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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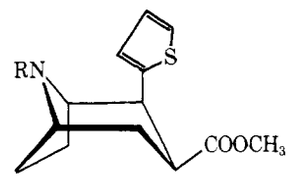
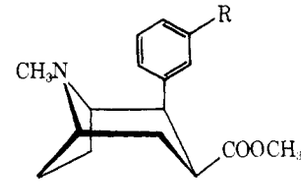
Tropanes bearing an exo substituent on carbon 2 show steric resistance to quaternization reactions. However, diethyl azodicarboxylate reacts readily to form adducts such as **3**. Attempts to demonstrate free-radical intermediates in the reaction by chemically induced dynamic nuclear polarization gave 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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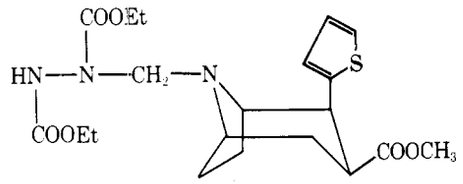
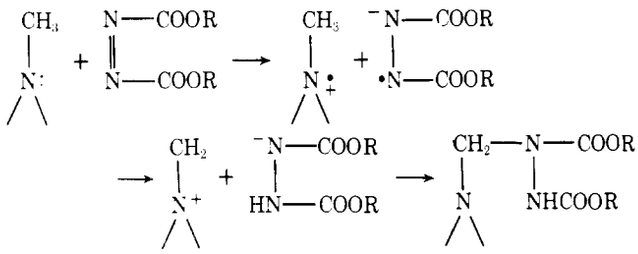


3

product from reaction of **1a** with dimethyl azodicarboxylate did crystallize and was formally characterized.

The mechanism generally ascribed to demethylation of amines by azodicarboxylic esters involves an initial coordination of the tertiary amine nitrogen with the electrophilic azo group. The resulting ion pair can then produce the structure actually formed by an ylide rearrangement.[3a-c]

Another reasonable explanation in the present instance would involve an initial single electron transfer from tertiary nitrogen to azoester, forming two ion radicals. Transfer of a



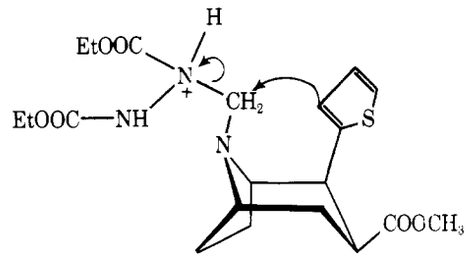
hydrogen atom from the readily accessible methyl group would then afford two charged species which could easily unite to form the observed product. A radical chain reaction mechanism for this type of transformation has been discounted by rate studies in the presence of inhibitors[3b] and, in the present work, by the failure of a radical initiator, 2,2′-azobis(2-methylpropionitrile), to accelerate the reaction.

Single electron transfer reactions which are rapid enough to build up a significant concentration of radical pairs exhibit chemically induced dynamic nuclear polarization (CIDNP), evident in NMR spectra as "negative" (emission) peaks.[4] The reaction of amine **1a** with dimethyl azodicarboxylate was 50% complete in about 35 min at 78 °C, the highest temperature available with the NMR spectrometer at hand. No peaks characteristic of CIDNP were evident, possibly because the reaction was too slow.

Hydrolysis of adduct **3** to produce the desired nortropane **1b** was best accomplished (65% yield) by aqueous methanolic pyridine hydroiodide at room temperature in 72 h. Diethyl hydrazodicarboxylate was formed at the same time in 73% yield. Pyridine hydrochloride afforded lower yields of the nortropane accompanied by a significant quantity of a cyclic product **5**. The best yield of this cyclized material (79%) was obtained when adduct **3** was heated under reflux for 3 h in methanol saturated with HCl.

