Synthesis and Biological Evaluation of 2,3-Diazabicyclo[2.2.1]heptane Derivatives as Prostaglandin Endoperoxide Analogs

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Abstract □ Three prostaglandin endoperoxide analogs that possess the 2,3-diazabicyclo[2.2.1]heptane skeleton were synthesized and evaluated for activity in human platelets and in the rat fundus. All three compounds were inactive in inhibiting or stimulating platelet aggregation. One compound possessed weak contracting activity on the rat fundus.

Keyphrases □ Platelet aggregation—evaluation of inhibition and stimulation by prostaglandin endoperoxide analogs □ Prostaglandin endoperoxide analogs—synthesis and evaluation for inhibition and stimulation of platelet aggregation

A recent report stated that the prostaglandin endoperoxide analog 9,11-azo-13-oxa-15-hydroxyprostanoic acid (I) is a potent inhibitor of platelet aggregation (1). Some of its congeners also possessed antiaggregatory activity.

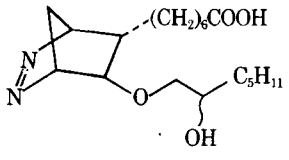
Because simple bicyclic systems, such as 2,3-dioxabicyclo[2.2.1]heptane and 2,3-diazabicyclo[2.2.1]hept-2-ene, were reported (2) to inhibit platelet aggregation in the millimolar concentration range, determination of whether less complex congeners of I containing only one side chain exhibit similar activity was of interest. The synthesis and biological evaluation of such compounds (II–IV) are described.

DISCUSSION

The preparation of II was accomplished *via* the olefin synthesis of Zweifel *et al.* (3) using diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (V) (4) (Scheme I). Two products, the desired *cis*-olefin (VII) (70%) and a ring-opened product, 4-(*N,N'*-dicarboethoxyhydrazino)cyclopentene (VIII) (10%), were obtained. The isolation of VII and VIII can be rationalized by the formation of an intermediate (VI), which can rearrange through two different but competitive pathways. Path a is the dominant alkyl carbanion migration pathway and yields VII; path b leads to rupture of the bicyclic system to give VIII[1]. Treatment of VII with base followed by air oxidation with cupric acetate as a catalyst (6) and acidolysis gave the target compound, II.

The coupling constant of the olefinic protons in II is ~10 Hz, which is within the range of the coupling constant for a *cis*-double bond (7). The *exo*-orientation of the side chain at C-5 is assigned by virtue of the reaction mechanism since hydroboration of bicyclic olefins proceeds by *cis*-addition (8) from the *exo*-face (8) and migration of an alkyl group from the boron atom to an electron-deficient carbon (path a in VI) occurs (9) with the retention of configuration.

Compounds III and IV were synthesized from the *exo*-mesylate (X)



