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(+)-Cocaine has been prepared from commercially available 3-tropinone in four steps. Synthetic procedures and experimental details are provided.

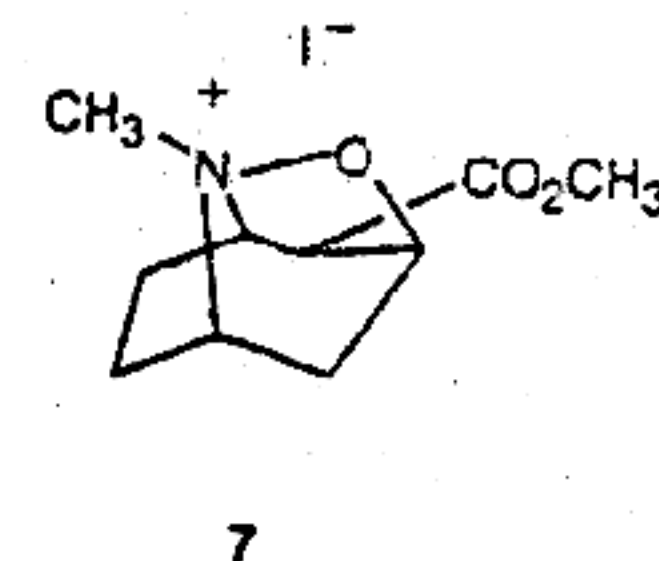
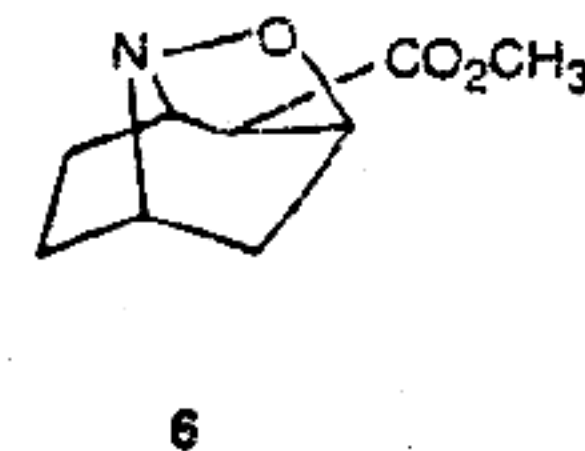
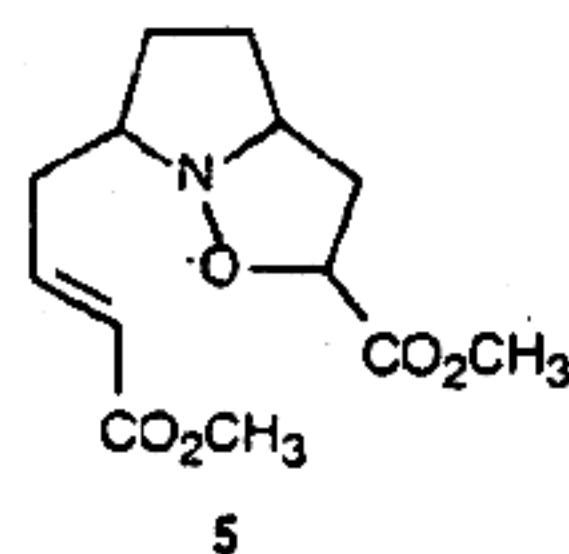
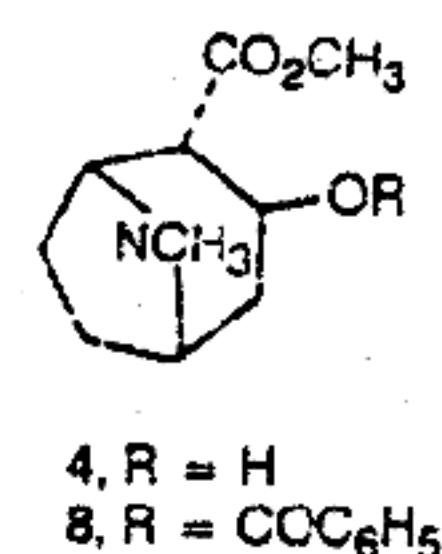
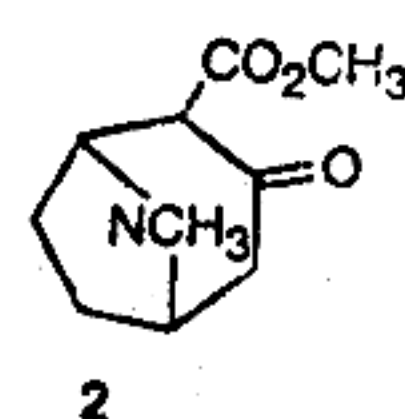
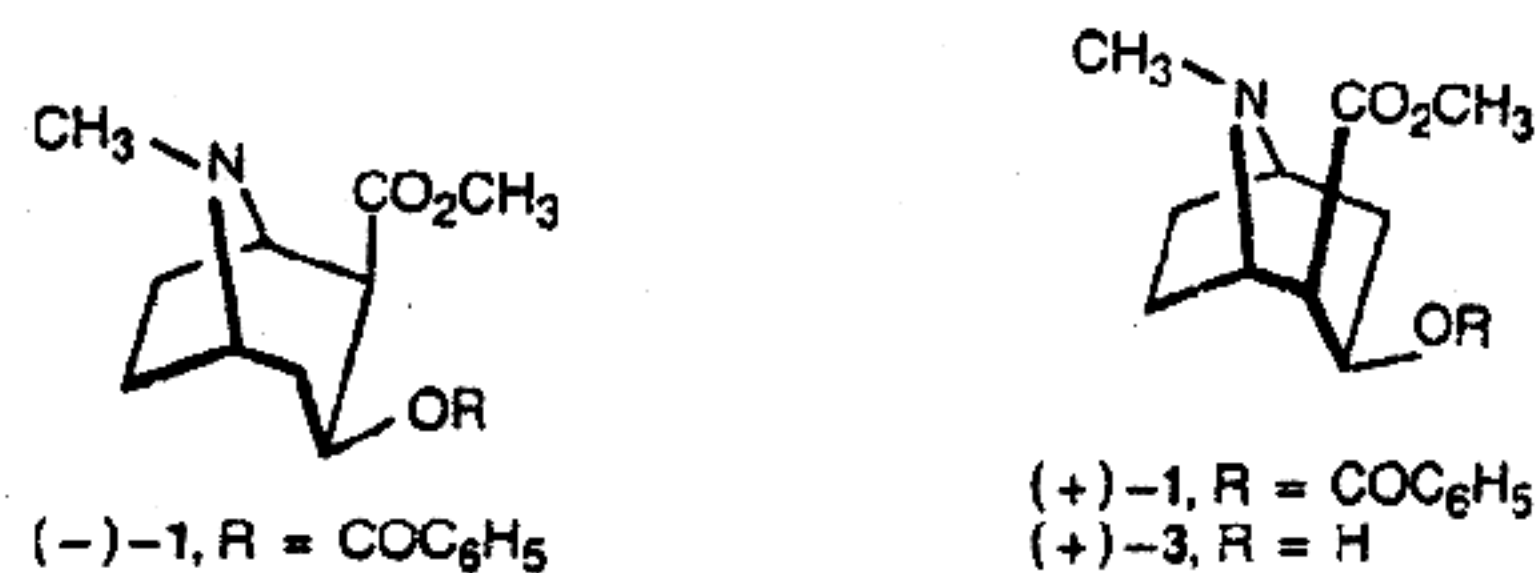
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Abuse of (-)-cocaine [(*-*)-1], an alkaloid obtained from the leaves of *Erythroxylan coca*, has grown from a relatively minor problem 12-15 years ago to a major public health threat today [1]. As a consequence there has been increased interest in both the natural [(*-*)-1] and unnatural [(+)-1] enantiomers. The need for unnatural cocaine [(+)-1] prompts us to report our synthesis, which combines several reported procedures. It is our hope that the availability of a relatively straightforward synthetic sequence to (+)-cocaine will promote research in comparative behavioral studies between the enantiomeric cocaines, in identification and investigation of a cocaine receptor and will aid in the legal prosecution of certain drug abuse cases.