The structure of **5** was deduced as follows. Elemental analysis indicated that the methylene attached to the tropane nitrogen in **4** had remained with the tropane moiety and, indeed, the NMR spectrum of **5** showed nonequivalent methylene signals at 4.02 and 4.32 ppm with J = 18 Hz (geminal coupling). The protonated form of **5** exhibited further coupling of this methylene, a condition which indicated that the methylene was attached to the nitrogen. No NCH_3 signal was present. The tertiary nature of the nitrogen was supported by its forming a quaternary salt with ethyl iodide and also an N oxide. The other side of the methylene group was attached to the 3 position of the thiophene ring since that hydrogen was no longer present in product **5**. The two aromatic hydrogens present showed the typical thiophene $J_{4,5}$ = 5 Hz coupling characteristic of that system.[5]

In ester **1a** the thiophene ring adopts a conformation which



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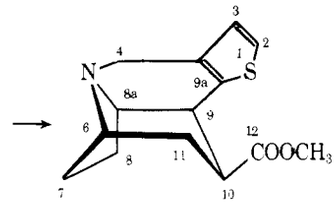


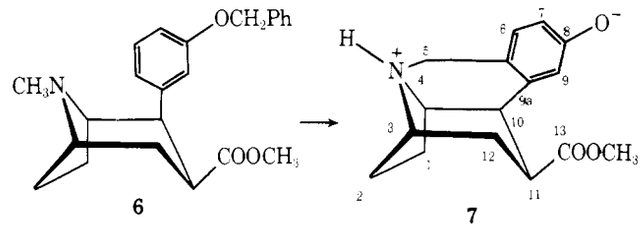
5

causes shielding of the OCH_3 hydrogens; a 3-proton singlet is present at 3.46 ppm.[6] In product **5** this thiophene ring is held rigidly in a position which is not able to cause this shielding and the OCH_3 signal is at 3.68 ppm, near that of 3.72 ppm found for the 3-endo ester series.[6]

Mixtures of cyclized product **5** and nortropane **1b** could be separated chemically by treatment with benzyl chloroformate. Tertiary amine **5** was not rendered neutral and could be extracted with acid. Cleavage of the benzyloxycarbonyl derivative of **1b** from the mixture with aqueous HBr then afforded **1b** as a hydrobromide salt.

A paper being published concurrently[6] describes some narcotic antagonists, one of the most potent being endo-ester **8**. It appeared of considerable interest to apply the presently reported cyclization reaction and determine the effect on activity of fixing in space this fully rotatable aromatic ring.

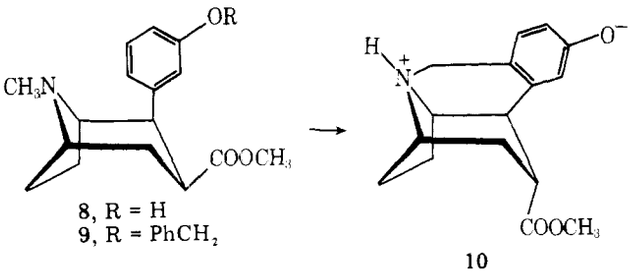
A pilot reaction with exo-ester **6**, containing a protected phenolic group, with diethyl azodicarboxylate produced the expected adduct similar to **3**. Treatment of this adduct with 4 N hydrochloric acid caused both cleavage of the benzyloxy group and cyclization, giving phenol **7** (22%, the only product



6 7

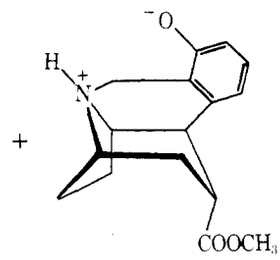
investigated) which appeared to exist as a zwitterion. Its IR spectrum showed broad, medium intensity absorption at 2300–2750 cm^{-1} typical of protonated nitrogen and the expected ester carbonyl absorption at 1723 cm^{-1}. Its NMR spectrum showed coupling of the methylene hydrogens adjacent to the nitrogen with hydrogen on nitrogen; the coupling disappeared upon addition of D_2O. The coupling pattern of the three aromatic hydrogens of this spectrum showed conclusively that the methylene bridge was attached para to the phenolic group. When the benzyloxy group was removed initially (by hydrogenation), no satisfactory reaction occurred with diethyl azodicarboxylate.

In the reaction of interest, treatment of endo-ester benzyl ether **9** with diethyl azodicarboxylate and hydrolysis of the resulting product with 4 N hydrochloric acid gave a 30% yield of **10** and a 7% yield of **11**. The NMR coupling pattern for the three aromatic hydrogens of **10** was like that of **7** and corresponded to bridging para to the phenolic group as represented by formula **10**. This spectrum showed coupling of a proton on



8, R = H
9, R = $PhCH_2$

10



11

nitrogen with the adjacent methylene signal which disappeared upon exchange by D_2O, an indication of zwitterion. The IR spectrum supported this salt structure.

