orously for 30 min, and the radioactivity was measured in a Packard B-2450 liquid scintillation counter. Nonspecific binding was determined by substituting nonradioactive diazepam (final concentration 3 μM) or clonazepam (final concentration 1 μM) for the test compound. Nonspecific binding was less than 10% of total binding under these conditions. Specific binding was defined as the difference in binding in the presence and absence of the large excess of nonradioactive benzodiazepine. Data were expressed as percent inhibition of specific binding, and IC_{50} values were estimated from semilogarithmic plots (see Figure 1). Inhibitory constants of compounds under study were calculated by the equation $K_i = IC_{50}/1 + [L]/K_D$, where [L] = ligand concentration (~2 nM), and the K_D for [^{3}H]diazepam was estimated to be 5.6 ± 0.34 nM in thrice-washed cerebral cortical membranes.[57] Hill coefficients for compounds under study were estimated using least mean squares regression analysis with values obtained from inhibition curves as described.[58]

Antagonism of the Anticonvulsant Effects of Diazepam. Mice were injected with sufficient diazepam (1.5–5.5 mg/kg, ip) to protect 80–90% against tonic–clonic convulsions induced by pentylenetetrazole (100 mg/kg, ip). This dose of PTZ elicits convulsions in 100% of mice pretreated with vehicle. Mice were injected with diazepam and 20 min later injected (ip) with either β-C or vehicle. Ten-minutes later, the animals were challenged with PTZ. In some studies with 3-formyl-β-carboline (**25**), the interval between administration of compound and PTZ was decreased to 5 min. Animals were scored as protected by diazepam if no appearance of seizures was noted for 10 min after injection of PTZ.

Antagonism of the Anxiolytic Actions of Diazepam and Meprobamate. Mice were treated with diazepam (2 mg/kg, ip) or meprobamate (50 mg/kg, ip) 20 min prior to injection with either vehicle or test compound. The number of light ⇌ dark transitions was measured in a chamber that was partitioned so that two-thirds of the chamber was illuminated and one-third was dark. A series of photocells records the number of light ⇌ dark transitions, which represent spontaneous exploratory activity, during a 10-min test period beginning 10 min after injection of the test compound or vehicle.[22]

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(±)-*cis*-2-Acetoxycyclobutyltrimethylammonium Iodide: A Semirigid Analogue of Acetylcholine

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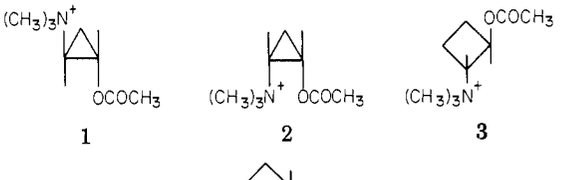
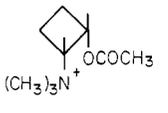
The title compound was prepared to complete a series of small ring (cyclopropane, cyclobutane) cis/trans 1,2-disubstituted semirigid congeners of acetylcholine. A multistep synthetic sequence, beginning with *cis*-cyclobutane-1,2-dicarboxylic anhydride, permitted unequivocal preparation of the (±)-cis target compound **4**. The geometry of **4** was confirmed by comparison with an authentic sample of the (±)-trans isomer. The cis and trans isomers were equipotent as muscarinic agonists, but they were much weaker than acetyl-β-methylcholine.

Prior communications from this laboratory have described the synthesis[1] and the remarkably high muscarinic effects[2] of (1*S*,2*S*)-*trans*-2-acetoxycyclopropyltrimethylammonium iodide ("*trans*-ACTM", **1**). The enantiomer



