

The Antiarrhythmic and Antiinflammatory Activity of a Series of Tricyclic Pyrazoles

Robert W. Hamilton

Department of Chemical Research, Searle Laboratories, Chicago, Illinois 60680

Received February 23, 1976

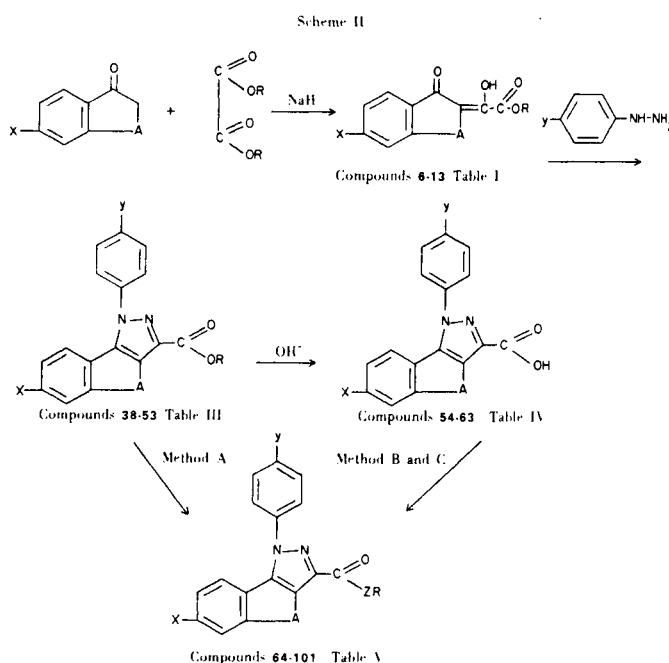
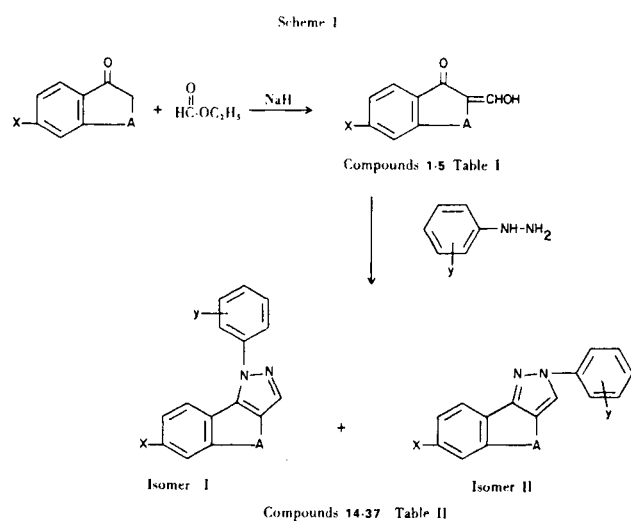
A series of tricyclic pyrazoles were prepared from intermediates available from steroid total synthesis and tested for antiarrhythmic and antiinflammatory activity.

J. Heterocyclic Chem., **13**, 545 (1976).

Pyrazoles have been used as analgesics and anti-inflammatory agents since Knorr prepared antipyrine in 1883 (1), and fused to the steroid A-ring, they have also been reported to enhance antiinflammatory activity (2). The work reported here combined these observations: a simpler three ring system was prepared containing the pyrazole nucleus, using A,B-ring intermediates available from steroid total syntheses. Since many antiinflammatory agents are carboxylic acids, these were prepared along with the esters, amides, and amino ester derivatives. Although the carboxylic acids had minimal antiinflammatory activity, the amides and amino esters showed antiarrhythmic activity and encouraged an expansion of the series. Compounds **66** and **99** showed activity comparable to quinidine and 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide (disopyramide, Table IV) but were not studied further because of side effects.

Chemistry.

Schemes I and II show the reaction sequences; The

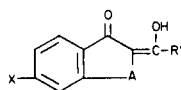


tables list the specific derivatives made.

The pyrazoles in Table II were prepared from the keto-aldehydes in Table I (Scheme I). Frequently both isomers were obtained, but could be separated by crystallization or chromatography. Wilshire (3) noted that in the nmr, the 3-proton shows a 0.83 ppm downfield shift for the 2-phenyl compared to the 1-phenyl substituted indazole in DMSO- d_6 , but not in deuteriochloroform. This shift was also noted for the benzindazoles, idenopyrazoles, and the benzocycloheptapyrazoles reported here. In addition a downfield shift of the 8-proton, due to the proximity of the phenyl group, was seen for the 1-phenyl compared to the 2-phenyl-benzindazoles in either deuteriochloroform or DMSO- d_6 .

Table I

Keto-aldehydes



| Compound | X | R' | A | Yield, % | Formula | M.p. °C. |
|----------|----------------------------------|------------------------------------|---|----------|--|--------------------|
| 1 | H | H | CH ₂ | 84 | C ₁₀ H ₈ O ₂ | 110-112 (a) |
| 2 | H | H | CH ₂ -CH ₂ | 100 | C ₁₁ H ₁₀ O ₂ | oil (b) |
| 3 | Cl | H | CH ₂ -CH ₂ | 96 | C ₁₁ H ₉ ClO ₂ | 53-54 |
| 4 | N(CH ₃) ₂ | H | CH ₂ -CH ₂ | 100 | C ₁₃ H ₁₅ NO ₂ | 95-96 |
| 5 | OCH ₃ | H | CH ₂ -CH ₂ | 97 | C ₁₂ H ₁₂ O ₃ | 67-69 (97-100) (c) |
| 6 | H | COOCH ₃ | CH ₂ -CH ₂ | 87 | C ₁₃ H ₁₂ O ₄ | 66-67 (d) |
| 7 | H | COOCH ₂ CH ₃ | CH ₂ -CH ₂ | | C ₁₄ H ₁₄ O ₄ | 45-47 (e) |
| 8 | Cl | COOCH ₃ | CH ₂ -CH ₂ | 95 | C ₁₃ H ₁₁ ClO ₄ | 93-94.5 |
| 9 | N(CH ₃) ₂ | COOCH ₂ CH ₃ | CH ₂ -CH ₂ | 79 | C ₁₆ H ₁₉ NO ₄ | 91-92 |
| 10 | OCH ₃ | COOCH ₃ | CH ₂ -CH ₂ | 75 | C ₁₄ H ₁₄ O ₅ | 61-66 (f) |
| 11 | H | COOCH ₃ | CH ₂ -CH ₂ -CH ₂ | 92 (g) | C ₁₃ H ₁₀ O ₃ (g) | 159 (g,h) |
| 12 | H | COOCH ₂ CH ₃ | CH ₂ | | C ₁₃ H ₁₂ O ₄ | 69-70 (i) |
| 13 | OCH ₃ (j) | COOCH ₂ CH ₃ | CH ₂ | 97 | C ₁₅ H ₁₆ O ₆ | 158-162- (k) |

