The desired product was purified by preparative tlc and recrystd from MeOH to afford 45 mg of **15**, mp 117–118°. Further recrystn gave the anal. sample: mp 117–118°; $[\alpha]^{22}D$ +9° (c, 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 17α-H), 2.03 (s, 17-OAc), 0.97 (s, 19-H_3), and 0.78 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O_2$) C, H.

3α-Trifluoromethyl-5α-androstan-17β-ol Acetate (17).—A soln of 200 mg of **11** in 50 ml of anhyd Et_2O was treated with 1 g of LAH and stirred for 1 day at room temp. After destroying the excess hydride by careful addition of EtOAc, the mixture was treated with a satd soln of Na-K tartarate. The Et_2O layer was sepd and the aq layer was extracted with Et_2O. The combined Et_2O extract was washed with H_2O, dried (Na_2SO_4), and evapd to give a gummy residue. The crude product (1 spot on tlc), 3α-trifluoromethyl-5α-androstan-17β-ol, was dissolved in 10 ml of pyridine and 2 ml of Ac_2O and left standing for 18 hr at room temp. The mixture was dild with H_2O and was extracted with Et_2O. The ethereal extract was washed with 5% HCl and H_2O, dried (Na_2SO_4), and evapd. The product was isolated by preparative tlc and recrystd from aq MeOH to give 50 mg of **17**, mp 99–100°. Further recrystn afforded the anal. sample: mp 100–101°; $[\alpha]^{22}D$ +7° (c, 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 17α-H), 2.03 (s, 17-OAc), 0.82 (s, 19-H_3), and 0.78 ppm (s, 18-H_3). *Anal.* ($C_{22}H_{33}F_3O_2$) C, H.

17α-Methyl-5α-androst-3-en-17β-ol (10).—To a soln of 1.1 g of 5α-androst-3-en-17-one[20] in 100 ml of Et_2O–THF (4:1) was added 25 ml of 3 *M* MeMgBr in Et_2O. The reaction mixture was refluxed overnight, poured into ice, and acidified with 10% HCl. The Et_2O layer was sepd and the aq layer was extracted with Et_2O. The combined extracts were washed with 5% Na_2CO_3 and H_2O, dried (Na_2SO_4), and evapd to give a gummy residue. The crude product was dissolved in C_6H_6 and adsorbed onto 50 g of neutral alumina. The column was eluted with C_6H_6–Et_2O (1:1 and 1:4). Recrystn from aq MeOH afforded 0.6 g of **10**, mp 140–141° (lit.[21] mp 139.5–140°) from a similar method).

3α-Trifluoromethyl-4β-iodo-17α-methyl-5α-androstan-17β-ol (12).—A quantity of 800 mg of **10** was allowed to react with excess CF_3I under the conditions described above. The product was isolated in the usual manner and recrystd from MeOH to afford 440 mg of **12**, mp 104–115°. Several recrystns from MeOH gave the anal. sample: mp 117–120°; $[\alpha]^{22}D$ −7° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 4.6 (m, 4α-H), 1.20 (s, 17-CH_3), 1.17 (s, 19-H_3), and 0.83 ppm, (s, 18-H_3). *Anal.* ($C_{21}H_{32}F_3IO$) C, H, I.

3α-Trifluoromethyl-17α-methylandrost-4-en-17β-ol (14).—A quantity of 366 mg of **12** was dissolved in 50 ml of 10% H_2O in MeOH containing 2 g of KOH. The mixture was refluxed for 2 hr. After cooling, H_2O was added to ppt the product. This was collected, washed with H_2O, and dried under vacuum. Recrystn from hexane afforded 124 mg of **14**, mp 149–151°. Further recrystn from hexane afforded the anal. sample: mp 149–150°; $[\alpha]^{22}D$ +77° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 5.28 (m, 4-H, 1.20 (s, 17-CH_3), 1.03 (s, 19-H_3), and 0.88 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{31}F_3O$) C, H.