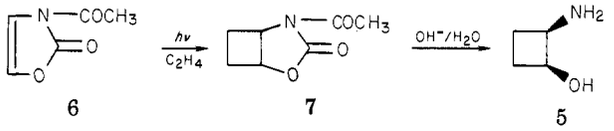
1 **2** **3**



4

1*R*,2*R* of **1** had only $^1/_{200}$ the muscarinic potency of **1**, and like **1**, it had almost no nicotinic activity. In contrast, (±)-*cis*-2-acetoxycyclopropyltrimethylammonium **2** was virtually inert in both nicotinic and muscarinic assays (one-twentieth as potent in a muscarinic assay and approximately equipotent in a nicotinic assay compared to (1*R*,2*R*)-*trans*-ACTM, the less active enantiomer). Subsequently,[3] the (±)-*trans*-cyclobutane analogue **3** of *trans*-ACTM was found to possess muscarinic activity, but the potency was decidedly less than that of (±)-*trans*-ACTM. The present work describes the synthesis and biological evaluation of (±)-*cis*-2-acetoxycyclobutyltrimethylammonium iodide (**4**) for completion of the series of cis and trans isomers of cyclopropane- and cyclobutane-derived congeners of acetylcholine.

Scheme I. Synthesis of *cis*-2-Aminocyclobutanol[a]



6 **7** **5**

[a] See ref 4.

Chemistry. Hartmann et al.[4] have reported the synthesis of (±)-*cis*-2-aminocyclobutanol (**5**) (Scheme I), and this compound would be an ideal precursor to the target species **4**. In the present study, all attempts to prepare adequate amounts of (±)-4-acetyl-2-oxa-4-azabicyclo-

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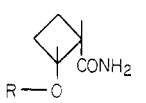
[3.2.0]heptane-3-one (**7**) by photochemical cycloaddition of ethylene to 3-acetyl-2(3*H*)oxazolone (**6**) using the procedure of Hartmann et al.,[4] or variations thereof, were unsuccessful.

An alternate strategy began with a 1,2-difunctionalized cyclobutane ring system with known cis geometry, bearing substituents which could be converted into acetoxy and trimethylammonium and which used functional group transformations which would permit unequivocal retention of the cis geometry. *cis*-Cyclobutane-1,2-dicarboxylic anhydride (**8**) was subjected to the sequence illustrated in Scheme II. The methyl ketones **11a,b** were the only synthetic intermediates that required careful handling to prevent epimerization to the trans geometry. This facile isomerization has been demonstrated[3] for **11a** (Scheme II). In the present work, **11a** could be quantitatively epimerized to methyl *trans*-2-acetylcyclobutanecarboxylate[3,5] by shaking with 5% HCl for 5 min. In order to avoid epimerization, the dimethylcadmium reaction (**10** → **11**) was quenched with a minimal amount of distilled water rather than with the more customary excess aqueous acid. The ethereal solvent was promptly evaporated, and remaining traces of water were azeotroped. When these precautions were followed, the cis isomer was obtained uncontaminated by trans material, according to gas chromatographic analysis.

In initial synthetic efforts, the anhydride **8** was treated with methanol, and the resulting methyl ester **9a** was utilized. However, all attempts to convert the carbomethoxy group of **12a** (Scheme II) into the primary amide **17**, for subsequent nitrene-mediated rearrangement to a



17, R = H or CH_3CO

primary amine, failed. Ammonolysis reactions of **12a** gave rise to complex intractable mixtures. Accordingly, the *cis*-anhydride **8** was treated with benzyl alcohol, and the sequence (Scheme II) was pursued on the benzyl ester **9b**. Initial attempts to isolate and purify the monobenzyl ester **9b**, the acid chloride **10b**, and the methyl ketone **11b** were hampered by contamination with *cis*-cyclobutane-1,2-dicarboxylic anhydride (**8**), which arises from elimination of the benzyl group from **9b**, **10b**, or **11b** in the presence of acid or upon standing in solution. Rapid workup of the reaction mixtures minimized the problem. The acid chloride **10b** decomposed on standing for a few hours, and successful reactions with **10b** were possible only with freshly distilled material.

Verification of the cis geometry of the target compound **4** was made by comparison of its physical, infrared spectral, and chromatographic properties with those of an authentic sample of the (±)-trans isomer **3**. It is reported[6,7] that, due to overlapping ranges of coupling constants, NMR spectral analysis is of little value in assigning cis or trans geometry in 1,2-disubstituted cyclobutane systems, and this was found to apply in the present work.