(a) Lit. (11) m.p. 112-113°. (b) After acidification the resultant oil was extracted with ether, dried (sodium sulfate) and solvent evaporated. The nmr and ir of the residue were as expected. Lit. (12) b.p. 153.5-154°. (c) Lit. (10) m.p. 65-66°, after standing 24 hours, 94-95°. (d) Lit. (13) m.p. 65.5-66.5°. (e) Lit. (14) m.p. 48°. (f) Lit. (15) m.p. 76.5-77.5°. (g) Obtained lactone, lit. (16) m.p. 157-158°. (h) Melts with gas evolution. Benzene used instead of ether as reaction solvent. (i) Lit. (17) m.p. 74-75°. (j) Compound **13** is the 5,6-dimethoxyindanone-1 derivative. (k) Lit. (18) m.p. 158-159°.

The uv spectra were distinctive for each set of isomers and were used when the nmr was complex.

The pyrazoles in Table III were prepared from the diketone esters in Table I (Scheme II). Even with careful examination of the mother liquors, only the 1-phenyl-benzindazole was found. The nmr spectra were superimposable with the corresponding analogues in Table II with the exception of the change at carbon-3.

The acids in Table IV were prepared by alkaline hydrolysis of the esters in Table III, and the amides and amino esters in Tables V and VI by several different methods as described in the Experimental Section (Scheme II).

Biology.

Compounds were tested for antiinflammatory activity in rats by one or more of several modified adjuvant arthritis assays (4). The most active compounds, **64**, **69**, **74**, and **88**, required 25 mg./kg. IG to show an approximately equivalent response to that from 2.5 mpk IG of indomethacin when given for 19 days to rats inoculated intradermally with *Mycobacterium butyricum* (4a).

Compounds were tested for activity against ventricular arrhythmia successively in the following assays: (1) aconitine induced ventricular tachycardia in an isolated rabbit heart (5), rated active if a bath concentration of 40 mg./l. produced a 50% or greater reduction of the

ventricular rate; (2) ouabain induced ventricular arrhythmia in an intact anesthetized dog (6), rated active if a dose of 20 mg./kg. I.V. produced a return to normal sinus rhythm for a period of 15 minutes or more in half or more of the dogs used; (3) the Harris two-stage, coronary-ligated dog (7), rated active if a dose of 20 mg./kg. I.V. produced a 25% or greater reduction in ectopic beats for at least 10 minutes in half or more of the dogs used. The compounds active in all three tests are listed in Table VI together with the standards quinidine and disopyramide; compounds **66** and **99** compare favorably. Study was discontinued on each of these because the dogs displayed one or more side effects as emesis, head tremors, rigidity, struggling or convulsions.

EXPERIMENTAL

Evaporations were carried out on a rotary still at reduced pressure (10-30 mm). Melting points determined on a Thomas-Hoover apparatus are uncorrected. Nmr (Varian Associates A-60-A and A-100, TMS standard), ir (Beckman IR-12) and uv (Beckman DK-2A) spectra were consistent with the assigned structures. Skellysolve B is a petroleum hydrocarbon fraction, b.p. 60-70°.

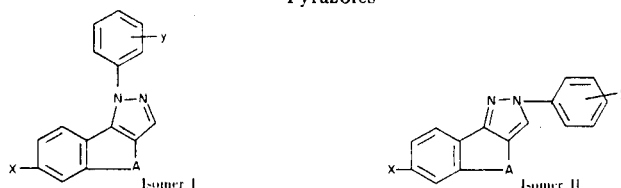
6-Chloro-1-tetralone.

This compound was prepared from 0.65 moles of 6-amino-1-tetralone (8) by the Sandmeyer reaction (9) in 70% yield, b.p. 146-148° (8 mm), n_{D}^{23} 1.5862.

Anal. Calcd. for C₁₀H₉ClO: C, 66.44, H, 5.02; Cl, 19.63. Found: C, 66.88; H, 5.03; Cl, 19.36.

Table II

Pyrazoles



| Compound (a) | X | y | Isomer | Reaction Solvent (b) | Purified Yield, % | Formula | M.p., °C | Crystallization Solvent (b) |
|--------------|----------------------------------|---------------------------|--------|----------------------|-------------------|---|-------------|-----------------------------|
| 14 | H | H | I | E (c) | 55 | C ₁₇ H ₁₄ N ₂ | 127-129 (d) | E |
| 15 | H | <i>p</i> -Cl | I | E | 69 | C ₁₇ H ₁₃ ClN ₂ | 117-120 | E-W |
| 16 | H | <i>p</i> -F | I | E | 23 | C ₁₇ H ₁₃ FN ₂ | 123-125 | B-S (e) |
| 17 | H | <i>p</i> -F | II | E | 18 | C ₁₇ H ₁₃ FN ₂ | 117-119 | B-S (e) |
| 18 | Cl | H | I | T (f) | 35 | C ₁₇ H ₁₃ ClN ₂ | 143-144 | B-S |
| 19 | Cl | <i>p</i> -Cl | I | X | 65 | C ₁₇ H ₁₂ Cl ₂ N ₂ | 174-176 | B-S |
| 20 | Cl | <i>o</i> -Cl | I | X | 32 | C ₁₇ H ₁₂ Cl ₂ N ₂ | (g) | (e) |
| 21 | Cl | <i>p</i> -F | I | X | 43 | C ₁₇ H ₁₂ ClFN ₂ | 166-168 | B-S |
| 22 | Cl | <i>m</i> -CH ₃ | I | T | 51 | C ₁₈ H ₁₅ ClN ₂ | 123-125 | B-S (e) |
| 23 | Cl | <i>m</i> -CH ₃ | II | T | 15 | C ₁₈ H ₁₅ ClN ₂ | 123-126 | B-S (e) |
| 24 | Cl | <i>p</i> -COOH | I | T (f) | 3 | C ₁₈ H ₁₃ ClN ₂ O ₂ | 254-256 | M |
| 25 | Cl | <i>p</i> -COOH | II | T (f) | 11 | C ₁₈ H ₁₃ ClN ₂ O ₂ | 304-307 | M |
| 26 | Cl | <i>o</i> -COOH | I | T (f) | 60 | C ₁₈ H ₁₃ ClN ₂ O ₂ | 210-212 | M |
| 27 | Cl | (h) | I | T | 67 | C ₂₁ H ₁₅ ClN ₂ | (i) | (e) |
| 28 | Cl | (h) | II | T | 2 | C ₂₁ H ₁₅ ClN ₂ | 177-178 | B-S (e) |
| 29 | OCH ₃ | H | I (j) | E | 55 | C ₁₈ H ₁₆ N ₂ O | 84-86 | B-S |
| 30 | OCH ₃ | <i>p</i> -F | I | X | 24 | C ₁₈ H ₁₅ FN ₂ O | 102-104 | B-S (e) |
| 31 | OCH ₃ | <i>p</i> -F | II | X | 7 | C ₁₈ H ₁₅ FN ₂ O | 112-113.5 | B-S (e) |
| 32 | OCH ₃ | <i>o</i> -CH ₃ | I | X | 20 | C ₁₉ H ₁₈ N ₂ O | 104-109 | B-S (e) |
| 33 | OCH ₃ | <i>o</i> -CH ₃ | II | X | 4 | C ₁₉ H ₁₈ N ₂ O | 90-92 | B-S (e) |
| 34 | N(CH ₃) ₂ | <i>o</i> -COOH | I | T | 27 | C ₂₀ H ₁₉ N ₃ O ₂ | 230-233 | E-W |
| 35 | OH | <i>p</i> -F | I | (k) | 68 | C ₁₇ H ₁₃ FN ₂ O | 279-283 | D-W |
| 36 | H | <i>p</i> -F | I | E | 21 | C ₁₆ H ₁₁ FN ₂ | 103-105 | B-S (e) |
| 37 | H | <i>p</i> -F | II | E | 2 | C ₁₆ H ₁₁ FN ₂ | 122-124 | S (e) |

