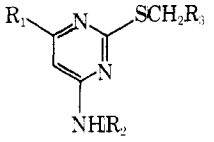
Table II. Antiarrhythmic Activity in the Anesthetized Dog



Compd	Dose (iv), mg/kg	Increase in fibrillatory threshold[a]
5a	20	0
5i	20	0
6a	20	+++
6b	20	+
6c	10	+
6d	20	0
6e	20	0
6f	20	+
6g	20	++
6h	20	0

[a] See the Experimental Section for explanation of terms.

and diphenylhydantoin. The fibrillatory threshold is measured in volts and the activity of the drug administered is determined according to Chart I.

Chart I

Increase in fibrillatory threshold	Voltage increase
no significant effect (0)	0-0.75 V
slight (+)	0.75-1.0 V
moderate (++)	1.0-2.0 V
marked (+++)	>2.0 V

In the screening procedure described above, a standard clinical compound such as quinidine elevated the fibrillatory threshold greater than 2.0 V with a dose of 20 mg/kg.[4] Diphenylhydantoin and procainamide elevated the fibrillatory threshold less than 2.0 V with doses of 20 and 25 mg/kg, respectively.

Chemistry. Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in either potassium bromide disks or pyridine, dimethyl sulfoxide, or chloroform solutions using a Perkin-Elmer (Model 21) spectrophotometer. Nuclear magnetic resonance spectra were obtained either with a Varian A-60 or JEOLC60-HL spectrometer. Elemental analyses of the compounds were obtained with a Perkin-Elmer (Model 24) elemental analyzer. The examples given are illustrative of the preparative procedures used for all the members of a series.

2-(4-Hydroxy-6-methyl-2-pyrimidinylthio)acetamide (3a). To a solution of 16.8 g (0.02 mol) of sodium bicarbonate in 300 ml of water was added 22.8 g (0.02 mol) of 6-methyl-2-thiouracil. The mixture was heated on a steam bath for 10 min. To this mixture was then added 18.6 g (0.02 mol) of 2-chloroacetamide, followed by 100 ml of absolute ethanol. The mixture was heated on a steam bath for 2 hr. The solution was cooled in an ice bath and the precipitate which formed was collected and recrystallized from a mixture of dimethylformamide and ethanol, affording 8 g of **3a.**

(4-Chloro-6-methyl-2-pyrimidinylthio)acetonitrile (4a). To a solution of 19.4 g (0.13 mol) of *N, N*-dimethylaniline in 250 ml of phosphorus oxychloride was added 25.8 g (0.13 mol) of **3a.** The mixture was heated under reflux for 1 hr. The phosphorus oxychloride was removed in a rotary evaporator and the residue was poured onto 1 l. of cracked ice. The precipitate which resulted was collected, dried, and recrystallized from heptane, giving 13.0 g of **4a.**

[4-(*p*-Chlorobenzylamino)-6-methyl-2-pyrimidinylthio]acetonitrile (5a). A stirred mixture of 5.97 g (0.03 mol) of **4a,** 4.2 g (0.03 mol) of 4-chlorobenzylamine, and 3.15 g (0.03 mol) of sodium carbonate in 150 ml of absolute ethanol was heated under reflux for 6 hr. The mixture was filtered and the filtrate was evaporated in a rotary evaporator. The residue was triturated with petroleum ether containing a little ethanol. The solid which crystallized was collected and recrystallized from ethyl acetate (petroleum ether was added to initiate precipitation), giving 3.2 g of **5a.**

2-[4-Methyl-6-(*p*-chlorobenzylamino)-2-pyrimidinylthio]acetamidoxime Dihydrochloride (6a). A mixture of 10.6 g (0.035 mol) of **5a,** 4.83 g (0.07 mol) of hydroxylamine hydrochloride, and 14.7 g (0.14 mol) of sodium carbonate in 10.0 ml of DMF was heated on a steam bath for 3 hr. The mixture was filtered and the filtrate was evaporated in a rotary evaporator. The residue was triturated with petroleum ether containing a little ethyl acetate. The solid which crystalized was collected and recrystallized from ethyl acetate, giving pure free base, mp 113–116°. This free base was dissolved in absolute ethanol and acidified with an ethereal hydrochloric acid solution, giving 3.5 g of **6a.**

Acknowledgments. The authors wish to thank Drs. T. Baum and R. Tomarelli for performing the pharmacological screening procedures and Mr. B. Hofmann for the microanalyses and infrared and nuclear magnetic resonance spectral determinations.