A sample of (±)-*cis*-2-aminocyclobutanol (**5**) was prepared by Red-Al reduction of (±)-*cis*-2-acetoxycyclobutylamine **16**. The melting point of the product of this reduction corresponds to that reported by Hartmann et al.[4] for **5**, and this was taken as further evidence for the retention of cis geometry of intermediates through structure **16**, Scheme II.

Scheme II. Preparation of (±)-2-Acetoxycyclobutyltrimethylammonium Iodide

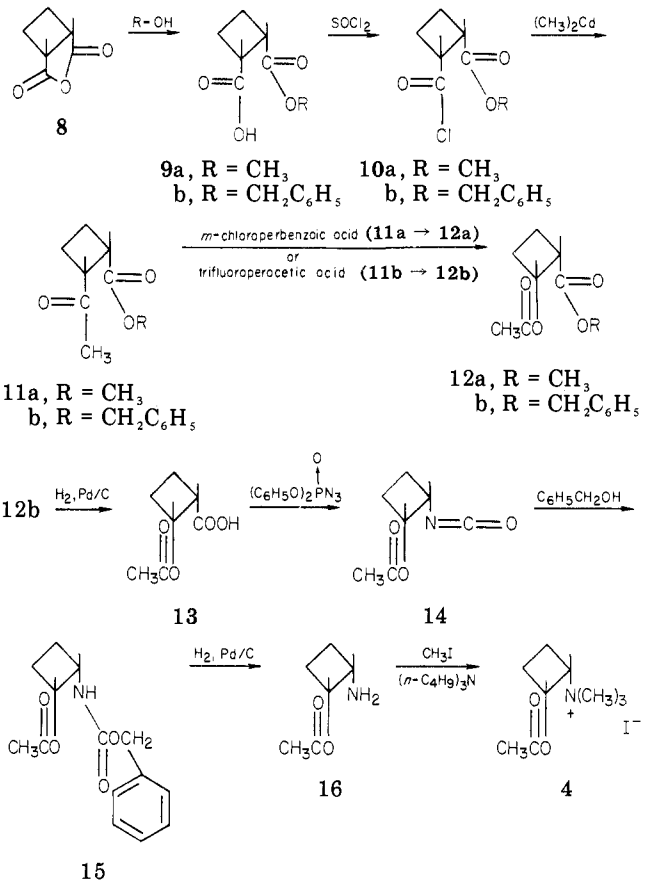


Table I. Muscarinic Effects of Cyclobutane-Derived Congeners of Acetylcholine

compd	ID_{50}, nmol (95% CL)
4 (cis isomer)	83 (58-117)
3 (trans isomer)	68 (48-95)
acetyl-β-methylcholine	0.11 (0.09-1.32)

Spectral (IR, NMR, MS) data for all compounds described herein were consistent with the proposed structures.

Pharmacology. Muscarinic activity was determined using isolated superfused guinea pig ilea according to standard literature procedures (see Experimental Section). Both the *cis*- (**4**) and the *trans*-2-acetoxycyclobutyltrimethylammonium iodide (**3**) induced contractile responses in a dose-dependent fashion. These contractions were completely abolished by atropine sulfate pretreatment. Both of the isomers demonstrated weak muscarinic activity (of the same order of magnitude) when compared to the muscarinic receptor agonist acetyl-β-methylcholine chloride (see Table I).

Both isomers (**4** and **3**) were concluded to be full muscarinic receptor agonists, since they produced dose–response curves that paralleled that produced by acetyl-β-methylcholine chloride, and they demonstrated the same efficacy. The muscarinic effects of the cyclobutane derivatives, unlike those of their cyclopropane congeners (**1** and **2**) seem unaffected by the stereochemistry of the ring system. It is appealing to speculate that the low order of muscarinic effects seen with **3** and **4** is nonspecific and is

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due merely to the presence of a trimethylammonium head on the molecules. The cyclobutane ring seems a poor choice for structure–activity studies of cholinergic agents.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of the theoretical values. IR spectra were recorded on a Beckman 4240 or Perkin-Elmer 267 spectrometer, as films on NaCl plates or as KBr pellets. ^{1}H NMR spectra were recorded on a Varian Associates T-60 or EM-360A spectrometer in $CDCl_3$ unless otherwise noted, using Me_4Si as the internal standard. Mass spectra were obtained using a Finnigan 3200 or 1015 S/L spectrometer. Photochemical reactions were performed in an Ace glass 7863 reaction vessel (Ace Glass Co., Vineland, NJ). The radiation source was an Ace-Hanovia 6515-34 450-W medium-pressure mercury quartz lamp.

