**Acknowledgment.** The crystallographic calculations were supported through the facilities of the Computer Science Center, University of Maryland. We wish to thank Professor W. Luttke, University of Gottingen, for many helpful discussions.

**Registry No.**—4, 16291-99-9; 6, 16292-01-6.

**Supplementary Material Available:** Tables of temperature factors and bond lengths and angles involving hydrogen atoms (4 pages). Ordering information is given on any current masthead page.

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# Absolute Configuration of (+)-Methyl 8-Methyl-8-azabicyclo[3.2.1]oct-2-ene-3-carboxylate

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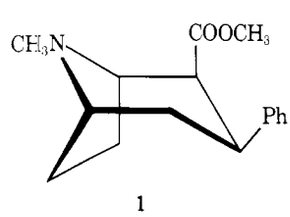
*Received May 5, 1978*

The absolute configurations of the enantiomers of ester **2** were needed in order to establish the configurations of a narcotic antagonist (**3**) and a hypoglycemic agent (**4**), wherein the biological activity resided in a single enantiomer. Ester **2** was resolved via its dibenzoyltartrate salts and its (+)-form was converted to ketone **8**, a compound that was also prepared from cocaine which is known to have a 1*R* configuration. Therefore, **(+)-2** has the 1*R* configuration.

Earlier a tropane molecule carrying an equatorial phenyl group on carbon 3 and an axial carbomethoxy group on carbon 2 (**1**) was shown to be a powerful CNS stimulant, the activity




**1**

residing in only one enantiomer.[1] Since the ester was prepared from (−)-anhydroecgonine methyl ester derived from cocaine, the absolute configuration was known.

Concurrently with the present work another aryltropanecarboxylic ester (**3**) is being reported which is a narcotic antagonist[2] while a third such ester (**4**) is a hypoglycemic agent.[3] In each of these cases only one enantiomer is active and they are derivable (separately) from the enantiomeric forms of **2** (see eq A and B). The absolute configuration of narcotic antagonist **3** is of particular interest since the compound constitutes a new structural form displaying this broadly studied biological activity. Assignment of absolute configurations to **3** and **4** hinges upon determination of the absolute configuration of one of the enantiomers of **2.** The present paper presents proof for the absolute configuration of **(+)2.**

Cocaine is known to have a 1*R* configuration.[4] The pattern for the present proof involved conversion of a known derivative of cocaine [**(−)-5**][5] to ketone **8** which could also be derived from **2. (−)-5** was treated with ethyl chlorocarbonate and the resulting urethane **6** was oxidized by Jones' reagent. Equilibration of the α-methyl ketone so formed (**7**) with sodium methoxide in methanol then provided **8** (1*R* configuration, $[\alpha]_D$ −24.4°). The remaining problem involved conversion of **2** to **8.**

