25 mL of CH_2Cl_2 was added at 0 °C, over a period of 0.5 h, a solution of 4-phenylbenzoyl chloride (0.83 g, 5.0 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to 25 °C over 14 h. It was then evaporated, the residue was dissolved in 20 mL of CH_2Cl_2 and washed with 1 × 10 mL of 1 N NaOH and 2 × 10 mL of 10% HCl, and the organic phase was dried and evaporated to leave 750 mg of residue. Chromatography (SiO_2, 5% acetone/CH_2Cl_2) afforded **30d**, pure by HPLC (Lichrosorb, 60% hexane/40% $CHCl_3$): mp 171–173 °C (after crystallization from ethyl acetate); NMR δ 2.8 (t, J = 6 Hz, 2 H, Ar CH_2C), 3.73 (s, 3 H, OCH_3), 3.5–4.0 (m, 3 H, CCH_2N), 4.65 (br s, 2 H, Ar CH_2N), 6.5–7.7 (m, 12 H, Ar H). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.4; H, 6.2; N, 4.1. Found: C, 79.9; H, 6.2; N, 4.0.

1-[4-(Benzyloxy)benzyl]-2-(4-*tert*-butylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (33b). To a 70 mL of THF was added 0.40 mL (0.29 g, 2.86 mmol) of diisopropylamine, followed by *n*-BuLi (2,3 M, 1.13 mL, 2.60 mmol) at −70 °C. After the mixture was stirred for 0.5 h, 280 mg (0.87 mmol) of isoquinoline **30b** was added as a solution in 3 mL of THF over a 5-min period. After 2 h at −70 °C, 4-(benzyloxy)benzyl bromide (100 mol %, 240 mg, 0.87 mmol) was added as a solution in 2 mL of THF, and after 5 min, 2 mL of 2-propanol was added and the solution was allowed to warm to 0 °C. The reaction mixture was added to 50 mL of hexane and 50 mL of H_2O, the organic layer was washed with 20 mL of 1 N NaOH and 20 mL of brine, and the combined aqueous layers were backwashed with 40 mL of $CHCl_3$. The combined organic layers were dried and evaporated to yield an oil, which was subjected to preparative TLC (two 2-mm SiO_2 plates, 1:1 ether/hexane, each plate developed twice), and the major product was rechromatographed (SiO_2, 2:1 ether/hexane), yielding 138 mg (0.27 mmol, 31%) of **33b**, which was recrystallized from $CHCl_3$/hexane: mp 175–177 °C; NMR δ 1.26 [s, 9 H, $C(CH_3)_3$], 2.3–4.0 (m, 6 H), 3.8 (br s, 3 H, OCH_3), 4.9 (br s, 2 H, Ar OCH_2), 4.7-5.3 (m, 1 H, Ar CHN), 6.3–7.5 (m, 16 H, Ar H). Anal. Calcd for $C_{35}H_{37}NO_3 \cdot 0.5H_2O$: C, 79.4; H, 7.2; N, 2.6. Found: C, 79.6; H, 7.2; N, 2.6.

1-[4-(Benzyloxy)benzyl]-2-(4-phenylbenzoyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (33d). A solution of 338 mg (0.98 mmol) of amide **30d** in 100 mL of dry THF was cooled to −70 °C and *tert*-butyllithium (1.05 M, 0.94 mL, 0.99 mmol, 100 mol %) was added dropwise, keeping the temperature below −65 °C. After 30 min at −70 °C, a solution of *p*-(benzyloxy)benzyl chloride (252 mg, 1.08 mmol, 110 mol %) in 5 mL of THF was added. The reaction mixture was allowed to warm to 0 °C over a 20-min period, at which time 2 mL of water was added, the solution was evaporated, and the residue was dissolved in 50 mL of ether and washed with 2 × 20 mL of H_2O and then 20 mL of brine. Drying and evaporating the organic phase left a residue, which was subjected to preparative TLC (four plates, 2-mm thick, SiO_2, eluting with 1.5% acetone in $CHCl_2$) and afforded a 20% recovery of educt **30d** and 325 mg (61% yield) of product **33d**: mp 146–147 °C (from ethyl acetate/hexane); NMR δ 2.5–3.2 (m, 2 H), 3.2–4.0 (m, 4 H), 3.75 (br s, 3 H, OCH_3), 4.6–5.3 (m, 3 H), 6.4–7.8 (m, 21 H, Ar H). Anal. Calcd. for $C_{37}H_{33}NO_3$: C, 82.3; H, 6.2; N, 2.6. Found: C, 82.0; H, 6.3; N, 2.6.

1-[4-(Benzyloxy)benzyl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (2c). To a solution of 200 mg (0.37 mmol) of **33d** in 75 mL of methanol was added 3.5 g of 3% sodium amalgam[20] in small chunks over 30 h. The reaction mixture was then filtered, and the filtrate was evaporated to an oil, which was taken up in CH_2Cl_2 and chromatographed on two preparative TLC plates (2 mm SiO_2, eluting with 10% methanol in CH_2Cl_2). The slowest band (R_f 0.5) consisted of the desired product **2c** (66 mg, 0.18 mmol, 50% yield): mp 94–96 °C (from ethyl acetate/hexane); NMR δ 1.74 (s, 1 H, NH), 2.4–3.5 (m, 6 H), 3.82 (s, 3 H, OCH_3), 4.32 (dd, J = 3 Hz, 10 H, Ar CHN), 5.02 (s, 2 H, OCH_2Ph), 6.5–7.5 (m, 12 H, Ar H). The HCl salt was crystallized from 1:1 ethanol/10% HCl: mp 178–179 °C. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C, 72.8; H, 6.6; N, 3.5. Found: C, 72.7; H, 6.7; N, 3.5.