The NMR pattern for the aromatic hydrogens of **11** corresponded to that expected for three adjacent hydrogens, the result of bridging ortho to the phenolic group. Coupling of a proton on nitrogen with the adjacent methylene was apparent here as with **10**, indicating a zwitterion here also.

The biological activities of **10** and **11** are discussed in the paper mentioned above[6] devoted to narcotic antagonists.

Experimental Section

NMR spectra were recorded on a Varian HA-100 spectrograph with Me_4Si as an internal standard. The IR spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer. All spectra on new compounds were completely compatible with the structures assigned with the exception of one crude product which is discussed. Melting ranges were determined in capillary tubes and are uncorrected. Preparative plate chromatography was done with a 1–1.5-mm thick layer of Brinckmann PF 254 silica gel on 20 × 40-cm glass plates.

Reaction of Tropane 1a with Diethyl Azodicarboxylate. Diethyl 1-[(*exo,exo*)-3-Methoxycarbonyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octan-8-ylmethyl]1,2-hydrazinedicarboxylate (3). A mixture of 16.5 g (0.062 mol) of tropane ester **1a**,[6] 50 g (0.29 mol) of diethyl azodicarboxylate, and 150 mL of dry benzene was heated under reflux for 8 h. Later experiments revealed that 2 mol of azoester per mol of tropane were adequate for this reaction. The product was extracted with 35, 25, and 25 mL of ice cold 2 N hydrochloric acid and each extract was washed quickly with Et_2O and drained into a single flask containing 15 mL of concentrated NH_4OH and 15 g of ice. Et_2O extraction of the liberated base gave 27.4 g (100%) of oily **3** which was about 95% pure by TLC (silica, 3:97 *i*-$PrNH_2$–Et_2O). The NMR spectrum was not definitive but contained no adverse characteristics. This product was used satisfactorily in this crude form.

Reaction of 1a with Dimethyl Azodicarboxylate. A solution of 0.66 g (0.0025 mol) of thienyl ester **1a** and 0.73 g (0.0050 mol) of dimethyl azodicarboxylate in 5 mL of tetrachloroethylene and 1 mL of benzene was heated under reflux for 7 h. Solvents were removed by warming in vacuo and the residue was chromatographed on 25 g of Brockmann grade II–III basic alumina using 175 mL of ether for elution followed by 150 mL of 4:1 EtOAc–Et_2O. The material which came off in the Et_2O was rechromatographed on 30 g of alumina using 4:1 Et_2O–pentane to elute starting material and then EtOAc to elute product. **Dimethyl 1-[(*exo,exo*)-3-methoxycarbonyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octan-8-ylmethyl]-1,2-hydrazinedicarboxylate** thus obtained (0.77 g, 76%) crystallized. Recrystallization from Et_2O gave 0.69 g (68%) of needles, mp 134–135 °C. The parent mass peak of the product was 264 ($M^+ - CH_3OOCNH - N - COOCH_3$). There was an NMR singlet at 4.08 ppm (NCH_2N).

Anal. Calcd for $C_{18}H_{25}N_3O_6S$: C, 52.53; H, 6.12; N, 10.21. Found: C, 52.73; H, 6.23; N, 10.42.

Effect of Radical Initiator on Azoester Reaction. Two identical reactions were assembled consisting of 1.00 g (3.8 mmol) of ester **1a**, 1.00 g (5.7 mmol) of diethyl azodicarboxylate, and 10 mL of dry benzene. To one of these was added 30 mg of 2,2′-azobis(2-methylpropionitrile). The rates of the two reactions were followed by spotting samples periodically on silica plates which were developed with 3:97 *i*-$PrNH_2$–Et_2O. After 1 h the reactions appeared to be only 25–30% complete so an additional 2 g of azoester was added to each and reflux was continued. After 4 h the reactions appeared complete. At no point did visual estimation of spots indicate that one reaction was faster than the other.