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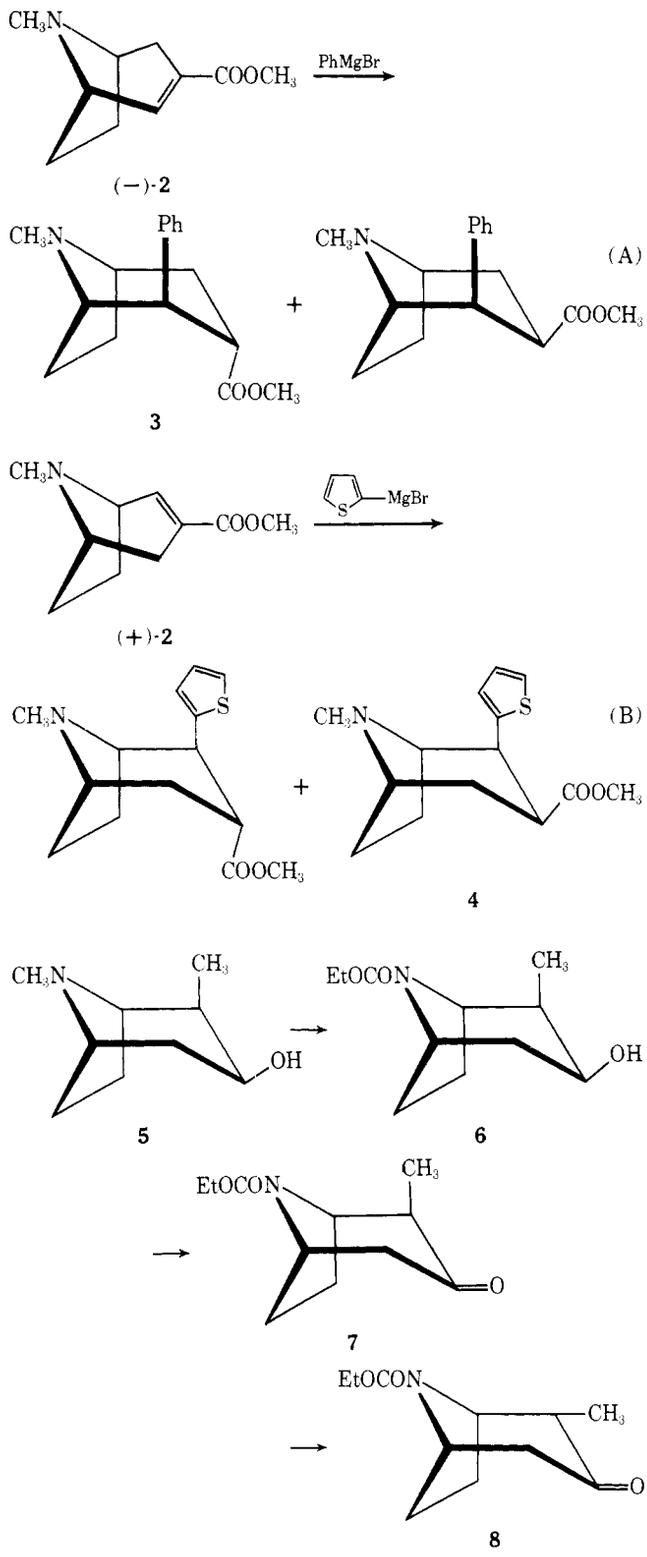
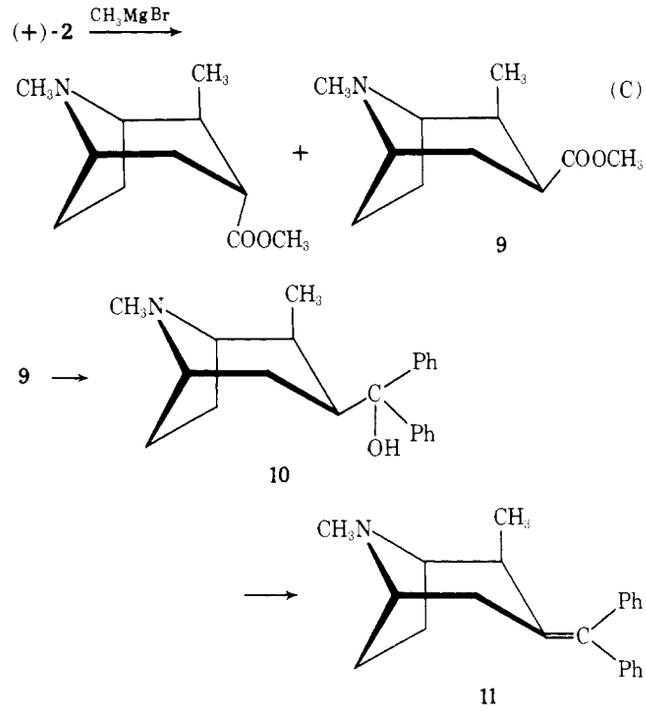


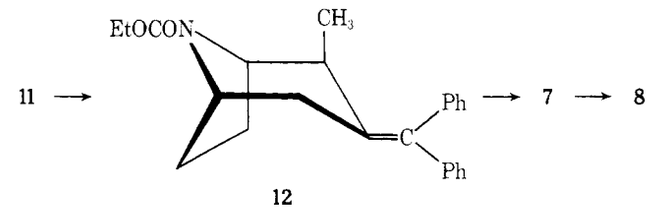

Unsaturated ester **2** was resolved via its dibenzoyltartrate salt, the (+) base precipitating in combination with the (−) acid in 1:1 ratio. **(+)-2** reacted with $CH_3MgBr$ at −25 to −30 °C in the expected manner except that a surprising 38% of starting material was recovered unchanged. The mixture of epimers formed (see eq C) was treated with sodium methoxide in methanol to give equatorial ester **9** (31%, $[\alpha]_D$ −33.9°).