Acknowledgment. This research was supported in part by the National Institute on Drug Abuse.

Registry No. 1a, 81625-16-3; **1a**·HCl, 4042-17-5; **1b**, 81625-17-4; **1b**·HCl, 81625-18-5; **1c**, 61273-84-5; **1c**·HCl, 81625-19-6; **2a**, 81625-20-9; **2a**·HCl, 81625-21-0; **2c**, 81625-22-1; **2c**·HCl, 81625-23-2; **3a**, 3979-58-6; **3c**, 76787-10-5; **4**, 2039-67-0; **5**, 591-31-1; **6**, 3179-09-7; **7**, 81625-24-3; **8a**, 93-40-3; **8c**, 6547-53-1; **9a**, 81625-25-4; **9c**, 76786-97-5; **9c**·HCl, 81625-26-5; **10**, 81625-27-6; **11**, 81625-28-7; **12**, 15184-99-3; **14**, 81625-29-8; **15**, 81625-30-1; **16**, 81625-31-2; **17**, 81625-32-3; **18**, 74904-29-3; **19**, 28281-58-5; **20**, 81625-33-4; **21**, 7306-46-9; **22**, 24693-44-5; **23**, 34146-68-4; **23**·HCl, 24693-40-1; **24**, 42923-77-3; **25**, 1723-70-2; **26c**, 836-43-1; **26d**, 836-42-0; **26e**, 5544-60-5; **26f**, 81625-34-5; **27**, 123-08-0; **27b**, 4397-53-9; **29**, 81625-35-6; **30a**, 81625-36-7; **30b**, 81625-37-8; **30c**, 81625-38-9; **30d**, 81625-39-0; **33b**, 81625-40-3; **33d**, 81625-41-4; pivaloyl chloride, 3282-30-2; *p*-*tert*-butylbenzoyl chloride, 1710-98-1; 4-phenylbenzoyl chloride, 14002-51-8.

(20) McDonald, R. N.; Reineke, C. E. *Org. Synth.* **1970**, *50*, 51.

Enantiomeric α-Aminopropiophenones (Cathinone): Preparation and Investigation

Bertold D. Berrang, Anita H. Lewin,* and F. Ivy Carroll*

Chemistry and Life Sciences Group, Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received October 19, 1981

The preparation of the optical antipodes of α-aminopropiophenone (cathinone) from norephedrine and an improved large-scale resolution of norephedrine are described. The characterization of cathinone and its salts and their stability in various solvents are discussed.

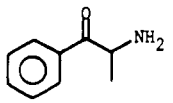
The chewing of the leaves of *Catha edulis* Forsk (Khat) by the natives of several Asian and African countries to provide rapid stimulation is extremely prevalent[1] and has been considered to be a serious problem of drug dependence not unlike that associated with amphetamine.[2] In fact, on the basis of the observations of Eddy et al.,[3] the United Nations Narcotics Laboratory undertook research on the chemistry of Khat and its components.[2]

Earlier in this century (+)-norpseudoephedrine, a CNS-active compound, was identified among the basic alkaloid components of Khat.[4] Later investigations[5-8]

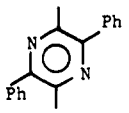
(1) Krikorian, A. D.; Getahun, A. *Econ. Bot.* **1973**, *27*, 378.
(2) United Nations Document MNAR/3/79.
(3) Eddy, N. B.; Halbach, H.; Isbell, H.; Seevers, N. H. *Bull. W. H. O.* **1965**, *32*, 721.
(4) Wolfes, O. *Arch. Pharm.* **1930**, *268*, 81.
(5) Parris, M. R.; Moyse, H. *Ann. Pharm. Fr.* **1957**, *15*, 89.

0022-3263/82/1947-2643$01.25/0

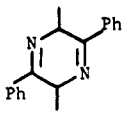
revealed the presence of other bases, but the isolation and characterization of the main constituent has only been reported within the last few years by the United Nations Narcotics Laboratory.[9,10] Specifically, the presence of (−)-α-aminopropiophenone [(−)-1][9] and its absolute con-



