

(-)-CATHINONE: IMPROVED SYNTHESIS AND  
CARBON-13 NMR ASSIGNMENTS

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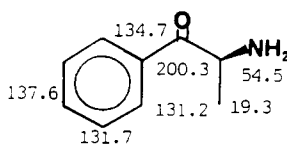
The khat plant, *Catha edulis* Forsk. (Celastraceae), is indigenous to East Africa and southern Arabia. Chewing the tender fresh leaves and twigs of this plant for their amphetamine-like effects is common in those areas. The phenethylamine alkaloid, (-)-cathinone [**1**], has been isolated (1) from freeze-dried khat leaves and found to be the principal active constituent. It has been the subject of numerous synthetic approaches, but the one reported by Berrang *et al.* (2) appears to be the most attractive. This note describes an analogous synthetic route that was found to be more reliable and less time consuming. It provided **1** in multigram amounts for pharmacological, spectroscopic, and biosynthetic studies.

The phenethylamine (+)-cathine [**2**], also known as (+)-norpseudoephedrine, was used as the starting material in the present synthetic scheme. Heating with HCOOH for 4 h resulted in a complete conversion to the key intermediate (+)-*N*-formylcathine [**3**] and the diformyl **4**. These two compounds were separable by column chromatography. Alternatively, shaking a CHCl<sub>3</sub> solution of the mixture of **3** and **4** with concentrated NH<sub>3</sub> for 5 min partially hydrolyzed **4** to **3**, which could now be readily obtained from (+)-cathine [**2**] in 84% yield as the sole product. Formylation of (+)-cathine [**2**] using this procedure is advantageous

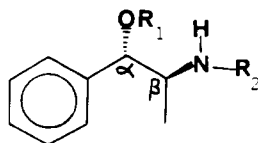
over formylation of **5** as the reaction is more complete. Furthermore, the diformyl **7** (**3**) was found to be more resistant to NH<sub>3</sub> hydrolysis than **4**. Pure **3** was oxidized to (-)-*N*-formylcathinone in 84% yield as reported (2) for **6**, which by acid hydrolysis yielded (-)-cathinone [**1**]. Because both enantiomers of cathine are commercially available, the procedure can be used to synthesize either of the enantiomers of cathinone.

It should be noted that the <sup>1</sup>H-nmr spectrum of **3** indicated the presence of two forms of this compound, a *cisoid* conformer [**3a**] and a *transoid* one [**3b**]. The <sup>13</sup>C-nmr signal at δ 50.2 with its minor satellite at 54.6, ascribed to the β-carbon, suggested the predominance of the *cisoid* form. This conclusion was based on the fact that in this conformation, the β-carbon was subjected to a shielding steric interaction with the carbonyl oxygen (4). The predominance of the *cisoid* form may be attributed to internal, electronic factors, such as hydrogen bonding which is only possible in this form.

While the <sup>13</sup>C-nmr assignments of most carbons of cathinone [**1**] were unambiguous and could be based on their chemical shift values, those of the *ortho* and *meta* carbons were not. The problem was resolved by obtaining a decoupled spectrum by irradiation at the frequency corresponding to the two *ortho* protons found characteristically downfield (5) at



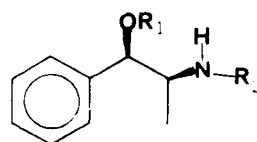
**1**



**2** R<sub>1</sub>=R<sub>2</sub>=H

**3** R<sub>1</sub>=H, R<sub>2</sub>=formyl

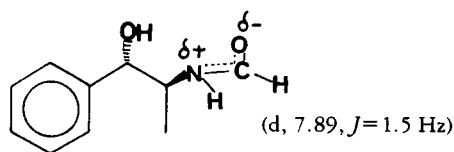
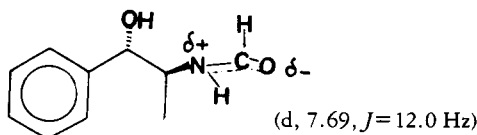
**4** R<sub>1</sub>=R<sub>2</sub>=formyl



**5** R<sub>1</sub>=R<sub>2</sub>=H

**6** R<sub>1</sub>=H, R<sub>2</sub>=formyl

**7** R<sub>1</sub>=R<sub>2</sub>=formyl

3a, *cisoid* 33b, *transoid* 3

$\delta$  8.10 (dd,  $J_{ortho}=7.5$  Hz,  $J_{meta}=2.5$  Hz). The nmr signal corresponding to the two *ortho* carbons collapsed to a singlet at  $\delta$  131.2. Complete assignments of all carbons are given on structure 1.

## EXPERIMENTAL

**GENERAL EXPERIMENTAL PROCEDURES.**—All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra and specific rotations were obtained on a Perkin-Elmer 5801R and a 241 MC, respectively.  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra were determined on a JEOL JNM-FX-100 FT spectrometer at 100 MHz and 25 MHz, respectively, and chemical shift values are given in  $\delta$  (ppm) with TMS as the internal standard, unless otherwise indicated (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). High- and low-resolution mass spectra were taken on a Finnigan 3200 mass spectrometer. Tlc was conducted on Si gel G plates with fluorescent indicator, using  $\text{CHCl}_3$ -MeCN (7:3) as the solvent system and using short wave uv light for detection (-)- and (+)-cathine (norpseudoephedrine) are commercially available from Fluka AG, CH-9470 Buchs, Switzerland.