3α-Trifluoromethyl-17α-methyl-5β-androstan-17β-ol (16).—To a soln of 100 mg of **14** in 75 ml of MeOH was added 300 mg of Pd-C. The mixture was hydrogenated at 0.2 kg/cm² for 4.5 hr. It was filtered and the filtrate was evapd to yield a solid residue. The residue was recrystd from hexane twice to afford 38.6 mg of **16**, mp 189–190°. Further recrystn from hexane afforded the anal. sample: mp 189–190°; $[\alpha]^{22}D$ −4° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.22 (s, 17-CH_3), 0.98 (s, 19-H_3), and 0.83 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{33}F_3O$) C, H.

3α-Trifluoromethyl-17α-methyl-5α-androstan-17β-ol (18).—A soln of 100 mg of **12** in 30 ml of anhyd Et_2O was treated with 400 mg of LAH and stirred overnight at room temp. After destroying the excess hydride with EtOAc, the mixture was treated with a satd soln of Na–K tartarate. The Et_2O layer was sepd, and the aq layer was extracted twice with Et_2O. The combined extracts were washed with H_2O, dried (Na_2SO_4), and evapd. The product was isolated by preparative tlc and recrystd from aq MeOH to give 31 mg of **18**, mp 131–134°. Further recrystn from MeOH gave the anal. sample: mp 134°; $[\alpha]^{22}D$ +2° (c 1, $CHCl_3$); nmr ($CDCl_3$) δ 1.21 (s, 17-CH_3). 0.85 (s, 19-H_3), and 0.82 ppm (s, 18-H_3). *Anal.* ($C_{21}H_{33}F_3O$) C, H.

(20) 5α-Androst-3-en-17-one was obtd from 5α-androst-3-en-17β-ol acetate (**9**) by hydrolysis of the 17-AcO group with 2% MeOH–KOH followed by CO_3 oxidn of the corresponding 17-OH group.

(21) P. D. Klimstra, U. S. Patent 3,166,578 (1965); *Chem. Abstr.*, **62**, 9207c (1965).

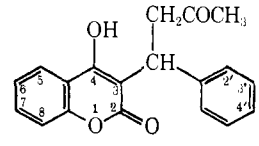
Studies on the 4-Hydroxycoumarins. Synthesis of the Metabolites and Some Other Derivatives of Warfarin[1]

M. A. HERMODSON, W. M. BARKER,* AND K. P. LINK

Department of Biochemistry, University of Wisconsin, Madison, Wisconsin 53706

Received June 22, 1970

Studies on the metabolism of warfarin [3-(α-acetonylbenzyl)-4-hydroxycoumarin] (I) in the rat have been described elsewhere.[2] The high physiological activity



I

of the anticoagulant precludes the isolation of excreted metabolic products in quantities large enough for classical chemical identification. Therefore, metabolic fate studies on warfarin were conducted using[4-^{14}C]warfarin sodium. The excreted radioactive metabolites from rats treated with the labeled compound were compared with known compounds, using chromatographic and isotope dilution techniques. This paper describes the syntheses of 5 compounds shown to be metabolites of warfarin, namely, 6-, 7-, 8-, and 4′-hydroxywarfarin and 2,3-dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-*c*]-[1]benzopyran. The syntheses of several hydroxylated warfarin derivatives which were not metabolites are also described.

Chemistry.—Warfarin may be synthesized by the Michael addition of 4-hydroxycoumarin to benzalacetone under a wide range of acidic or basic conditions.[3] The 4-hydroxycoumarin used in this reaction can be easily prepared by the method of Dickenson,[4] using *o*-hydroxyacetophenone and diethyl carbonate. However, this method did not prove successful for the synthesis of any of the desired dihydroxycoumarins from appropriate dihydroxyacetophenones, possibly due to the extreme insolubility of the disodium salts in the reaction solvent, benzene. Blocking the nonortho OH group by formation of a benzyl ether provided an intermediate which would undergo the desired reaction with $(EtO)_2CO$.