(a) A is -CH₂CH₂- for all compounds except **36** and **37** for which it is -CH₂-. (b) B, benzene; D, DMSO; E, ethanol, M, butanone; S, Skellysolve B; T, toluene; X, xylene. (c) Phenylhydrazone base was used. (d) Lit. (12) m.p. 127-128°. (e) Chromatography used. (f) Phenylhydrazone base and one equivalent of *p*-toluenesulfonic acid monohydrate were used. (g) B.p. 170-175° (0.1 mm). (h) 1-Naphthyl replaces phenyl. (i) B.p. 210-215° (0.1 mm). (j) Isomer H was present but not isolated. (k) Two g. of compound **30**, 50 ml. of acetic acid, and 20 ml. of 48% hydrobromic acid were refluxed 3 hours and concentrated. The residue was suspended in 10% sodium hydroxide and filtered. The filtrate was acidified to yield product.

Preparation of Compounds in Table I.

The ketones, all commercially available except 6-chloro-1-tetralone and 6-dimethylamino-1-tetralone (**8**), were condensed (**10**) with ethyl formate or dialkyl oxalate. If the ketone was insoluble in ether, benzene was substituted as solvent. The products were crystallized from benzene-Skellysolve B.

Preparation of Pyrazoles, Tables II and III.

A mixture of 0.1 moles of ketone (Table I), 0.11 moles of a hydrazine hydrochloride and 250 ml. of solvent were refluxed until the reaction was complete as indicated by tlc or by measurement of water evolved, generally 3-8 hours. The solvent was evaporated and the residue was partitioned between water and ether or chloroform. The organic layer was separated, washed with water, dried (potassium carbonate), and the solvent evaporated. The residue was crystallized from the solvent indicated.

Ester Hydrolysis.

Esters were hydrolyzed with 10% aqueous sodium hydroxide in methanol at reflux. The acids obtained after dilution and acidification were crystallized (dimethylsulfoxide-water) except where indicated (Table IV).

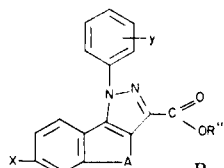
Preparation of Amides and Amino Esters.

Method A.

A solution of the ester (Table III) in excess amine was refluxed for 5 hours. After evaporation of excess amine the residue was dissolved in dilute hydrochloric acid and washed twice with ether. The solution was made alkaline (ammonium hydroxide), the suspension extracted with ether, which was dried (potassium carbonate), and evaporated. The residue was crystallized from benzene-Skellysolve B or converted to the hydrochloride or oxalate salt which was crystallized from ethanol-ether.

Table III

3-Carboalkoxy-pyrazoles

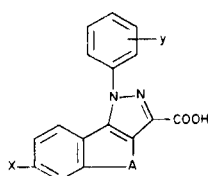


| Compound | X | y | A | R' | Reaction Solvent (a) | Yield, % | Formula | M.p., °C (b) |
|----------|----------------------------------|----------------------------|---|-------------------------------|----------------------|----------|---|--------------|
| 38 | H | H | CH ₂ CH ₂ | C ₂ H ₅ | T | | | 152-154 (c) |
| 39 | H | <i>p</i> -Cl | CH ₂ CH ₂ | CH ₃ | T | 79 | C ₁₉ H ₁₅ ClN ₂ O ₂ | 198-199 |
| 40 | H | <i>p</i> -F | CH ₂ CH ₂ | CH ₃ | T | 63 | C ₁₉ H ₁₅ FN ₂ O ₂ | 158-160 |
| 41 | Cl | H | CH ₂ CH ₂ | CH ₃ | T | 90 | C ₁₉ H ₁₅ ClN ₂ O ₂ | 190-192 |
| 42 | Cl | <i>o</i> -COOH | CH ₂ CH ₂ | CH ₃ | T (d) | 65 | C ₂₀ H ₁₅ ClN ₂ O ₄ | 239-244 |
| 43 | Cl | <i>p</i> -OCH ₃ | CH ₂ CH ₂ | (e) | T | | | |
| 44 | Cl | <i>p</i> -F | CH ₂ CH ₂ | (e) | T, | | | |
| 45 | N(CH ₃) ₂ | H | CH ₂ CH ₂ | C ₂ H ₅ | T | 82 | C ₂₂ H ₂₃ N ₃ O ₂ | 172.5-174 |
| 46 | N(CH ₃) ₂ | <i>p</i> -Cl | CH ₂ CH ₂ | C ₂ H ₅ | T | 50 | C ₂₂ H ₂₂ ClN ₃ O ₂ | 196-198 |
| 47 | OCH ₃ | <i>p</i> -Cl | CH ₂ CH ₂ | CH ₃ | T | 72 (f) | C ₂₀ H ₁₇ ClN ₂ O ₃ | 187.5-189 |
| 48 | Cl | H | CH=CH | CH ₃ | (g) | 72 | C ₁₉ H ₁₃ ClN ₂ O ₂ | 205-207.5 |
| 49 | H | H | CH ₂ -CH ₂ -CH ₂ | C ₂ H ₅ | E (h) | 48 | C ₂₁ H ₂₀ N ₂ O ₂ | 110-111 |
| 50 | H | H | CH ₂ | C ₂ H ₅ | T | | | 112-114 (i) |
| 51 | H | <i>p</i> -F | CH ₂ | C ₂ H ₅ | E | 67 | C ₁₉ H ₁₅ FN ₂ O ₂ | 185-187 |
| 52 | OCH ₃ (j) | H | CH ₂ | C ₂ H ₅ | E | 93 | C ₂₁ H ₂₀ N ₂ O ₄ | 171-172.5 |
| 53 | H | (k) | CH ₂ CH ₂ | C ₂ H ₅ | E | 54 | C ₁₇ H ₂₀ N ₂ O ₂ | 102-104 |