The first total synthesis of (+)-cocaine, reported by Wilstatter in 1923 [2], involved condensation of acetonedicarboxylic acid monomethyl ester, methylamine and succinaldehyde to give (\pm)-2-(carbomethoxy)-3-tropinone (2), which was reduced by sodium amalgam to a mixture of (\pm)-ecgonine methyl ester (3) and (\pm)-pseudoecgonine methyl ester (4). The latter, 4, being less soluble, was separated by crystallization; the mother liquor yielded ecgonine methyl ester (3) hydrochloride. Benzoylation of the free base 3 with benzoic anhydride gave racemic cocaine which was resolved *via* its bitartrate salt to give (+)-cocaine [(+)-1].

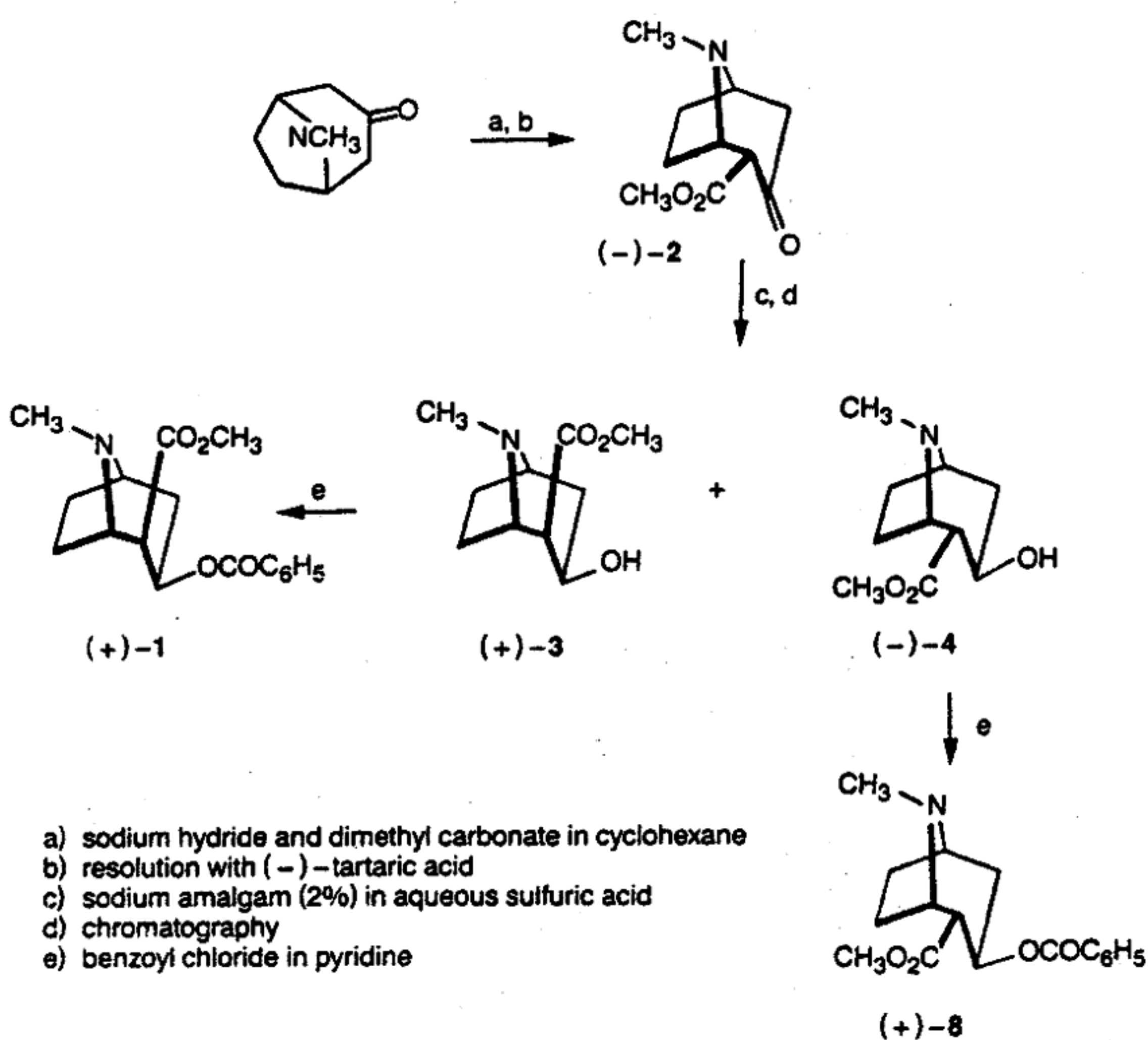
In addition to this specific synthesis of (+)-cocaine, there are three reports of the synthesis of (\pm)-cocaine, which, in principle, could be resolved to give (+)-cocaine. A Russian group reported [3,4] the synthesis of (\pm)-cocaine following the Wilstatter [2] pathway but utilizing an alternative synthesis of (\pm)-2-(carbomethoxy)-3-tropinone (2). They reported a 35% yield of (\pm)-ecgonine methyl ester (3) from (\pm)-2-(carbomethoxy)-3-tropinone (2) and utilized benzoyl chloride at 100° either neat [3] or in benzene with sodium carbonate [4] to prepare (\pm)-cocaine in 84% [3] and 61% [4] yield, respectively.

