Chemical Aspects of Propranolol Metabolism: 1,1-Diethoxy-3-(1-naphthoxy)-2-propanol and Related Ring-Closure Products *cis*- and *trans*-4-Ethoxy-3-hydroxy-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran

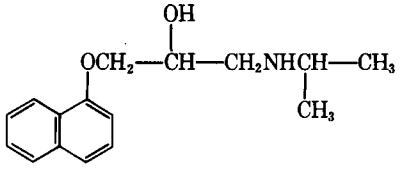
CHING-HSIU CHEN and WENDEL L. NELSON ˣ

Received March 22, 1982, from the *Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, WA 98195.* Accepted for publication July 1, 1982.

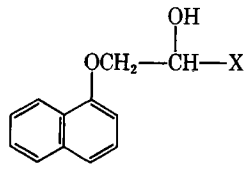
Abstract □ 1,1-Diethoxy-3-(1-naphthoxy)-2-propanol (V), the diethyl acetal of an important aldehyde intermediate in the metabolic *N*-dealkylation of propranolol, was prepared from compound X, the product of the reaction of the lithium salt of methyl methylsulfinylmethyl sulfide with 2-(1-naphthoxy)-acetaldehyde. Compound X, as a mixture of three diastereomeric α-hydroxydithioacetal derivatives, when treated with ethyl orthoformate afforded the desired acetal V as well as two ring-closure products, the dihydronaphtho[1,2-*b*]pyrans VI and VII. Compounds VI and VII were characterized on the basis of mass spectral and ^{1}H- and ^{13}C-NMR data. The stereochemistry of these compounds was assigned on the basis of the 300-MHz ^{1}H-NMR spectra of their acetate esters (XI and XII).

Keyphrases □ Propranolol—metabolite synthesis, 1,1-diethoxy-3-(1-naphthoxy)-2-propanol □ Metabolism—of propranolol, synthesis of the diethyl acetal of an aldehyde intermediate, 1,1-diethoxy-3-(1-naphthoxy)-2-propanol □ 1,1-Diethoxy-3-(1-naphthoxy)-2-propanol—synthesis, diethyl acetal of an aldehyde intermediate in propranolol metabolism

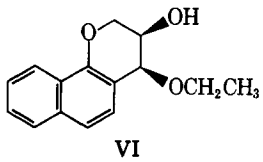
Propranolol (I) is a β-adrenergic receptor antagonist used extensively in the treatment of various cardiovascular disorders, including hypertension and angina pectoris (1–3). In humans, a major metabolic process is oxidative *N*-dealkylation, which consists of at least two multistep pathways that result in the ultimate formation of both 3-(1-naphthoxy)-2-hydroxypropionic acid (II) and 3-(1-naphthoxy)propane-1,2-diol (III) (4–6). These metabolites are thought to arise from the oxidation and reduction of a common intermediate, 3-(1-naphthoxy)-2-hydroxypropionaldehyde (IV) (7). This aldehyde (IV) probably arises to a small extent directly from propranolol, but to a much greater extent by way of desisopropylpropranolol (7–10). Preparation of an easily characterized derivative of IV to be used in the further study of these *N*-dealkylation pathways was sought. In this paper, the synthesis of the diethyl acetal of IV (V) and the characterization of two dihydronaphtho[1,2-*b*]pyrans (VI and VII), ring-cyclized products formed during the synthesis of V, are reported.