References and Notes

(1) Taken in part from the M.S. Thesis of one of the authors (A.C.S.), St. Joseph's College, Philadelphia, Pa., 1974.
(2) (a) A. A. Santilli, A. C. Scotese, and R. M. Tomarelli, *Experientia,* **30,** 1110 (1974). (b) Presented before the Division of Medicinal Chemistry, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974.
(3) J. Druey, U.S. Patent 2,530,570 (1950) [*Chem. Abstr.,* **45,** 3428 (1951)].
(4) T. Baum, D. K. Eckfeld, A. T. Skropshire, G. Rowles, and L. L. Varner, *Arch. Int. Pharmacodyn.,* **193,** 149 (1971).

Synthesis and Analgesic Activities of 2,5-Dimethyl-2′-hydroxy-9α- and -β-propyl-6,7-benzomorphans

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The 2,5-dimethyl-2′-hydroxy-9α- and -β-propyl-6,7-benzomorphans were synthesized from 4-methyl-3-propylpyridine in five steps, in an overall yield of 14 and 5%, respectively. The required 4-methyl-3-propylpyridine was prepared in an overall yield of 34% by a four-step sequence. The benzomorphans were about as potent as, or more potent than, morphine in vivo.

Although 2,9α- and -β-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphans have been synthesized,[1,2] the isomeric 5-methyl-9-propyl compounds have not been prepared due to the commercial unavailability of 4-methyl-3-propylpyri-

dine, a starting material. We have been interested in synthesizing 2,5-dimethyl-2′-hydroxy-9α- and -β-propyl-6,7-benzomorphans (**10** and **11**) because of the various types of structure–activity correlations which could be made.

It can be seen in Table I that if a uninodal activity curve could be anticipated, maximal analgesic effect is reached in the 9β-methyl series (compounds **12–15**) when C-5 is substituted with an ethyl group. The 9α-methyl series (compounds **16–19**) similarly does not intuitively look promising for further synthetic work. Table I might indicate, however, that at least in the 5-methyl-9α-alkyl series (compounds **20, 17,** and **21**) maximal potency had not yet been achieved. The achievement of maximal potency in the 9β-alkyl series (compounds **20, 13,** and **22**) is problematic. It is difficult to predict, intuitively, at what point the activity of a series will level off.[3]

Chemistry. The synthesis of **10** and **11** was achieved by utilizing the well-known Steven's rearrangement.[4] The required starting material, 4-methyl-3-propylpyridine (**4**), was synthesized by a four-step sequence in an overall yield of about 35%. 3-Cyano-2,6-dihydroxy-4-methyl-5-propylpyridine (**1**) was prepared from cyanoacetamide and ethyl 2-propylacetoacetate in alkaline medium. Although optimization of yield was not attempted, a number of different bases and varied reaction conditions were tried. The use of alcoholic KOH (see the Experimental Section) gave the best yield of **1**. Treatment of **1** with 48% HBr gave **2,** quantitatively. Conversion of the dihydroxypyridine **2** to its dichloro derivative **3** was accomplished with $POCl_3$ at 180–200°. Little or no **3** could be obtained when **2** was refluxed with $POCl_3$ alone (110°) or in the presence of dimethylaniline. The use of PCl_5 gave a multicomponent mixture, possibly containing some of the desired **3,** although separation of the mixture was not feasible. The desired **4** was obtained by hydrogenolysis of **3** with Pd on charcoal. An attempted hydrogenolysis of **3** using P in HI gave a mixture of products. An alternative approach to **4,** the reaction of 3-propylpyridine[5] with formic–acetic anhydride and zinc,[6,7] gave a mixture of, mostly, what was presumed to be (from GLC) 4-ethyl-3-propylpyridine, some of the desired **4,** and a fair amount of starting material (Scheme I).