Ester **9** reacted readily with phenylmagnesium bromide in THF to form carbinol **10** in 46% yield; $[\alpha]_D$ = −20.0°. The corresponding 2-desmethyl analogue is reported by Zirkle et al.[6] from reaction of methyl 3β-tropanecarboxylate with phenyllithium. Reflux of carbinol **10** with $POCl_3$ in pyridine then furnished olefin **11**, $[\alpha]_D$ +135.6°. At this point the amine




function was protected for the projected oxidation step by 1.5-h reflux with ethyl chlorocarbonate, giving urethane **12**, $[\alpha]_D$ +111.7°.

Attempted cleavage of the double bond of **12** with $NaIO_4$–




$RuO_2$ in $CCl_4$ resulted in only 15% reaction (by TLC). Addition of 1.54 N sodium hypochlorite, however, caused consumption of essentially all of the starting material.[7] Failure of oxidation to go to completion in the first instance may have involved a ruthenium complex which did not allow $RuO_4$ regeneration.

Workup of the oxidation mixture afforded 44% of benzophenone and 43% of the expected tropan-3-one. Equilibration of this *exo*-methyl ketone (**7**) with $NaOCH_3$ then furnished the requisite ketone **8**. It was purified by high-pressure liquid chromatography using a hexane–*i*-PrOH solvent system and finally by plate chromatography using $Et_2O$–pentane, the latter step insuring that no traces of *i*-PrOH remained in the oily product. After this considerable manipulation the yield of **8** was only 23%; $[\alpha]^{25}_D$ −26.4° compared with $[\alpha]^{25}_D$ −24.4° for **8** prepared from cocaine. The IR spectra and $R_f$ values of the two samples of **8** were identical. The NMR spectra were essentially identical but a faint trace of impurity showed in that of **8** derived from cocaine. This trace impurity could account for the small difference in optical rotations observed for the two products.

The experiments described demonstrate that (+)-unsaturated ester **2** has the 1*R* configuration. It follows that hypoglycemic agent **4** belongs to the 1*R* series whereas narcotic antagonist **3** is of the 1*S* series.

## Experimental Section

Melting points were determined in capillary tubes in an oil bath and are uncorrected. Optical rotations were measured on 1% solutions in $CHCl_3$ unless noted otherwise. All preparative plate chromatography

was done using 20 × 40-cm glass plates coated with a 1.0–1.5-mm layer of Brinckmann Instruments grade $PF_{254}$ silica gel.

The NMR, IR, and mass spectra of all compounds reported were compatible with assigned structures. NMR spectra were recorded on a Varian HA-100 spectrometer using $Me_4Si$ as an internal standard. IR spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer and mass spectra were measured with a Joelco JMS-1-OCS mass spectrograph.

**Ethyl (1*R*-*exo*,*exo*)-3-Hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (6).** A mixture of 2.37 g (0.0153 mol) of (1*R*-*exo*,*exo*)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-ol (**5**)[5] and 30 mL of ethyl chlorocarbonate was heated under reflux for 2.75 h and the excess chlorocarbonate was removed by warming in vacuo. Addition of concentrated $NH_4OH$, extraction with $Et_2O$, and concentration of the extracts gave 2.78 g of an oily mixture of mono- and di(ethoxycarbonylated) products (TLC).

The oily material in 10 mL of MeOH was treated with 4 g of $NaHCO_3$ in 15 mL of $H_2O$ and heated under reflux for 3 h. Concentration by warming in vacuo and extraction of the residue with $Et_2O$ gave 1.36 g of oil which was chromatographed on four silica preparative plates ($Et_2O$). Elution of the principal band gave 1.00 g (31%) of oily **6**: $[\alpha]^{25}_D$ −53.2°; IR (oil film) 3410 (broad, OH) and 1684 $cm^{-1}$ (C=O); mass spectra $M^+$ 213, $M^+ - OH$ 196, $M^+ - OEt$ 168, $M^+ - COOEt$ 140 (s). This product (**6**) still contained 2–3% impurity (TLC) but was sufficiently pure for use in the next reaction.

**Ethyl (1*R*-*endo*)-2-Methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (8) Derived from Cocaine.** A solution of 1.00 g (4.7 mmol) of alcohol **6** in 35 mL of acetone was treated with 1.25 mL (9.8 mequiv) of 7.86 N Jones' reagent in 10 min with stirring and cooling by ice–$H_2O$. MeOH (1 mL) was added to destroy excess reagent, the solvents were removed by warming in vacuo, and the residue was extracted thoroughly with ether. Concentration of the extracts gave 0.83 g of oil which was apparently >95% 2-exo isomer by TLC (silica, $Et_2O$).