Chemically Induced Dynamic Nuclear Polarization Study. A solution of 0.33 g (1.2 mmol) of thienyl ester **1a** and 0.36 g (2.5 mmol) of dimethyl azodicarboxylate in 0.75 mL of C_6D_6 was inserted in the probe of a Jeol FX-60 NMR spectrometer which was held at 78 °C. The spectrum was recorded at 1, 3, 6, 10, 20, 30, 40, 50, 60, 75, 105, and 165 min. Only the faintest trace of the *N*-methyl peak was visible on the 165-min scan. Other peaks disappeared or appeared in an expected manner but at no time was an emission peak apparent. The reaction was approximately 50% complete in 35 min.

Hydrolysis of Adduct 3 with Pyridine·HI. A solution of 262.8 g (0.598 mol) of intermediate **3** in 1.6 L of MeOH, 320 mL of pyridine, and 500 mL of H_2O was chilled to 15 °C, divided into two portions, and each treated with 220 mL of cold (5 °C) 47% aqueous HI. The resulting solutions were left at room temperature for 3 days and then concentrated to solid residues by warming to 60 °C in vacuo. Each residue was slurried with 175 mL of H_2O, the slurries were filtered, and the filter cakes were washed with two 25-mL portions of water and air dried.

Trituration of the combined crystalline solids (246 g) with a mixture of 100 mL each of concentrated NH_4OH and H_2O, agitation of the mixture with 600 mL of Et_2O, and filtration separated 68.7 g of crystalline diethyl 1,2-hydrazinedicarboxylate. The layers of the filtrate were separated, the water layer was extracted with Et_2O, and the combined Et_2O layers were concentrated to a residual oil in order to remove NH_3. Dilution of the oily residue with Et_2O, addition of excess gaseous HCl, and collection of the precipitated crystalline salt gave 108.0 g (62%) of **methyl (*exo,exo*)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate (1b)·HCl,** mp 235–6 °C, with intumescence. Its IR, NMR, and mass spectra were consistent with its structure and were in accord with starting material and analogues of this substance reported separately.[6] Recrystallization from CH_3CN (90 mL/g and concentrated to 25% of volume) afforded the analytical sample, mp 239–240 °C (intumescence).

Anal. Calcd for $C_{13}H_{17}NO_2S$·HCl: C, 54.25; H, 6.30; Cl, 12.32. Found: C, 54.07; H, 6.33; Cl, 12.18.

Concentration of the filtrate from precipitation of the **1b**·HCl above afforded 7.6 g more of the diethyl hydrazine-1,2-dicarboxylate giving a total yield of 73%.

The aqueous filtrate from separation of the 246 g of solid above was concentrated to a residue by warming in vacuo. Trituration with 200 mL of half-concentrated NH_4OH and extraction with ether separated more basic products. Concentration of the Et_2O extracts to remove NH_3, dilution of the residue with Et_2O, filtration from a small insoluble residue, and addition of gaseous HCl precipitated 29.3 g of gummy salts. Trituration with 75 mL of acetone, collection of the insoluble portion, and dual washing of the cake with acetone gave 4.4 g more of the nortropane **1b** which appeared to be about 95% pure by TLC. The total yield of demethylated product **1b** was 65% of theoretical.

Treatment of Adduct 3 with Methanolic Hydrogen Chloride. A solution of 2.0 g (4.5 mmol) of adduct **3** in 50 mL of MeOH was saturated with gaseous HCl without cooling and the solution was then heated under reflux with a slow stream of HCl bubbled in for 2.5 h. After standing for 18 h at room temperature the solution was concentrated by warming in vacuo and 25 mL of H_2O was added. Filtration separated some crystalline diethyl hydrazodicarboxylate. Basification of the filtrate with concentrated NH_4OH and extraction with Et_2O separated 1.43 g of basic material which was chromatographed on five 20 × 40-cm silica preparative plates using two solvent passes of 2% *i*-$PrNH_2$–98% Et_2O. The band containing the major product, **methyl (9a/12-*Z*)-4,6,7,8,8a,9-hexahydro-6,9-ethanothieno[3,2-*f*]indolizine-10-carboxylate (5),** afforded 0.95 g (79%) of colorless, crystalline solid, mp 97–104 °C. In a separate run this base was recrystallized from ether with pentane added to give massive prisms: mp 101.5–103 °C; IR (KBr) 1730 cm^{-1} (C=O), M^+ 263. The NMR ($CDCl_3$) showed no NCH_3 but did show OCH_3 as a singlet at 3.68 ppm and a $-CH_2-$ as an AB pattern with A = 4.02 and B = 4.32 ppm with J = 18 Hz (geminal coupling). The HCl salt of **5** (in CF_3COOD) showed further coupling of this methylene with hydrogen on nitrogen. The nonequivalent AB pattern had A = 4.66 ppm (J = 18 Hz) and B = 4.92 ppm (J = 18.5 Hz). Dilution with D_2O caused the 5-Hz coupling to collapse, giving only the 18-Hz coupling. Two thiophene hydrogens