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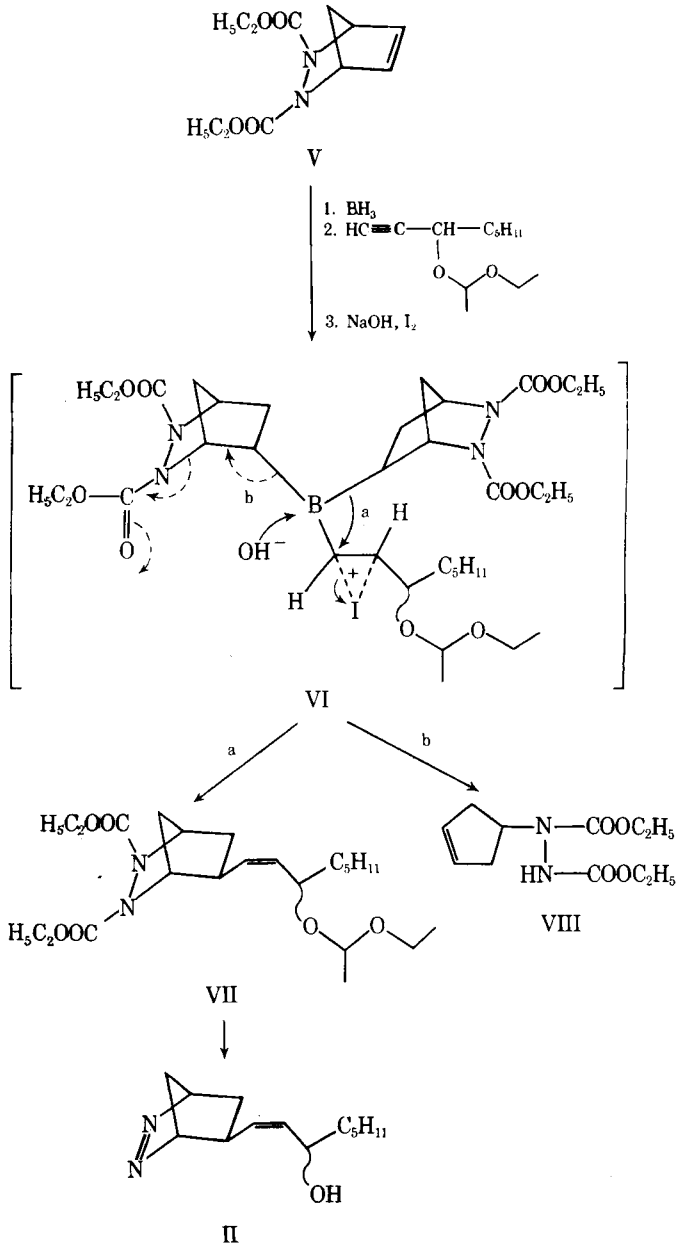

V, VI, VII, VIII, II

Scheme I

(Scheme II) using the aluminum-mediated condensation developed by Nagishi and Baba (10). Compound X, which was prepared from the corresponding alcohol (IX), was reacted with tri-1-octynylalane to yield III (46%) (Scheme II). Deprotection and oxidation of III gave the azo product, IV.

The NMR spectrum of III indicates that the 1-octynyl side chain at C-5 is *exo*. After decoupling of the C-6 *exo*-proton and the C-3' methylene protons of the alkyne side chain, the C-5 methine proton appeared as a broad doublet at δ 2.65. The coupling constant (J = 7 Hz) of this doublet

[1] A similar ring-opened product was reported in the hydroboration–oxidation of dimethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (5).

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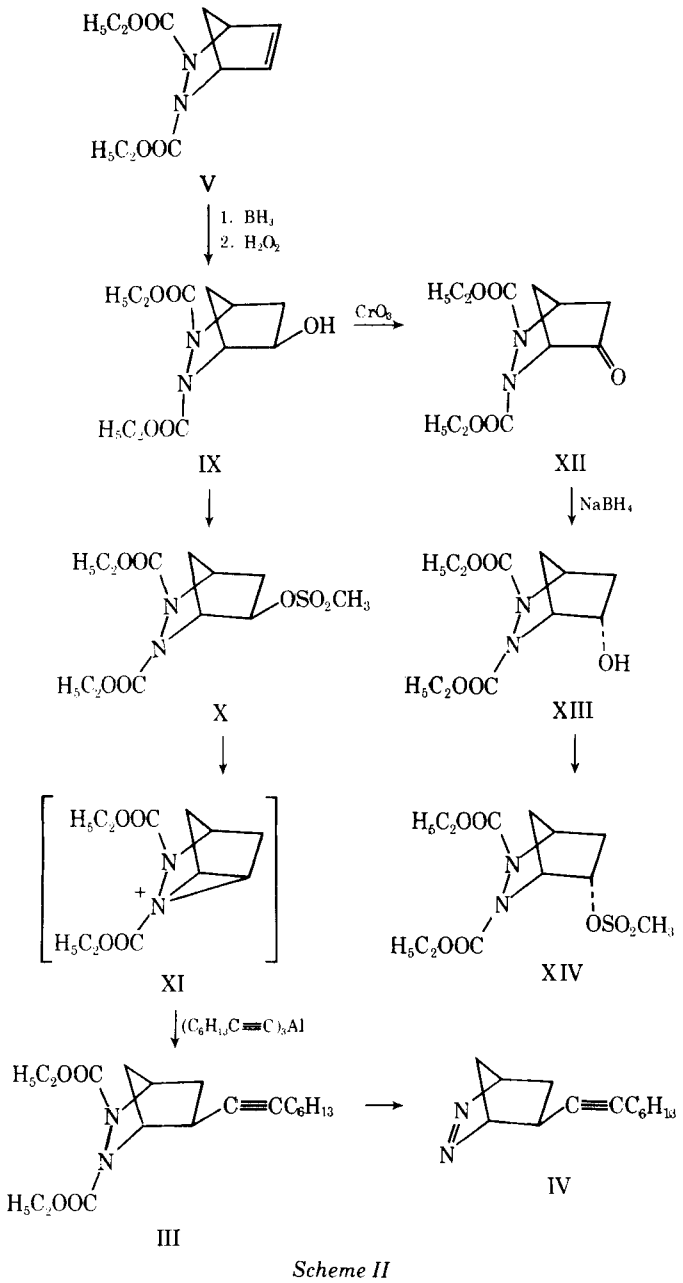