1



2



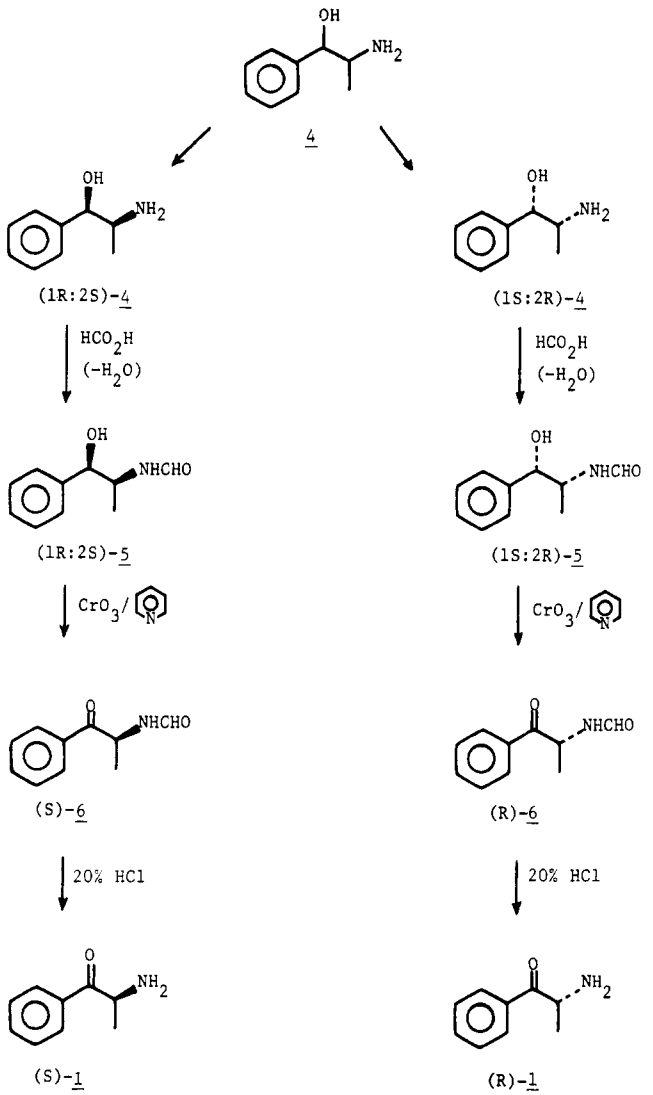
3

figuration,[10] as well as the presence of 3,6-dimethyl-2,5-diphenylpyrazine (2),[9] were reported. Since this information is only available in the United Nations Documents, which are somewhat hard to come by,[11] it will be briefly summarized here. Extraction of freeze-dried plant material with methanol, followed by separation of the nonpolar and weakly basic species and purification by acid–base extractions gave an odiferous yellow oil which, after treatment with oxalic acid, gave a solid: mp 157–160 °C; $[\alpha]^{20}$ −36° (MeOH).[9] This compound was identified as α-aminopropiophenone oxalate by its UV, IR, ^{1}H NMR, and mass spectra.[9] In another report[10] the absolute configuration of the plant extract was deduced from comparison of the CD curve observed for a separately isolated sample of oxalate salt with those of model compounds. It was concluded[10] that natural α-aminopropiophenone has the *S* configuration, which is biogenetically consistent with the configurations of both (+)-norpseudoephedrine and (−)-norephedrine at the corresponding asymmetric center.

These reports do, however, contain some puzzling results. The stereospecific synthesis of (−)-α-aminopropiophenone [(−)-1] by bromination of propiophenone followed by the Gabriel synthesis is claimed.[10] Indeed, the melting point (175 °C) reported for the hydrochloride salt of the synthetic product differs substantially from that reported previously for racemic α-aminopropiophenone (1) hydrochloride (184,[12] and 187 °C[13]) and is in agreement with the melting point reported by Takamatsu (175–176 °C[14]) for (+)-α-aminopropiophenone [(+)-1] hydrochloride. Furthermore, it was reported[10] that when this salt was converted to an amine oxalate, a solid with a melting point of 172–175 °C, which showed no melting point depression with natural cathinone [(−)-1] oxalate, was obtained. These results seem to suggest that the stereospecific synthesis of (−)-α-aminopropiophenone [(−)-1] hydrochloride from propiophenone had been accomplished without the benefit of optically active reagents, solvents, or resolution.

Other apparent inconsistencies appear in the literature relating to 1. For example, the report[14] that treatment of α-aminopropiophenone [(±)-1] with ethanolic hydrochloric acid gave (+)-α-aminopropiophenone hydrochloride [(+)-1: mp 175–176 °C; $[\alpha]^{26}_D$ +47.1°] would appear to be an error; presumably the *l*-mandelate salt of (+)-α-aminopropiophenone [(+)-1] was treated with ethanolic hydrochloric acid.

Scheme I



In the light of increased interest in expanding the pharmacological and medical investigations of the major constituents of Khat[2] and because known methods of resolution of racemic α-aminopropiophenone (1) were inadequate for the preparation of gram quantities of the required antipodes of 1, we undertook the development of an improved synthetic pathway to optically active 1. At the same time, having pure 1 and its optical antipodes in hand, we were able to establish some of the properties and chemical behavior of 1 and of its salts and to explain some of the literature discrepancies.

Results and Discussion

Attempts to resolve (±)-α-aminopropiophenone [(±)-1] via the mandelate salt by following the reported procedures[7,14] yielded only minute quantities of product in spite of the care taken to exclude light. Somewhat better results were obtained with tartaric acid. Thus, (+)-α-aminopropiophenone [(+)-1] crystallized with (−)-tartaric acid, and the (−) enantiomer [(−)-1] crystallized with (+)-tartaric acid. For both antipodes the yields were small, probably due to the strong tendency of α-aminopropiophenone (1) to cyclize to 3,6-dimethyl-2,5-diphenyldihydropyrazine (3), with subsequent oxidation to 3,6-dimethyl-2,5-diphenylpyrazine (2) when it is not stabilized by the presence of strong acids.[13] Consequently, an alternative route to optically active cathinone (1) was developed (see Scheme I). Norephedrine (4) was resolved in high yield into its (+)

