

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

I.(+)-2-Tropinone¹

BY M. R. BELL AND S. ARCHER

RECEIVED MARCH 3, 1960

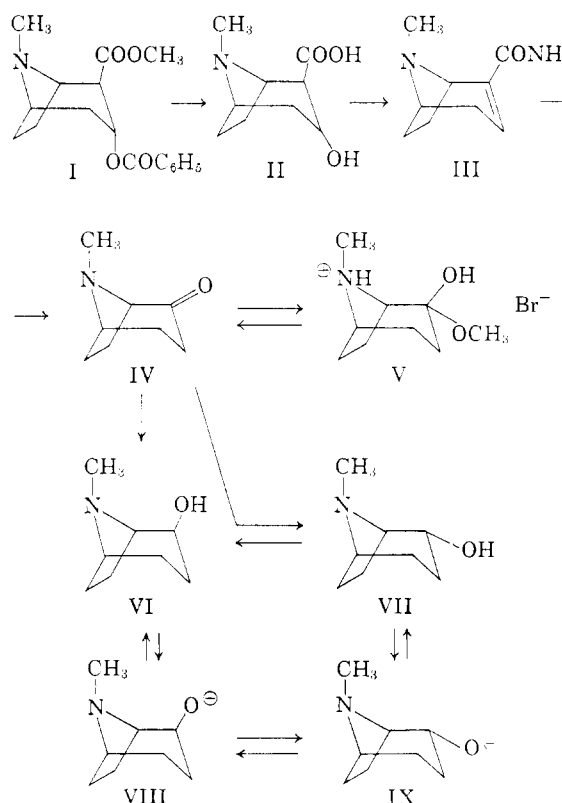
The title compound was prepared from cocaine by the following steps: hydrolysis to ecgonine, treatment with phosphorus oxychloride and then ammonia to give anhydroecgonine amide, followed by a Hofmann rearrangement to L(+)-2-tropinone. Reduction of the latter with lithium aluminum hydride furnished the expected equatorial alcohol. This proved to be identical with a degradation product of dioscorine, thus establishing the absolute configuration of the alkaloid. By proper choice of conditions it was possible to prepare the axial 2-tropanol substantially free of the equatorial isomer by means of a sodium-3-pentanol reduction.

Although 3-tropinone is a well known substance and has been the starting point in the preparation of many compounds of potential and actual biological interest, at the time this work was conceived there were no recorded syntheses of either of the other possible tropinones. We were particularly interested in having a supply of 2-tropinone for synthetic work, an interest which was intensified by the disclosure that it was this ketone and not 6-tropinone that was a degradation product of dioscorine.²

The synthesis from cocaine (I), whose absolute configuration had been established,³ proceeded through ecgonine (II).⁴ Treatment with phosphorus oxychloride furnished the unisolated acid chloride of anhydroecgonine⁵ which with aqueous ammonia afforded anhydroecgonine amide (III). Sodium hypochlorite in cold aqueous methanol followed by acid hydrolysis led to 2-tropinone (IV) contaminated with the other hydrolytic product, methylurethan. The latter proved to be a stubborn impurity that was best removed by converting IV to the hydrobromide or hydrochloride salt. The hydrobromide V crystallizes from methanol as a methanolate which is devoid of carbonyl absorption in the infrared. A similar case was reported by Lyle⁶ who found that 1-methyl-3-piperidone yielded a hydrochloride which formed a stable hydrate that was transparent in the carbonyl region of the infrared spectrum.

When V was converted to IV, a pure specimen of the ketone was obtained that had a band at 5.82 μ which is in the normal range for a six-membered ring ketone. Similarly, 1-methyl-3-piperidone absorbed at 5.82 μ .⁶ The ketone IV gave a methiodide which was obtained solvent-free but absorbed at 5.76 μ . This lack of solvation *vis-à-vis* V may be due to (a) the lack of opportunity for stabilization by hydrogen bonding which is possible in V and (b) the presence of an extra methyl group on the nitrogen can introduce a severe 1,3 diaxial interaction in a solvate of the methiodide which would favor a solvent-free state. However the proximity of the positive charge on the nitrogen in the salts of 2-tropinone is

probably responsible for both the solvation in the hydrobromide and this shift in carbonyl absorption to lower wave length in the methiodide.