Scheme II

is in the range of *endo-endo* coupling (J = 6–7 Hz) in the norbornane system (11) and is identical to that reported (12) for a related compound.

The *endo*-mesylate isomer (XIV) (Scheme II) did not react with tri-1-octynylalane under identical conditions. This isomer was prepared by a similar procedure (5) and included oxidation of the alcohol (IX) followed by hydride reduction of the resulting ketone (XII) to the *endo*-alcohol (XIII) (Scheme II).

The fact that only the *exo*-mesylate underwent this reaction can be explained by a carbonium-ion mechanism (10) with the assumption that departure of the *exo*-mesylate group is assisted by the electrons of the neighboring carbamate nitrogen. This action would give a symmetrical aziridinium-ion intermediate (XI), which opens on reaction with the alkyne. A similar type of ring opening was reported (12) with a structurally related aziridinium ion to give an *exo*-substituted product. Therefore, the predictable stereochemical consequence of the aziridinium-ion (XI) mechanism is that the newly introduced group at C-5 in III and IV is *exo*. In contrast, the stereochemistry of the *endo*-methanesulfonate group in XIV makes it difficult or impossible to form an aziridinium ion because departure of the *endo*-methanesulfonate function receives no assistance from the neighboring nitrogen.

At 10^{-4} M, none of the compounds (II–IV) induced aggregation of human platelets or inhibited the aggregation induced by 8.2×10^{-4} M arachidonic acid or by 8.5×10^{-7} M of 9,11-methanoepoxy prostaglandin H_2[2] (13). In view of the finding (1) that all analogs of I that possess the carboxyhexyl side chain showed inhibition of the aggregation induced by 9,11-methanoepoxy prostaglandin H_2, the carboxyhexyl side chain might be more important in receptor or enzyme binding relative to the other side chain. The activity of II–IV on the rat fundus also was evaluated. Compound III showed contracting activity at 10^{-4} M but was much less potent ($\sim 3 \times 10^5$-fold) than prostaglandin E_2. The other two compounds were inactive in this test.

EXPERIMENTAL[3]

Diethyl 5-*exo*-[3-[(1-Ethoxy)ethoxy]-*cis*-1-octenyl]-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (VII)—To 9.5 ml of diborane–tetrahydrofuran (1.09 M, 10 mmoles) at 0° under nitrogen was added 4.8 g (20 mmoles) of V (4) in tetrahydrofuran (10 ml). After the mixture was stirred at 0° for 6 hr, 1.98 g (10 mmoles) of 3-[(1-ethoxy)-ethoxy]oct-1-yne (14) was added dropwise. Stirring was continued for 1 hr at 0° followed by 1.5 hr at 25°. The mixture then was cooled to 0°, and migration of the diazabicyclic system was induced by addition of sodium hydroxide (6 N, 6 ml) followed by iodine (2.54 g, 10 mmoles) in 15 ml of tetrahydrofuran.