Therefore 6-, 7-, and 8-hydroxywarfarin were synthesized as shown in Scheme I.

The synthesis of 5-hydroxywarfarin, which could not be achieved by Scheme I, proceeded by the route shown in Scheme II.

It was found later that this method of synthesis also gave 6-, 7-, and 8-hydroxywarfarin in considerably bet-

* To whom inquiries concerning this work should be addressed at the Pharmacology Department, International Minerals and Chemical Corp., Libertyville, Ill. 60048.

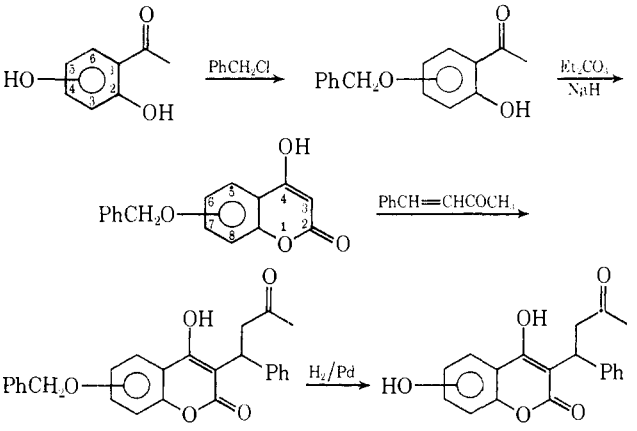
(1) The work described herein was submitted in partial fulfillment of the requirements for the Ph.D. degrees of M. A. Hermodson and W. M. Barker, University of Wisconsin, Madison, Wis.

(2) W. M. Barker, M. A. Hermodson, and K. P. Link, *J. Pharm. Exp. Ther.*, **171**, 307 (1970).

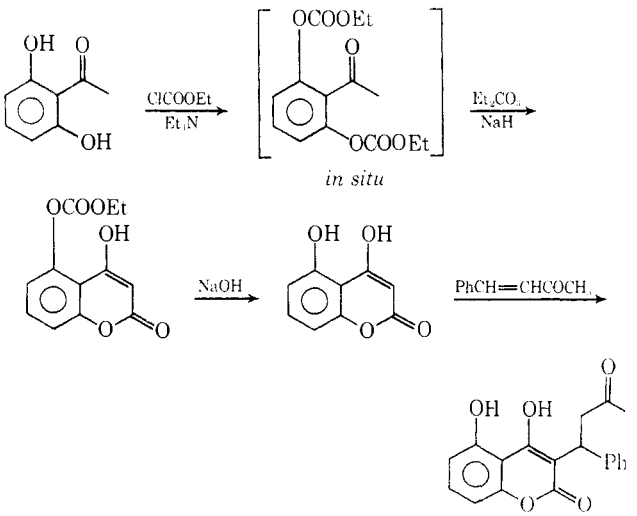
(3) C. Schroeder, Ph.D. Thesis, University of Wisconsin, Madison, Wis. (1955).

(4) H. G. Dickenson (to Ward, Blenkinsop and Co., Ltd.), cyclic lactones, U. S. Patent 2,449,162, Sept 14, 1948 [*Chem. Abstr.*, **43**, 694 (1949)].

SCHEME I

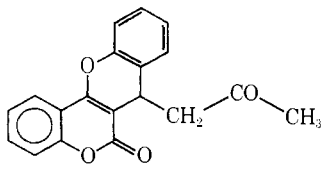


SCHEME II



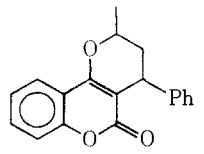
ter yields than were obtained *via* Scheme I. In addition 4′,6-, 4′,7- and 6,7-dihydroxywarfarin were synthesized from the appropriate starting materials by Scheme II.