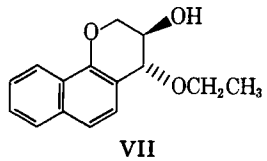
I



II: X = COOH
III: X = CH_2OH
IV: X = CHO
V: X = $CH(OEt)_2$



VI

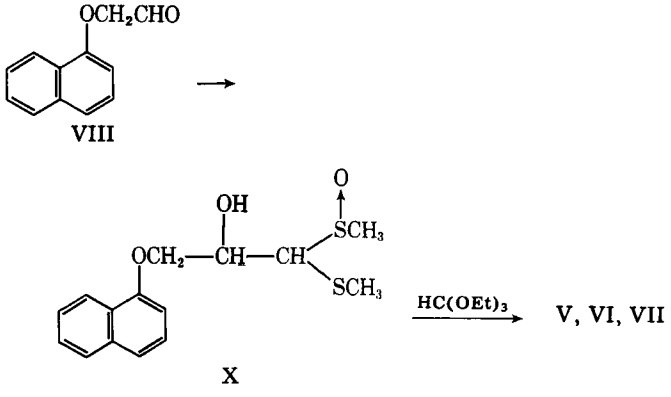


VII

RESULTS AND DISCUSSION

The initial attempt to prepare V was based on partial reduction of the cyanohydrin of 2-(1-naphthoxy)acetaldehyde (VIII), suitably protected as a dihydropyranyl ether. Sodium bis(2-methoxyethoxy)aluminum hydride has been reported to be successful in the partial reduction of some cyanohydrin acetals to form α-hydroxyaldehydes (11). However, over-reduction occurred and 1-naphthol, a product of ring cleavage, was formed, thus requiring an alternate approach.

The successful synthesis of the desired acetal V was accomplished by allowing VIII to react with an anionic formaldehyde equivalent, the lithium salt of methyl methylsulfinylmethyl sulfide (IX) (12). Three diastereomers of X were formed, which were separated. Each of these diastereomers (X*a*, X*b*, and X*c*), when treated with ethyl orthoformate, gave the desired acetal V, as well as cyclized products VI and VII. The most successful and direct method for preparation of V, however, was to subject the mixture of the diastereomers of X, without prior separation, to these conditions. Conversion of the mixture of diastereomers of X to the acetal V (ethyl orthformate and acid catalysis) was attempted to prevent possible isomerization of the α-hydroxyaldehyde, expected from direct hydrolysis of X, to an α-hydroxyketone, as reported in related systems by Ogura and Tsuchihashi (12).



VIII

X

Crystallization and chromatographic separation of the products of the conversion of X to V afforded a 58% yield of the desired acetal V and two other components, which were characterized as VI and VII, obtained in 9 and 30% yields, respectively. Attempts to use milder conditions or shorter times for the conversion of X to V failed to reduce the relative amounts of VI and VII formed, suggesting that the activation energies for their formation are similar to that for formation of the desired acetal V.

The structures of compounds VI and VII were assigned on the basis of CI–MS data, ^{1}H- and ^{13}C-NMR data, and elemental analysis. Methane CI–MS of VI and VII each demonstrated the loss of the elements of ethanol. QM = *m/z* 245 rather than *m/z* 291; their 60-MHz ^{1}H-NMR spectra also showed the loss of one ethoxy substituent. In the aromatic region of the ^{1}H-NMR spectra, the signal of H_8 (the most downfield proton in V and other 1-alkoxynaphthalenes) was retained and the signal of H_2 (the most upfield aromatic proton in V and other 1-alkoxynaphthalenes) was lost, indicating cyclization at C_2 of the naphthalene ring. Comparison of the ^{13}C-NMR spectrum of VII with the spectrum of V

0022-3549/83/0800-0863$01.00/0

(Table I), confirmed the structural assignment. Assignment of the signals of all the carbons in the naphthalene ring was accomplished by comparison with published spectra of 1-methoxynaphthalene and 2-methylnaphthalene (13). The most distinguishing feature was the difference in the chemical shift of C_2 in the aromatic ring of V and the corresponding carbon atom C_{4a} of VII. This signal was shifted upfield in the dihydronaphtho[1,2-*b*]pyran VII. A similar upfield shift was noted for the signal of the acetal carbon $C_{1'}$ when it was converted to the benzylic carbon C_4 in VII.