were present at 7.08 and 6.81 ppm with J = 5 Hz (thiophene shows J for $H_{4,5}$ = 5 Hz).[5]

The hydrochloride salt of **5** formed needles from CH_3CN, mp 240–241 °C dec. Anal. Calcd for $C_{14}H_{17}NO_2S$·HCl: C, 56.09; H, 6.05; Cl, 11.82. Found: C, 56.02; H, 5.99; Cl, 12.04.

Compound 5·Ethiodide. A mixture of 3.50 g (0.0133 mol) of ester **5**, 3.25 mL (6.24 g, 0.0399 mol) of ethyl iodide, and 10 mL of CH_3CN was heated under reflux for 0.5 h and allowed to stand at room temperature for 65 h. Et_2O (25 mL) was added and the mixture was filtered to give 4.9 g of the quaternary salt of **5**, mp 246–248 °C dec. Recrystallization from 200 mL of EtOH concentrated to a 100-mL volume afforded 4.4 g of needles, mp 247–249 °C dec. Concentration of the filtrate gave 0.2 g more salt with the same melting point; yield 82%.

Anal. Calcd for $C_{16}H_{22}INO_2S$: C, 45.83; H, 5.29; I, 30.26. Found: C, 45.92; H, 5.30; I, 30.15.

Compound 5·Oxide. A solution of 5.00 g (0.019 mol) of ester **5** in 225 mL of Et_2O was treated with 4.25 g (0.021 mol) of 85% *m*-chloroperbenzoic acid and the mixture was stirred for 1.5 h. H_2O (15 mL) was added, the layers were separated, and the water layer was washed twice with Et_2O. The combined Et_2O layers were washed with two 5-mL portions of H_2O and the combined water layers were concentrated by warming in vacuo (finally heated at 70–90 °C for 2 h at the oil pump). The residue was dissolved in 50 mL of EtOH and this solution was concentrated. A solution of the residue in 200 mL of acetone was concentrated progressively to give 2.30 g (43%) of desired N-oxide monohydrate (as two crops), mp 162–165 °C (intumescence).

Anal. Calcd for $C_{14}H_{17}NO_3S$·H_2O: C, 56.54; H, 6.43; N, 4.71. Found: C, 56.48; H, 6.38; N, 4.65.

Chemical Separation of 1b and 5. A mixture (18.66 g, about 0.07 mol) of **1b** and **5** resulting from hydrolysis of **3** with pyridine hydrochloride instead of pyridine hydroiodide was dissolved in 90 mL of THF. Solid $NaHCO_3$ (18.7 g, 0.22 mol) and 35 mL of H_2O were added, the mixture was cooled in an ice bath, and 19.1 g (0.11 mol) of benzyl chloroformate in 65 mL of THF was added dropwise with stirring in 1 h. After 1 h of further stirring while cold, the THF was removed in vacuo and the residual paste was acidified with 2 N HCl. Extraction with Et_2O separated the neutral material.

The aqueous acid portion was made basic with concentrated NH_4OH and the liberated base was extracted with Et_2O. Concentration of the extract gave an oil (5.89 g) which crystallized when seeded with **5**. It was recrystallized from Et_2O with pentane added to give 3.50 g of **5**, mp 97–99 °C.

The neutral oil was dissolved in 15 mL of HOAc and the solution was saturated with gaseous HBr. The resulting solution was warmed on the steam bath for 15 min, by which time CO_2 evolution ceased. The solution was cooled and diluted with 125 mL of Et_2O and the precipitated gum was triturated with Et_2O to effect crystallization. Recrystallization of this salt from 100 mL of absolute EtOH with concentration to a 45-mL volume gave 11.6 g of **1b·HBr**, mp 220–221 °C (intumescence). A 1-g sample, recrystallized from EtOH for analysis, melted at 218–219 °C (intumescence).