Pharmacology. Determination of Muscarinic Activity. Muscarinic activity was determined using isolated guinea pig ilea.[8,9] Animals were killed with a blow to the head and were exsanguinated. A 4- to 5-cm segment of proximal ileum was constantly superfused with oxygenated (95% O_2, 5% CO_2) Tyrode solution at 37 °C, which contained 20 μM choline chloride, 1 μM propranolol hydrochloride, and 83 μM hexamethonium bromide. The solution was superfused at a rate of 6.0 mL/min, using a Gilson minipuls 2 rotary head pump.

Compounds **3** and **4** and acetyl-β-methylcholine chloride were dissolved in distilled H_2O. Increasing amounts of each substance were injected into the superfusate in a volume of 20 μL, and ensuing contractions were determined with a Statham G 10 B force transducer and were displayed on a Beckman RM611 multichannel recorder. Each agent was tested on a minimum of four ilea from separate animals. After initial dose–response curves had been obtained, sensitivity to muscarinic receptor antagonism was determined by adding 0.29 nM atropine sulfate to the superfusate and allowing it to equilibrate for 15 min. The preparation was then rechallenged with the highest dose of the putative muscarinic receptor agonist being tested.

The ID_{50} with the corresponding 95% confidence intervals were determined by probit analysis. Deviation from linearity and parallelism of the dose–response curves were determined by 3 × 3 parallel line bioassay. The significance of the antagonism of the maximal response induced by the putative muscarinic agonists in the presence of atropine sulfate was determined with the student's paired t test. Significant differences were assumed at the $\alpha \leq 0.05$ level.

Methyl (±)-*cis*-2-Acetylcyclobutanecarboxylate (11a). A solution of Me_2Cd (~0.2 mol) was prepared by stirring $CdCl_2$ (38.49 g, 0.21 mol), MeMgBr (0.4 mol in Et_2O, Aldrich Chemical Co.), and 150 mL of dimethoxyethane under N_2 at 0 °C for 1 h and then at 25 °C for 23 h. The supernatant was siphoned (leaving the insoluble Mg salts behind) into a flask containing 29.95 g (0.17 mol) of (±)-*cis*-2-carbomethoxycyclobutanecarbonyl chloride (**10a**),[5] followed by an additional 350 mL of dimethoxyethane washings of the inorganic salts. The resulting mixture was stirred at 0 °C for 1 h and then at 70 °C for 27 h. Tetrahydrofuran (69 mL) was added, and the mixture was stirred at 65 °C for 1 h. It was then cooled and quenched by slow addition of a minimal amount of H_2O, until effervescence ceased. The volatiles were removed under reduced pressure; remaining traces of H_2O were removed by azeotroping with toluene. The residue was taken up in dry toluene and filtered, and the filtrate was concentrated under reduced pressure. Distillation of the oily residue gave 11.9 g (42%) of product, bp 70 °C (0.8 mm). Anal. ($C_8H_{12}O_3$) C, H, O.

Methyl (±)-*trans*-2-Acetylcyclobutanecarboxylate (18). Compound **11a** (7.14 g, 0.046 mol) was shaken with 5% HCl at 25 °C for 5 min. The mixture was extracted with Et_2O, and the ethereal extract was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. Distillation of the residue, bp 63–66 °C (0.25 mm) gave 7.01 g (98%) of material whose IR and NMR spectra were identical with similar spectra recorded for an authentic sample[5] of **18** [lit.[5] bp 99–101 °C (12 mm)].

