1 in 50 ml of 98–100% HCO_2H was heated under reflux for 1 hr and then concentrated at 90° *in vacuo*. The residual solid, 22.3 g, melted at 117–119°. Recrystallization from EtOAc gave 17.8 g (64% yield) of **3**: mp 125–127°; ν (mineral oil) 3340 (s), 3100 (s), 2700–2400 (s, broad), 1665 cm^{-1} (s).

Anal. Calcd for $C_5H_6N_2O \cdot HCO_2H$: C, 46.13; H, 5.17; N, 17.94; neut equiv, ($HClO_4$ in glacial AcOH), 156. Found: C, 46.11; H, 5.11; N, 18.00; neut equiv, 157. (Note: 2-aminopyridines are monobasic toward $HClO_4$ in glacial ACOH, *e.g.*, 2-aminopyridine, mol wt 94, gives neut equiv 93).

When **1** and 98–100% HCO_2H were heated for 24 hr, **3** was the only product; **1** and HCO_2H–Ac_2O gave **3**; **1** and HCO_2COCH_3 gave **3**; **1**, HCO_2H, and $C_6H_{11}N{=}C{=}NC_6H_{11}$ in EtOAc gave only highly colored, high-melting materials that could not be identified; and **1** and HCO_2Me or HCO_2Et heated in sealed tubes for 18 hr at 125–150° gave only **3** as the identifiable product.

Formic Acid Salt of 2 (4).—A solution of 18.0 g (0.16 mol) of **2** and 90 ml of HCO_2COCH_3 was heated at 60° for 21 hr and then concentrated at 70° *in vacuo*. The residual oil crystallized spontaneously; it weighed 21.2 g (83% yield), mp 72–74°. Recrystallization from $(i\text{-Pr})_2O$ gave 17.2 g (69% yield) of **4**: mp 78–80°; ν (KBr) 3370 (s), 2840 (m), 1680 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{11}BrN_2O \cdot HCO_2H$: C, 48.02; H, 4.03; N, 8.62. Found C, 48.21; H, 3.96; N, 8.88.

Alternative procedures, *e.g.*, heating **2** with HCO_2H, with or without Ac_2O, under reflux or heating **2** HCl, HCO_2Na, and HCO_2H under reflux, gave **4**; **2** and Cl_3CCHO in $CHCl_3$ did not react.

Reaction of 1 with PhO_2CCH_3. Preparation of 8.—A mixture of 1.0 g (0.091 mol) of **1** and 2.2 g of PhO_2CCH_3 was kept at 0° and then at 25° for 4 days; only **1** was recovered. No reaction occurred following the addition of 0.5 g of PhOH. When the same reactants were heated for 4 hr at 65° and the mixture was concentrated *in vacuo*, a residue, 1.0 g, mp 93–99°, was obtained. This was dissolved in 10 ml of boiling PhMe, the hot solution filtered, and the filtrate cooled to give 0.15 g of **1**. Concentration of the filtrate to dryness gave 0.60 of crude **8**, mp 102–105°. Recrystallization from $(i\text{-Pr})_2O$ gave 0.30 g (22% yield) of **8**: mp 102–104°; ν ($CDCl_3$) 3400 (s), 3000–2600 (s, broad), 1655 cm^{-1} (s).

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.31; N, 18.41. Found: C, 55.19; H, 5.44; N, 18.61.