Quaternization of **4** with methyl iodide, followed by $NaBH_4$ reduction, gave the terahydropyridine **6.** Reaction of **6** with *p*-methoxybenzyl bromide (**7**) rather than the usual chloride[4b] was advantageous, because the quaternary bromide (**8**) was much less hygroscopic than the corresponding chloride. Stevens rearrangement of **8** (PhLi) gave a mixture of four products (by GLC).[4a] Pure **9** could be obtained readily through the HBr salt. Cyclization of **9** was achieved by refluxing in 48% HBr to give, after work-up, a mixture of the 9α- and -β-benzomorphans **10** (61%) and **11** (21%), separated by fractional crystallization. The overall yield of **10** and **11** (from **4**) was about 14 and 5%, respectively.

The 9α- and -β-benzomorphans were easily distinguished by a methiodide rate-formation study. After 24 hr **10** and **11** were converted to their methiodides to the extent of 99 and 14%, respectively, in complete accord with previous similar studies.[8,9]

Biological Studies and Conclusion. The analgesic activities of **10** and **11** were determined by the hot-plate[10,11] and Nilsen[12] methods and are shown in Table I. Both **10** and **11** are potent analgesics.

It can be seen, in Table I, that in the 5-methyl-9-alkyl series, maximal potency was achieved with the 9α-ethyl compound **21** and, apparently, the 9β-methyl or ethyl compound (**13** and **22**). The increase in bulk at the C-9 position of **10** and **11** did not increase the potency of the benzomorphan beyond that obtained with the lower alkyl members.[13]

However, it may be anticipated, from the difference in potencies found by the Eddy hot-plate and Nilsen test, that **11** will eventually prove to have agonist–antagonist properties. These studies are presently being carried out.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Microanalyses were performed by the Laboratory's Section on Microanalytical Services and Instrumentation and are within ±0.4% of the calculated values. Ir (Perkin-Elmer 21) and NMR spectra (Varian A-60 or HR-220) were consistent with the assigned structures.

3-Cyano-2,6-dihydroxy-4-methyl-5-propylpyridine (1). Using a modification of the method of Bobbit and Scola,[14] a solution of KOH (5.6 g, 0.1 mol) in MeOH (70 ml) was added during 1.5 hr to a stirred, refluxing solution of cyanoacetamide (16.8 g, 0.2 mol) and ethyl 2-propylacetoacetate (17.2 g, 0.1 mol) in absolute EtOH (150 ml). A heavy, white precipitate separated during the