(6) Ristic, Th.; Thomas, a. *Arch. Pharm.* **1962**, *295*, 254.
(7) Karawya, M. S. *J. Pharm. Sci. UAR.* **1968**, *9*, 147.
(8) Rücker, G. *Planta Med.* **1973**, *24*, 61.
(9) United Nations Document MNAR/11/1975.
(10) United Nations Document MNAR/7/1978.
(11) These documents were unavailable from either the United Nations Library in New York or from the document library of the University of North Carolina at Chapel Hill which serves as a regional depository of the United Nations Documents. We obtained copies of the documents from the National Institute on Drug Abuse.
(12) Behr-Bergowski, L. *Chem. Ber.* **1897**, *30*, 1515.
(13) Gabriel, S. *Chem. Ber.* **1908**, *41*, 1127–1156.
(14) Takamatsu, H. *Yakugaku Zasshi* **1956**, *76*, 1219–1222; *Chem. Abstr.* **1957**, *51*, 4303c.

and (−) antipodes with *O,O*-dibenzoyl-*d*-tartaric acid.[15] Each enantiomer was converted to its *N*-formyl derivative (**5**) and oxidized with chromium trioxide in pyridine. Hydrolysis with 20% hydrochloric acid at 40 °C gave optically pure α-aminopropiophenone (**1**) hydrochloride without racemization. In this manner there was obtained, from racemic norephedrine (**4**), (−)-α-aminopropiophenone [(−)-**1**] in 39% overall yield and the (+) enantiomer [(+)-**1**] in 40% overall yield. It should be noted that use of an *N*-acetyl blocking group in the oxidation of norephedrine (**4**) to α-aminopropiophenone (**1**) was unsuitable because removal of the acetyl group led to racemization (~60%). Similarly, if deprotection of *N*-formyl-α-aminopropiophenone (**6**) was carried out with weaker acid (<20% HCl) and at higher temperature (>40 °C), racemization was observed.

An approach to the stereospecific synthesis of (*S*)-cathinone [(*S*)-**1**] from (*S*)-*N*-(methoxycarbonyl)alanine has been recently published.[17] The Friedel–Crafts yield was reported to be 50–60%; assuming a 90% yield in removal of the *N*-methoxycarbonyl protecting group, the overall yield obtained would be slightly higher than that obtained by our method. However, whereas our approach leads to both enantiomers on using a natural (and therefore relatively inexpensive) tartaric acid derivative, preparation of (*R*)-cathinone [(*R*)-**1**] by the procedure of McClure et al.[17] requires nonnatural alanine.

Surprisingly, the melting points obtained by us for racemic and optically active α-aminopropiophenone (**1**) hydrochloride were practically the same (racemic, mp 190–191 °C; optically active, mp 189–191 °C). Furthermore, our melting points for the optical antipodes were substantially higher than those previously reported (175–176 °C).[13] Our experiments suggest that the low melting point was observed when the samples were insufficiently dried.

Because it had been found that optically active α-aminopropiophenone (**1**) racemized readily in the absence of strong acids,[18] it occurred to us that the plant extract obtained by using dilute acetic acid at room temperature might have racemized to some extent during the extraction procedure and/or while present as the salt of a weak acid such as oxalic acid. The hydrochloride salts of (−)-α-aminopropiophenone [(−)-**1**] and of the racemate were therefore converted to the oxalate salts. The optically active and racemic oxalate salts had very similar melting points (optically active, mp 173–175 °C; racemic, mp 172–173 °C), as we had found for the hydrochloride salts. In addition, they did not exhibit melting point depression when admixed. Thus, although optical resolution by direct crystallization of mixtures of interconverting enantiomers is possible in principle,[19] the strong tendency of α-aminopropiophenone (**1**) to racemize and/or cyclize when it is not stabilized by the presence of a strong acid[13,18] may account for the apparent identity of the oxalate salt of the plant extract and of synthetic α-aminopropiophenone observed.[10] Clearly, in this case the melting points cannot serve as criteria for optical purity. The specific rotation reported[10] for the oxalate salt of the plant extract was −34.4° (*c* 0.7, methanol); the value obtained by us for the oxalate salt of (−)-α-aminopropiophenone [(−)-**1**] in separate experiments was −40.5° and −42.1° (*c* 0.3, methanol). It thus appears that the oxalate salt of the plant extract[10] had partially racemized. It should be noted that a concentration of 0.3 g/100 mL of methanol could be achieved only with difficulty. In fact, gentle heating was required which may account for the slight racemization observed upon dissolution (see Table I) and for the small difference in [α] obtained by us for the same salt (−40.5°, −42.1°). In order to achieve a concentration of 0.7 g/100 mL, the sample may have had to be heated by the authors,[10] causing further loss of optical activity. The tendency of the (−)-**1** oxalate to exhibit reduced optical rotation after being kept in solution was confirmed by our observation that, after the sample had been allowed to stand at room temperature for 3 days, the rotation had decreased in two separate experiments to −20.0° and −16.6°; similary, after a methanol solution of the (−)-**1** oxalate salt was warmed at 60 °C for 15 min, the rotation recorded was −27.0°.

Table I. Stability of (−)-α-Aminopropiophenone Oxalate in Methanol

Δ*t*, h	$[\alpha]_{obsd}$[a], deg	% racemization: calcd from $[\alpha]_{obsd}$[b]	% racemization: obsd by HPLC
0	−42.1	6	6
24	−31.2	30	9
48	−23.9	47	24
96	−16.6	63	34

[a] *c* = 0.3. [b] Calculated by assuming [α] 42.1° to be due to 6% racemization as observed by HPLC.