Earlier efforts by Ikawa[5] to prepare 2′-hydroxywarfarin had shown that the compound was unstable. Condensation of 4-hydroxycoumarin with *o*-hydroxybenzalacetone yielded a cyclic ether II which resulted from the loss of H_2O between the phenolic and enolic OH groups to form a stable 6-membered ring. Because

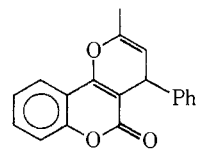


II

most ingested ketones are metabolized to some extent by reduction to the corresponding alcohols,[6] the reduction product of the acetone side chain of warfarin was also considered as a possible metabolite. As with 2′-hydroxywarfarin, however, this compound might by expected to undergo spontaneous intramolecular dehydration to yield 2,3-dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][1]benzopyran (III). Accordingly, III was prepared by low pressure hydrogenation of 2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-*c*][1]benzopyran (IV) which had been prepared by a previous worker.[7]



III



IV

Experimental Section[8]

All melting points are uncorrected from a Fisher-Johns melting point apparatus.

2-Hydroxy-5-benzyloxyacetophenone.—A mixture of 2,5-dihydroxyacetophenone (50 g), $PhCH_2Cl$ (41.8 g), KI (5 g), and anhyd K_2CO_3 (50 g) in 750 ml of Me_2CO (dried over $CaCl_2$), was refluxed for 4 hr. After cooling to room temp, the mixture was filtered and evapd to dryness *in vacuo*. The resulting residue was recrystd from MeOH, yielding 56.4 g (71.4%) of product, mp 69–70°. *Anal.* ($C_{15}H_{14}O_3$), C, H.

In a similar manner, 2,4-dihydroxyacetophenone yielded **2-hydroxy-4-benzyloxyacetophenone,** mp 105–106° (lit.[9] mp 104–104.5°).

2,3-Dihydroxyacetophenone, made by the method of Clauson-Kaas, *et al.*,[10] and Boehme and Scharpf,[11] was monobenzylated by this procedure to give **2-hydroxy-3-benzyloxyacetophenone** in 43% yield, bp 122–130° (0.05 mm). *Anal.* ($C_{15}H_{14}O_3$) C, H.

4-Hydroxy-6-benzyloxycoumarin.—A mixture of 25 g of 50% NaH in mineral oil and 500 ml of dry PhH was stirred and heated to boiling. When the distg temp reached 80°, 2-hydroxy-5-benzyloxyacetophenone (56.4 g) in 1000 ml of dry PhH was added dropwise at a rate which kept the total reaction vol constant. $(EtO)_2CO$ (55 g) in 500 ml of dry PhH was then added in the same manner. Distillation was allowed to proceed slowly for 5 hr with occasional addns of dry PhH to maintain the vol at approximately 500 ml. The reaction mixture was cooled and poured slowly into a mixture of 1000 g of ice in excess HCl. Enough EtOAc was added to dissolve the solid product, and the layers were sepd. The organic layer was evapd *in vacuo*, and the product was recrystd from MeOH; yield 30.5 g (54%), mp 230–231°. *Anal.* ($C_{16}H_{12}O_4$) C, H.

4-Hydroxy-7-benzyloxycoumarin was obtained in 36% yield in a similar manner from 2-hydroxy-4-benzyloxyacetophenone, mp 272–273° (from MeOH). *Anal.* ($C_{16}H_{12}O_4$), C, H. 2-Hydroxy-3-benzyloxyacetophenone, under the same reaction conditions gave a 30% yield of **4-hydroxy-8-benzyloxycoumarin,** mp 195–196° (from MeOH). *Anal.* ($C_{16}H_{12}O_4$) C, H.