Scheme I

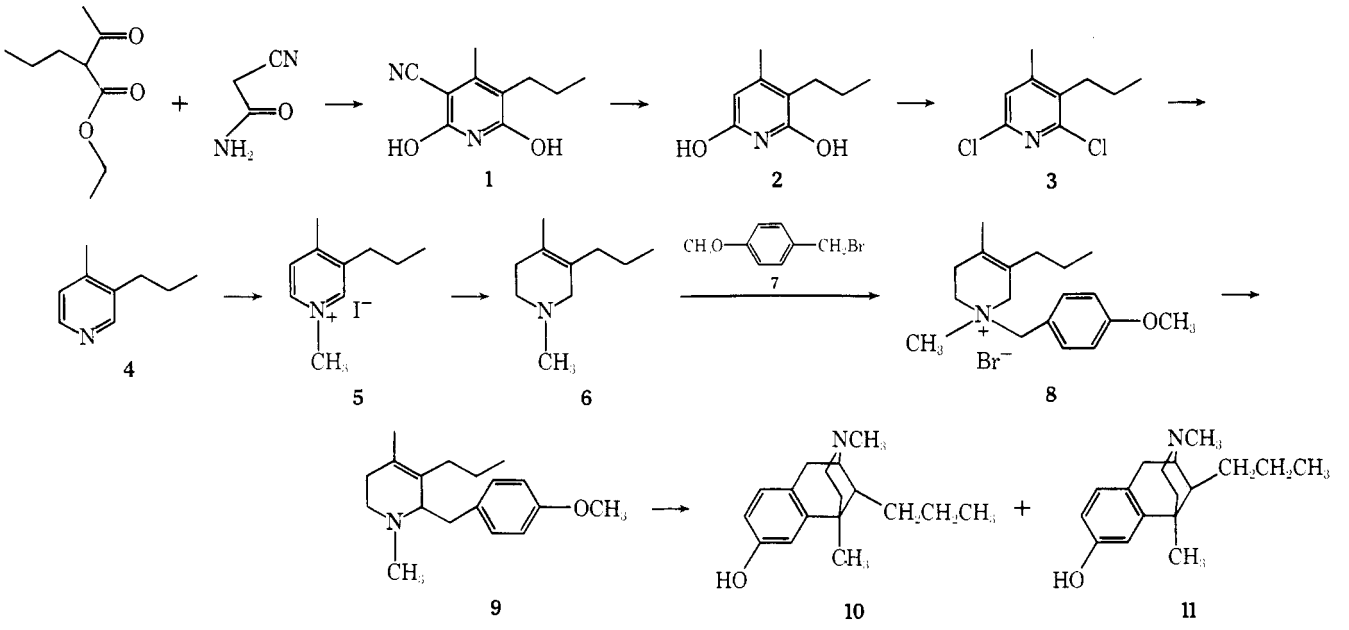

Table I. Analgesic Activity of Some 2′-Hydroxy-5,9α- or -β-substituted 6,7-Benzomorphans

Compd no.	Substituents C-5	C-9α	C-9β	ED_{50}, mg/kg[a] (95% SE limits)[c]	ED_{50}, mg/kg[b] (95% SE limits)[c]
10[d]	Me	*n*-Pr	H	1.61 (1.03–2.52)	1.8 (1.3–2.6)
11[d]	Me	H	*n*-Pr	0.69 (0.50–0.96)	0.35 (0.26–0.49)
12[e]	H	H	Me	1.1 (0.8–1.4)[f]	
13[g]	Me	H	Me	0.22 (0.18–0.26)	
14[g]	Et	H	Me	0.03 (0.03–0.04)	
15[e]	*n*-Pr	H	Me	0.12 (0.11–0.14)	
16[e]	H	Me	H	4.3 (3.1–5.9)	
17[g]	Me	Me	H	1.18 (1.05–1.33)	
18[g]	Et	Me	H	2.47 (1.95–3.12)	
19[e]	*n*-Pr	Me	H	2.06 (1.66–2.55)	
20[g]	Me	H	H	3.28 (2.55–4.24)	
21[g]	Me	Et	H	0.75 (0.67–0.84)	
22[g]	Me	H	Et	0.24 (0.21–0.27)	
Morphine[g]				1.2 (0.9–1.3)	0.8 (0.6–1.2)

[a]Eddy hot-plate test, subcutaneous injection (H_2O solution of salt form), in mice. [b]Nilsen test (injection, solution, and animal as in a. [c]SE limits determined by probit analysis. [d]Free base (dilute HCl added for solution). [e]Hydrobromide salt. [f]Weak antagonist (as determined in single-dose suppression studies in monkeys, Medical College of Va., 1974). [g]Hydrochloride salt.

addition. Absolute EtOH (100 ml) was added. After the addition was complete, stirring and refluxing were continued 3 hr. The mixture was then cooled and filtered and the solid was washed with EtOH and then with Et_2O. It was dissolved in H_2O (200 ml) and acidified with 37% HCl. The tan, crystalline material (10.1 g) that resulted was washed with H_2O and dried. Recrystallization from *i*-PrOH with filtering through Celite gave 9.4 g (49%) of **1**: needles; mp 229.5–231.5°. Recrystallization from Me_2CO–H_2O gave pure **1**·H_2O: irregular prisms; mp 230.5–231.5° (lit.[15] mp 221–222°). Anal. ($C_{10}H_{12}N_2O_2 \cdot H_2O$) C, H, N.

In a run 25 times the scale described above, the yield of recrystallized material was 41%.

2,6-Dihydroxy-4-methyl-3-propylpyridine (2). To 48% HBr (700 ml) was added **1** (212.7 g, 1.1 mol). The mixture was refluxed 24 hr (CO_2 was liberated and the mixture became homogenous). The HBr was then evaporated at the water pump, leaving a semisolid paste. H_2O (480 ml) was added and the solution neutralized to pH 1–2 (Hydrion paper) with 40% aqueous KOH. After cooling to 25°, the resulting white solid was filtered, washed well with cold H_2O, and dried to give 183.0 g (99%) of **2**: mp 148–150°. A portion of this material was sublimed at 130° (0.1 mm) for analysis: mp 152–153.5°. Anal. ($C_9H_{13}NO_2$) C, H, N.