The mixture was maintained at ice temperature for 5 hr and at 25° for an additional 3 hr. Excess iodine in the mixture was destroyed by addition of an aqueous solution of sodium thiosulfate. The organic layer was separated, and the aqueous phase was extracted three times with ether (50 ml). The organic layers were combined and dried (anhydrous magnesium sulfate), and the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (100 g, 3 × 35 cm) using (*a*) 20% ethyl acetate in petroleum ether (30–60°) (300 ml), (*b*) ethyl acetate in petroleum ether (30–60°) (200 ml), (*c*) ethyl acetate (300 ml), and (*d*) 2% methanol in ethyl acetate (300 ml).

The major product, VII, was eluted with ethyl acetate fractions (3.08 g, 70%). Rechromatography of VII on silica gel (100 g, 3 × 35 cm) using 3% isopropanol in chloroform afforded analytically pure VII; IR (liquid film): 1700 and 1750 (C=O) cm^{-1}; NMR (carbon tetrachloride): δ 0.7–1.57 (m, 25H, C_5H_{11}, 2 $COOCH_2CH_3$, $CHCH_3$, OCH_2CH_3, and 2 methylene protons at C-6), 1.65 (broad s, 3H, 2 bridge protons at C-7 and 1 methine proton at C-5), 3.2–3.7 (m, 2H, OCH_2CH_3), 3.98–4.8 (m, 8H, 2 $COOCH_2CH_3$, bridgehead protons at C-1 and C-4, C=CCH, and O–CH–O), and 5.0–5.65 (m, 2H, olefinic protons); mass spectrum (70 ev): m/e 440 (M^+).

Anal.—Calc. for $C_{23}H_{40}N_2O_6$: C, 62.70; H, 9.15; N, 6.36. Found: C, 62.53; H, 9.28; N, 6.18.

The ring-opened product (VIII) (0.48 g, 10%) was isolated from the 2% methanol in ethyl acetate eluent; IR (liquid film): 3300 (NH) and 1510 (CON) cm^{-1}; NMR (chloroform-d_6): δ 1.13 (t, 6H, 2 $COOCH_2CH_3$), 2.39 (d, 4H, $CH_2C{=}CH_2$), 4.05 (q, 4H, 2 $COOCH_2CH_3$), 4.8 (m, 1H, >CHN), 5.5 (s, 2H, $CH{=}CH$), and 6.8 (s, 1H, NH); mass spectrum (70 ev): m/e 242 (M^+).

Anal.—Calc. for $C_{11}H_{18}N_2O_4$: C, 54.53, H, 7.49; N, 11.57. Found: C, 54.73; H, 7.63; N, 11.32.

5-*exo*-(3-Hydroxy-*cis*-1-octenyl) -2,3- diazabicyclo[2.2.1]hept-2-ene (II)—Compound VII (0.44 g, 1 mmole) was dissolved in ethylene glycol (1 ml) and mixed with a solution of potassium hydroxide (0.336 g, 6 mmoles) in ethylene glycol (6 ml). The mixture was heated at 115° for 4.5 hr followed by the addition of water (50 ml). The aqueous solution was extracted with two 100-ml portions of ether. The volume of the ether was reduced to ~10 ml and mixed with methanol (10 ml) containing a catalytic amount (0.01 g) of cupric acetate. Air was bubbled into the mixture at 0° for 2 hr.

The resulting mixture was partitioned between water (50 ml) and ether (2 × 200 ml). The ether layer was separated and removed *in vacuo* to give an oil, which was chromatographed on silica gel (10 g, 1.3 × 30 cm) with ether to afford 5-*exo*-[3-(1-ethoxy)ethoxy-*cis*-1-octenyl]-2,3-diazabicyclo[2.2.1]hept-2-ene (0.183 g, 65%); IR (liquid film): 1490 (N=N) cm^{-1}; mass spectrum (70 ev): m/e 294 (M^+). Deprotection of the alcohol was achieved by dissolving this product in ethyl acetate–water–tetrahydrofuran (3:1:1) (10 ml) and heating to 45° for 3 hr.