More recently Tufariello [5] reported a multistep synthesis of (\pm)-cocaine which involved the preparation of hexahydropyrrolo[1,2-*b*]isoxazole (5) as a key intermediate. When 5 was refluxed in xylene, methyl acrylate was expelled and the resulting nitron spontaneously cyclized to 6. Methylation of 6 with methyl iodide gave the methiodide 7 which on treatment with activated



zinc in aqueous acetic acid provided, stereospecifically, (\pm)-ecgonine methyl ester (3). Benzoylation of 3 afforded (\pm)-cocaine (1).

Even though the Tufariello [5] synthesis provides an efficient and highly stereoselective synthesis of (\pm)-cocaine, two factors led us to investigate the original Wilstatter approach for the synthesis of gram quantities of (\pm)-cocaine. First, it appeared to involve less steps, and second, it held the promise of higher yield. Thus, whereas the Tufariello synthesis involved six steps and gave (\pm)-ecgonine methyl ester (3) in 18% overall yield, starting from commercially available 3-tropinone and following the Wilstatter route involves two steps proceeding in 80% and 35% yield, respectively, to give (\pm)-ecgonine methyl ester (3) in 28% overall yield. In fact, using commercially available 3-tropinone, our initial synthesis followed the Wilstatter procedure. Specifically, (\pm)-2-(carbomethoxy)-3-tropinone (2) was prepared in 80% yield by the sodium hydride catalyzed carbomethoxylation of 3-tropinone [6], and reduction



none *via* its bitartrate salt is known [9,10], and since Findlay had shown [10] that natural cocaine could be degraded to (+)-2-(carbomethoxy)-3-tropinone, it was obvious that the (-)-enantiomer would be the required precursor for (+)-cocaine. In addition, since the separation of cocaine (1) from pseudococaine (8) had proven to be tedious, it was decided to separate ecgonine methyl ester (3) from pseudoecgonine methyl ester (4) prior to benzylation. A final modification of the synthesis was the utilization of the benzylation procedure of Sinnema [11] to convert ecgonine methyl ester to cocaine.

An outline of the preferred synthetic route from 3-tropinone to (+)-cocaine is shown in Chart 1. Resolution of (\pm)-2-(carbomethoxy)-3-tropinone with (-)-tartaric acid gave (-)-2-(carbomethoxy)-3-tropinone [(-)-2] in about 35% yield. [Treatment of the free base from the mother liquors with (+)-tartaric acid followed by free basing of the mother liquor from the (+)-tartrate salt and retreatment with (-)-tartaric acid raises the actual recovery to about 50%.] Ecgonine methyl ester [(+)-3] was separated from the product mixture of the sodium amalgam reduction by column chromatography in overall yield of 30%. Benzylation with benzoyl chloride in pyridine afforded 89% of (+)-cocaine which, after purification had physical properties matching those of (-)-cocaine.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary tube apparatus or on a Koffler hot stage. All optical rotations were recorded at the sodium D line with a Perkin-Elmer Model 141 polarimeter (1-dm cell).

(\pm)-2-Carbomethoxy-3-tropinone (2).

The title compound was prepared by the previously reported [6] procedure.