(a) See footnote b, Table II. (b) The compounds were crystallized from benzene-Skellysolve B except **38**, **42**, **43**, **44**, and **50**, which were reacted without crystallization. (c) Lit. (14) m.p. 155°. (d) Hydrazine base was used. (e) The product was a mixture of methyl and ethyl esters from inadvertently using ethanol to hydrolyze the preceding reaction. (f) Crude yield. Crystallized a sample only. (g) Compound **41** (7.6 g.) and 10.2 g. of DDQ in 100 ml. of dioxane was refluxed for 20 hours, cooled, filtered, and the solvent evaporated. The residue was dissolved in benzene, washed once with aqueous sodium hydroxide, twice with water, dried (potassium carbonate) and the solvent evaporated. (h) Lactone (compound **11**) was used as starting material. (i) Lit. (17) m.p. 117-118°. (j) Compound **52** is a 6,7-dimethoxyindanopyrazole derivative. (k) (CH₃)₂CH represents phenyl.

Table IV

3-Carboxypyrazoles



| Compound | X | A | Crude Yield, % | Formula | M.p., °C | Crystallization Solvent (a) |
|----------|----------------------------------|----------------|---|---|-------------|-----------------------------|
| 54 | H | H | CH ₂ CH ₂ | C ₁₈ H ₁₄ N ₂ O ₂ | 248-251 (b) | |
| 55 | H | <i>p</i> -Cl | CH ₂ CH ₂ | C ₁₈ H ₁₃ ClN ₂ O ₂ | 270 (c) | |
| 56 | Cl | H | CH ₂ CH ₂ | C ₁₈ H ₁₃ ClN ₂ O ₂ | 282 (c) | |
| 57 | Cl | <i>o</i> -COOH | CH ₂ CH ₂ | C ₁₉ H ₁₃ ClN ₂ O ₄ | 302-303 (c) | D-W |
| 58 | OCH ₃ | <i>p</i> -Cl | CH ₂ CH ₂ | C ₁₉ H ₁₅ ClN ₂ O ₃ | 227-228 (c) | E |
| 59 | N(CH ₃) ₂ | <i>p</i> -Cl | CH ₂ CH ₂ | C ₂₀ H ₁₈ ClN ₃ O ₂ | 280-281 (c) | D-W |
| 60 | Cl | H | CH=CH | C ₁₈ H ₁₁ ClN ₂ O ₄ | 287-289 (c) | D-W |
| 61 | H | H | CH ₂ -CH ₂ -CH ₂ | C ₁₉ H ₁₆ N ₂ O ₂ | 196-199 | B-S |
| 62 | H | H | CH ₂ | C ₁₇ H ₁₂ N ₂ O ₂ | 250 (c,e) | |
| 63 | H | (f) | CH ₂ CH ₂ | C ₁₅ H ₁₆ N ₂ O ₂ | 193.5-195.5 | |

(a) See footnote b, Table II. (b) Lit. (14) m.p. 248°. (c) Melts with gas evolution. (d) Purified yield. (e) Lit. (17) m.p. 250-251 dec. (f) (CH₃)₂CH- replaces phenyl.