In a recent review of the chemistry of dioscorine, Ulbricht⁷ pointed out that it was reported that 2-tropinone methiodide was unexpectedly unstable in weakly basic solution. Prior to the appearance of this paper we found that this quaternary salt was stable under conditions that were even more drastic than those specified earlier.⁷

When 2-tropinone was reduced with lithium aluminum hydride, VII was obtained crystalline as the major product. Direct comparison of this alcohol and its derivatives with the corresponding ones obtained from the dioscorine degradation was carried out by Büchi.⁸ This comparison served not only to confirm the identity of the alkaloid but to relate it to cocaine (I) stereochemically and thus establish its absolute configuration.³

(1) For a preliminary communication see M. R. Bell and S. Archer, *THIS JOURNAL*, **80**, 6147 (1958).

(2) Professor G. Büchi privately informed one of us (S.A.) of this development at the San Francisco Meeting of the American Chemical Society in April, 1958, some time prior to the appearance of Pinder's paper on this subject, J. B. Jones and A. R. Pinder, *Chemistry & Industry*, 1000 (1958).

(3) E. Hardegger and H. Ott, *Helv. Chim. Acta*, **38**, 312 (1955).

(4) F. Wohler, *Ann.*, **121**, 372 (1862).

(5) A. Einhorn, *Chem. Ber.*, **20**, 1221 (1887).

(6) R. E. Lyle, R. E. Adel and G. G. Lyle, *J. Org. Chem.*, **24**, 342 (1959).

(7) T. L. V. Ulbricht, *Tetrahedron Letters*, **1**, 5 (1959).

(8) D. E. Ayer, G. Büchi, P. R. Warnhoff and D. W. White, *THIS JOURNAL*, **80**, 6146 (1958).

It was possible to isolate from the filtrate of the lithium aluminum hydride reduction a small amount of the isomeric tropanol VI by taking advantage of the reverse solubility of the hydrochlorides. The alcohol VI was eventually obtained as a pure liquid whose infrared spectrum showed strong intramolecular hydrogen bonding. This feature was absent in the spectrum of VII and on this basis it was assigned the alpha (equatorial) configuration and the liquid 2-tropanol the beta (axial) one. The pK_a values⁸ supported this assignment.

When 2-tropanone was reduced by a slight modification of Dev's method⁹ (one mole of ketone: three moles of sodium: four moles of isopropyl alcohol) a mixture of 2-tropanols was obtained which from vapor phase chromatography (V.P.C.) appeared to be about 60% axial and 40% equatorial. This was surprising in view of the fact that lithium aluminum hydride reduction gave predominantly equatorial alcohol. Under normal circumstances unhindered ketones usually give the same product by these methods.¹⁰ This result is understandable if it is true that the anion IX by virtue of its equatorial configuration is more stable than the anion VIII derived from VI and that VI because of its strong hydrogen bond is more stable than the alcohol VII. In our Dev reduction when all the ketone and sodium have been consumed there are three moles of alkoxide and two of alcohol. In this situation an appreciable amount of VI can be present together with the anion IX. The concentration of these species and their postulated relative stabilities can account for the observed result. The concentration of IX can be reduced and that of VI be increased by changing the ratio of reactants to one ketone:three sodium:six isopropyl alcohol. In this way the amount of available alcohol at the end of the reduction rises from two moles to four. Reduction under these conditions gave a crude product in which the ratio of VI to VII was about 9:1 (V.P.C.). When 3-pentanol was substituted for isopropyl alcohol, thereby raising the reaction temperature and hastening the attainment of equilibrium, V.P.C. of the reaction product revealed that there was 5% or less of the α -isomer VII in the crude 2-tropanol fraction.

Starting with pure VII it was possible to effect an 85% conversion to VI with sodium 3-pentoxide in 3-pentanol containing 10 mole percent of fluorenone. Thus it is clear that at equilibrium the axial isomer of 2-tropanol is more stable than the equatorial one.

Experimental¹¹

L-Anhydroecgonine Amide (III).—A solution of 141.8 g. of cocaine hydrochloride in 2.5 l. of aqueous hydrochloric acid (prepared by adding 200 ml. of 12 *N* hydrochloric acid to 3 l. of water) was refluxed for 15 hours, extracted several times with ether and the aqueous phase evaporated to dryness to leave 92 g. (99% yield) of crude L-ecgonine hydrochloride.¹²

(9) S. Dev, *J. Indian Chem. Soc.*, **33**, 769 (1956).

(10) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(11) Analyses and rotations were carried out under the supervision of Mr. M. E. Auerbach. Spectra were determined under Dr. F. C. Nachod's supervision.