**FORMYLATION OF (+)-CATHINE [2] TO 3 AND 4.**—(+)-Cathine [2] (2 g) was heated with 99%  $\text{HCOOH}$  (2 ml) in a boiling  $\text{H}_2\text{O}$  bath for 4 h. The solution was diluted with  $\text{H}_2\text{O}$  (5 ml) and extracted with  $\text{CHCl}_3$  (50 ml) which was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , then evaporated in vacuo to afford an oily residue (2 g). Flash chromatography (6) on Si gel, using  $\text{CHCl}_3$ -MeCN (7:3) as solvent, provided two fractions that yielded 3 and 4 as follows:

Fraction 1 (0.5 g) contained 4, tlc Rf 0.55; crystallized from hexane/ $\text{Et}_2\text{O}$ , mp 56-57°;  $[\alpha]^{25}_D+81^\circ$  (c 1.0,  $\text{CHCl}_3$ ); ir (KBr)  $\nu$  max (KBr) 1715 (O.CO) and 1660  $\text{cm}^{-1}$  (NH.CO);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.09 (with a similar minor signal at 1.21) (3H, d,  $J=6.0$  Hz, Me), 4.59 (3.82) (1H, m,  $\beta$ -CH), 5.83 (5.72) (1H, d,  $J=7.0$  Hz,  $\alpha$ -CH), 6.05 (1H, br d, slowly exchangeable, NH), 7.34 (5H, s, Ar H), 8.12 (2H, br s, 2 HCO);  $^{13}\text{C}$  nmr  $\delta$  160.6, 160.1 (with two minor signals at 164.1 and 159.7) (d, 2CO), 136.3 (s, C-1), 128.6, 126.9 (128.7 and 125.9) (d, o, and

m-C, undistinguished), 77.0 (77.9) (d,  $\alpha$ -C), 47.4 (58.8) (d,  $\beta$ -C), 17.4 (18.1) (q-Me); ms  $m/z$  207 (5%)  $[\text{M}]^+$  with the base peak at  $m/z$  72; Found C, 63.66; H, 6.51; N, 6.77.  $\text{C}_{11}\text{H}_{13}\text{NO}_3$  requires C, 63.75; H, 6.32; N, 6.76%.

Fraction 2 (1.5 g) contained 3, tlc Rf 0.40; crystallized from  $\text{Et}_2\text{O}$ , mp 66-67°;  $[\alpha]^{25}_D+46^\circ$  (c, 1.0,  $\text{CHCl}_3$ ); ir  $\nu$  max (KBr)  $\text{cm}^{-1}$  3200 (OH) and 1650 (N.CO);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  1.04 with minor signal at 1.08 (d,  $J=6.6$  Hz, Me), 4.16 (3.50) (1H, m,  $\beta$ -CH), 4.33 (1H, br, s, OH), 4.47 (4.36) (1H, d,  $J=5.3$  Hz,  $\alpha$ -CH), 6.50 (1H, br d, slowly exchangeable, NH), 7.26 (5H, s, ArH), 7.89 (d,  $J=1.5$  Hz, HCO *cisoid*), 7.69 (d,  $J=12.0$  Hz, HCO *transoid*), and both *cisoid* and *transoid* collapsed into singlets upon  $\text{D}_2\text{O}$  exchange;  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$  161.9 with satellite signal at 165.0 (d, -CO), 141.5 (141.3) (s, C-1), 128, 126.4 (double intensity d, o, and m-C, indistinguishable), 127.6 (d, p-C) with all Ar d showing partially overlapping satellite signals, 76.3 (76.8) (d,  $\alpha$ -C), 50.2 (54.6) (d,  $\beta$ -C) and 17.6 (18.2) (q-Me); ms  $m/z$  179  $[\text{M}]^+$  (4%) with the base peak at  $m/z$  105; found C, 67.11; H, 7.42; N, 7.90.  $\text{C}_{10}\text{H}_{13}\text{NO}_2$  requires C, 67.02; H, 7.31; N, 7.82%.

Alternatively, the  $\text{CHCl}_3$  solution of 3 and 4 obtained from reacting 20 g of 2 was thoroughly shaken with concentrated  $\text{NH}_3$  (300 ml) for 5 min, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , then evaporated in vacuo to afford 20 g (84%) of pure 3, identical to the substance obtained above.

**CONVERSION OF 3 TO (-)-CATHINONE HYDROCHLORIDE.**—(+)-N-Formylcathine [3] (3 g) was oxidized with  $\text{CrO}_3$  as previously reported (2) for 6 to provide (-)-N-formylcathinone as a colorless oil (2.5 g, 84%) with  $^1\text{H}$ -nmr signals as those reported (2);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$  198.4 (s,  $\alpha$ -C), 160.8 (d, HCO.), 133.9 (d and s, p-C and C-1, respectively), 128.8 (double intensity d, m-C), 128.6 (double intensity d, o-C, distinguished from previous signal by selective band decoupling), 48.7 (d,  $\beta$ -C) and 19.3 (q, Me).

Hydrolysis of N-formylcathinone to 1 HCl was accomplished by treatment with 10% HCl as previously described (2), to give a product mp 175-176° (without drying over  $\text{P}_2\text{O}_5$ ),  $[\alpha]_D-47^\circ$  (c 1,  $\text{H}_2\text{O}$ ) [literature (2) 175-176° and -47.1°, respectively]; with  $^1\text{H}$ -nmr signals in agreement with those reported (2); for the  $^{13}\text{C}$ -nmr assignments ( $\text{D}_2\text{O}$ , DSS as reference) see structure 1.

## ACKNOWLEDGMENTS

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