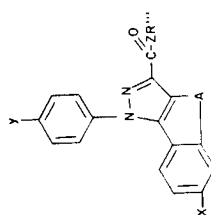


Table V
3-Carboxyamides and Esters









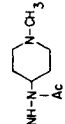
| Compound | X | Y | A | ZR'' | Method | Yield, % | Formula | M.p., °C |
|----------|----------------------------------|------------------|---|--|--------|----------|---|---------------|
| 64 | H | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 75 | C ₂₄ H ₂₈ N ₄ O·HCl | 178-180 |
| 65 | H | Cl | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 63 | C ₂₄ H ₂₇ ClN ₄ O·HCl | 220-221 |
| 66 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 83 | C ₂₄ H ₂₇ ClN ₄ O·HCl | 231-233 (a) |
| 67 | Cl | F | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 61 | C ₂₄ H ₂₆ ClFN ₄ O | 109-110 |
| 68 | Cl | OCH ₃ | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 63 | C ₂₅ H ₂₉ ClN ₄ O ₂ | 121-123 |
| 69 | OCH ₃ | Cl | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 71 | C ₂₅ H ₂₉ ClN ₄ O ₂ ·HCl | 241-242 (a) |
| 70 | N(CH ₃) ₂ | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 34 | C ₂₆ H ₃₃ N ₅ O·2HCl | 239-241 (a,b) |
| 71 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | (c) | 63 | C ₂₅ H ₃₀ ClN ₄ O | 244-245 (a) |
| 72 | H | H | CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 67 | C ₂₃ H ₂₆ N ₄ O·HCl | 179-181 |
| 73 | OCH ₃ (d) | H | CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 67 | C ₂₅ H ₃₀ N ₄ O ₃ ·HCl | 245-246 (a) |
| 74 | H | H | CH ₂ -CH ₂ -CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 89 | C ₂₅ H ₃₀ N ₄ O·C ₄ H ₄ O ₄ | 173-174 |
| 75 | Cl | H | CH=CH | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 87 | C ₂₄ H ₂₅ ClN ₄ O·HCl | 216-219 |
| 76 | H | (e) | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 44 | C ₂₁ H ₃₀ N ₄ O·HCl | 131-134 (a) |
| 77 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 80 | C ₂₂ H ₂₃ ClN ₄ O | 161.5-162.5 |
| 78 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | A | 52 | C ₂₆ H ₃₁ ClN ₄ O·HCl·C ₂ H ₆ O | 218-225 (f) |
| 79 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N  | A | 63 | C ₂₄ H ₂₅ ClN ₄ O | 121-124 |
| 80 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N  | A | 67 | C ₂₅ H ₂₇ ClN ₄ O | 116.5-118 |
| 81 | H | H | CH ₂ | NH-CH ₂ -CH ₂ -N  | A | 61 | C ₂₃ H ₂₄ N ₄ O ₂ | 130-131 |
| 82 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N  | A | 73 | C ₂₄ H ₂₆ N ₄ O ₂ | 125-127 |
| 83 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -N  | A | 27 | C ₂₈ H ₃₁ ClN ₄ O ₂ ·HCl·0.5 H ₂ O | 246-249 (a,b) |
| 84 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ | A | 72 | C ₂₃ H ₂₅ ClN ₄ O | 98-99 |
| 85 | OCH ₃ | Cl | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ | A | 81 | C ₂₄ H ₂₇ ClN ₄ O ₂ ·HCl | 255.5-256 (b) |
| 86 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -CH ₂ -N  | B | 71 | C ₂₆ H ₂₉ ClN ₄ O | 141.5-142.5 |
| 87 | H | H | CH ₂ CH ₂ | NH ₂ | B (g) | 71 | C ₁₈ H ₁₅ N ₃ O | 200-201 |
| 88 | H | H | CH ₂ CH ₂ | NHClH ₃ | B (g) | 83 | C ₁₉ H ₁₇ N ₃ O | 174-175 |

Table V (Continued)

| Compound | X | y | A | ZR'' | Method | Yield, % | Formula | M.p., °C |
|------------|----|----|---|--|--------|----------|---|-------------|
| 89 | Cl | H | CH ₂ CH ₂ | NHNH ₂ | A (h) | 89 | C ₁₈ H ₁₅ ClN ₄ O | 166-168 (i) |
| 90 | Cl | H | CH ₂ CH ₂ | NHOH | (j) | 28 | C ₁₈ H ₁₄ ClN ₃ O ₂ | 207-208 (k) |
| 91 | Cl | H | CH ₂ CH ₂ | NH-CH ₂ -CH ₂ -OH | A | 86 | C ₂₀ H ₁₈ ClN ₃ O ₂ | 144-146 |
| 92 | H | H | CH ₂ |  | B | 69 | C ₂₂ H ₂ N ₄ O | 150-151 |
| 93 | Cl | H | CH ₂ CH ₂ |  | B | 61 | C ₂₃ H ₂ ClN ₄ O | 142-143 |
| 94 | H | H | CH ₂ |  | B | 41 | C ₂₅ H ₂ 7N ₅ O ₂ | 210-213 |
| 95 | H | H | CH ₂ CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 59 | C ₂₄ H ₂₇ N ₃ O ₂ ·HCl | 179-181 |
| 96 | H | Cl | CH ₂ CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | C | 25 | C ₂₄ H ₂₆ ClN ₃ O ₂ | 102-103 |
| 97 | Cl | H | CH ₂ CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 37 | C ₂₄ H ₂₆ ClN ₃ O ₂ ·HCl | 190-192 |
| 98 | Cl | F | CH ₂ CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 64 | C ₂₄ H ₂₅ ClFN ₃ O ₂ ·HCl | 202-204 |
| 99 | H | H | CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 72 | C ₂₃ H ₂₅ N ₃ O ₂ ·HCl | 220-221 |
| 100 | H | H | CH ₂ -CH ₂ -CH ₂ | OCH ₂ -CH ₂ -N(C ₂ H ₅) ₂ | B | 39 | C ₂₅ H ₂₉ N ₃ O ₂ ·C ₄ H ₄ O ₄ | 127-129 |
| 101 | Cl | H | CH ₂ CH ₂ | OCH ₂ -CH ₂ -CH ₂ -N(CH ₃) ₂ | C (l) | 41 | C ₂₃ H ₂₄ ClN ₃ O ₂ | 111-112 |

(a) Melted with gas evolution. (b) Added 5-10% water when crystallizing. (c) Dissolved 4 g. of the base of compound **66** and 6 g. of iodomethane in 100 ml. of chloroform, sealed, heated at 60° for 16 hours and then evaporated solvent. (d) Compound **73** is a 6,7-dimethoxyindanopyrazole derivative. (e) (CH₃)₂CH-replaces phenyl. (f) The ethanolate evolves gas at about 140° when melted slowly. (g) An excess of the amine was bubbled into the reaction mixture. (h) Ethanol (400 ml.) and an excess of hydrazine hydrate was used. (i) Double m.p. at 181°. (j) Compound **41** (5 g.), 1.1 g. of hydroxylamine hydrochloride and 1.7 g. of sodium methoxide heated at reflux for 20 hours, acidified with dilute hydrochloric acid and the resultant solid crystallized from butanone. (k) Crystallized from butanone. (l) 1-Butanol was used instead of 2-propanol.