Preparation of Phenyl Formate.—To 470.0 g (5.0 mol) of phenol and 1100 g (23.5 mol) of 98–100% HCO_2H was added in 0.5 hr 1120.0 g (7.3 mol) of $POCl_3$, and then, in one portion, 30.0 g (0.225 mol) of $AlCl_3$. The temperature rose spontaneously to 40°. The mixture was stirred without cooling for 2 hr and heated so that the internal temperature rose to 70° in 2 hr, and the temperature was maintained at 70° for 5 hr. The ice-cooled mixture was agitated and then diluted slowly with 1500 ml of ice-cooled H_2O-saturated Et_2O and then with 1500 g of ice. The H_2O layer was separated, 1500 ml of H_2O added, and the cooled mixture treated with solid $NaHCO_3$ until the pH was 7.5. The H_2O layer was again separated, and the Et_2O layer was washed with 500 ml of saturated H_2O–NaCl, dried, and concentrated. The residue weighed 615.3 g, $n^{26}D$ 1.5195, d^{20}_{20} 1.12. Analyses by glc indicated 65% phenyl formate, 33% phenol, and 2% unidentified impurities. The yield was 65%. The undistilled material was suitable for use; it could be distilled, bp 72–74° (13 mm), but the distilled material had the same composition as the crude product.

Registry No.—**3**, 31354-43-5; **4**, 31354-44-6; **5**, 31354-45-7; **6**, 26372-72-5; **7**, 1864-94-4; **8**, 31354-48-0; **9**, 31354-49-1.

A Total Synthesis of the Four Isomeric 2-Tropanols

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As part of an extensive study of pharmacologically active derivatives of L(+)-2α-tropanol and L(−)-2β-tropanol, it was necessary to demonstrate the feasibility of a total synthesis of these alcohols from commercially available raw materials; the quantities that might be required could not be prepared from available supplies of cocaine by the Bell and Archer synthesis.[1] It was also important to prepare the hitherto undescribed D(−)-2α-tropanol and D(+)-2β-tropanol to permit parallel studies of their derivatives.

Two total syntheses of L(+)-2α-tropanol from pyrrole in overall yields of 10–18% have been described;[2] optical resolution was achieved at the 2-tropanone stage. Recently R. E. Lyle and his associates[3] reported that the hydroboration–oxidation of tropidine gave L(+)-2α-tropanol in 43% yield, along with 50% of 3α-tropanol and small amounts of the β isomers. Since tropidine can be prepared from 3α-tropanol, and the latter by the well-known Robinson–Schöpf reaction, Lyle's work completes another total synthesis of the 2-tropanols. The novel total synthesis of anhydroecgonine[4,5] from benzene and diazoacetic ester by way of cycloheptatrienecarboxylic acid constitutes the first portion of still another total synthesis, for anhydroecgonine amide is an intermediate in the Bell and Archer synthesis. A study of the process economics of all these routes showed that they were unsatisfactory for large-scale synthesis.

We have used the synthesis shown in Scheme I to prepare racemic 2α-tropanol (**6**) from commercially available acetonedicarboxylic acid and 2,5-diethoxytetrahydrofuran in 25% overall yield; the starting materials can be made in high yield from citric acid and furan, respectively. The route shown was a simple combination of Findlay's synthesis[6,7] of **3** (now known[8] to be allopseudoecgonine) with the procedures used by Bell and Archer for the conversion of ecgonine to L(+)-**6**. Optical resolution of racemic **6** was achieved in high yield through appropriate salts of (+)-and (−)-tartaric acids. The novel D-(−)-2α-tropanol was epimerized to the novel D(+)-2β-tropanol by a procedure used previously for epimerization of the L(+)-2α isomer.[1]

Experimental Section[9]

2-Methoxycarbonyl-3-tropanone (1).—Findlay's procedure[6] was carried out at two–four times the scale used by him. The