[2] U46619.

[3] Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Ariz. IR spectra were obtained with a Perkin-Elmer model 237B grating spectrophotometer. NMR data (δ) were recorded with Varian models A-60D and T-60 spectrometers. Mass spectral analyses were performed with a Hitachi Perkin-Elmer model RMU-6D spectrometer by the Mass Spectrometry Service Laboratory, School of Chemistry, University of Minnesota.

The solvents were removed *in vacuo* at 25° to leave an oily residue, which was chromatographed on silica gel (10 g, 1.3 × 30 cm) with ether to give II (0.13 g, 59%). This product was a mixture of two racemates; IR (liquid film): 3400 (OH), 1700 (*cis*-C=C), and 1490 (N=N) cm^{-1}; NMR (carbon tetrachloride): δ 1.95–2.2 (broad d, 1H, methine proton at C-5), 3.9–4.5 (m, 1H, C*H*OH), 4.75, 4.9 (2 broad s, 1H, bridgehead proton assigned to the two diastereomers at C-4), 4.95–5.6 (m, 2H, *cis*-C*H*=C*H*, J = 10 Hz), and 5.13 (broad s, 1H, bridgehead proton at C-1); mass spectrum (70 ev): m/e 176 ($M^+ - N_2 - H_2O$); UV: λ_{max} 338 (N=N) nm.

Anal.—Calc. for $C_{13}H_{22}N_2O$: C, 70.22; H, 9.98; N, 12.60. Found: C, 70.07; H, 9.87; N, 12.54.

Diethyl 5-*exo*-Hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (IX)—Compound IX was obtained from diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (V) (4) (1 g, 3.7 mmoles) by hydroboration and oxidation *via* a procedure similar to that described by Allred and Smith (5). The oily product was chromatographed on silica gel and eluted with ethyl acetate–ether (3:2) to give 0.7 g (75%) of the *exo*-alcohol (IX) as a colorless oil, R_f 0.31 (silica gel, 10% ethanol in ether); IR (liquid film): 3475 (OH), 1720, and 1750 (C=O) cm^{-1}; NMR (carbon tetrachloride): δ 1.27 (t, 6H, 2 $COOCH_2CH_3$), 1.58 (m, 2H, bridge protons at C-7), 1.78–2.2 (m, 2H, CHOH-CH_2), 4.1 (broad s, 1H, bridgehead proton at C-1), and 4.47 (broad s, 1H, bridgehead proton at C-4); mass spectrum (70 ev): m/e 258 (M^+).

Anal.—Calc. for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85. Found: C, 50.96; H, 7.24; N, 10.69.

Diethyl 5-*exo*-Methanesulfonyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (X)—To a solution of IX (3.64 g, 14.1 mmoles) in pyridine–toluene (1:1) (40 ml) was added 1.78 g (15.5 mmoles) of methanesulfonyl chloride in pyridine (20 ml) at 0°. The mixture was allowed to stir at 25° for 12 hr, and the pyridinium hydrochloride salt which precipitated was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was partitioned between water (50 ml) and methylene chloride (2 × 100 ml). Removal of the methylene chloride afforded an oil, which was chromatographed on silica gel (50 g, 2.3 × 35 cm) using benzene–ether (8:2) to give X.

Compound X was crystallized from carbon tetrachloride–ether to afford a white solid (3.8 g, 80%), R_f 0.52 (silica gel, ether), mp 87.5–88°; NMR (chloroform-d_6): δ 1.26 (2 t, 6H, 2 $COOCH_2CH_3$), 1.5–2.6 (m, 4H, methylene protons at C-6 and bridge protons at C-7), 3.02 (s, 3H, OSO_2CH_3), 4.16 (2 q, 4H, 2 $COOCH_2CH_3$), and 4.45–4.9 (m, 3H, bridgehead protons at C-1 and C-5 and methine proton at C-5); mass spectrum (70 ev): m/e 336 (M^+).