2,6-Dichloro-4-methyl-3-propylpyridine (3). To $POCl_3$ (267 g, 1.75 mol) in a 300-ml steel bomb was added **3** (70 g, 0.42 mol). The bomb was capped, heated in an oil bath at 180–200° for 4 hr, and cooled and the contents were poured onto crushed ice. The oil that separated was extracted with ligroine (2 × 400 ml, bp 30–60°), the extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated to give 85.5 g of a light-tan oil. This material and the corresponding material from a run using 60 g of **2** were combined and distilled to give 137 g (86.5%) of **3**, bp 89–91° (0.1 mm), which did not form crystalline picrate or HCl salts. Redistillation gave pure material. Anal. ($C_9H_{11}Cl_2N$) C, H, N.

4-Methyl-3-propylpyridine (4). $NaOAc \cdot 3H_2O$ (61 g, 0.45 mol), 10% Pd/C (5.5 g), and MeOH (300 ml) were combined and prereduced at an initial pressure of 48 psi using a standard Parr apparatus. When uptake of H_2 had ceased, **3** (40 g, 0.2 mol) was added and shaking was begun at 47 psi. After 18 hr, uptake of H_2 had ceased at ~105% of theory. The catalyst and NaCl formed in the reaction were filtered through Celite and the filter was washed well with MeOH. The filtrate was rendered acidic with 37% HCl and evaporated at the water pump to a semisolid. Sufficient H_2O to just dissolve the solids was added and the solution extracted with Et_2O (2 × 100 ml). This Et_2O extract was discarded and the aqueous layer made strongly basic with KOH. The oil that separated was extracted with Et_2O (3 × 160 ml) and the extracts were dried ($MgSO_4$), filtered, and evaporated to give 27.0 g of crude **4**. A total of 135.0 g of **3** was reduced in four runs using the above method and the crude material from each combined and distilled to give 87.1 g (97.5%) of **4**: bp 103–105° (18 mm). The compound **4a** was characterized as its **picrate**: yellow needles from Me_2CO; mp 140–141.5°. Anal. ($C_{15}H_{16}N_4O_7$) C, H, N.

4-Methyl-3-propylpyridine Methiodide (5). To a solution of **4** (91.6 g, 0.7 mol) in Me_2CO (170 ml) was added MeI (194 g, 1.37 mol), during 0.5 hr, while stirring and cooling. As the exothermic reaction proceeded, refluxing began and crystalline material separated. When the addition was complete, the mixture was stirred 2 hr at room temperature. EtOAc (200 ml) was added and the mixture cooled to 5° for 0.5 hr. The solid was filtered, washed with cold EtOAc–Me_2CO (1:1), and dried to give 180.8 g (96.5%) of **5**, mp 139.5–141.5°. Recrystallization from Et_2O–MeOH gave pure material as needles: mp 141–143°. Anal. ($C_{10}H_{16}NI$) C, H, N.

***p*-Methoxybenzyl Bromide (7).** This material was prepared using a procedure similar to that of Kornblum.[16] The compound could be distilled: bp 92–95° (0.2 mm) [lit.[17] bp 105–110° (8 mm)]. However, occasionally, extensive decomposition was noted on attempted distillation. The crude material was essentially pure and was used directly, since the use of distilled material offered no advantage.

1,4-Dimethyl-1-(*p*-methoxybenzyl)-3-propyl-1,2,5,6-tetrahydropyridinium Bromide (8). To 1 *N* NaOH (935 ml) was added **5** (181 g, 0.65 mol), $NaBH_4$ (36.0 g, 0.95 mol), and MeOH (189 ml). Stirring was begun without external heating or cooling. The temperature rose to 63° during the first 0.5 hr and was maintained in the range 60–65° for an additional 2.5 hr. The reaction mixture was then cooled, saturated with NaCl, and extracted with four 200-ml portions of Et_2O. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give 97.8 g (0.64 mol, 98%) of crude **6**. This material was dissolved directly in Me_2CO (220 ml) and **7** (130 g, 0.65 mol) was added dropwise, with stirring and cooling (22–27°). EtOAc (320 ml) was added 0.5 hr after the addition was complete and the product allowed to crystallize overnight at 5°. The material was then filtered, washed with EtOAc–Me_2CO (3:2, 400 ml) at 0° and then Et_2O, and dried at 65° in vacuo to give 162.8 g (71.5%) of **8**: mp 150–152°. Recrystallization from 2-butanone gave pure **8**: mp 155–157°. Anal. ($C_{18}H_{28}BrNO$) C, H, N.