6-Benzyloxywarfarin.—A mixture of 4-hydroxy-6-benzyloxycoumarin (15 g), benzalacetone (10.5 g), and Et_3N (5.6 g) in H_2O (200 ml) was stirred and refluxed 2 days. The cooled reaction mixture was adjusted to pH 9 to 10 with 5% NaOH and extd (Et_2O). The aq layer was acidified with HCl and cooled, the product removed by filtn and recrystd from Me_2CO; yield 18.5 g (80.3%), mp 166–167°. *Anal.* ($C_{26}H_{22}O_5$) C, H.

Similarly, **7-benzyloxywarfarin** was obtained from 4-hydroxy-7-benzyloxycoumarin in 58% yield, mp 143–144° (from Et_2O).

(5) M. Ikawa, Ph.D. Thesis, University of Wisconsin, Madison, Wis. (1948).

(6) R. T. Williams, "Detoxication Mechanisms," Wiley, New York, N. Y., 1959, pp 335–341.

(7) M. Seidman, Ph.D. Thesis, University of Wisconsin, Madison, Wis. (1951).

(8) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(9) L. Jurd and L. A. Rolle, *J. Amer. Chem. Soc.*, **80**, 5527 (1958).

(10) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **6**, 55 (1952).

(11) W. Boehme and W. Scharpf, *J. Org. Chem.*, **26**, 1692 (1961).

Journal of Medicinal Chemistry, 1971, Vol. 14, No. 2 169

Anal. ($C_{26}H_{22}O_5$) C, H. **8-Benzyloxywarfarin** was obtained from 4-hydroxy-8-benzyloxycoumarin in 67% yield, mp 165–166° (from Et_2O). *Anal.* ($C_{26}H_{22}O_5$) C, H.

6-Hydroxywarfarin.—A mixture of 6-benzyloxywarfarin (10 g) and 1.46 g of 10% Pd–C (60 g/mole) in 100 ml of 90% EtOH was shaken for 2 hr under H_2 pressure of 3.16 kg/cm². The catalyst was removed by filtration, and the solvent was evapd *in vacuo*. The residue was recrystd from $CHCl_3$;[12] yield 4.8 g (61.5%), mp 219–220°. *Anal.* ($C_{19}H_{16}O_5$) C, H.

Likewise, **7-hydroxywarfarin** was prepared from 7-benzyloxywarfarin in 77% yield, mp 208–210° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) C, H. **8-Hydroxywarfarin** was prepared from 8-benzyloxywarfarin in 60% yield, mp 189–191° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) C, H.

4,5-Dihydroxycoumarin.—2,6-Dihydroxyacetophenone (15.2 g) and Et_3N (21 g) were mixed with stirring in 500 ml of dry PhH and cooled in an ice bath. EtOCOCl (21.7 g) in 100 ml of dry PhH was added dropwise, while the temp was maintained at 0–5°. After addn of the reactants, the mixture was stirred and allowed to warm to room temp for 0.5 hr, then filtered. $(EtO)_2CO$ (12 g) and NaH (15 g, 50% in mineral oil) were added to the filtrate and the mixture was stirred and slowly distd for 8 hr. Dry PhH was added to the mixture periodically to maintain the reaction vol. The mixture was cooled and poured slowly into a mixture of 1000 g of ice in excess HCl. EtOAc was added to the mixture to dissolve the ppt. After phase separation the organic solvents were evapd *in vacuo*. The residue was dissolved in 200 ml of 10% NaOH, stirred at room temp for 4 hr, and then acidified with HCl and the product collected by filtration. The 4,5-dihydroxycoumarin was crystd from EtOH, yielding 9.5 g (60%), mp 218°.

In like manner, **4,6-dihydroxycoumarin** was synthesized from 2,5-dihydroxyacetophenone in 75% yield and crystd from EtOH, mp 300° (dec >290°). **4,7-Dihydroxycoumarin** was similarly prepared from 2,4-dihydroxyacetophenone and crystd from EtOH (25% yield), mp 282°; and **4,6,7-trihydroxycoumarin** from 2,4,5-trihydroxyacetophenone[13] in 40% yield, mp above 300° (undetd) (from MeOH).