Table II. Stability of (−)-α-Aminopropiophenone in Methanol

Δ*t*, h	$[\alpha]_{obsd}$,[a] deg	Δ*t*, h	$[\alpha]_{obsd}$,[a] deg
0	−46.8	24	−16.6
0.3	−46.0	48	−9.5

[a] *c* = 0.24.

These observations suggest that racemization and/or dimerization and possibly subsequent oxidation may be taking place in the solution of the oxalate salt. In order to gain further insight into this problem, we sought an independent measure of the *optical* purity of the samples. A possible approach was to take advantage of the reaction of amines with isocyanates, known to be rapid and quantitative,[20] to prepare diastereomeric, unsymmetrical ureas and analyze the products by HPLC.[21] To this end, commercially available (*S*)-(−)-α-methylbenzyl isocyanate[22] was added to a slurry of racemic cathinone in tetrahydrofuran. HPLC analysis on silica gel gave two equally intense, well-separated signals for the diastereomeric ureas. In order to avoid racemization, we needed a procedure to derivatize the cathinone salts directly. This was accomplished by treating a slurry of the salt in tetrahydrofuran with the isocyanate followed by the addition of triethylamine. Analysis of the cathinone (**1**) salts by this method confirmed that they were all >98% optically pure.

When this procedure was used to follow the apparent racemization of (−)-cathinone [(−)-**1**] oxalate in methanol solution, a slow increase in the concentration of the (+) enantiomer [(+)-**1**] was observed, but it accounted for only a fraction of the observed decrease in the absolute value

(15) The resolution of norephedrine with tartaric acid has been reported.[16] In our hands *O,O*-dibenzoyltartaric acid was a more satisfactory resolving agent.

(16) Nagai, W. N.; Kanao, S. *Justus Liebigs Ann. Chem.* **1929**, *470*, 156–182.

(17) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431–2433.

(18) Takamatsu, H. *Yakugaku Zasshi* **1956**, *76*, 1223–1226.

(19) Collet, A.; Brienne, M.-J.; Jacques, J. *Chem. Rev.* **1980**, *80*, 215–230.

(20) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592–601.

(21) Rice, K. C., private communication.

(22) The material supplied by Aldrich has the incorrect configurational assignment. Thus, the catalog reads "(*R*)-(−)-2-methylbenzyl isocyanate"; it is in fact the (*S*)-(−) enantiomer. This has been confirmed by Aldrich.

of the optical rotation (Table I). In fact, careful HPLC and TLC analyses revealed the presence of decomposition products. A similar situation obtained with a solution of the (−)-cathinone [(−)-1] free base in methanol (Table II). In this case the racemization could not be followed by HPLC because evaporation of the methanol (required prior to derivatization with isocyanate) led to decomposition. However, the optical rotation decreased to 36% of its initial value in 48 h, and TLC indicated the same decomposition products to be present that had been observed for (−)-cathinone [(−)-1] oxalate. To our surprise, a methylene chloride solution of the (−)-cathinone [(−)-1] free base was quite stable at room temperature over a 24-h period. Thus, the optical rotation was constant, no racemization was observed by HPLC, and no new products were observed by either HPLC or TLC. Evaporation to dryness and redissolution gave a TLC identical with that obtained from the methanol solution of (−)-cathinone [(−)-1] after 48 h. Isolation of the major decomposition product showed it to be the dimethyldiphenylpyrazine **2**. Thus, it appears that cathinone (1) is fairly stable in nonpolar, nonhydroxylic media. However, in hydroxylic solvents and in the absence of any solvents, it racemizes and dimerizes quite rapidly. Weak acids such as oxalic acid form a stable salt, but solutions of the salt undergo slow racemization and/or decomposition as well.

Because the cathinone (1) free base was found to be quite stable in methylene chloride, the quantitative interconversion of cathinone salts without racemization appeared feasible. Indeed, it was found that when the *d*-camphor-β-sulfonate salt of (−)-α-aminopropiophenone [(−)-1] was prepared as described,[14] carefully treated with base, extracted, and acidified with hydrochloric acid, the product, after crystallization, was optically pure.

Conclusions

(1) The optical antipodes of α-aminopropiophenone can be prepared in high yield by oxidation of optically active *N*-formylnorephedrine, followed by deblocking of the amino group. The resolution of norephedrine is best carried out by using *O,O*-dibenzoyltartaric acid.

(2) Melting points cannot be used as criteria of the optical purity of cathinone derivatives because of the (a) similarity of the melting points of the racemic and optically active compound and (b) lack of melting point depression upon admixing of opposite antipodes and/or racemic and optically active compounds.

(3) The cathinone free base racemizes and dimerizes readily in a hydroxylic medium. Similar behavior is observed for solutions of the oxalate salt but at a somewhat reduced rate; therefore, the plant extract of Schorno[10] may have been partially racemized.

(4) The cathinone free base is fairly stable as a dilute solution in nonpolar, nonhydroxylic media, and, consequently, strong acid salts of optically active cathinone can be interconverted without racemization.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus or on a Koffler hot stage. Proton NMR spectra were recorded on a Varian EM-360 spectrometer, and mass spectra were obtained on an AEI MS-902 spectrometer. All optical rotations were recorded at the sodium D line with a Perkin-Elmer Model 141 polarimeter (1-dm cell). Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Il.