The assignment of the relative stereochemistry of VI and VII was not apparent from their ^{1}H-NMR spectra because of similarities in the chemical shifts of the dihydropyran ring protons. The 300-MHz ^{1}H-NMR spectra of their acetate esters (XI and XII, respectively) provided sufficient signal separation to allow assignment of the stereochemistry of the esters and thus of VI and VII. The 300-MHz ^{1}H-NMR data of the dihydropyran ring protons of XI and XII are given in Table II. Comparison with ^{1}H-NMR data of the related structures *cis*- and *trans*-3,4-diacetoxy-3,4-dihydro-2*H*-pyran (15) and some related 3,4-substituted flavans (16–19) aided in assignment of the relative stereochemistry.

Several spectral similarities were noted when these data were compared with data from the model dihydropyrans. In the spectra of XI and XII, $J_{3,4}$ = 3.7 and 2.6 Hz, respectively, compared with $J_{3,4}$ = 4.12 and 2.87 Hz for *cis- and trans*-3,4-diacetoxy-dihydro-2*H*-pyran, respectively (15). In XI, assigned the *cis* stereochemistry, $J_{3,2}$ = 7.2 Hz. In both XI and XII, other $J_{2,3}$ and $J_{2',3}$ coupling constants are small (2.9 Hz in XI, 2.6 and 1.5 Hz *in XII*), *consistent* with data from the model dihydropyrans (15). Also, a larger long-range coupling ($J_{2,4}$ = 1.6 Hz) is observed in the spectrum of XII and in the reported data for the *trans* model dihydropyran, likely due to the contribution of a zigzag or W conformation (20).

Both XI and XII seem likely to exist in solution as a mixture of half-chair and/or twist boat conformations. In a series of structurally related conformationally flexible flavans with similar substituents in the 3- and 4-positions (16–19), the values of $J_{3,4}$ are of similar size. In these model flavans, $J_{3,4}$ of 3.2–4.5 Hz are observed in the spectra of *cis*-3,4-disubstituted compounds, and $J_{3,4}$ is ~2.3 Hz in the spectra of *trans*-3,4-disubstituted compounds. These comparisons, and those in the flexible dihydropyrans, strongly indicate the relative stereochemistry of the 3- and 4-substituents is *cis* in XI and *trans* in XII. Thus, VI and VII are assigned the *cis* and *trans* relative stereochemistry, respectively.

The synthesis and characterization of the acetal V and related naphtho[1,2-*b*]pyrans VI and VII will facilitate additional experiments on the metabolic *N*-dealkylation of propranolol. Compound V has been used successfully in experiments to trap intermediate aldehyde IV as an *O*-methyloxime (21).

EXPERIMENTAL[1]

2-(1-Naphthoxy)acetaldehyde (VIII)—This aldehyde was prepared from 1-naphthol and α-bromoacetaldehyde diethyl acetal as previously reported (22).

1-Methylthio-1-methylsulfinyl-3-(1-naphthoxy)-2-propanol (X)—To a solution of 1.24 g (1.1 ml, 10 mmoles) of methyl methylsulfinylmethyl sulfide (IX) in 20 ml of tetrahydrofuran at 0° was added slowly 6.6 ml (10.3 mmoles) of 1.55 *M* methyllithium solution, followed by 1.86 g (10 mmoles) of 2-(1-naphthoxy)acetaldehyde (VIII) in 5 ml of tetrahydrofuran. The mixture was stirred at 0° for 1 hr, water was added, and the mixture was extracted with ether. The ether extract was dried (magnesium sulfate) and evaporated to dryness. The residue, containing three diastereomers (X*a*, X*b*, and X*c*), was fractionally crystallized from a mixture of ethyl acetate–methanol (19:1) affording 200 mg (6.5%) of X*a* (R_f 0.30 ethyl acetate–methanol, 19:1) and 359 mg (11%) of X*c* (R_f 0.21). X*a*, mp 172–173.5°; ^{1}H-NMR (DMSO-d_6): δ 2.20 (s, 3, SCH_3), 2.80 (s, 3, $SOCH_3$), 3.35 (s, 1, OH), 3.97–4.16 (m, 1, C*H*OH), 4.16–4.50 (m, 2, OCH_2), 4.57–4.96 (m, 1, C*H*SCH_3), and 6.85–8.50 (m, 7, naphthalene protons); CI–MS: *m/z* 311 (QM), 293, 246, and 229. X*c*, mp 147–152°; ^{1}H-NMR (methanol-d_4): δ 2.25 (s, 3, SCH_3), 2.84 (s, 3, $SOCH_3$), 4.02–4.30 (m, 1, C*H*OH), 4.30–4.50 (m, 1, C*H*SCH_3), 4.60 (d, 2, OCH_2), and 6.90–8.65 (m, 7, naphthalene protons); CI–MS: *m/z* 311 (QM), 293, 246, and 229.