Anal.—Calc. for $C_{12}H_{20}N_2O_7S$: C, 42.85; H, 5.99; N, 8.33. Found: C, 42.58; H, 5.86; N, 8.16.

Diethyl 5-*exo*-(1-Octynyl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (III)—To a solution of *n*-oct-1-yne (0.9 g, 9.6 mmoles, purified by distillation over anhydrous sodium sulfate) in dry *n*-hexane (15.4 ml) was added, under nitrogen, 3.84 ml of *n*-butyl lithium (2.5 *M*, 9.6 mmoles) in hexane at 0°. The suspension was stirred at 0° for 0.5 hr, and 0.43 g (3.2 mmoles) of aluminium chloride was added. The resulting mixture was stirred at 0° for 0.5 hr, and the solvent was removed *in vacuo* at 25° to give a residue of trioctylalane; this residue was dissolved in 25 ml of dry dichloroethane (dried over phosphorus pentoxide and distilled) under nitrogen.

The trioctylalane solution was cooled to 0°, and a solution of 1.0 g (3 mmoles) of X in 5 ml of dichloroethane was added. After stirring at 25° for 24 hr, the mixture was added to another batch of freshly prepared trioctylalane (9.6 mmoles). Stirring was continued at 25° for another 24 hr, and the mixture then was partitioned between 2% HCl (50 ml) and chloroform (2 × 100 ml). The organic layer was separated, dried (anhydrous sodium sulfate), and filtered, and the solvent was removed *in vacuo* to give an oil; this oil was chromatographed on silica gel (10 g, 1.3 × 30 cm) with ether–pentane (4:1) to afford III (0.43 g, 46%).

Compound III showed a single peak on GLC (3% OV-1, 1.8 m; 200°; nitrogen flow rate, 10 ml/min; retention time, 5 min); NMR (carbon tetrachloride): δ 0.66–1.06 (m, 3H, CH_2CH_3), 1.65 (broad s, 2H, protons at C-7), 1.83 (broad s, 1H, *endo*-proton at C-6), 2.06 (broad s, 3H, 2 C=C-CH_2 and C-6 *exo*-proton), and 2.65 (broad s, 1H, >CH-C≡C-; after decoupling of the δ 2.06 peak, J = 7 Hz); mass spectrum (68 ev, high resolution): calc. M^+ for $C_{19}H_{30}N_2O_4$, m/e 350.2205; found, 350.2212.

Anal.—Calc. for $C_{19}H_{30}N_2O_4$: C, 65.16; H, 8.64; N, 8.00. Found: C, 65.47; H, 8.82; N, 7.97.

5-*exo*-(1-Octynyl)-2,3-diazabicyclo[2.2.1]hept-2-ene (IV)—Compound IV was prepared from III (0.7 g, 2 mmoles) by base hydrolysis and oxidation according to the procedure employed for the preparation of II. The product was extracted with ether after oxidation. The ether was removed *in vacuo*, and the residue was chromatographed on silica gel (10 g, 1.3 × 30 cm) with 10% isopropanol in petroleum ether (30–60°) to give IV (0.37 g, 90%); IR (liquid film): 1590 (N=N) cm^{-1}; NMR (carbon tetrachloride): δ 1.7–2.3 (m, 3H, C*H*-C≡C-CH_2) and 4.9–5.15 (m, 2H, bridgehead protons at C-1 and C-4); mass spectrum (70 ev): m/e 204 (M^+).

Anal.—Calc. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.72. Found: C, 76.64; H, 9.96; N, 13.75.

Diethyl 2,3-Diazabicyclo[2.2.1]heptane-5-one-2,3-dicarboxylate (XII)—A mixture of chromium trioxide (8.92 g, 88.2 mmoles), 200 ml of methylene chloride (dried over a 3-Å molecule sieve), and 7.0 g (88.2 mmoles) of pyridine (dried over potassium hydroxide pellets) was allowed to stir at 25° for 15 min. A solution containing 3.93 g (14.7 mmoles) of IX in methylene chloride (10 ml) was added to this mixture and stirred for 15 min. The reaction mixture then was filtered, and the methylene chloride was removed *in vacuo*. The residue was dissolved in ether (100 ml) and filtered again to obtain a clear filtrate.