1,4-Dimethyl-2-(*p*-methoxybenzyl)-3-propyl-1,2,5,6-tetrahydropyridine (9) Hydrobromide. To a slurry of **8** (169 g, 0.48 mol) in dry Et_2O (300 ml) was added 1.8 *M* PhLi (800 ml, 1.44 mol) in C_6H_6–Et_2O (70:30) as rapidly as possible with efficient stirring. The brisk refluxing subsided after a few minutes; stirring was continued for 2.5 hr. The mixture was then poured onto crushed ice and the organic phase separated. The aqueous layer was washed with Et_2O (200 ml) and the combined organic extract was shaken with 1.5 *N* HCl (350 ml) and then with additional 1.5 *N* HCl (2 × 100 ml). The combined aqueous extracts were washed with Et_2O (200 ml) and made alkaline with 12 *M* NH_4OH. The oil that separated was shaken into Et_2O (3 × 300 ml) and the combined Et_2O extract washed with H_2O (100 ml) and brine (2 × 100 ml). The Et_2O extract was dried (Na_2SO_4) and evaporated to give 121.7 g of an amber oil that was dissolved in EtOAc–Me_2CO (90:10, 300 ml). While stirring and cooling to maintain a temperature of 20–25°, the solution was acidified with HBr gas to pH 3–4 (moist Hydrion paper). When crystallization was complete (~0.5 hr), the

solid was filtered, washed with EtOAc–Me_2CO (9:1), and dried to give 64.4 g (38%) of **9**: mp 151–156.5°. Recrystallization from methyl isobutyl ketone gave 55.7 g (33%) of essentially pure **9**, mp 159.5–161°; rods from *i*-PrOH, mp 160–161.5°. Anal. ($C_{18}H_{28}BrNO$) C, H, N.

2,5-Dimethyl-2′-hydroxy-9α-propyl-6,7-benzomorphan (10). To 48% HBr (600 ml) was added **9**·HBr (61.4 g, 0.17 mol) and the solution refluxed 20 hr. The reaction mixture was cooled, poured onto crushed ice, and made alkaline with 12 *M* NH_4OH. The semisolid that resulted was dissolved in $CHCl_3$ (2.0 l), washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent left 42.8 g (96%) of tan crystalline material which was recrystallized from dioxane (400 ml) to give 25.4 g (56.8%) of **10**: mp 212–216.5°. An additional crystallization from dioxane and finally from absolute EtOH gave fine needles of pure **10**: mp 217.5–219°. Anal. ($C_{17}H_{25}NO$) C, H, N.

2,5-Dimethyl-2′-hydroxy-9β-propyl-6,7-benzomorphan (11) Hydrochloride Dihydrate. The filtrate from the 25.4 g of **10** above was evaporated to give a solid to which H_2O (50 ml) was added. After addition of 37% HCl to pH 1–2 (Hydrion paper), the slurry was heated to solution and filtered hot (Celite), and the filter was washed with 10 ml of hot H_2O. The combined filtrate and washing were cooled to 0° and the resulting crystals filtered, washed with ice–H_2O, and air-dried to give 8.9 g (17.4%) of **11**·HCl·$2H_2O$, mp 267.5–270.5°; oblong prisms from H_2O, mp 270–272.5°. Anal. ($C_{17}H_{26}ClNO·2H_2O$) C, H, N.

Treatment of an aqueous solution of **11**·HCl with NH_4OH gave a solid which was recrystallized twice from absolute EtOH to give cubes of **11** (base), mp 182.5–184°. Anal. ($C_{17}H_{25}NO$) C, H, N.

The filtrate from the 8.9 g of **11**·HCl above was made alkaline with NH_4OH and the resulting base mixture reprocessed as described for the isolation of **10** and **11**. In this manner additional **10** (1.8 g) and **11** (1.8 g) were obtained (total isolated yield of **10** and **11**, 60.6 and 20.9%, respectively).