The combined mother liquors were evaporated and the residue purified by column chromatography on 100 g of silica gel eluting with 500 ml of ethyl acetate–methanol (19:1) to give 1.18 g (38%) of a mixture of X*a*, X*b*, and X*c* and 127 mg (4%) of X*b* as a liquid (R_f 0.25); ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3, SCH_3), 2.68 (s, 3, $SOCH_3$), 3.38 (s, 1, OH), 4.17–4.57 (broad s, 4, $CH_2CHOHCHSCH_3$), and 6.67–8.54 (m, 7, naphthalene protons); CI–MS: *m/z* 311 (QM), 293, 246, and 229.

Anal.—Calc. for $C_{15}H_{18}O_3S_2$ (X*c*): C, 58.04; H, 5.85. Found: C, 58.35; H, 5.96.

1,1-Diethoxy-3-(1-naphthoxy)-2-propanol (V)—To a solution of the mixture of diastereomers of X (10.18 g, 32.8 mmoles) in 30 ml of ethanol was added 6.3 ml (38.1 mmoles) of ethyl orthoformate and 0.60 g of concentrated sulfuric acid. The mixture was heated at 60° for 24 hr. The reaction mixture was neutralized with 1.0 ml of concentrated aqueous ammonia and evaporated to dryness. The mixture was partitioned between water and ether, and the ether extract was evaporated to dryness. The residue was purified by column chromatography on 200 g of silica gel. Elution with 1 liter of chloroform–ethanol (99:1) gave 0.750 g (9.3%) of VI (R_f 0.39 in chloroform–ethanol, 99:1), 5.50 g (58%) of V (R_f 0.29), and 2.43 g (30%) of VII (R_f 0.18).

An analytical sample of the acetal V was obtained by rechromatographing crude V on 150 g of silica gel. Elution with 500 ml of benzene–ethyl acetate (4:1) afforded V as an oil; ^{1}H-NMR ($CDCl_3$): δ 0.85–1.40 [2t, 6, $CH(OCH_2CH_3)_2$], 2.80–3.18 (broad s, 1, OH), 3.28–3.90 [m, 4, $CH(OCH_2CH_3)_2$], 3.90–4.30 (m, 3, OCH_2CHOH), 4.74 [d, J = 5 Hz, 1, $CH(OCH_2CH_3)_2$], 6.75 (dd, J = 6 and 3 Hz, 1, naphthalene H_2), 7.15–7.55 (m, 4, naphthalene H_3, H_4, H_6, H_7), 7.70 (m, 1, naphthalene H_5), and 8.30 (distorted dd, J = 5 and 3 Hz, 1, naphthalene H_8); ^{13}C-NMR ($CDCl_3$): see Table I; CI–MS: *m/z* 291 (QM), 245, 227, and 199.

Anal.—Calc. for $C_{17}H_{18}O_4$: C, 70.32; H, 7.64. Found: C, 70.21; H, 7.67.