5-Hydroxywarfarin.—4,5-Dihydroxycoumarin (1.78 g), benzalacetone (3.0 g), and Et_3N (0.073 ml)[14] were stirred and refluxed in 75 ml of H_2O for 8 hr. The mixture was cooled, 75 ml of satd $NaHCO_3$ added, and the mixture extd (Et_2O). The H_2O layer was made acidic with HCl, and the product collected by filtration. The 5-hydroxywarfarin was crystd from Me_2CO–H_2O and from PhH, mp 166° (70% yield). *Anal.* ($C_{19}H_{16}O_5$) C, H.

6,7-Dihydroxywarfarin was synthesized in 65% yield from 4,6,7-trihydroxycoumarin, mp 221–222° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_6$) H; C: calcd 67.05; found 64.73.[15]

4',6-Dihydroxywarfarin, mp 256° [(from $CHCl_3$) *Anal.* ($C_{19}H_{16}O_6$) C, H], and **4',7-dihydroxywarfarin,** mp 237° [(from $CHCl_3$[12]) *Anal.* ($C_{19}H_{16}O_6$) C, H], were prepared as above from the appropriate dihydroxycoumarins and *p*-hydroxybenzalacetone.

3'-Hydroxywarfarin was prepared from *m*-hydroxybenzalacetone and 4-hydroxycoumarin as above, mp 188–189° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) H; C: calcd 70.36; found 69.35.[15]

2,3-Dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-c][1]benzopyran.—2-Methyl-4-phenyl-5-oxo-α-pyrano[3,2-*c*][1]benzopyran (4 g) was suspended in 100 ml of 95% EtOH and 5 ml of AcOH with 100 mg of 10% Pd–C. The mixture was shaken with H_2 (3.16 kg/cm²) for 4 hr at room temp. The catalyst was removed by filtration and the solvent evapd *in vacuo*. The product was crystd from MeOH; mp 188–189°, yield, 90%. The pmr spectrum showed 16 H atoms with the assignments fitting the desired compd.

(12) All hydroxywarfarins, except 5-hydroxywarfarin, were purified by dissolving in a minimum of Me_2CO, then adding at least 6 vol of $CHCl_3$ and removing the Me_2CO by boiling. The products crystd from the cooled $CHCl_3$ soln.

(13) M. B. Knowles (to Eastman Kodak Co.), U. S. Patent 2,763,691, Sept 18, 1956 [*Chem. Abstr.*, **51**, 8791 (1957)].

(14) It was critical that the Et_3N concn be 5 mole % (based on the coumarin derivative concn) when condensing di- or trihydroxycoumarins with benzalacetone. Too much base prevented condn.

(15) This compd was chromatographically pure and gave a satisfactory ir spectrum. A change in crystal structure near the mp suggested a fair amount of solvation.

Conformationally Rigid Neurotransmitters. Acetylcholine Analogs in the Bicyclo[2.2.2]octane System[1a,b]

WENDEL L. NELSON* AND RAYMOND S. WILSON[1c]

College of Pharmacy, University of Washington, Seattle, Washington 98105

Received July 23, 1970

Steric and electronic effects have long been offered as at least partial explanations for differences in biological activity of variously substituted analogs of acetylcholine (ACh).[2] Hypotheses delineating the architectural features of the cholinergic receptor have been based on such observations of activity. Conformational aspects of ACh and its analogs have been studied in solution[3a-c] and in the solid state[3d-i] and extended Hückel theory calculations[3j,k] have been applied in attempts to determine the conformational aspects of the cholinergic receptor.