The product was dissolved in 10 mL of MeOH, 0.1 g of $NaOCH_3$ was added, and the solution was allowed to stand at room temperature overnight. Solvent was removed and the product isolated with $Et_2O$. There was produced a 15:85 mixture of exo and endo isomers respectively; the endo isomer was less polar. Preparative plate chromatography (three plates, $Et_2O$) afforded 0.48 g (48%) of the desired 2-endo product **8** (oil); $[\alpha]^{25}_D$ −24.3°.

Faint traces of impurities were still visible by TLC, so the sample was processed through an LC apparatus using 70:29:1 hexane–EtOAc–*i*-PrOH for elution: column 2.5 × 25 cm of EM Reagents silica gel 60; flow rate 8 mL/min; monitoring at 280 nm. Repeat of the process using a 1:9 *i*-PrOH–hexane solvent system gave apparently clean **8** (TLC) with $[\alpha]^{25}_D$ −24.4°. The NMR spectrum of this product (from cocaine) showed a trace impurity peak which was not present in **8** prepared from synthetic sources.

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.44; H, 8.23; N, 6.52.

**Resolution of Methyl 8-Methyl-8-azabicyclo[3.2.1]-oct-2-ene-3-carboxylate (2).**[2] A solution of 40.0 g (0.221 mol) of **2**[2] in 40 mL of EtOAc was added to a solution of 83.2 g (0.221 mol) of (−)-dibenzoyltartaric acid monohydrate (derived from the natural form of tartaric acid) in 150 mL of acetone. Addition of 150 mL of EtOAc and scratching with a rod induced crystallization. The mixture was stirred for 2 h at room temperature and filtered to give 82.88 g (31% over theory for one diastereoisomer) of principally **(+)-2·(−)-DBT** salt, mp 126–131 °C dec; $[\alpha]^{25}_D$ −77.0° (2% in $CH_3OH$).

The salt was divided into two equal portions, each of which was added to 1.5 L of boiling water with vigorous stirring. A small amount failed to dissolve. Cloudiness developed when the solutions were cooled to 88 °C. The temperature fell to 75 °C before seed crystals became effective. At this point the cloudy solutions were decanted from 5 and 4 g of precipitated oil and stirred with slow cooling as heavy needles and long prisms developed.

Cooling overnight at 5 °C and filtration gave 24.2 and 25.3 g (77%) of **(+)-2·(−)-DBT** salt: mp 132–136 °C dec; $[\alpha]^{25}_D$ −77.4° (2% in $CH_3OH$). This product was recrystallized again in two portions from 1.2-L volumes of boiling water to which 30 mL of EtOH was added after slight cooling. The temperature was lowered to 70 °C without formation of cloudiness, at which point seeding was effective. Cooling to 5 °C and filtration gave a total of 39.9 g (62%) of **(+)-2·(−)-DBT** salt [dried for 6 h at 25 °C (0.5 mm)] which again melted at 132–136 °C dec, $[\alpha]^{25}_D$ −76.8° (2% in MeOH). Water (Karl-Fischer) = 2.29%. Anal. Calcd for $C_{10}H_{15}NO_2 \cdot C_{18}H_{14}O_8$: C, 62.33; H, 5.42; N, 2.60. Found (dry basis): C, 62.55; H, 5.33, N, 2.59.

The filtrates from the original collection of the **(+)2·(−)-DBT** salt and its first recrystallization were concentrated by warming in vacuo and the residue was shaken with 100 mL of 2 N HCl and $Et_2O$. The $Et_2O$ layer was extracted with 10 mL of 2 N HCl and the combined acid layers were saturated with $K_2CO_3$. The liberated base was extracted with $Et_2O$ giving 22.05 g of oil enriched in **(−)-2.**