(S)-2-(Carbomethoxy)-3-tropinone [(-)-2].

To a solution of (\pm)-2-(carbomethoxy)-3-tropinone (33.8 g, 0.172 mol) in absolute ethanol (100 ml) was added a solution of (-)-tartaric acid (25.7 g, 0.171 mole) in absolute ethanol (100 ml). Eventually, crystallization to give (S)-(-)-2-(carbomethoxy)-3-tropinone bitartrate took place. The solid, after filtration and drying, weighed 12.4 g and had $[\alpha]_D^{25} - 15.1^\circ$ (c 2, water), Findlay [10] reported $[\alpha]_D^{20} - 15.4^\circ$ (c 2, water) while Clarke and co-workers [9] reported $[\alpha]_D^{25} + 16.4^\circ$ for the opposite enantiomer. The free base was obtained by dissolution in aqueous sodium carbonate and extraction with dichloromethane. After solvent evaporation and drying, 5.7 g (34%) of (S)-(-)-2-(carbomethoxy)-3-tropinone [(-)-2] $[\alpha]_D^{25} - 20.2^\circ$ (c 1, methanol) [lit [10] -18.0° (c 1, methanol)] was obtained. In another experiment, 11 g (52% yield) of the title compound was obtained from 42.2 g of (\pm)-2-(carbomethoxy)-3-tropinone.

(+)-Ecgonine Methyl Ester [(+)-3] and (-)-Pseudoecgonine Methyl Ester [(-)-4].

The sodium-amalgam reduction [2,3] of (S)-(-)-2-(carbomethoxy)-3-tropinone was carried out on 6-8 g batches. A typical procedure is as follows. To an ice-cold solution of (S)-(-)-2-(carbomethoxy)-3-tropinone (7.0 g, 0.036 mole) in pH 3.4 sulfuric acid (100 ml) was added 1100 g of 1.5% sodium amalgam over a 3.5 hour period. Throughout the temperature was maintained between -2° and $+7^\circ$, and the pH was

with sodium amalgam provided (\pm)-ecgonine methyl ester (3) and (\pm)-pseudoecgonine methyl ester (4), as reported [2]. It was tempting, however, to explore other, more modern, reduction procedures to establish whether greater selectivity could be achieved. In fact, a predominance of (\pm)-allopseudoecgonine methyl ester was obtained by the use of sodium borohydride in methanol at -30° [6]. Strikingly, none of the other reagents which were tried gave *any* of the ecgonine methyl ester isomers [7]. Similarly, attempts to reduce the known [2] *O*-benzoyl derivative of 2-(carbomethoxy)-3-tropinone failed to produce any of the cocaine isomers [8]. It thus appears that sodium amalgam reduction is still the viable synthetic route from 2-(carbomethoxy)-3-tropinone (2) to ecgonine methyl ester (3). In our hands, the ratio of (\pm)-pseudoecgonine methyl ester (4) to (\pm)-ecgonine methyl ester (3) varied from 1:2 to 2:3, and the overall yield ranged between 50% and 70%.

Benzylation of the product mixture [(\pm)-ecgonine methyl ester (3) and (\pm)-pseudoecgonine methyl ester (4)] with benzoic anhydride in the presence of DBU gave a mixture of (\pm)-cocaine (1) and (\pm)-pseudococaine (8) in 75% yield. The isomers were separated by fractional crystallization or chromatographically, and (\pm)-cocaine was subsequently resolved *via* its tartrate salt to give (+)-cocaine in 24% yield. Since the overall yield from 3-tropinone was only about 5% (or 10% correcting for the resolution), this meant that large amounts of material would have to be handled, particularly through the sodium amalgam reduction step, in order to prepare gram quantities of (+)-cocaine. We therefore considered the possibility of performing a resolution at the earliest possible stage of the synthesis, *i.e.* of (\pm)-2-(carbomethoxy)-3-tropinone. Indeed, the resolution of (\pm)-2-(carbomethoxy)-3-tropi-

maintained between 3 and 4 (bromophenol blue indicator) by periodic addition of 30% sulfuric acid. Water was also added to dissolve some of the salts which precipitated. After the addition of the amalgam was complete, stirring at pH about 3.5 was continued for 35 minutes. After separation of the mercury, the solution was brought to pH 11 with ammonium hydroxide and extracted with chloroform (7 x 200 ml). Analysis of the extract by gc showed it to contain a 2:1 mixture of (+)-ecgonine methyl ester [(+)-3] and (-)-pseudoecgonine methyl ester [(-)-4]. Evaporation of the dried (sodium sulfate) extract afforded 8.24 g of a greenish syrup. This material was chromatographed on a silica gel-60