Removal of the ether afforded an oily product (XII) (7.2 g, 82%), which was relatively pure as judged by NMR analysis. This product was used without further purification for the synthesis of XIII because of its instability. A small quantity of pure XII was isolated by using a Florisil column (50 g, 2.3 × 35 cm) with methylene chloride; IR (liquid film): 1775 (C=O) cm^{-1}; NMR (carbon tetrachloride): δ 1.3 (2 t, 6H, 2 $COOCH_2CH_3$), 1.98 (s, 2H, bridge protons at C-7), 2.22 (s, 2H, CH_2C=O), 4.15 (2 q, 4H, 2 $COOCH_2CH_3$), 4.22 (broad s, 1H, bridgehead proton at C-1), and 4.8 (s, 1H, bridgehead proton at C-4); mass spectrum (70 ev): m/e 256 (M^+).

Anal.—Calc. for $C_{11}H_{16}N_2O_5$: C, 52.30; H, 6.29; N, 10.93. Found: C, 52.17; H, 6.50; N, 10.80.

Diethyl 5-*endo*-Hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (XIII)—To a solution of bicyclic ketone (XII) (4.1 g, 1.6 mmoles) in methanol (46 ml) maintained at −25° were added divided portions of sodium borohydride (0.6 g, 16 mmoles) in methanol–water (80:20) (49 ml). After stirring at −25° for 15 min, the reaction was quenched by addition of dilute hydrochloric acid to pH 7. The methanol was removed *in vacuo*, and the remaining aqueous solution was extracted with methylene chloride (2 × 50 ml). Removal of the methylene chloride *in vacuo* afforded an oily product (XIII), which was purified by column chromatography using silica gel (60 g, 2.3 × 3.5 cm) and eluted first with 250 ml of ether and then with 10% ethanol in ether to obtain the pure alcohol (XIII) (2.26 g, 55%), R_f 0.51 (silica gel, 10% ethanol in ether); IR (liquid film): 3475 (OH) cm^{-1}; NMR (carbon tetrachloride): δ 1.25 (t, 6H, 2 $COOCH_2CH_3$), 1.66 (s, 2H, bridge protons at C-7), 1.5–2.4 (m, 4H, 2 bridge protons at C-6 and 2 bridge protons at C-7), 4.15 (2 q, 4H, 2 $COOCH_2CH_3$), 4.2 (m, 1H, methine proton at C-5 observed after decoupling of the δ 1.25 triplet), 4.28 (s, 1H, bridgehead proton at C-1), and 4.44 (s, 1H, bridgehead proton at C-4); mass spectrum (20 ev): m/e 258 (M^+).

Anal.—Calc. for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85. Found: C, 51.14; H, 6.99; N, 10.88.

Diethyl 5-*endo*-Methanesulfonyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (XIV)—Compound XIV was prepared from XIII (0.85 g, 3.3 mmoles) in the manner described for the preparation of X. The crude product was purified on silica gel (10 g, 1.3 × 30 cm) with 20% ethyl acetate in ether to afford an oil. This oil was crystallized from carbon tetrachloride to give pure XIV (10 g, 92%), R_f 0.37 (silica gel, ether), mp 120–120.5°; NMR (chloroform-d_6): δ 3.05 (s, 3H, OSO_2CH_3), 4.48 (broad s, 1H, bridgehead proton at C-1), and 4.92–5.2 (m, 2H, bridgehead proton at C-4 and methine proton at C-5); mass spectrum (70 ev): m/e 336 (M^+).

Anal.—Calc. for $C_{12}H_{20}N_2O_7S$: C, 42.85; H, 5.99; N, 8.33. Found: C, 42.72; H, 6.02; N, 8.28.

Platelet Aggregation Studies—Platelet-rich plasma was prepared according to the method of Gerrard *et al.* (15) and was incubated with II–IV (10^{-4} *M*) at 37.5° for 1.5 min. It then was added to a cell containing a standard quantity of arachidonic acid or 9,11-methanoepoxy prostaglandin H_2. Aggregation (or inhibition of aggregation) was monitored for 5 min on a dual-channel aggregometer[4].