A solution of the 22.05 g (0.122 mol) of oil in 22 mL of EtOAc was added to a solution of 45.8 g (0.122 mol) of (+)-dibenzoyltartaric acid monohydrate in 80 mL of acetone and a further 80 mL of EtOAc was added. After the seeded mixture was stirred 2 h at room temperature the **(−)2·(+)-DBT** salt was collected and washed with 2 × 25 mL of 2:3 acetone–EtOAc. Air drying furnished 54.0 g of salt which was recrystallized once from water with added ethanol in the manner used above for the second recrystallization of the enantiomeric salt. The pure **(−)-2·(+)-DBT** salt weighed 43.0 g (67%). An analytical aliquot showed mp 132–136 °C dec; $[\alpha]^{25}_D$ +77.5° (2% in MeOH); 2.62% $H_2O$ by Karl Fischer after it had been dried for 6 h at 25 °C (0.5 mm). Anal. Calcd for $C_{10}H_{15}NO_2 \cdot C_{18}H_{14}O_8$: C, 62.33; H, 5.42; N, 2.60. Found (dry basis): C, 62.16; H, 5.46; N, 2.54.

The **(+)-2·(−)-DBT** salt (39.3 g, 0.071 mol) was shaken with 50 mL of 2 N HCl and 200 mL of $Et_2O$ and the $Et_2O$ layer was washed with 10 mL of 2 N HCl. The combined acid layers were saturated with $K_2CO_3$ and the liberated base was extracted with two portions of $Et_2O$. Distillation of the base gave 11.79 g (92% from the salt) of **(+)-2:** bp 86.5–88 °C (0.7 mm); $[\alpha]^{25}_D$ +49.0° (4% in $CHCl_3$). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.21; H, 8.41; N, 7.61.

The **(−)-2·(+)-DBT** salt (37.8 g, 0.068 mol) was converted in the same manner to **(−)-2** base: bp 80–81 °C (0.3 mm); 11.4 g (92% from the salt); $[\alpha]^{25}_D$ −48.4° (2% in $CHCl_3$). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.41; H, 8.16; N, 7.78. In a subsequent reaction of these enantiomers of **2** with PhMgBr,[3] evidence appeared for the presence of about 3% of the optical antipodes in these supposedly pure enantiomers.

**Methyl (1*R*-*exo*,*exo*)-2,8-Dimethyl-8-azabicyclo[3.2.1]-octane-3-carboxylate (9).** A solution of 4.90 g (0.0271 mol) of dextrorotatory unsaturated ester **2** in 25 mL of $Et_2O$ was added with stirring in 15 min to 15 mL (0.041 mol) of 2.7 M ethereal methylmagnesium bromide and 100 mL of $Et_2O$ which was held at −25 to −30 °C. The resulting suspension of white solid was stirred for 2 h at this same temperature and then poured into 35 mL of 2 N HCl and 50 g of ice. The layers were separated, the ether layer was washed once with 2 N HCl, and the combined acid layers were saturated with $K_2CO_3$. Three extractions of this mixture with $Et_2O$ gave 5.14 g of a mobile oil.

This mixture of esters, epimeric at C-3, was heated under reflux with 0.2 g of $NaOCH_3$ and 50 mL of MeOH for 6 h. The solvent was removed by warming in vacuo, 5 mL of brine was added, and the product was extracted with $Et_2O$. Concentration of the extracts gave 4.73 g of crude material which contained considerable starting material (TLC). It was chromatographed on 19 preparative plates which were developed with 3:97 *i*-$PrNH_2$–$Et_2O$. A strong UV-absorbing band was eluted to give 1.84 g (38%) of starting material. The desired ester **9**, an oil, appeared as a less polar, non-UV-absorbing band and amounted to 1.66 g (31%), $[\alpha]^{25}_D$ −33.9°. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.71; N, 7.10. Found: C, 67.24; H, 9.67; N, 7.15.

**(1*R*-*exo*,*exo*)-2,8-Dimethyl-α,α-diphenyl-8-azabicyclo-[3.2.1]octane-3-methanol (10).** To a stirred mixture of 55 mL (0.165 mol) of 3 M phenylmagnesium bromide (in $Et_2O$) and 80 mL of THF was added a solution of 8.02 g (0.041 mol) of ester **9** in 35 mL of THF in 3 min without external cooling. This mixture was heated under reflux for 2 h, cooled, and added to 125 mL of 2 N hydrochloric acid and 50 g of ice. The THF and $Et_2O$ were removed by warming in vacuo, 200 mL of $Et_2O$ was added, and the product, in the form of an insoluble HCl salt, was collected on a filter.