Methyl (±)-*cis*-2-Acetoxycyclobutanecarboxylate (12a). A mixture of 10.87 g (0.07 mol) of **11a**, 42.39 g (0.21 mol) of 85% *m*-chloroperbenzoic acid, and 100 mL of dry $CHCl_3$ was stirred under N_2 in the dark at 25 °C for 15 days. The mixture was then filtered, and the filtrate was washed with 5% NaOH and then with H_2O and dried (Na_2SO_4), and the $CHCl_3$ was removed under reduced pressure. Distillation of the residual oil gave 7.24 g (61%) of the product, bp 54–56 °C (0.3 mm). Anal. ($C_8H_{12}O_4$) C, H, O.

(±)-*cis*-Cyclobutane-1,2-dicarboxylic Acid Monobenzyl Ester (9b). A solution of 70.03 g (0.56 mol) of *cis*-cyclobutanecarboxylic anhydride (**8**) and 172.4 mL (1.67 mol) of benzyl alcohol in 110 mL of dry benzene was stirred under N_2 under reflux for 4 h, until the carbonyl band (1782 cm^{-1}) of the starting material **8** could not be detected by IR analysis of the solution. The benzene was removed under reduced pressure, and the excess benzyl alcohol was distilled from the mixture. The residual oil was dissolved in benzene, and this solution was extracted with saturated $NaHCO_3$ solution. The aqueous extract was acidified with 10% HCl and was then extracted with benzene. This extract was dried (Na_2SO_4), and the volatiles were removed under reduced pressure. Crystallization of the oily residue from CCl_4–petroleum ether (bp 35–60 °C) gave 108.09 g (83%) of product, mp 66 °C. Anal. ($C_{13}H_{14}O_4$) C, H, O.

(±)-*cis*-Carbobenzoxycyclobutanecarbonyl Chloride (10b). A mixture of 6.75 g (0.029 mol) of **9b**, 0.8 mL of pyridine, and 20 mL of benzene was stirred with cooling in an ice–H_2O bath, and 8.05 g (0.063 mol) of oxalyl chloride was added in one portion. After 1 h, the mixture was warmed to 55 °C, and stirring was continued for an additional 23 h. The volatiles were removed under reduced pressure, and the residual oil was distilled, bp 125–133 °C (0.15 mm). Redistillation, bp 126–128 °C (0.09 mm), gave 4.1 g (56%) of product: MS, m/e 252 (M^+).

Benzyl (±)-*cis*-2-Acetylcyclobutanecarboxylate (11b). A solution of Me_2Cd (~0.29 mol) was prepared from 55.0 g (0.3 mol) of $CdCl_2$, MeMgBr (0.57 mol in Et_2O, Aldrich Chemical Co.), and 250 mL of dimethoxyethane, as described for **11a**. The Me_2Cd solution was siphoned into a flask containing freshly prepared **10b** (16.01 g, 0.06 mol), followed by an additional 500 mL of dimethoxyethane washings of the inorganic salts from the Me_2Cd reaction residue. The mixture was stirred at 0 °C for 1 h and then at 72 °C for 107 h. Tetrahydrofuran (50 mL, 0.62 mol) was added, and the mixture was stirred at 68 °C for 1 h. The mixture was then cooled and quenched by slow addition of a minimal amount of H_2O until effervescence ceased. The volatiles were removed under reduced pressure; remaining traces of H_2O were removed by azeotroping with toluene. The residue was taken up in toluene and filtered, and the filtrate was concentrated under reduced pressure. Distillation of the yellow oily residue, bp 126–130 °C (0.1 mm) gave 61.5 g (42%) of product. Anal. ($C_{14}H_{16}O_3$) C, H, O.