Rat Fundus Studies—A 0.2 × 2.5-cm section of the fundus was cut from the outer curvature of the stomach from male Sprague–Dawley rats and suspended in a tissue bath. The tissue bath was perfused continuously with Krebs solution, and one end of the stomach was tied to an isotonic heart–smooth muscle transducer connected to a recorder[5].

[4] Payton.
[5] Beckman R411 Dynograph.

Compounds II–IV were added to the bath, and muscle contraction was monitored for 1.5 min. Prostaglandin E_2 was used to obtain standard contraction.

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Potential Organ- or Tumor-Imaging Agents XIX: Radioiodinated Antiarrhythmic Drugs as Potential Myocardial Imaging Agents

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Abstract □ Iodinated and radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol were synthesized wherein an iodophenyl moiety replaced the naphthalene ring of the parent drug. These new compounds were evaluated not only for their β-adrenergic blocking and antiarrhythmic activities but also for their ability to accumulate selectively in myocardial tissue. Like propranolol, the iodinated analogs displayed comparable β-blocking and antiarrhythmic activity, and the order of potency was *ortho-* > *meta-* > *para*-iodophenyl. Quaternization of propranolol and the iodinated analogs eliminated the β-adrenergic blocking activity but retained the antiarrhythmic property of the secondary amine precursors. Among the quaternary salts, the antiarrhythmic potency was *meta-* > *ortho-* > *para*-iodophenyl. Tissue distribution of the radioiodinated derivatives revealed that only the quaternary derivatives were selectively accumulated in myocardial tissue. These results demonstrate that an iodophenyl ring can substitute for the naphthalene ring in propranolol and its quaternary salt without significant alteration of pharmacological properties. The radioiodinated quaternary derivatives may be useful pharmacological tools in experiments aimed at relating antiarrhythmic activity to myocardial uptake.

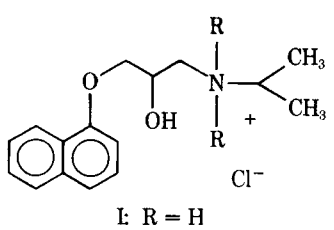
Keyphrases □ Antiarrhythmic agents—iodinated and radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol, synthesis and evaluation of activity, tissue distribution of radioiodinated analogs, potential as myocardial imaging agents □ Propranolol—iodinated and radioiodinated analogs, synthesis and testing for β-adrenergic blocking and antiarrhythmic activity, tissue distribution of radioiodinated analogs, potential as myocardial imaging agents □ Radionuclide imaging—radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol, tissue distribution, potential as myocardial imaging agents

The synthesis of a compound that selectively concentrates in the myocardium and that also can act as a carrier molecule for a γ-emitting nuclide has been a goal of this laboratory for several years (1–3). The approach has been to select a compound with known or suspected propensity for the target organ and then to modify the structure to allow incorporation of a γ-emitting nuclide while retaining the localizing properties of the parent compound.

BACKGROUND

One possible carrier molecule for myocardial localization is the β-adrenergic blocking agent propranolol (I). Its antiarrhythmic actions were demonstrated in a wide variety of experimentally induced arrhythmias (4, 5) as well as in clinically occurring arrhythmias (6, 7). Tissue distribution studies with [^{14}C]propranolol (8, 9) demonstrated its uptake by the heart, but not to the degree expected in view of the potent action of propranolol in blocking the cardiac effects of catecholamines (8). Instead, other tissues such as the lungs and brain contained higher levels of radioactivity (8, 9).

Previous studies in this laboratory showed that quaternization of propranolol produced a drug (II) that retained the antiarrhythmic activity but eliminated the β-adrenergic blocking property of propranolol (10). Subcutaneous administration of ^{14}C-labeled II to rats revealed a rapid and selective localization of radioactivity in the heart (23 times the blood



I: R = H
II: R = CH_3

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