Work in rigid systems, designed to represent various conformations of cholinergic agents, *e.g.*, cyclopropane,[4a,b] tropane,[4c] *trans*-decalin,[4d,e] cyclohexane,[4f,g] cyclopentane,[4h] and isoquinuclidine,[4i] has produced some evidence concerning conformational aspects of the cholinergic drug–receptor interaction. In most cases evidence has been accumulated supporting an extended or transoid conformation of ACh in the drug–receptor complex at the muscarinic receptor and in the enzyme–substrate interaction of AChE, although not without some exceptions.[5] Evidence in the dioxolane series also supports a maximum $N^+ \rightarrow O$ distance at the muscarinic site.[6a-d]

* To whom correspondence should be addressed.

(1) (a) A preliminary account of this work was presented to the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstract M-2. (b) This work was supported in part by the National Institute of Mental Health, U. S. Public Health Service, under Grant MH-13,514. (c) Mead Johnson Undergraduate Research Award participant, 1966–1967.

(2) For reviews see, (a) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, Wiley, New York, N. Y., 1964. (b) H. L. Friedman, in "Drugs Affecting the Peripheral Nervous System," A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, pp 79–132.

(3) (a) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 537 (1966). (b) F. G. Canepa and E. F. Moody, *Nature (London)*, **207**, 78 (1965). (c) M. Martin-Smith, G. Smail, J. Stenlake, *J. Pharm. Pharmacol.*, **19**, 649 (1967). (d) F. G. Canepa, P. Pauling, and H. Sörum, *Nature (London)*, **210**, 907 (1966). (e) C. Chothia and P. Pauling, *ibid.*, **219**, 1156 (1968). (f) C. Chothia and P. Pauling, *Chem. Commun.*, 626 (1969). (g) C. Chothia and P. Pauling, *ibid.*, 746 (1969). (h) C. Chothia and P. Pauling, *Proc. Nat. Acad. Sci. U. S.*, **65**, 477 (1970). (i) E. Shefter and O. Kennard, *Science*, **153**, 1389 (1966). (j) L. B. Kier, *Mol. Pharmacol.*, **3**, 487 (1967). (k) L. B. Kier, in "Fundamental Concepts in Drug–Receptor Interaction," J. F. Danielli, J. F. Moran, and D. J. Triggle, Ed., Academic Press, New York, N. Y., 1970, pp 15–28.

(4) (a) C. Y. Chiou, J. P. Long, J. G. Cannon, and P. O. Armstrong, *J. Pharmacol. Exp. Ther.*, **166**, 243 (1969). (b) P. D. Armstrong, J. G. Cannon, and J. P. Long, *Nature (London)*, **220**, 65 (1968). (c) S. Archer, A. M. Lands, and T. R. Lewis, *J. Med. Pharm. Chem.*, **5**, 423 (1962). (d) E. E. Smissman, W. L. Nelson, and J. B. LaPidus, *J. Med. Chem.*, **9**, 458 (1966). (e) E. E. Smissman and G. L. Chappell, *ibid.*, **12**, 432 (1969). (f) H. D. Baldridge, Jr., W. J. McCarville, and S. L. Friess, *J. Amer. Chem. Soc.*, **77**, 739 (1955). (g) J. B. Kay, J. B. Robinson, B. Cox, and D. Polkonjak, *J. Pharm. Pharmacol.*, **22**, 214 (1970). (h) S. L. Friess and H. D. Baldridge, Jr., *J. Amer. Chem. Soc.*, **78**, 2482 (1956). (i) W. L. Nelson and R. S. Wilson, *J. Pharm. Sci.*, **59**, 98 (1970).

(5) M. Martin-Smith, G. A. Smail, and J. B. Stenlake, *J. Pharm. Pharmacol.*, **19**, 565 (1967).

(6) (a) H. F. Ridley, S. S. Chattergee, J. F. Moran, and D. J. Triggle, *J. Med. Chem.*, **12**, 931 (1969). (b) D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle, *ibid.*, **12**, 130 (1969). (c) M. May and D. J. Triggle, *J. Pharm. Sci.*, **57**, 511 (1968). (d) M. May, H. F. Ridley, and D. F. Triggle, *J. Med. Chem.*, **12**, 320 (1969).