Resolution of Norephedrine (4). A solution of 80 g (0.53 mol) of (±)-norephedrine in 400 mL of EtOH was combined at 60 °C with a solution of 95 g (0.27 mol) of *O,O*-dibenzoyl-*d*-tartaric acid in a mixture of 100 mL of EtOH and 250 mL of *i*-PrOH. When the mixture had cooled slightly, some seed crystals were added, and the salt was allowed to crystallize undisturbed for 3 days. The clear supernatant was carefully decanted from the crystal cake of (+)-norephedrine *O,O*-dibenzoyl-*d*-tartrate. The solid was washed thoroughly with EtOH–*i*-PrOH, and the washings were filtered into the supernatant. This operation usually caused the crystallization of (−)-norephedrine *O,O*-dibenzoyl-*d*-tartrate in the filtrate. After 2 days, the (−)-norephedrine salt was collected by filtration, washed with THF and dried at 120 °C. The yield was 75 g (86%) of (−)-norephedrine *O,O*-dibenzoyl-*d*-tartrate and 68 g (78%) of (+)-norephedrine *O,O*-dibenzoyl-*d*-tartrate. Both products had a melting point of 196–200 °C dec. For conversion to the corresponding hydrochlorides, the salts were each treated with 150 mL of 7% ethanolic hydrochloric acid at 60 °C for 30 min. After evaporation of the solvent, the residue was triturated with THF which caused spontaneous crystallization. The solid was washed with THF and EtOH and vacuum dried. From the filtrates was obtained a second crop upon cooling. The following results were obtained. (−)-Norephedrine [(−)-4] hydrochloride: 40 g (81%); mp 170–172 °C; $[\alpha]^{20}_D$ −32.7° (*c* 1, H_2O) (lit.[15] mp 171–172 °C; $[\alpha]^{20}_D$ −33.7°). (+)-Norephedrine [(+)-4] hydrochloride: 37 g (74%); mp 170–172 °C; $[\alpha]^{20}_D$ +33.0° (*c* 1, H_2O) (lit.[15] mp 171–172 °C; $[\alpha]^{20}_D$ +33.40°).

(+)-*N*-Formylnorephedrine [(+)-5]. A solution of 110 g (0.73 mol) of (+)-norephedrine [(+)-4] in 250 mL of THF was cooled in an ice bath while a mixture of 35 g (0.73 mol) of 95% formic acid was added dropwise with stirring over 1 h. The pasty product was diluted with ether to give 134 g (94%) of the crystalline formate of (+)-4.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.71; H, 7.52; N, 7.06.

The formate was dissolved in 700 mL of toluene and refluxed for 2 days, with the water produced being separated in a Dean–Stark trap. The syrupy product (+)-5, which remained after evaporation of the solvent and vacuum drying, weighed 115 g (92%): NMR ($CDCl_3$) δ 0.93 (d, CH_3CH), 4.37 (m, CH(OH)–CH), 4.79 (d, CH(OH)–CH), 8.0 (s, NCHO).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.03; H, 7.45; N, 7.71.

(+)-*N*-Formyl-α-aminopropiophenone [(+)-6].[23] An ice-cold mixture of 3 L of CH_2Cl_2 and 190 g (2.4 mol) of pyridine was treated with 120 g (1.2 mol) of dry CrO_3 which was added in portions within a 30-min period. The purple-brown mixture was stirred at room temperature for 2 h. A solution of 38 g (0.21 mol) of (±)-5 in 200 mL CH_2Cl_2 was added to the CrO_3 mixture all at once with vigorous mechanical stirring. After 15 min, the yellow solution was decanted from a black, sticky precipitate and immediately extracted with 1 L of 5% NaOH solution followed by 1 L of 10% HCl solution. The organic phase was filtered through a bed of Na_2SO_4 and evaporated to a clear, light yellow syrup. After vacuum drying overnight, the product (+)-6 weighed 31 g (83% yield): NMR ($CDCl_3$) δ 1.42 (d, CH_3CH); 5.56 (d, q, $CHCH_3$); 8.20 (s, NHCHO). The material was sufficiently pure for further synthesis.

(+)-α-Aminopropiophenone [(+)-1] Hydrochloride. A suspension of 21 g (0.12 mol) of (+)-6 in 200 mL of 20% HCl was vigorously stirred at 40 °C until a clear solution resulted (~5 h). The mixture was evaporated to dryness, and the residue was crystallized from *i*-PrOH–Et_2O. After the sample was dried overnight (P_2O_5–KOH), 16 g (72%) of (+)-1·HCl was obtained: mp 186–189 °C; $[\alpha]^{24}_D$ +43.5° (*c* 1, H_2O). One recrystallization from *i*-PrOH–THF gave a product: mp 189–190 °C dec; and $[\alpha]^{23}_D$ +47.3° (*c* 1, H_2O).

Anal. Calcd for $C_9H_{12}ClNO$; C, 58.22; H, 6.52; N, 7.55. Found: C, 58.34; H, 6.67; N, 7.35.

A 1-g sample of this material was exposed to air for 2 days after which its melting point was 175–177 °C and its specific rotation was $[\alpha]^{21}_D$ +46.9° (*c* 1, H_2O) [lit.[12] mp 175–176 °C; [α] +47.1° (H_2O)]. Vacuum drying of the air-exposed sample over P_2O_5 and KOH for 16 h raised the melting point to 189–191 °C and the rotation to $[\alpha]^{21}_D$ +47.3° (*c* 1, H_2O) with a concomitant weight loss of approximately 0.7%.