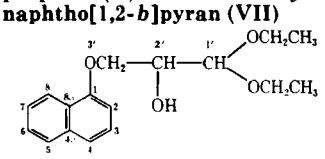
Compound V, in the presence of semicarbazide hydrochloride at pH 4–5 (ethanol, 60°, 2.5 hr), afforded the semicarbazone of IV as a white solid, mp 205–207°; CI–MS: *m/z* 274 (QM).

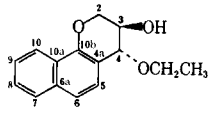
Anal.—Calc. for $C_{14}H_{15}N_3O_3$: C, 61.35; H, 5.33; N, 15.38. Found: C, 61.49; H, 5.72; N, 15.31.

***cis*-4-Ethoxy-3-hydroxy - 2*H*-3,4-dihydronaphtho[1,2-*b*]pyran (VI)**—Compound VI further purified twice by column chromatography on 15 g of silica gel eluting with 70 ml of chloroform–ethanol (199:1) was obtained as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3, OCH_2CH_3), 2.60–2.90 (broad d, J = 7 Hz, 1, OH), 3.68 (q, J = 7 Hz, 2, OCH_2CH_3), 4.10–4.30 (m, 3, OCH_2CHOH), 4.42 (m, 1, $CHOC_2H_5$), 7.06–7.92 (m, 5, naphthalene H_3, H_4, H_5, H_6, H_7), and 8.20 (distorted dd, J = 5.5 and 2.5 Hz, 1, naphthalene H_8); CI–MS: *m/z* 245 (QM).

Anal.—Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.50; H, 6.60.

Table I—^{13}C-NMR Data for 1,1-Diethoxy-3-(1-naphthoxy)-2-propanol (V) and *trans*-4-Hydroxy-3-ethoxy-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (VII)



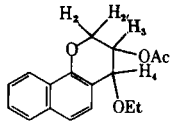


Compound V		Compound VII	
Carbon	Chemical shift, ppm	Carbon	Chemical shift, ppm
C_1	154.44	C_{10b}	149.46
C_2	105.03	C_{4a}	113.42
C_3	125.82	C_5	126.80
C_4	120.60	C_6	120.55
C_{4a}	134.51	C_{6a}	134.47
C_5	127.50	C_7	128.32
C_6	126.41	C_8	127.44
C_7	125.20	C_9	124.90
C_8	121.92	C_{10}	122.17
C_{8a}	125.68	C_{10a}	125.49
$C_{3'}$	71.14[a]	C_2	66.70, 65.63
$C_{2'}$	68.50[a]	C_3	
$C_{1'}$	102.53	C_4	74.66
OCH_2CH_3	64.16, 63.57	OCH_2CH_3	64.64
OCH_2CH_3	15.36, 15.20	OCH_2CH_3	15.62

[a] Tentative assignment consistent with the reported ^{13}C-NMR chemical shift assignments of carbons in the propanolamine side chain of propranolol (14).

[1] Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 727B spectrophotometer. Routine ^{1}H-NMR spectra were recorded on a Varian EM-360A spectrometer, using TMS as internal standard. Notations used in the ^{1}H-NMR descriptions are as follows: (s) singlet; (d) doublet; (t) triplet; (q) quartet; (m) multiplet. High-field ^{1}H-NMR spectra were recorded on the Brucker 300-MHz spectrometer, using TMS as internal standard. ^{13}C-NMR spectra were recorded on the Varian CFT-20 spectrometer, using TMS as internal standard. Mass spectra were recorded on a Biospect mass spectrometer, operated in the CI mode with methane (0.5 torr) as the reagent gas. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Table II—300-MHz ^{1}H-NMR Data for the Dihydropyran Ring Protons of XI and XII