Benzyl (±)-*cis*-2-Acetoxycyclobutanecarboxylate (12b). A solution of trifluoroperacetic acid was prepared by adding 14.7 mL (0.1 mol) of trifluoroacetic anhydride in 35 mL of CH_2Cl_2 dropwise to 2.3 mL (0.09 mol) of 90% H_2O_2 and stirring at 0 °C for 1 h. This solution was added dropwise to a mixture of 5.03 g (0.022 mol) of **11b**, 29.6 g (0.21 mol) of Na_2HPO_4, and 100 mL of CH_2Cl_2. The mixture warmed rapidly, and it was stirred under reflux for 2 h. The inorganic salts were removed by filtration and were washed on the filter with CH_2Cl_2. The combined filtrate and washings were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated. Distillation of the oily residue through a short-path apparatus gave 4.33 g (81%) of material, bp 134–136 °C (0.35 mm). Anal. ($C_{14}H_{16}O_4$) C, H.

(±)-*cis*-2-Acetoxycyclobutanecarboxylic Acid (13). Compound **12b** (4.18 g, 0.017 mol) was hydrogenolyzed at 25 °C in 65 mL of EtOAc over 0.45 g of 5% Pd/C at an initial pressure of 50 psig. After the consumption of 1 equiv of H_2 (18 h), the catalyst was removed and the solvent was evaporated under reduced pressure. Distillation of the resulting oil through a short-path apparatus gave 2.64 g (99%) of product, bp 98–101

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°C (0.06 mm). Anal. ($C_7H_{10}O_4$) C, H, O.

Benzyl *N*-(±)-*cis*-2-Acetoxycyclobutylcarbamate (15). Compound **13** (2.58 g, 0.016 mol), triethylamine (2.3 mL, 0.016 mol), 3.5 mL (0.016 mol) of diphenylphosphoryl azide, and 16 mL of dry benzene were combined under N_2 at 25 °C; then the mixture was warmed and stirred under reflux for 4 h until the evolution of N_2 ceased. Benzyl alcohol (8.5 mL, 0.082 mol) was added, and the resulting mixture was stirred under reflux for 15 h. The benzene was then removed under reduced pressure, and excess benzyl alcohol was distilled off. The residual oil was taken up in benzene, and this solution was washed with H_2O, saturated $NaHCO_3$, and H_2O and dried (Na_2SO_4). Concentration of the solution gave 4.32 g (100%) of the product as an oil, which was determined by GC to be greater than 99% pure. This was used in the next step without purification. An analytical sample was distilled (with considerable loss by charring), bp 152–154 °C (0.1 mm). Anal. ($C_{14}H_{17}NO_4$) C, H, N.

(±)-*cis*-2-Acetoxycyclobutylamine (16). Compound **15** (1.21 g, 0.0046 mol) was hydrogenolyzed at 25 °C in 50 mL of EtOAc and 2 mL of glacial AcOH over 0.5 g of 10% Pd/C at an initial pressure of 50 psig. The theoretical amount of H_2 was consumed in 1 h; hydrogenation was continued for 40 h. The catalyst was removed, and the solvent was evaporated. The residual material was taken up in 20 mL of EtOAc, this solution was washed with saturated Na_2CO_3 (19 mL, 0.041 mol), and this washing was washed twice with EtOAc. The combined organic phases were washed with 10 mL of H_2O, which was back-extracted twice with EtOAc, and the combined EtOAc solutions were evaporated. Distillation of the yellow, oily residue through a short-path apparatus gave 0.44 g (74%) of product: bp 79–80 °C (1.0 mm); MS, *m/e* 129 (M^+).

(±)-*cis*-2-Acetoxycyclobutyltrimethylammonium Iodide (4). Freshly prepared **16** (0.2 g, 0.0016 mol), 0.81 mL (0.0034 mol) of tri-*n*-butylamine, and 7 mL of EtOAc were combined at 0 °C, and 0.32 mL (0.0051 mol) of MeI was added. The mixture was stirred at 25 °C for 18 h in the dark. The white precipitate that formed was collected on a filter under N_2 and was washed on the filter with EtOAc. Recrystallization of the residue on the filter from 1-butanol–heptane gave 0.269 g (58%) of white needles, homogeneous by TLC (R_f 0.19, silica GF, MeOH): mp 174–176.5 °C; IR ($CHCl_3$) 3000 (strong, C–H *as*), 1740 (acetoxy C=O), 1440 (m, C–H *bend*), 1429 (vw, C–H *bend*), 1420 (m, C–H *bend*) cm^{-1}; MS, *m/e* 157 ($M^+ - CH_3I$); NMR (CD_3OD) δ 2.0–2.3 (m, superimposed singlet at δ 2.05, total integration 7 H, $\overline{NCHCH_2CH_2CCHO}$), 2.05 (s, $COCH_3$), 3.2 (s, 9 H, NCH_3), 4.05–4.45 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$), 5.1–5.4 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$). Anal. ($C_9H_{18}INO_2$) C, H, N.