(12) Material obtained in this way in another run had the following constants: m.p. 240–244°, $[\alpha]_D^{25} - 45.2 \pm 0.1$ (0.5% in H₂O). Lit. values: m.p. 246°, $[\alpha]_D^{25} - 57.1^\circ$. C. Lieberman, *Chem. Ber.*, **21**, 2342 (1888); O. Hesse, *ibid.*, **22**, 665 (1889).

A suspension of the above salt in 800 ml. of phosphorus oxychloride was refluxed for one hour⁵ and then evaporated to dryness *in vacuo* on the steam-bath. The viscous residue was cooled in a Dry Ice-acetone-bath and treated with 750 ml. of concentrated ammonia that had been pre-cooled to the same temperature. The mixture was allowed to warm to room temperature over a period of about 15 minutes with swirling and occasional cooling to moderate the reaction. Most of the ammonia was removed *in vacuo* on the steam-bath and the resulting yellow solution was treated with a large excess of potassium carbonate until a thick slurry was formed. This was thoroughly extracted with methylene chloride and the extracts were dried and evaporated to leave 59 g. (85% yield) of crude L-anhydroecgonine amide suitable for use in the next step.

The product was purified by passage of a chloroform solution through a column of Florisil followed by evaporation of the eluates and recrystallization of the residue from ethyl acetate. The jagged white needles melted at 142.5–145°, $[\alpha]_D^{25} - 51.2^\circ$ (1% in H₂O).

Anal. Calcd. for C₉H₁₄O₂: C, 65.03; H, 8.49; N, 16.86. Found: C, 65.27; H, 8.35; N, 16.66.

L-(+)-2-Tropanone.—To a stirred solution of 6.64 g. of L-anhydroecgonine amide (m.p. 140–144.5°) in 60 ml. of methanol was added over a 15-minute period 53.6 ml. (7% excess) of 0.798 *N* sodium hypochlorite¹³ while the temperature was carefully kept below -5°. After the completion of the addition there was an excess of hypochlorite, but when the solution was placed in an ice-water bath for 10 minutes the temperature of the reaction mixture rose to 3° and the starch-iodide test was negative. The bath was removed and after 30 minutes the solution was heated at 60–65° for 10 minutes. The warm solution was treated cautiously with 15 ml. of 12 *N* hydrochloric acid and boiled until the internal temperature reached 90° (10 minutes). After 15 minutes more of heating on the steam-bath the solution was cooled and a large excess of solid potassium carbonate was added. The mixture was thoroughly extracted with methylene chloride and the dried extracts were evaporated to leave the crude products. At this point the infrared spectrum showed a strong carbonyl peak at 5.82 μ and bands characteristic of methyl urethan but none of the starting amide. Vapor phase chromatography showed that the urethan was present to about 15%.

The residue was dissolved in dry ether and treated with dry hydrogen chloride. The crude-2-tropanone hydrochloride weighed 5.7 g. and melted at 230–235°. This was converted to the free base with excess potassium carbonate and taken up in methylene chloride. The dried organic layers were distilled at 0.55 mm. to give the fractions: 1, b.p. 60°, 0.19 g., $n_D^{25} 1.4910$; 2, b.p. 60–61°, 1.48 g., $n_D^{25} 1.4912$; and 3 b.p. 61°, 0.55 g., $n_D^{25} 1.4912$; total weight 2.12 g. (40% yield).

The following data were obtained on fraction 2: vapor phase chromatography indicated a purity of >99%, λ_{max} 5.82 μ (neat and in CHCl₃), λ_{max} ϵ 150, $[\alpha]_D^{25} + 23.2^\circ$ (1.6% in H₂O). The pure ketone crystallized in the refrigerator, m.p. ca. 27°.

Anal. Calcd. for C₈H₁₃NO: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.36; H, 9.46; N, 9.89.

In another experiment 67 g. of the crude amide was dissolved in 550 ml. of methanol and cooled to -15 to -20° while 553 ml. of a 0.781 *N* solution of sodium hypochlorite was added in 15 minutes at that temperature. The Dry Ice-bath was replaced by an ice-water-bath and the temperature of the reaction mixture reached 3° in 30 minutes. The starch-iodide test was negative. The bath was removed and the solution was stirred for another 30 minutes before being warmed at 60° for 10 minutes. Then 154 ml. of 12 *N* hydrochloric acid was added cautiously. The solution was heated to 90° and allowed to stand overnight in the refrigerator. The solution was concentrated to 200 ml. and extracted with chloroform. It was then made strongly alkaline with potassium carbonate and the resulting slurry was extracted eight times with methylene chloride. The dried solution was concentrated and distilled at 31 mm. to give the fractions: 1, b.p. 95–104°, wt. 3 g. This solidified and was undoubtedly largely methylurethan; 2, b.p. 104–106°, wt. 2.8 g.; and 3, b.p. 106–126° (mainly 122–126°), wt. 43 g. This was 2-tropanone but the infrared spectrum

(13) R. A. Weerman, *Ann.*, **401**, 1 (1913).

showed a band at 6.35μ indicating the presence of the urethan.