The free base was liberated with dilute NaOH and separated with ether. Plate chromatography (5:0.5:94.5 MeOH–*i*-$PrNH_2$–THF) of the resulting 10.05 g of oil gave an oil (6.7 g) which crystallized (mp 91–94 °C) in the presence of pentane. Recrystallization of this 6.7 g of crystalline **10** from 4 mL of warm hexane with 10 mL of pentane added gave 3.4 g (46%) of colorless prisms: mp 99–100.5 °C; $[\alpha]^{25}_D$ −20.0°. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.46; H, 8.24; N, 4.27.

**(1*R*-*exo*)-2,8-Dimethyl-3-diphenylmethylene-8-azabicyclo[3.2.1]octane (11).** A mixture of 5.94 g (18.5 mmol) of tropanol **10**, 40 mL of pyridine, and 20 mL of $POCl_3$ was heated under reflux for 12 h. The volatile components were removed by warming in vacuo and the residue was treated with 10 mL of $H_2O$ and 10 mL of concentrated $NH_4OH$. Extraction with $Et_2O$ gave 5.33 g of an oily product which was converted to a somewhat hygroscopic HCl salt. Two recrystallizations from acetone gave only 0.97 g of pure **11** hydrochloride: mp 268–269 °C; $[\alpha]^{25}_D$ +167.7° (1% in EtOH). Anal. Calcd for $C_{22}H_{25}N \cdot HCl$: C, 77.74; H, 7.71; Cl, 10.43. Found: C, 78.02; H, 7.68; Cl, 10.17.

A portion of this salt was converted to free base 11 which melted at 89–91 °C without recrystallization.

All of the reaction product with the exception of the pure salt above was chromatographed (as base) on 14 preparative plates which were developed with 3:97 *i*-$PrNH_2$–$Et_2O$. The major band gave 3.69 g of crystalline product, mp 77–88 °C. One recrystallization from MeOH (3.7 mL) gave 2.70 g of 11 base: mp 89–90 °C; $[\alpha]^{25}_D$ +135.6°; total yield 64%.

**Ethyl (1*R-exo*)-3-Diphenylmethylene-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (12).** A mixture of 4.14 g (0.0137 mol) of amine 11 and 20 mL of ethyl chlorocarbonate was warmed to 60 °C whereupon gas evolution began. Lively evolution occurred in the 75–80 °C range. The solution was heated (finally under reflux) for a total of 1.5 h, cooled, diluted with $Et_2O$, and washed with 2 mL of 2 N HCl, 3 mL of $H_2O$, and 5 mL of brine. Concentration of the $Et_2O$ solution gave 4.7 g of viscous oil which was chromatographed on 16 preparative plates (1:1 $Et_2O$–pentane). The 4.42 g (90%) of pure oily 12 thus obtained showed $[\alpha]^{25}_D$ +111.7°. Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.92; H, 7.86; N, 3.87.

**Ethyl (1*R-endo*)-2-Methyl-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate (8) from the Synthetic Source.** To a suspension of 0.75 g of $RuO_2 \cdot 2H_2O$ in 50 mL of $CCl_4$ containing 4.40 g (0.0122 mol) of olefin at room temperature (29 °C) was added with stirring in 5 min a warm (45 °C) solution of 10.5 g (0.049 mol) of $NaIO_4$ in 60 mL of $H_2O$ with cooling to keep the temperature less than 35 °C. After 30 min a TLC plate indicated about 15% reaction. In an earlier experiment the amount of product did not further increase with time. After 45 min a solution (85 mL) of 1.54 N NaOCl (Chlorox) was added in 20 min with cooling to prevent temperature elevation. TLC (1:1 $Et_2O$ pentane) then showed 85% reaction. Addition of 35 mL more NaOCl consumed the last of the starting material.

The mixture was stirred for 30 min more and filtered. The organic layer was separated and the water layer was extracted twice with $CH_2Cl_2$, once with ether, and twice with $CHCl_3$, the water's being saturated with salt before the last two extractions. Concentration of the extracts gave 3.55 g of oil which was chromatographed on twelve 20 × 40-cm silica gel preparative plates. The benzophenone produced (IR, NMR, mp, TLC) showed an $R_f$ of about 0.8 and amounted to 1.13 g (44%). The desired tropanone (1.12 g, 43%) (with the C-2 methyl still in the exo configuration) showed an $R_f$ of 0.35.