(230-400 mesh, 300 g) low pressure column (6 cm i. d.) eluting with chloroform-*t*-butylmethyl ether-ammonium hydroxide (95:5:1) to give 2.39 g of slightly impure (+)-ecgonine methyl ester [(+)-3] and 1.79 g (25%) of (-)-pseudoecgonine methyl ester [(-)-4]. Treatment of a diethyl ether solution of [(+)-3] with methanolic hydrochloric acid and recrystallization of the resultant [(+)-3] hydrochloride from methanol-diethylether (2:1) gave 2.33 g (28%) of pure (+)-ecgonine methyl ester [(+)-3] hydrochloride, mp 213.5-214.5°, $[\alpha]_D^{24} + 52.3^\circ$ (c 1, methanol). The literature values [12] for the (-)-enantiomer are 213-213.5° and $[\alpha]_D^{24} - 50^\circ$ (c 1, methanol). Recrystallization of [(-)-4] from diethylether gave crystalline solid, mp 114-115°, $[\alpha]_D^{24} - 22.5^\circ$ (c 1, water). The literature [13] values for the (+)-enantiomer are: mp 114-116° and $[\alpha]_D^{20} + 22.8^\circ$ (c 1.7, water).

(+)-Cocaine [(+)-1].

To a slurry of (+)-ecgonine methyl ester [(+)-3] hydrochloride (7.8 g, 0.0332 mole) in 70 ml of dry pyridine cooled in an ice bath was added, slowly and with stirring, a solution of benzoyl chloride (5.8 g, 0.0497 mole) in dry pyridine (30 ml). After overnight stirring at ambient temperature, the solid was removed by filtration and dried thoroughly. The crude yield of (+)-cocaine hydrochloride was 14.5 g. The salt was dissolved in aqueous potassium carbonate and the solution extracted with chloroform (6 x 200 ml). The organic phase was dried and evaporated to give 9.9 g (98%) of [(+)-1] as an off-white solid. Purification by elution through a short silica gel 60 (230-400 mesh, 200 g) column (7 cm i. d.) with hexane-*t*-butyl methyl ether-ammonia (50:50:1) gave 8.9 g (89%) of white solid; mp 96-98°, $[\alpha]_D^{24} + 15.5^\circ$ (c 1, chloroform), $[\alpha]_D^{24} + 35.7^\circ$ (c 1, 50% aqueous ethanol). Reported [12] values for [(-)-1] are: mp 98°; $[\alpha]_D^{20} - 16^\circ$ (c 4, chloroform); $[\alpha]_D^{18} - 35^\circ$ (c 1, 50% aqueous ethanol).

(-)-Pseudococaine [(-)-8].

To a solution of (-)-pseudoecgonine methyl ester (2.60 g, 0.013 mole) in dry pyridine (25 ml) was added dropwise in ½ hour a solution of benzoyl chloride (3.48 g, 0.0225 mole) in dry pyridine (100 ml) and stirred at ambient temperature for 24 hours. The volatiles were evaporated affording 4.5 g of crude (-)-pseudococaine hydrochloride. The salt was dissolved in aqueous potassium carbonate and extracted with chloroform (6 x 200 ml). The extract was dried over sodium sulfate, filtered and evaporated, yielding 3.56 g of syrupy material which was converted to the hydrochloride salt in diethyl ether with methanolic hydrochloric acid. Crystallization from methanol-diethyl ether (1:1) gave 4.1 g (93%), mp

210-212°, $[\alpha]_D^{24} - 43^\circ$ (c 1, methanol) and $[\alpha]_D^{24} - 42.3^\circ$ (c 1, water). For the (+)-enantiomer the reported [12] values are: mp 210° and $[\alpha]_D^{20} + 41^\circ$ (c 5, water).

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