Table VII
Analytical Data

| Compound No. | | C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found | Cl Calcd. | Cl Found |
|--------------|---|----------|---------|----------|---------|----------|---------|-----------|----------|
| 1 | C ₁₀ H ₈ O ₂ | | | | | | | | |
| 2 | C ₁₁ H ₁₀ O ₂ | | | | | | | | |
| 3 | C ₁₁ H ₉ ClO ₂ | 63.32 | 63.59 | 4.35 | 4.46 | | | 17.04 | 16.76 |
| 4 | C ₁₃ H ₁₅ NO ₂ | 71.86 | 71.63 | 6.96 | 7.00 | 6.45 | 6.15 | | |
| 5 | C ₁₂ H ₁₂ O ₃ | | | | | | | | |
| 6 | C ₁₃ H ₁₂ O ₄ | 67.23 | 67.14 | 5.21 | 5.40 | | | | |
| 7 | C ₁₄ H ₁₄ O ₄ | | | | | | | | |
| 8 | C ₁₃ H ₁₁ ClO ₄ | 58.55 | 58.76 | 4.16 | 4.41 | | | 13.30 | 13.01 |
| 9 | C ₁₆ H ₁₉ NO ₄ | 66.42 | 66.22 | 6.62 | 6.64 | 4.84 | 4.64 | | |
| 10 | C ₁₄ H ₁₄ O ₅ | | | | | | | | |
| 11 | C ₁₃ H ₁₀ O ₃ | | | | | | | | |
| 12 | C ₁₃ H ₁₂ O ₄ | | | | | | | | |
| 13 | C ₁₅ H ₁₆ O ₆ | 61.63 | 61.33 | 5.52 | 5.45 | | | | |
| 14 | C ₁₇ H ₁₄ N ₂ | 82.90 | 83.22 | 5.73 | 5.71 | | | | |
| 15 | C ₁₇ H ₁₃ ClN ₂ | | | | | 9.98 | 9.99 | 12.63 | 12.82 |
| 16 | C ₁₇ H ₁₃ FN ₂ | 77.25 | 77.18 | 4.96 | 4.91 | 10.60 | 10.82 | | |
| 17 | C ₁₇ H ₁₃ FN ₂ | 77.25 | 77.15 | 4.96 | 4.69 | 10.60 | 10.82 | | |
| 18 | C ₁₇ H ₁₃ ClN ₂ | 72.77 | 73.06 | 4.67 | 4.88 | 9.98 | 10.20 | | |
| 19 | C ₁₇ H ₁₂ Cl ₂ N ₂ | | | | | 8.89 | 8.67 | 22.50 | 22.50 |
| 20 | C ₁₇ H ₁₂ Cl ₂ N ₂ | | | | | 8.89 | 9.12 | 22.50 | 22.03 |
| 21 | C ₁₇ H ₁₂ ClFN ₂ | 68.34 | 68.60 | 4.05 | 4.05 | 9.38 | 9.26 | | |
| 22 | C ₁₈ H ₁₅ ClN ₂ | | | | | 9.51 | 9.62 | 12.03 | 12.09 |
| 23 | C ₁₈ H ₁₅ ClN ₂ | | | | | 9.51 | 9.51 | 12.03 | 12.12 |
| 24 | C ₁₈ H ₁₃ ClN ₂ O ₂ | 66.75 | 66.61 | 4.03 | 4.02 | 8.63 | 8.46 | 10.92 | 11.06 |
| 25 | C ₁₈ H ₁₃ ClN ₂ O ₂ | | | | | 8.63 | 8.23 | 10.92 | 10.78 |
| 26 | C ₁₈ H ₁₃ ClN ₂ O ₂ | | | | | 8.63 | 8.79 | 10.92 | 10.86 |
| 27 | C ₂₁ H ₁₅ ClN ₂ | | | | | 8.47 | 8.40 | 10.72 | 10.77 |
| 28 | C ₂₁ H ₁₅ ClN ₂ | | | | | 8.47 | 8.39 | 10.72 | 10.87 |
| 29 | C ₁₈ H ₁₆ N ₂ O | 78.23 | 78.15 | 5.84 | 6.02 | 10.14 | 10.24 | | |
| 30 | C ₁₈ H ₁₅ FN ₂ O | 73.45 | 73.62 | 5.14 | 5.09 | 9.52 | 9.52 | | |
| 31 | C ₁₈ H ₁₅ FN ₂ O | 73.45 | 73.56 | 5.14 | 5.04 | 9.52 | 9.34 | | |
| 32 | C ₁₉ H ₁₈ N ₂ O | 78.59 | 78.35 | 6.25 | 6.36 | 9.65 | 9.44 | | |
| 33 | C ₁₉ H ₁₈ N ₂ O | 78.59 | 78.26 | 6.25 | 6.49 | 9.65 | 9.40 | | |
| 34 | C ₂₀ H ₁₉ N ₃ O ₂ | 72.05 | 72.40 | 5.74 | 5.57 | 12.61 | 12.66 | | |
| 35 | C ₁₇ H ₁₃ FN ₂ O | 72.84 | 73.01 | 4.67 | 4.76 | 10.00 | 9.82 | | |
| 36 | C ₁₆ H ₁₁ FN ₂ | 76.78 | 76.94 | 4.43 | 4.68 | 11.19 | 11.32 | | |
| 37 | C ₁₆ H ₁₁ FN ₂ | 76.78 | 76.60 | 4.43 | 4.53 | 11.19 | 11.12 | | |
| 38 | | | | | | | | | |
| 39 | C ₁₉ H ₁₅ ClN ₂ O ₂ | | | | | 8.27 | 7.96 | 10.47 | 10.58 |
| 40 | C ₁₉ H ₁₅ FN ₂ O ₂ | 70.79 | 70.82 | 4.69 | 4.93 | 8.69 | 8.69 | | |
| 41 | C ₁₉ H ₁₅ ClN ₂ O ₂ | | | | | 8.27 | 8.14 | 10.47 | 10.30 |
| 42 | C ₂₀ H ₁₅ ClN ₂ O ₄ | 62.75 | 62.49 | 3.95 | 4.07 | 7.32 | 7.39 | 9.26 | 9.02 |
| 43 | | | | | | | | | |
| 44 | | | | | | | | | |
| 45 | C ₂₂ H ₂₃ N ₃ O ₂ | 73.10 | 72.94 | 6.41 | 6.28 | 11.63 | 11.53 | | |
| 46 | C ₂₂ H ₂₂ ClN ₃ O ₂ | | | | | 10.61 | 10.78 | 8.96 | 9.19 |
| 47 | C ₂₀ H ₁₇ ClN ₂ O ₃ | | | | | 7.60 | 7.73 | 9.61 | 9.65 |
| 48 | C ₁₉ H ₁₃ ClN ₂ O ₂ | 67.76 | 67.81 | 3.89 | 3.89 | 8.32 | 8.26 | | |
| 49 | C ₂₁ H ₂₀ N ₂ O ₂ | 75.88 | 75.88 | 6.07 | 6.14 | 8.43 | 8.36 | | |
| 50 | | | | | | | | | |
| 51 | C ₁₉ H ₁₅ FN ₂ O ₂ | 70.79 | 70.91 | 4.69 | 4.89 | 8.69 | 8.39 | | |
| 52 | C ₂₁ H ₂₀ N ₂ O ₄ | 69.21 | 69.20 | 5.53 | 5.54 | 7.69 | 7.76 | | |
| 53 | C ₁₇ H ₂₀ N ₂ O ₂ | 71.80 | 71.89 | 7.09 | 7.10 | 9.85 | 9.93 | | |
| 54 | C ₁₈ H ₁₄ N ₂ O ₂ | | | | | | | | |
| 55 | C ₁₈ H ₁₃ ClN ₂ O ₂ | | | | | 8.63 | 8.58 | 10.92 | 11.09 |
| 56 | C ₁₈ H ₁₃ ClN ₂ O ₂ | | | | | 8.63 | 8.38 | 10.92 | 10.92 |
| 57 | C ₁₉ H ₁₃ ClN ₂ O ₄ | | | | | 7.60 | 7.49 | 9.62 | 9.36 |