Hydrolysis of (+)-6 with 2% HCl gave (+)-1·HCl: mp 167–176 °C; $[\alpha]^{23}_D$ +23.5° (*c* 1, H_2O).

(23) Ratcliffe, R.; Rodelhorst, R. *J. Org. Chem.* **1970**, *35*, 4000–4002.

(-)-*N*-Formylnorephedrine [(-)-5]. The free base isolated from 115 g (0.62 mol) of (-)-norephedrine [(-)-4] hydrochloride by $CHCl_3$–aqueous $NaHCO_3$ partition was dissolved in 250 mL of THF. While a temperature of 5 °C was maintained, a mixture of 30 g (0.7 mol) of 95% formic acid and 30 mL of THF was added dropwise over 2 h. The resulting thick suspension was diluted with 520 mL of Et_2O and stored at room temperature for 1 h. Filtration and washing with Et_2O gave 122 g of (-)-norephedrine [(-)-4] formate, mp 144–145 °C.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.03; H, 7.44; N, 7.02.

The dried formate was refluxed for 2.5 days with 800 mL of toluene in a Dean–Stark trap until all the water was removed. The solvent was then evaporated, and vacuum drying gave 106 g (96%) of (-)-*N*-formylnorephedrine [(-)-5] as a slightly yellow syrup.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.78; H, 7.20; N, 7.57.

(-)-α-Aminopropiophenone [(-)-1] Hydrochloride. The oxidation of (-)-5 was carried out in four portions of 26.5 g with chromium trioxide–pyridine complex as described for the (+) antipode. The corresponding (-)-*N*-formyl-α-aminopropiophenone [(-)-6] produced (91 g, 83%) had the same NMR characteristics as (+)-6. Hydrolysis of 90 g (0.5 mol) of (-)-6 with 6 N hydrochloric acid (500 mL, 3 mol) at 40 °C and evaporation of the excess acid provided (-)-1·HCl as a tan solid, 65 g (69.5%). Two recrystallizations from *i*-PrOH–Et_2O gave pure product (mp 175–176 °C) which after vacuum drying over P_2O_5–KOH had a melting point of 188–190 °C dec. The salt weighed 56 g (60%) and had $[\alpha]^{21}_D$ −46.9° (*c* 1, H_2O). A mixture melting point with the other antipode or with racemic 1·HCl gave a depression to 176–177 °C dec.

Anal. Calcd for $C_9H_{12}ClNO$: C, 58.22; H, 6.52; N, 7.55. Found: C, 58.45; H, 6.83; N, 7.52.

Resolution of α-Aminopropiophenone (1). (a) With *d*-Tartaric Acid. A solution of 1.8 g (0.01 mol) of 1·HCl in 10 mL water was added all at once to an emulsion prepared by shaking 100 mL of CH_2Cl_2 and 10 mL of 1 M $NaHCO_3$ solution. After the mixture was shaken for 20 s, the organic phase was separated as soon as possible and immediately added to a solution of 0.8 g (0.005 mol) of *d*-tartaric acid in 35 mL of EtOH. After 2 days at room temperature, 450 mg (17%) white crystals [mp 162–164 °C dec; $[\alpha]^{23}_D$ +15.5° (*c* 1, H_2O)] were separated. Treatment of the salt with ethanolic HCl gave (+)-1·HCl: 280 mg (75%) from tartarate); mp ~176 °C dec; $[\alpha]^{24}_D$ −46.8° (*c* 1, H_2O).

(b) With *d*-Camphor-β-sulfonic Acid.[14] In 5 mL of water were dissolved successively 0.8 g (0.02 mol) of NaOH, 4.7 g (0.02 mol) of *d*-camphor-β-sulfonic acid, and 3.7 g (0.02 mol) of 4·HCl. The resulting orange-yellow solution was kept at 5 °C for 2 days. A white crystalline precipitate was separated by filtration and washed with *i*-PrOH–Me_2CO to give 0.5 g of salt: mp 200–202 °C dec; $[\alpha]^{23}_D$ +6.5° (*c* 1, H_2O) (lit.[14] mp 202–202.5 °C; $[\alpha]^{25}_D$ +1.2°). The combined filtrate and washings were cooled at −15 °C for 3 days to yield an additional 1.1 g of the above product; the total yield was 1.6 g (42%). A 200-mg sample which was treated with $NaHCO_3$–CH_2Cl_2 as above and the organic phase immediately reacted with ethanolic HCl to give 52 mg (55%) of (-)-1·HCl: mp 173–176 °C; $[\alpha]^{24}_D$ −45.0° (*c* 1, H_2O).

α-Aminopropiophenone (1) Oxalate.[10] A 100-mg (0.054 mmol) sample of (-)-1·HCl was converted to the free base as described above. The CH_2Cl_2 solution of (-)-4 was immediately added to a solution of 50 mg (0.0055 mol) of oxalic acid in 7 mL of EtOH. After the mixture was allowed to stand at room temperature for 15 h, the fine precipitate of (-)-1 oxalate was separated by filtration and vacuum dried. This material had the following: mp 173–175 °C; $[\alpha]^{25}_D$ −40.5° (*c* 0.3, MeOH), −46.5° (*c* 1, H_2O) [lit.[8] mp 172–175 °C; $[\alpha]^{21}_D$ −34.4° (*c* 0.7, MeOH)]. After the methanolic solution had been stored at room temperature for 3 days, it showed $[\alpha]^{22}_D$ −20.0° (*c* 0.3, MeOH). A methanolic solution of the (-)-1 oxalate was heated at 60 °C for 15 min. After this treatment, the specific rotation had decreased to $[\alpha]^{22}_D$ −27.0° (*c* 0.3, MeOH).