Anal. Calcd for $C_{13}H_{17}NO_2S$·HBr: C, 46.99; H, 5.46; Br, 24.05. Found: C, 46.69; H, 5.51; Br, 23.81.

Treatment of Methyl (*exo,exo*)-8-Methyl-2-[3-(phenylmethoxy)phenyl]-8-azabicyclo[3.2.1]octane-3-carboxylate (6) with Diethyl Azodicarboxylate. A mixture of 7.45 g (0.020 mol) of exo-ester **6**,[6] 7.10 g (0.040 mol) of diethyl azodicarboxylate, and 30 mL of freshly boiled benzene was heated under reflux for 16 h. A silica TLC plate developed with 3:97 *i*-$PrNH_2$–Et_2O showed complete consumption of starting ester with the product represented by a single spot.

The cooled reaction solution was extracted with three 10-mL portions of 2 N hydrochloric acid and the combined extracts were treated with 10 mL of concentrated and 150 mL of 4 N hydrochloric acid. Reflux of the 4 N solution for 4 h caused formation of $PhCH_2Cl$ which was then separated by extraction with Et_2O. Concentration of the aqueous solution by warming in vacuo gave a pasty solid which was swirled with 20 mL of MeOH and again concentrated to remove residual H_2O.

The solid carboxylic acid hydrochloride present at this point was dissolved in 200 mL of MeOH and the solution was saturated with gaseous HCl and allowed to stand for 17 h. Filtration to remove a small amount of white powder and concentration of the filtrate by warming in vacuo gave an oil which crystallized in the presence of 25 mL of CH_3CN. The collected solid was treated with excess 2 N NaOH and ether, the clear layers were separated, and the alkaline layer was immediately treated with excess gaseous CO_2. Extraction with ether and concentration of the extracts to a small volume caused precipitation of 1.23 g (22%) of prisms of **methyl (9a/13-*Z*)-1,2,10,10a-tetrahydro-8-hydroxy-3*H*,5*H*-3,10-ethanopyrrolo[1,2-*b*]isoquinoline-11-carboxylate (7),** mp 206–9 °C. Recrystallization from 100 mL of acetone concentrated to a 15-mL volume furnished 1.05 g of needles: mp 210–2 °C; *m/e* 273; IR (KBr) showed a salt band at 2300–2750 cm^{-1} and an ester carbonyl at 1723 cm^{-1}; NMR (CF_3COOD) showed three aromatic hydrogens (one at 6.70 ppm meta coupled with J = 2 Hz, one at 7.02 ppm ortho and meta coupled with J = 8, 2 Hz, and one at 7.18 ppm ortho coupled with J = 8 Hz). An OCH_3 singlet appeared at 3.78 ppm and a $-CH_2-$ was present as a broadened AB pattern with A at 4.66 ppm and B at 4.86 ppm. Signal overlap made measurement difficult but J was approximately 18 Hz. The signal sharpened considerably upon addition of D_2O and presented a standard pattern of geminal coupling with J = 18 Hz.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.1; H, 6.7; N, 5.1.

Treatment of Methyl (2-*exo*,3-*endo*)-8-Methyl-2-[3-(phenylmethoxy)phenyl]-8-azabicyclo[3.2.1]octane-3-carboxylate (9) with Diethyl Azodicarboxylate. A mixture of 3.44 g (0.0094 mol) of endo-ester **9**,[6] 4.0 g (0.023 mol) of diethyl azodicarboxylate, and 25 mL of freshly boiled benzene was refluxed and worked up as described for the exo-ester **6** immediately above. The crude phenolic product precipitated from alkaline solution by CO_2 (1.78 g) was chromatographed on ten 20 × 40-cm silica preparative plates which were developed by three passes of 3:97 *i*-$PrNH_2$–Et_2O. The largest band (R_f about 0.25) was eluted with acetone and the solution was concentrated to precipitate 0.77 g (30%) of colorless plates of **methyl (9a/13-*E*)-1,2,10,10a-tetrahydro-8-hydroxy-3*H*,5*H*-3,10-ethanopyrrolo[1,2-*b*]isoquinoline-11-carboxylate (10),** mp 213–5 °C with slight darkening. Recrystallization from 100 mL of acetone boiled down to a 15-mL volume gave 0.67 g of **10**: mp 216–8 °C; *m/e* 273; IR (KBr) 2300–2750 (salt band), 1721 cm^{-1} (C=O); NMR (CF_3COOD) showed three aromatic hydrogens (one at 6.94 ppm meta coupled with J = 2–3 Hz, one at 7.06 ppm ortho and meta coupled with J = 8, 2 Hz, and one at 7.22 ppm ortho coupled with J = 8 Hz). An OCH_3 singlet appeared at 4.04 ppm and a $-CH_2-$ was present as a broadened AB pattern with A = 4.65 ppm (J = 18 Hz) and B = 4.92 ppm (J = 18, 5 Hz). Addition of D_2O caused the 5-Hz signal to collapse.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.2; H, 7.0; N, 5.3.