Epimerization at C-2 was accomplished by heating the 1.12 g with 0.075 g of $NaOCH_3$ in 10 mL of MeOH under reflux for 45 min and then allowing the solution to stand overnight. The MeOH was removed, brine was added, and the product was extracted with $Et_2O$. Silica gel TLC (1:9 *i*-PrOH–hexane) showed about an 85:15 mixture of endo–exo epimers at C-2. The pure 2-endo epimer was isolated by LC using an EM Reagent silica gel-60 column (2.5 × 25 cm; mean pore diameter 60 Å) with a flow rate of 8 mL/min, a 1:9 *i*-PrOH–hexane solvent system, and a 100-mg sample weight per injection. Monitoring was done with a UV spectrometer set at 290 nm. In order to insure that the oily product was completely free from traces of *i*-PrOH, it was spread on four 20 × 40-cm preparative chromatoplates which were developed with 4:1 $Et_2O$–pentane. Elution with ether and pumping at 80 °C (15 mm) for 1.5 h gave 0.59 g (23%) of pure **8**: $n^{25}_D$ 1.4852 (*Z* 18.3), $[\alpha]^{25}_D$ −26.4°. The NMR and IR spectra and $R_f$ value were identical with those of compound 8 prepared from cocaine except for a faint trace of impurity in the latter sample. No 2-exo epimer was visible in the NMR spectrum.

**Acknowledgments.** Appreciation is extended to the members of the Analytical Department of the Sterling-Winthrop Research Institute for spectral and optical rotational measurements.

**Registry No.**—(+)-**2**, 67597-97-1; (−)-**2**, 67650-63-9; (±)-**2**, 67650-64-0; (+)-**2**·(−)-DBT salt, 67650-65-1; (−)-**2**·(+)-DBT salt, 67737-74-0; **5**, 67597-98-2; **6**, 67597-99-3; **7**, 67598-00-9; **8**, 67650-66-2; **9**, 67598-01-0; **10**, 67598-02-1; **10**·HCl, 67650-67-3; **11**, 67598-03-2; **11**·HCl, 67650-68-4; **12**, 67598-04-3; methyl (1*R-exo,endo*)-2,8-dimethyl-8-azabicyclo[3.2.1]octane-3-carboxylate, 67650-69-5; ethyl chlorocarbonate, 541-41-3; methyl bromide, 74-83-9; phenyl bromide, 108-86-1.

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# Reaction of 2-Aryltropanes with Diethyl Azodicarboxylate

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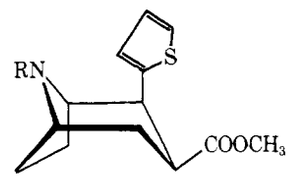
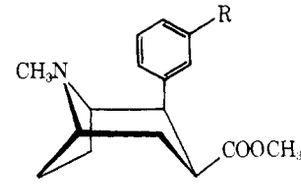
*Received May 5, 1978*

Tropanes bearing an exo substituent on carbon 2 show steric resistance to quaternization reactions. However, diethyl azodicarboxylate reacts readily to form adducts such as **3**. Attempts to demonstrate free-radical intermediates in the reaction by chemically induced dynamic nuclear polarization gave no positive results. Conventional acid hydrolysis of **3** produced some of the expected nortropane but primarily gave **5**. Conditions were maximized for production of either **5** or the nortropane. The same type of bridging reaction occurred when a *m*-benzyloxyphenyl group replaced the 2-thienyl moiety, attack occurring both ortho and para to the benzyloxy function.

A study of the structural requirements for observed hypoglycemic activity of tropane carboxylic ester **1a**[1] required the production of norester **1b**. Catalytic debenzylation of *N*-benzyl ester **1c**[1] was not satisfactory. Demethylation of **1a** by ethyl chloroformate (in boiling benzene) or cyanogen bromide failed owing to steric inhibition of quaternary ammonium ion formation with tropanes carrying exo substituents on carbon 2.[2] (Ethyl iodide failed to react with **1a** in 7 h at 35 °C and methyl iodide gave only 3% reaction with **2a** in 24 h at 25 °C.) It was, therefore, a considerable surprise when the demethylating reagent diethyl azodicarboxylate[3] reacted essentially quantitatively with **1a** in 8 h in boiling benzene to form **3**. This




**1a**, R = $CH_3$
**b**, R = H
**c**, R = $PhCH_2$




**2a**, R = H
**b**, R = OH

product was characterized only spectrally since it could not be crystallized, distilled, or converted to a crystalline salt. The

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