Fractions 2 and 3 were combined, dissolved in 400 ml. of ether containing 40 ml. of methanol and treated with 60 ml. of a 30% solution of hydrogen bromide in acetic acid. The hydrobromide-methanolate was collected and washed with ether; wt. 71 g., m.p. 255–258° dec. It was converted to the base in our usual way and the 2-tropinone was collected at 118–119° (30 mm.), wt. 35.5 g. (63.7% yield).

The hydrobromide which crystallized as a methanolate was prepared by dissolving 1.0 g. of the ketone in methanol acidifying with excess hydrogen bromide-acetic acid solution and precipitating the salt with ether. After two crystallizations from methanol it melted at 266–266.5°. The infrared spectrum (KBr disk) was transparent in the carbonyl region.

Anal. Calcd. for $C_8H_{13}NO \cdot HBr \cdot CH_3O$: C, 42.86; H, 7.19; Br, 31.69; CH_3O , 12.31. Found: C, 42.78; H, 6.84; Br, 32.21; CH_3O , 11.78.

The di-*p*-toluyl-D-tartrate, prepared in acetone and crystallized from the same solvent, melted at 163° dec.

Anal. Calcd. for $C_{20}H_{23}NO \cdot C_{20}H_{19}O_4$: C, 63.99; H, 6.14; N, 2.67. Found: C, 64.14; H, 6.21; N, 2.61.

The methiodide was prepared from 340 mg. of the ketone and 0.2 ml. of methyl iodide in 2 ml. of acetonitrile. The salt that separated was leached with methanol; wt. 580 mg., m.p. 332° dec. It could be recrystallized from water with a 90% recovery.

Anal. Calcd. for $C_8H_{13}INO$: I, 45.14. Found: I, 45.28.

To test its stability, the methiodide (100 mg.) was added to a solution of 20 mg. of sodium carbonate in 0.5 ml. of water. The mixture was heated until a clear solution resulted and then placed in a bath at 55°. After 15 minutes the salt started to crystallize. The suspension was rewarmed to redissolve the crystals and then it was placed in the bath again. After another 15 minutes the solution was cooled. The solid that separated weighed 65 mg. and proved to be the starting methiodide.

2(α)-Tropanol (VII).—A solution of 5.6 g. of 2-tropinone in 20 ml. of dry ether was added dropwise in 15 minutes to a stirred solution of 2.0 g. of lithium aluminum hydride in 100 ml. of dry ether. After 30 minutes of reflux the mixture was cooled and decomposed with 2.0 ml. of water. The solid was filtered off and boiled with two 50-ml. portions of methylene chloride. The filtrate and extracts were combined, dried and concentrated to leave 5.7 g. of an oil which solidified on cooling. After crystallization from hexane there was obtained 3.58 g. of the tropanol, m.p. 72–76°, raised to 73–76° after crystallization from ether-pentane. Repeated crystallizations from hexane gave white needles, m.p. 75.5–77°, $[\alpha]^{25}_D + 14.5^\circ$ (1% in H_2O).

Anal. Calcd. for $C_8H_{13}ClNO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.84; H, 10.52; N, 9.98.

When the first hexane filtrate was evaporated an oil remained which afforded a crystalline hydrochloride which melted at 326–328° dec. after two crystallizations from isopropyl alcohol. This proved to be the salt of the 2 β -tropanol (see below).

The hydrochloride of 2 α -tropanol was prepared from the crystalline 2 α -tropanol in ether and crystallized twice from isopropyl alcohol, m.p. 268–269.5°, $[\alpha]^{25}_D + 19.8^\circ$ (1% in H_2O).

Anal. Calcd. for $C_8H_{13}NO$: N, 7.88. Found: N, 7.81.

The methiodide was prepared in acetonitrile and melted at >330° after two crystallizations from methanol.

Anal. Calcd. for $C_8H_{13}INO$: C, 37.91; H, 6.36. Found: C, 37.94; H, 6.57.