In the plate chromatography described above a band of R_f about 0.07 was scraped and eluted. This material was rechromatographed to give 18 mg (7%) of crystalline **methyl (9a/13-*E*)-1,2,10,10a-tetrahydro-6-hydroxy-3*H*,5*H*-3,10-ethanopyrrolo[1,2-*b*]isoquinoline-11-carboxylate (11):** mp 217–24 °C; *m/e* 273; IR (KBr) 2300–2750 (protonated nitrogen), 1720 cm^{-1} (C=O); NMR (CF_3COOD) showed three adjacent aromatic hydrogens (one H at 7.32 ppm with two ortho couplings, J = 8, 8 Hz, the other two hydrogen signals superimposed at 6.92 ppm with ortho coupling, J = 8 Hz). An OCH_3 singlet was at 4.02 ppm and a $-CH_2-$ appeared as a nonequivalent AB pattern, B being further coupled: A = 4.66 ppm (J = 18 Hz), B = 4.94 ppm (J = 18, 6 Hz). Addition of D_2O caused the 6 Hz coupling of B to collapse.

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Registry No.—**1a**, 67597-72-2; **1b**·HCl, 67597-73-3; **1b**·HBr, 67597-74-4; **3**, 67597-75-5; **5**, 67597-76-6; **5**·HCl, 67650-58-2; **5**·ethiodide, 67597-77-7; **5**·oxide, 67597-78-8; **6**, 67597-79-9; **7**, 67597-80-2; **7**·free acid, 67632-53-5; **7**·HCl, 67650-61-7; **9**, 67650-59-3; **10**, 67650-60-6; **11**, 67597-81-3; dimethyl 1-[(*exo,exo*)-3-methoxycarbonyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octan-8-ylmethyl]-1,2-hydrazinedicarboxylate, 67632-52-4; diethyl azodicarboxylate, 1972-28-7; dimethyl azodicarboxylate, 2446-84-6; diethyl 1-[(*exo,exo*)-3-methoxycarbonyl-2-[3-(phenylmethoxy)phenyl]-8-azabicyclo[3.2.1]octan-8-ylmethyl]-1,2-hydrazinedicarboxylate, 67597-82-4.

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Biologically Oriented Organic Sulfur Chemistry. 19. Synthesis and Properties of 2-Amino-5-mercapto-5-methylhexanoic Acid, a Bishomologue of Penicillamine. Use of Boron Trifluoride Etherate for Catalyzing Markownikoff Addition of a Thiol to an Olefin[1a-f]

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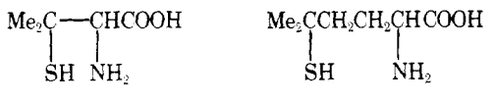
Synthesis is reported of 2-amino-5-mercapto-5-methylhexanoic acid (**2**) as a bishomologue of penicillamine (**1**). In this synthesis, alkylation of diethyl acetamidomalonate gave ethyl 2-acetamido-2-carbethoxy-5-methyl-4-hexenoate (**4**). Addition of α-toluenethiol to **4** using BF_3·Et_2O then gave ethyl 2-acetamido-2-carbethoxy-5-benzylthio-5-methylhexanoate (**6**) in 63–74% yield; this reaction appears to be the first use of BF_3·Et_2O as a catalyst for effecting Markownikoff-type addition of a thiol to an alkene. The bishomologue **2** was obtained from **6** either by decarboxylation to the amide (**5**), debenzylation of **5** to **7**, and hydrolysis, or (preferably) by decarboxylation and hydrolysis to the amino acid **8** in one step and debenzylation. The bishomologue **2** resisted hot strong acid. It reacts with formaldehyde, Fe(III), or Cu(II) much less readily than does **1** and therefore affords a promising means of probing biological properties of **1** where it is unclear whether these properties depend upon ring formation involving SH and NH_2 or upon independent action of functional groups.