Racemic 1 oxalate prepared in the same manner as above had a melting point of 172–173 °C (lit.[10] 172–175 °C). A mixture of (+)-1 oxalate and (-)-1 oxalate had a melting point of 172–175 °C.

Stability Study of (-)-α-Aminopropiophenone [(-)-1] Oxalate. The optical rotation of a solution of 30 mg of (-)-α-aminopropiophenone oxalate in 10 mL of MeOH was checked at 24-h intervals (Table I) by using a 1-mL cell with a 10-cm path length and a Perkin-Elmer 141 polarimeter. Simultaneously with each polarimeter reading, 0.3-mL aliquot was evaporated to dryness and the residue slurried in 0.3 mL of dry THF. The slurry was treated with 10 μL of (-)-(*S*)-α-methylbenzyl isocyanate followed by 5 μL of dry Et_3N. The resulting solution was analyzed by HPLC. After 2 weeks, the solution ([α] −13.9°) was evaporated to ca. 0.7 mL, applied to a 10 × 5 cm analytical silica gel plate and eluted with $CHCl_3$/Me_2CO/NH_4OH (8:3:1). The band of R_f 0.28, representing the major component, was isolated and analyzed by mass spectroscopy: calcd for $C_{18}H_{16}N_2$, *m/e* 260.1312; found, *m/e* 260.1314.

Stability Study of (-)-α-Aminopropiophenone [(-)-1] in Methanol. To a biphasic mixture of 100 mg of Na_2CO_3 in 5 mL of H_2O and 10 mL of Et_2O was added 30 mg of (-)-α-aminopropiophenone hydrochloride. After the mixture was shaken for 5 s, the organic phase was separated, added to 10 mL of MeOH, and evaporated to ca. 8 mL. The volume was then adjusted to 10 mL with MeOH, and aliquots were removed periodically for measurement of the optical rotation. Evaporation of the methanol invariably led to the observation of a racemate by HPLC. TLC analysis after a week showed the same product mixture as obtained for (-)-1 oxalate.

Stability Study of (-)-α-Aminopropiophenone [(-)-1] in Methylene Chloride. To an emulsion of 100 mg of Na_2CO_3 in 5 mL of H_2O and 10 mL of CH_2Cl_2 was added 30 mg of (-)-α-aminopropiophenone hydrochloride. After the mixture was shaken for 5 s, the organic phase was separated. Aliquots were checked by HPLC, and the optical rotation was measured over a 24-h period. The initial rotation was $[\alpha]^{26}_D$ −26.5° (*c* 0.24, CH_2Cl_2); after 24 h, the rotation was $[\alpha]^{23}_D$ −25.8° (*c* 0.24, CH_2Cl_2). TLC analysis did not show any noticeable amount of decomposition.

Analysis of Decomposition Product of (-)-α-Aminopropiophenone [(-)-1] in Methylene Chloride. After partitioning 100 mg of (-)-α-aminopropiophenone hydrochloride between CH_2Cl_2 and aqueous Na_2CO_3, the organic phase was evaporated under N_2 at −10 °C to give a pale yellow oil. After warming to ambient temperature and standing for 30 min, the oil turned bright yellow. At the end of 40 min, a yellow solid crystallized out. It was dissolved in CH_2Cl_2; after 2 h, the yellow color had faded. TLC indicated no starting material. Evaporation of the solvent and washing of the crystalline solid with MeOH gave pale yellow crystals: mp 116–120 °C; mass spectrum, *m/e* 260.1314. The reported melting point for dimethyldiphenylpyrazine is 125–126 °C,[12] and the calculated mass for $C_{18}H_{16}N_2$ is 260.1312.

HPLC Analysis. The reaction mixture resulting from treatment of α-aminopropiophenone (salt or free base) with α-methylbenzyl isocyanate was analyzed on a Radial Pak B (Waters Associates) column by using an isocratic solvent mixture of 1% AcOH and 9% *i*-PrOH in isooctane with a flow rate of 1 mL/min as the eluant with monitoring at 260 nm. Typical retention times were 4–5 min.

Acknowledgment. This work was supported under Contract 271-79-3618 with the National Institute on Drug Abuse (NIDA), Research Technology Branch, Division of Research.

Registry No. (+)-1, 80096-54-4; (+)-1·HCl, 76333-53-4; (+)-1 oxalate, 81626-15-5; (+)-1 tartrate, 81626-16-6; (-)-1, 71031-15-7; (-)-1·HCl, 72739-14-1; (-)-1 oxalate, 81626-17-7; (-)-1 *d*-camphor-β-sulfonate, 81655-26-7; 2, 54600-85-0; (+)-4, 37577-28-9; (+)-4 *O,O*-dibenzoyl-*d*-tartrate, 81626-18-8; (+)-4·HCl, 40626-29-7; (+)-4 formate, 81626-19-9; (-)-4, 492-41-1; (-)-4 *O,O*-dibenzoyl-*d*-tartrate, 81626-20-2; (-)-4·HCl, 3198-15-0; (-)-4 formate, 53630-90-3; (+)-5, 81626-21-3; (-)-5, 77387-33-8; (+)-6, 81626-22-4; (-)-6, 81626-23-5; (-)-(*S*)-methylbenzyl isocyanate, 21872-32-2.