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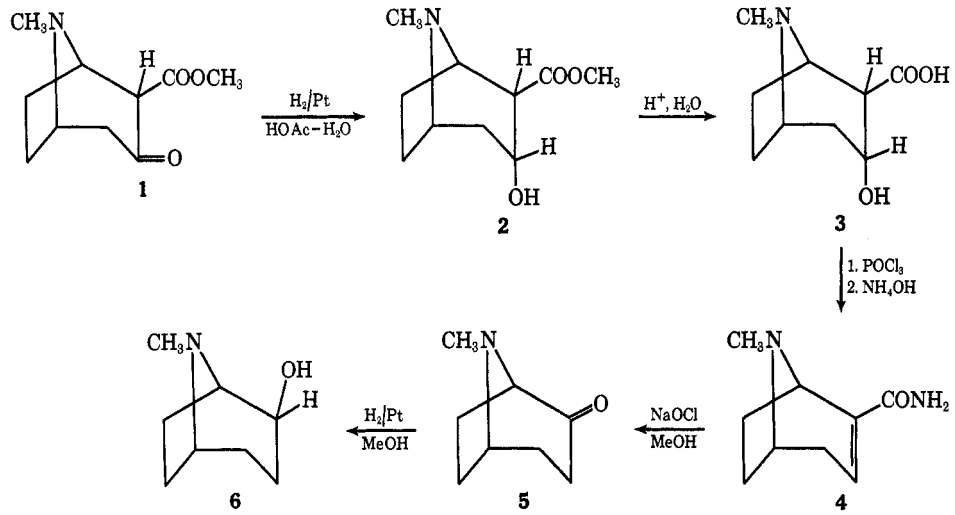
(7) S. P. Findlay, *ibid.*, **24**, 1540 (1959).

(8) A. Sinnema, L. Maat, A. J. Van der Gugten, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **87**, 1027 (1968). This article reviews all earlier syntheses and establishes the correct configuration for the four isomeric ecgonines and the cocaines derived therefrom. The assigned configurations differ from those assigned by some earlier workers.

(9) Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Dr. S. M. Nagy (Belmont, Mass.). Satisfactory ir and nmr spectra were recorded for all compounds. Analytical glc procedures for the 2-tropanols involved the use of an F & M 1609 instrument with a flame ionization detector. The 6-ft stainless steel column contained 5% Carbowax 20M on Haloport F and was operated at 150° with helium as a carrier gas at 20 ml/min. Under these conditions the retention times were for 2β-tropanol, 7–8 min; 2-tropanone, 11–12 min; 2α-tropanol, 16–17 min. The relative retention times were similar to those reported for analogous compounds in the 3-tropanol series by H. S. Aaron, G. E. Wicks, and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

SCHEME I



preparation of the succindialdehyde solution was simplified in several runs by using hydrochloric acid. Thus, in a 0.2-mol run, 32 g of 2,5-diethoxytetrahydrofuran was stirred with 160 ml of 0.2 *N* HCl until the solution became homogeneous. Most of our runs were allowed to proceed for 3 days at room temperature. The olive-green crude product (80–90%) melted over 4° ranges between 89 and 94°. When we were unable to reduce it catalytically, a variety of purification procedures were examined. Sublimation at 85° (0.1 mm) separated the bulk of the material from a nonvolatile tar but the sublimate, mp 92–97°, reduced very slowly. Recrystallization of the sublimate from aqueous acetone gave material, mp 103–105°, that reduced smoothly. We usually recrystallized the crude from aqueous acetone before carrying out the sublimation. The yield of purified material was 50%. We were unable to study the wide variety of alternative procedures that have been described for Robinson–Schöpf reactions of this type.[10-14]

(±)-**Allopseudoecgonine** (**3**).—Findlay[7] and others[8] had isolated the methyl ester **2** by way of an intermediate hydroacetate salt and obtained **2** as a crystalline solid in 54–80% yield. In a typical run a solution of 5 g of purified **1** in a mixture of 150 ml of HOAc and 25 ml of H_2O was hydrogenated over 0.6 g of PtO_2 at room temperature and 3.5 kg/cm² for 60 hr. A conventional work-up gave 80–100% yields of **2** as a yellow oil. No significant absorption of hydrogen was observed when crude **1** was reduced at room temperature in methanol or in aqueous acetic acid even at 175 kg/cm². Reduction of **1** over Raney nickel[15] gave poor quality material even after use of Findlay's work-up procedure[7] to eliminate unreduced **1**.

The ester **2** (18 g, 0.09 mol) was dissolved in 50 ml of concentrated HCl and 500 ml of H_2O was added. The solution was refluxed for 4 hr and then was taken to dryness under vacuum. The residue was triturated with acetone and dried to give 21 g (0.09 mol) of **3** HCl, mp 221–223° dec (lit.[8] mp 221–222°).

