) was heated in a boiling water-bath with 99% HCO_2H (5.0 ml) for 10 hr. Evaporation left an oily residue which showed two spots on TLC, R_f values 0.60 and 0.40. Flash chromatography [6] using $CHCl_3$–MeCN (7:3) provided the following in the order of elution.

Diformylnorephedrine (**4**) crystallized from Et_2O–hexane to give colourless needles (1.07 g), mp 80–81°; $[\alpha]_D^{25}$ −77° (*c* 0.1; $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: two CO bands at 1655 (N–CO) and 1717 (O–CO); ^{1}H NMR ($CDCl_3$): δ1.11 (*d*, *J* = 6 Hz) with a similar minor *d* at δ1.18 (Me), 4.50 (*m*, HCN), 5.97 (*d*, *J* = 4 Hz) with a similar minor signal at δ5.70 (OCH), 6.40 (*br s*, exch. slowly, NH), 7.30 (*s*, ArH), 7.93 (*br s*, HCO) and 8.10 (*s*, HCO); ^{13}C NMR ($CDCl_3$): δ160.6, 160.1 (*s*, 2CO) with two minor signals at 163.7 and 159.7, 136.1 (*s*) with a minor signal at 134.9 (C-1), two double intensity doublets at 128.5 and 126.3 with accompanying minor signals at 127.0 and 128.6 (*o*- and *m*-C), 128.3 (*d*, *m*-C), 76.9 (*d*) with minor signals at 77.5 (OCH), 47.3 with minor signal at 51.4 (HCN) and 14.9 with minor signal at 17.4 (Me); MS *m/z*: 207 $[M]^+$ (< 1%) with the peak at *m/z* 73. (Found: C, 63.60; H, 6.50; N, 6.66. $C_{11}H_{13}NO_3$ (207) requires: C, 63.75; H, 6.32; N, 6.76%.)

(−)-*N*-formylnorephedrine (**1**) crystallized from Et_2O–hexane to give colourless needless (4.03 g) with mp, mmp, $[\alpha]_D$ and spectral data indistinguishable from those of the natural material.

Acknowledgements—This work was supported by a grant from the Saudi Arabian National Center for Science and Technology (SANCST). The authors would like to thank Mr. K. Madana Gopal of the Department of Chemistry, King Saud University, and Mr. Essam Lotfi of the Department of Pharmaceutical Chemistry, for their technical assistance.

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