Table VII (Continued)

| Compound No. | Formula | Analytical Data | | | | | | | |
|--------------|---|-----------------|---------|-----------|-----------|----------|---------|-----------|----------|
| | | C Calcd. | C Found | H Calcd. | H | N Calcd. | N Found | Cl Calcd. | Cl Found |
| 58 | C ₁₉ H ₁₅ ClN ₂ O ₃ | 64.32 | 64.44 | 4.26 | 4.26 | 9.99 | 10.17 | | |
| 59 | C ₂₀ H ₁₈ ClN ₃ O ₂ | | | | | 11.42 | 11.53 | 9.64 | 9.98 |
| 60 | C ₁₈ H ₁₁ ClN ₂ O ₄ | 66.98 | 67.13 | 3.44 | 3.66 | 8.68 | 8.66 | | |
| 61 | C ₁₉ H ₁₆ N ₂ O ₂ | 74.98 | 75.17 | 5.30 | 5.38 | 9.21 | 9.20 | | |
| 62 | C ₁₇ H ₁₂ N ₂ O ₂ | | | | | | | | |
| 63 | C ₁₅ H ₁₆ N ₂ O ₂ | 70.29 | 70.16 | 6.29 | 6.44 | 10.93 | 10.79 | | |
| 64 | C ₂₄ H ₂₈ N ₄ O·HCl | | | | | 13.18 | 13.03 | 8.34 | 8.16 |
| 65 | C ₂₄ H ₂₇ ClN ₄ O·HCl | 62.74 | 62.74 | 6.17 | 6.11 | 12.20 | 11.99 | 15.44 | 15.53 |
| 66 | C ₂₄ H ₂₇ ClN ₄ O·HCl | | | | | 12.20 | 12.40 | 15.44 | 15.23 |
| 67 | C ₂₄ H ₂₆ ClFN ₄ O | 65.37 | 65.48 | 5.94 | 6.08 | 12.71 | 12.70 | | |
| 68 | C ₂₅ H ₂₉ ClN ₄ O ₂ | 66.28 | 66.35 | 6.45 | 6.34 | 12.37 | 12.19 | | |
| 69 | C ₂₅ H ₂₉ ClN ₄ O ₂ ·HCl | | | | | 11.45 | 11.73 | 14.49 | 14.64 |
| 70 | C ₂₆ H ₃₃ N ₅ O·2 HCl | | | | | 13.88 | 13.73 | 14.05 | 14.03 |
| 71 | C ₂₅ H ₃₀ ClN ₄ O | | | 22.47 (a) | 22.51 (a) | 9.92 | 9.74 | 6.28 | 6.49 |
| 72 | C ₂₃ H ₂₆ N ₄ O·HCl | | | | | 13.64 | 13.60 | 8.63 | 8.63 |
| 73 | C ₂₅ H ₃₀ N ₄ O ₃ ·HCl | 63.75 | 63.35 | 6.63 | 6.76 | 11.90 | 11.64 | | |
| 74 | C ₂₅ H ₃₀ N ₄ O·C ₄ H ₄ O ₄ | 67.16 | 67.00 | 6.61 | 6.79 | 10.81 | 10.66 | | |
| 75 | C ₂₄ H ₂₅ ClN ₄ O·HCl | | | | | 12.25 | 12.45 | 15.51 | 15.23 |
| 76 | C ₂₁ H ₃₀ N ₄ O·HCl | 64.51 | 64.72 | 7.99 | 8.18 | 14.33 | 14.48 | | |
| 77 | C ₂₂ H ₂₃ ClN ₄ O | 66.91 | 67.00 | 5.82 | 6.06 | 14.19 | 13.93 | 8.98 | 8.81 |
| 78 | C ₂₆ H ₃₁ ClN ₄ O·HCl·C ₂ H ₆ O | 63.03 | 63.43 | 7.18 | 7.09 | 10.50 | 10.51 | 13.29 | 13.37 |
| 79 | C ₂₄ H ₂₅ ClN ₄ O | | | | | 13.31 | 13.30 | 8.42 | 8.31 |
| 80 | C ₂₅ H ₂₇ ClN ₄ O | 69.02 | 69.06 | 6.25 | 6.46 | 12.88 | 13.00 | | |
| 81 | C ₂₃ H ₂₄ N ₄ O ₂ | 71.11 | 70.94 | 6.23 | 6.36 | 14.42 | 14.16 | | |
| 82 | C ₂₄ H ₂₆ N ₄ O ₂ | 65.97 | 66.11 | 6.23 | 5.85 | 12.82 | 12.70 | | |
| 83 | C ₂₈ H ₃₁ ClN ₄ O ₂ ·HCl·0.5 H ₂ O | 64.61 | 64.70 | 6.39 | 6.47 | 10.77 | 10.73 | | |
| 84 | C ₂₃ H ₂₅ ClN ₄ O | | | | | 13.70 | 13.80 | 8.67 | 8.74 |
| 85 | C ₂₄ H ₂₇ ClN ₄ O ₂ ·HCl | | | | | 11.79 | 11.73 | 14.92 | 14.91 |
| 86 | C ₂₆ H ₂₉ ClN ₄ O | 69.55 | 69.78 | 6.51 | 6.60 | 12.48 | 12.73 | | |
| 87 | C ₁₈ H ₁₅ N ₃ O | 74.72 | 74.48 | 5.23 | 5.19 | 14.53 | 14.40 | | |
| 88 | C ₁₉ H ₁₇ N ₃ O | 75.22 | 75.37 | 5.65 | 5.82 | 13.85 | 13.74 | | |
| 89 | C ₁₈ H ₁₅ ClN ₄ O | 63.81 | 63.79 | 4.46 | 4.54 | 16.54 | 16.32 | | |
| 90 | C ₁₈ H ₁₄ ClN ₃ O ₂ | | | | | 12.37 | 12.17 | 10.44 | 10.40 |
| 91 | C ₂₀ H ₁₈ ClN ₃ O ₂ | | | | | 11.42 | 11.69 | 9.64 | 9.59 |
| 92 | C ₂₂ H ₂₂ N ₄ O | 73.72 | 73.94 | 6.19 | 6.47 | 15.63 | 15.75 | | |
| 93 | C ₂₃ H ₂₃ ClN ₄ O | 67.89 | 67.61 | 5.70 | 5.54 | 13.77 | 13.75 | | |
| 94 | C ₂₅ H ₂₇ N ₅ O ₂ | 69.90 | 69.94 | 6.34 | 6.28 | 16.30 | 16.29 | | |
| 95 | C ₂₄ H ₂₇ N ₃ O ₂ ·HCl | | | | | 9.87 | 10.03 | 8.32 | 8.41 |
| 96 | C ₂₄ H ₂₆ ClN ₃ O ₂ | | | | | 9.91 | 9.96 | 8.37 | 8.32 |
| 97 | C ₂₄ H ₂₆ ClN ₃ O ₂ ·HCl | | | | | 9.13 | 9.01 | 15.40 | 15.64 |
| 98 | C ₂₄ H ₂₅ ClFN ₃ O ₂ ·HCl | | | | | 8.78 | 8.46 | 14.82 | 14.73 |
| 99 | C ₂₃ H ₂₅ N ₃ O ₂ ·HCl | | | | | 10.20 | 10.35 | 8.61 | 8.60 |
| 100 | C ₂₅ H ₂₉ N ₃ O ₂ ·C ₄ H ₄ O ₄ | 67.03 | 66.80 | 6.40 | 6.58 | 8.09 | 7.87 | | |
| 101 | C ₂₃ H ₂₄ ClN ₃ O ₂ | | | | | 10.23 | 10.33 | 8.66 | 8.75 |