(±)-**2-Tropanone** (**5**).—The 21 g of **3** HCl was converted to (±)-anhydroecgonine amide (**4**) by Bell and Archer's procedure.[1] The crude solid product (85%) was then converted[1] to racemic **5** (73%) isolated as an oil, bp 80–120° (10 mm) [lit.[2] 99–99.5° (11 mm)]. The infrared spectrum was identical with that of L(+)-2-tropanone.[1]

(±)-**2α-Tropanol** (**6**).—A solution of 3 g of **5** in 100 ml of anhydrous MeOH was hydrogenated over 0.1 g of PtO_2 at room temperature and 3.5 kg/cm²; the calculated absorption of hydrogen occurred during 1 hr. A conventional work-up gave a quantitative yield of **6** HCl, mp 262–265°, whose ir spectrum was identical with that of authentic L(+)-2α-tropanol hydrochloride,[1] mp 268–269°. The product was entirely free from the 2β isomer (glc) and was identical with that prepared by the racemization of authentic L(+)-2α-tropanol.[16]

Both L(+)- and *rac*-**5** have been reduced to the corresponding 2α-tropanols in about 85% yield by lithium aluminum hydride.[1,2] A variety of azabicyclic ketones have been reduced catalytically,[12,14,17] but in the case of 2-tropanone hydrogenolysis to tropane occurred when the reduction was carried out in acid solution over platinum.[2,18]

Optical Resolution of (±)-2α-Tropanol.—The procedure was developed using racemic 2α-tropanol prepared by the racemization of L(+)-2α-tropanol.[16] A warm solution of 105 g (0.7 mol) of (+)-tartaric acid in 500 ml of anhydrous MeOH was added to a warm solution of 99 g (0.7 mol) of racemic 2α-tropanol in 500 ml of anhydrous MeOH. The mixture was cooled to room temperature, 500 ml of EtOAc was added, and the mixture was stored at 0° overnight. There was obtained 84 g (82%) of **L(+)-2α-tropanol (+)-tartrate**, mp 171–174°, $[\alpha]^{24}D$ +22° (*c* 2, H_2O). A reference sample prepared from L(+)-2α-tropanol (from cocaine) had mp 174–175°, $[\alpha]^{32}D$ +22.9° (*c* 3, H_2O).

Anal. Calcd for $C_{12}H_{21}NO_7$: C, 49.47; H, 7.27; N, 4.81. Found: C, 49.46; H, 7.04; N, 4.69.

L(+)-2α-Tropanol was obtained from the above salt in the usual way and was identical with that prepared from cocaine.[1]

The filtrate from the above salt was diluted with H_2O, saturated with K_2CO_3, filtered, and evaporated to give 54 g of enriched D(−)-2α-tropanol of about 75% optical purity. By neutralization with (−)-tartaric acid this was converted to 80 g (78%) of **D(−)-2α-tropanol (−)-tartrate**, mp 173–174°, $[\alpha]^{28}D$ −22.1° (*c* 3, H_2O).

D(−)-2α-Tropanol was obtained from this latter salt in the usual way. Except for the sign of rotation it was identical with the L(+)-2α isomer.

D(+)-2β-Tropanol.—Epimerization of D(−)-2α-tropanol was carried out by the procedure used for the epimerization of L(+)-2α-tropanol.[1] The product (70%), bp 84–85° (11 mm), $[\alpha]^{25}D$ +19° (*c* 2, H_2O), was identical, except for the sign of optical rotation, with L(−)-2β-tropanol made by the epimerization of L(+)-2α-tropanol.

Registry No.—**1**, 26863-83-2; L(+)-2α-tropanol (+)-tartrate, 31354-40-2; D(−)-2α-tropanol (−)-tartrate, 31354-41-3; D(+)-2β-tropanol, 31354-42-4.

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