Penicillamine (**1**) gives rise to an astonishing multiplicity of significant biomedical and biological effects. Illustratively,



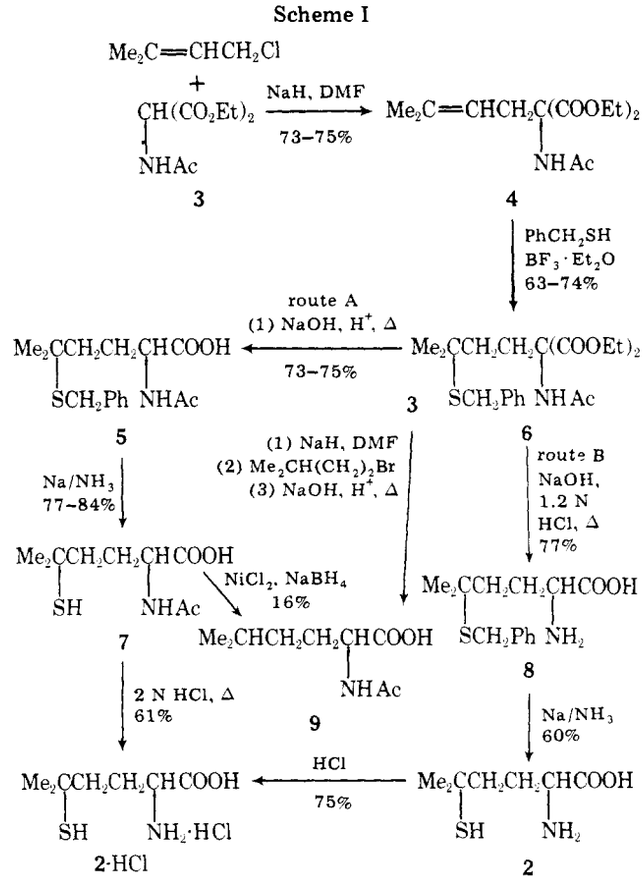
1 **2**

it has been of interest in treating a wide variety of diseases,[2a] inhibits lysyl oxidase,[2b] shows immunological properties,[1b] reduces skin-tensile strength of rats (apparently through formation of thiazolidines with aldehyde groups of collagen),[1a] and is a good chelating agent,[2c] a property that is biomedically important.[2c-e] The last two of these, formation of thiazolidines and chelation, depend on the capability of **1** to form five-membered rings involving SH and NH_2, but whether most other biological functions of **1** depend on this proclivity or simply on independent action of one or more of the functional groups is unknown. A bishomologue of **1** that could lead only to more difficultly formed seven-membered rings would be useful because it could be compared with **1** in the multifold biological activities of **1** and thus could help to clarify the question of five-membered ring involvement vs. independent action of functional groups. This paper reports synthesis of the bishomologue **2**. The key to the synthesis of **2** was a novel BF_3-catalyzed Markownikoff-type addition of a thiol to an alkene that warrants general attention as a new synthetic tool. The bishomologue **2** was indeed found to react much less readily than **1** with a model aldehyde and in forming metal chelates.

In the synthesis of **2** (Scheme I), alkylation of **3** produced the requisite carbon skeleton (confirmed below).

For insertion of SH, although Markownikoff addition of H_2S and anti-Markownikoff addition of thiols to alkenes are well known, a report of Ipatieff, Pines, and Friedman that H_2SO_4 catalyzes the requisite Markownikoff addition of thiols was one of a very few guides that were attractive.[3] With α-toluenethiol and **4**, however, the principal or sole product using H_2SO_4 was benzyl disulfide (presumably produced by oxidation of the thiol by H_2SO_4). Use of BF_3·Et_2O at ~25 °C and **4** for several days led to no reaction with α-toluenethiol and led only to intractable mixtures with thioacetic acid. However, use of BF_3·Et_2O as both catalyst and solvent with

Scheme I



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