(a) Iodine.

Method B.

A suspension of 0.10 moles of acid (Table IV), and 0.2 moles of thionyl chloride was heated until the gas evolution ceased. The excess thionyl chloride was evaporated, 50 ml. of benzene was added, and then evaporated. To this residue suspended in 50 ml. of benzene, 0.012 moles of amine or amino alcohol was added rapidly with stirring. The mixture was allowed to stand for 1 hour and worked up by Method A.

Method C.

A solution of 0.10 moles of acid (Table IV), 0.011 moles of a dialkylaminoalkyl chloride and 100 ml. of 2-propanol were refluxed 16 hours, then worked up by Method A.

Table VI
Activity Against Ventricular Arrhythmia

| Compound | Ouabain (n) (a) | Coronary Artery Ligation (n) (a) |
|------------------|-----------------|----------------------------------|
| 64 | 15 (1/2) | 15 (1/2) |
| 66 | 15 (1/1) | 5 (1/2) |
| 92 | 15 (1/2) | 15 (2/3) |
| 99 | 5 (1/1) | 5 (2/4) |
| 100 | 20 (1/1) | 15 (1/2) |
| Quinidine | 7.5 (2/2) | 10 (2/2) |
| Disopyramide (b) | 6.6 (2/2) | 7.5 (2/2) |

(a) Minimum effective dose (mg./kg.) (no. active/total dogs used).

(b) Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide.

Acknowledgements.

The author wishes to thank Mr. E. Zielinski and staff for elemental analyses, Mr. A. Damascus and staff for spectra determinations, Mr. R. Nicholson and staff for chromatographies, and Dr. J. Witt and staff for the large-scale preparation of several intermediates. Dr. R. Aspinall and Mr. W. Pautsch and their staffs furnished data from adjuvant arthritis assays, and Dr. R. Dean and Mrs. E. Muir and their staffs supplied the data from the antiarrhythmia assays. Special thanks are extended to Dr. R. Bible for extensive discussions and interpretations of spectra.

REFERENCES AND NOTES

- (1) W. C. Cutting, "Handbook of Pharmacology," Appleton-Century Crofts, 5th Ed., New York, N.Y., 1972, p. 520.
- (2) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H.

Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Am. Chem. Soc.*, **86**, 1520 (1964).

(3) J. F. K. Wilshire, *Aust. J. Chem.*, **19**, 1935 (1966).

(4a) J. B. Hill, R. Ray, H. Wagner, and R. L. Aspinall, *J. Med. Chem.*, **18**, 50 (1975); (b) R. L. Aspinall and P. S. Cammarata, *Nature*, **224**, 1320 (1969); (c) R. L. Aspinall, P. S. Cammarata, A. Nakao, J. Jiu, M. Miyano, D. E. Baker, and W. F. Pautsch, "Advances in the Biosciences," Vol. 9, Pergamon Press-Vieweg, Oxford, England, 1973, p. 419.

(5) B. R. Lucchesi, *J. Pharmacol. Exp. Ther.*, **137**, 291 (1962).

(6) B. R. Lucchesi and H. F. Hardman, *ibid.*, **132**, 372 (1961).

(7) A. S. Harris, A. Estandia, T. J. Ford, Jr., and R. F. Tillotson, *Circulation*, **4**, 522 (1951).

(8) R. Pappo, U. S. Patent 3,318, 907 (1967).

(9) C. S. Marvel and S. M. McElvain, "Organic Synthesis," Collect. Vol. I, 2nd Ed., Wiley, New York, N.Y. 1941, p. 170.

(10) J. C. Dubois, A. Horeac, and H. B. Kagan, *Bull. Soc. Chim. France*, 1830 (1967).

(11) S. Ruhemann and S. I. Levy, *J. Chem. Soc.*, **101**, 2542 (1912).

(12) K. V. Auwers and C. Wiegand, *J. Prakt. Chem.*, **134**, 82 (1932).

(13) W. E. Bachmann and D. G. Thomas, *J. Am. Chem. Soc.*, **63**, 598 (1941).

(14) K. V. Auwers and C. Wiegand, *J. Prakt. Chem.*, **134**, 97 (1932).

(15) W. E. Bachmann and D. G. Thomas, *J. Am. Chem. Soc.*, **64**, 94 (1942).

(16) W. J. Horton, C. E. Hummel, and H. W. Johnson, *ibid.*, **75**, 944 (1953).

(17) S. Ruhemann, *J. Chem. Soc.*, **101**, 1729 (1912).

(18) R. Robinson and R. C. Shah, *ibid.*, 610 (1933).