Recrystallization of (±)-*trans*-2-Acetoxycyclobutyltrimethylammonium Iodide (3). An authentic sample was recrystallized twice from 1-butanol–heptane to afford white crystals, homogeneous by TLC (R_f 0.53, silica GF, MeOH): mp 166–167.5 °C. [lit[3] mp 164–166 °C]. The IR spectrum ($CHCl_3$) was identical with that recorded for **4** with the following exceptions: 1433 (m, C–H *bend*), 1415 (w, C–H *bend*) cm^{-1}; NMR (CD_3OD) δ 2.0–2.3 (m, superimposed singlet at δ 2.05, total integration 7 H, $\overline{NCHCH_2CH_2CHO}$), 2.05 (s, $COCH_3$), 3.2 [s, 9 H, $N(CH_3)_3$], 4.05–4.5 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$), 5.1–5.4 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$).

(±)-*cis*-2-Aminocyclobutanol (5). A solution of 0.1 g (0.007 mol) of **16** in 10 mL of benzene was added dropwise to a solution of 70% *Red-Al* (0.67 mL, 0.0023 mol, Aldrich Chemical Co.) in 10 mL of benzene. The mixture was stirred under N_2 under reflux for 4 h, and then the excess *Red-Al* was destroyed by careful addition of EtOH. The volatiles were removed under reduced pressure, and the residue was dissolved in 10% NaOH. Liquid/liquid extraction of this solution with Et_2O for 4 days, followed by concentration of the organic solution, gave a brown oil. An ion-exchange column was prepared: Amberlite IRC-50 (40.0 g, Mallinckrodt) was washed with 10% glacial AcOH in EtOAc, EtOAc (4 times), and 2-PrOH (4 times) and was packed into a glass column. A solution of the brown oil in 2 mL of 2-PrOH was placed on the column, and impurities were eluted with 400 mL of 2-PrOH. The product was then eluted with 350 mL of 10% Et_3N in 2-PrOH. The eluate was evaporated to give an oily residue, homogeneous by GC. Crystallization from Et_2O–petroleum ether (bp 35–60 °C) gave 0.31 g (46%) of product, mp 56–59 °C (lit.[4] mp 58–60 °C).

Notes

Antimalarials. 14. 5-(Aryloxy)-4-methylprimaquine Analogues. A Highly Effective Series of Blood and Tissue Schizonticidal Agents

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A series of five 5-(aryloxy)-4-methylprimaquine analogues has been prepared and evaluated for antimalarial activity. The compounds were tested for suppressive activity against *Plasmodium berghei* in mice and for radical curative activity against *Plasmodium cynomolgi* in the rhesus monkey. The compounds were not only significantly superior to primaquine as radical curative agents but also were suprisingly highly effective as suppressive agents.

Primaquine, over the years, has been the clinical drug of choice with widespread use in the treatment of relapsing *Plasmodium vivax* and *P. ovale* malaria. Primaquine, used clinically as the diphosphate salt, is a radical curative drug that is effective in clearing tissue parasites but has minimal suppressive activity; i.e., it is relatively ineffective as a blood schizonticide. In man, the toxicity of primaquine precludes administration of a single curative dose. Thus, to achieve a radical cure of *P. vivax* in man, the drug is ordinarily given in divided doses over 14 or 21 days and is accompanied by a 3-day course of chloroquine to clear the blood of schizonts.

As part of early attempts to improve primaquine, the side chain was variously modified as part of the extensive Army World War II Program, but no significant improvement was achieved.

Later in 1955, Elderfield and co-workers[1] reported the

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