Rates of Methiodide Formation of 10 and 11. Using the procedure previously described,[8] the predominant **10** and lesser **11** isomers produced in the cyclization of **9** were shown to be converted to the corresponding methiodides to an extent of 99 and 14%, respectively, during 24 hr. The assigned relative stereochemistry of **10** and **11** is thereby confirmed.

Acknowledgment. We thank Mrs. L. Atwell, Medicinal Chemistry Section, for the analgesic assay data.

References and Notes

(1) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).
(2) C. F. Chignell, J. H. Ager, and E. L. May, *J. Med. Chem.*, **8**, 235 (1965).
(3) A preliminary, quantitative structure–activity (QSAR) calculation by one of us (A.E.J.) gave intriguing predictions about the potencies of these compounds. Although these equations are not, as yet, theoretically satisfactory, they indicated to us that the syntheses should be attempted.
(4) (a) A. E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966); (b) A. E. Jacobson and R. T. Parfitt, *ibid.*, **32**, 1894 (1967).
(5) A. D. Miller and R. Levine, *J. Org. Chem.*, **22**, 168 (1957).
(6) J. P. Wibaut and S. Vromen, *Recl. Trav. Chim. Pays-Bas*, **67**, 545 (1948).
(7) D. Taub, R. D. Hoffsommer, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **30**, 3229 (1965).
(8) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).
(9) T. Oh-ishi, A. E. Jacobson, R. S. Wilson, H. J. C. Yeh, and E. L. May, *J. Org. Chem.*, **39**, 1347 (1974).
(10) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953).
(11) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965), see ref 8 therein.
(12) T. D. Perrine, L. Atwell, I. B. Tice, A. E. Jacobson, and E. L. May, *J. Pharm. Sci.*, **61**, 86 (1972).
(13) The equations derived from the QSAR study accurately predicted the potency of **10** and came quite close to the Nilsen ED_{50} for **11**.
(14) J. M. Bobbit and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).
(15) I. Guareschi, *Mem. R. Accad. Sci. Torino*, 55 [through *Chem. Zentralbl.*, II, 681 (1905)].
(16) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).
(17) E. S. Huyser, *J. Am. Chem. Soc.*, **82**, 391 (1960).

Synthesis and Neuroleptic Activity of Isomeric Thieno[1,4]benzothiazines

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To investigate the influence of electronic properties of the tricyclic thiazine system on neuroleptic activity, a series of the isomeric *N*-dimethylaminopropylthienobenzothiazines was synthesized. All compounds were screened for neuroleptic activity in mice and rats. For the active compounds lowest active doses in the antiamphetamine test were determined. Activity appeared to be dependent on the mode of annelation of the thiophene molecule: compounds bearing the same substituent and side chain with the thiophene molecule in 2,3 and 3,4 annelation were active, while those compounds with a 3,2 annelation seemed to be devoid of activity at the given dose.

In previous papers we described the synthesis of some isomers of the dithienothiazine system.[1] Attempts to synthesize promazine analogs, however, were unsuccessful due to oxidation of the intermediate N-unsubstituted dithienothiazines.

As was shown in some preliminary experiments the thienobenzothiazines, in which one thiophene molecule is replaced by the less reactive benzene nucleus, were more stable compounds. In addition, we have a tool to enhance the stability of the thiazine system by the introduction of electron-withdrawing groups. These groups hamper the formation of the radical cation,[2] the first step in disproportionation and decay reactions.[3,4] In our studies we investigate to what extent the electronic structure of thiazines influences their neuroleptic activity.

Differences in electronic properties can be achieved by preparing isomeric thienobenzothiazines, varying in the mode of annelation of the thiophene molecule. In order to reduce the physicochemical differences to a minimum, all isomers should bear the same substituent and side chain.

In this paper the synthesis and preliminary pharmacology of thienobenzothiazine analogs of promazine, chlorpromazine, and triflupromazine are reported.

Chemistry. For the synthesis of isomeric thienobenzothiazine systems we used the reaction scheme developed in our previous investigations. All isomers were prepared using a synthetic sequence as outlined for the thieno[3,2-*b*][1,4]benzothiazine substituted with a trifluoromethyl group in the benzene ring (Scheme I).

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