Dev Reductions of 2-Tropinone. (A) **1 Mole Ketone:3 Moles Sodium:4 Moles Isopropyl Alcohol.**—Magnetic stirring was used in all the experiments described in this section. All reactions were carried out in a nitrogen at-

mosphere. The 2-tropinone used was purified through the hydrobromide-methanolate and boiled at 118–119° (30 mm.). To a suspension of 2.49 g. of powdered sodium in 15 ml. of dry toluene, a solution of 5.13 g. of IV in 8.28 ml. of isopropyl alcohol was added dropwise in 45 minutes. The mixture was refluxed for 1.2 hours and allowed to stand overnight. The next morning all the sodium had not disappeared so that 3 ml. more isopropyl alcohol was added and heating was continued for 1.5 hours more. Thus the total amount of isopropyl alcohol added was four moles.

The mixture was cooled and treated with 12 ml. of water. The layers were separated and aqueous phase made basic with potassium carbonate and then extracted with methylene chloride. The organic layers were combined, dried and distilled to give two fractions: 1, b.p. 102–110° (28 mm.), wt. 2.76 g.; and 2, b.p. 110–130° (28 mm.), wt. 1.30 g. Vapor phase chromatography showed that they were both mixtures; fraction 1 was richer in the β -isomer VI and fraction 2 was mainly VII. The ratio of VI to VII in the alcohol fractions was about 60:40.

(B) **1 Mole Ketone:3 Moles Sodium:6 Moles Isopropyl Alcohol.**—The solution of 5.13 g. of 2-tropinone in 16.5 ml. of isopropyl alcohol was added to the sodium in 20 minutes. The sodium had not quite disappeared after 3 hours. The mixture was refluxed overnight for a total of 20 hours. A clear yellow solution resulted. It was allowed to cool and while still warm was treated with 7 ml. of water. The mixture was then worked up as described above to give 3.37 g. of an oil, b.p. 102–108° (28 mm.). Vapor phase chromatography indicated that this was about 90% VI.

(C) **1 Mole Ketone:3 Moles Sodium:6 Moles 3-Pentanol.**—The solution of 5.13 g. of IV in 23.3 ml. of redistilled 3-pentanol was added to the sodium in toluene in 30 minutes. The sodium disappeared about 30 minutes after the last of the ketone-alcohol mixture had been added. The solution became red about a quarter of the way through the addition and remained so. The mixture was refluxed for a total of 20 hours and worked up essentially as directly above. The fraction b.p. 104–117° (30 mm.) (wt. 4.75 g.) was analyzed by vapor phase chromatography and proved to be about 95% VI. The other peaks were probably due to small quantities of neutral material and some equatorial isomer.

In another experiment the reaction was carried out in the same way but after the solvents were removed the residue was converted to the hydrochloride in ether rather than distilled. The salt was collected on a filter, washed with ether and dried, wt. 5.3 g. (81.5%), m.p. 312–318° dec. It was converted to the base in the usual way. Evaporation of the dried extracts left an oil (wt. 4.03 g.) the vapor phase chromatogram of which indicated only traces of the equatorial alcohol VII.

Distillation gave a colorless oil, b.p. 89–93° (13 mm.), n^{25}_D 1.4886, $[\alpha]^{25}_D - 11.9^\circ$ (1% in H_2O).

Anal. Calcd. for $C_8H_{13}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.23; H, 10.39; N, 9.69.

The hydrochloride melted at 330–331° dec. when crystallized from isopropyl alcohol; $[\alpha]^{25}_D - 14.6^\circ$ (1% H_2O).

Anal. Calcd. for $C_8H_{13}ClNO$: C, 54.07; H, 9.08. Found: C, 54.21; H, 8.89.

Conversion of 2 α -Tropanol to 2 β -Tropanol.—A solution of sodium 3-pentoxide (from 0.13 g. of sodium), 260 mg. of VII, 0.75 ml. of toluene and 28.6 mg. (10 mole per cent.) of fluorenone in 1.2 ml. of 3-pentanol was stirred magnetically under reflux for 20 hours, cooled and treated with 1.2 ml. of water. The layers were separated after the addition of ether and the aqueous phase was made alkaline and ether extracted. The dried combined organic layers were treated with alcoholic hydrogen chloride and the salt that separated was converted to the base in our usual way. Vapor phase chromatography indicated that the mixture contained about 85% of the axial isomer VI and the remainder was mainly VII.

RENSELAER, N. Y.