Proton	Chemical Shift (δ)	Apparent Coupling Constants
		Compound XI (*cis*)
H_4	4.74	$J_{3,4}$ = 3.7 Hz, line broadening[a]
H_3	5.47	$J_{3,2}$ = 7.4 Hz, $J_{3,4}$ = 3.7 Hz, $J_{3,2'}$ = 2.9 Hz
H_2	4.55	J_{gem} = 11.1 Hz, $J_{2,3}$ = 7.4 Hz
$H_{2'}$	4.36	J_{gem} = 11.1 Hz, $J_{2',3}$ = 2.9 Hz, $J_{2',4}$ = 1.0 Hz
		Compound XII (*trans*)
H_4	4.32	$J_{3,4}$ = 2.6 Hz, $J_{2,4}$ = 1.6 Hz
H_3	5.25	$J_{3,4}$ = 2.6 Hz, $J_{3,2}$ = 2.6 Hz, $J_{3,2'}$ = 1.5 Hz
H_2	4.56	J_{gem} = 12.1 Hz, $J_{2,3}$ = 2.6 Hz, $J_{2,4}$ = 1.6 Hz
$H_{2'}$	4.43	J_{gem} = 12.1 Hz, $J_{2',3}$ = 1.5 Hz

[a] Coupling constant $J_{2',4}$ was assigned on the basis of decoupling experiments and from the signal for $H_{2'}$.

***cis*-3-Acetoxy-4-ethoxy - 2*H*-3,4-dihydronaphtho[1,2-*b*]pyran (XI)**—To a solution of VI (120 mg, 0.49 mmole) in 5 ml of ether at room temperature was added triethylamine (717 mg, 7.1 mmoles), followed by the addition of acetyl chloride (569 mg, 7.1 mmoles). The reaction mixture was stirred for 2 hr, filtered, and evaporated to dryness. The residue was purified by column chromatography on 10 g of silica gel. Elution with 60 ml of chloroform gave 65 mg (46%) of XI as a colorless oil. An analytical sample was obtained by rechromatographing on 10 g of silica gel, eluting with 40 ml of chloroform; ^{1}H-NMR ($CDCl_3$): δ 1.27 (t, J = 7 Hz, 3, OCH_2CH_3), 2.10 (s, 3, $COCH_3$), 3.72 and 3.75 (overlapping q, J = 7 Hz, 2, OCH_2CH_3), 4.30–4.60 (m, 2, OCH_2), 4.70 (d, J = 3.5 Hz, 1, $CHOC_2H_5$), 5.25–5.65 (dt, J = 7, 3.5, and 3.5 Hz, 1, $CHOCOCH_3$), 7.00–7.97 (m, 5, naphthalene H_3, H_4, H_5, H_6, H_7), and 8.20 (dd, J = 6.5 and 3 Hz, 1, naphthalene H_8); partial 300-MHz ^{1}H-NMR spectrum: see Table II; CI-MS: m/z 287 (QM).

Anal.—Calc. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.15; H, 6.57.

***trans*-4-Ethoxy-3-hydroxy - 2*H*-3,4-dihydronaphtho[1,2-*b*]pyran (VII)**—Compound VII further purified by column chromatography on 60 g of silica gel, eluting with 300 ml of benzene–ethyl acetate (4:1) was obtained as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 1.10 (t, J = 7 Hz, 3, OCH_2CH_3), 2.53–3.00 (broad d, 1, OH), 3.50 (q, J = 7 Hz, 2, OCH_2CH_3), 3.65–3.96 (m, 1, $CHOH$), 4.06 (d, J = 2 Hz, 1, $CHOC_2H_5$), 4.16 (d, J = 2 Hz, 2, OCH_2), 7.03–7.94 (m, 5, naphthalene H_3, H_4, H_5, H_6, H_7), and 8.17 (distorted dd, J = 5 and 2.5 Hz, 1, naphthalene H_8); ^{13}C-NMR ($CDCl_3$): see Table I; CI-MS: m/z 245 (QM).

Anal.—Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.60; H, 6.89.

***trans*-3-Acetoxy-4-ethoxy - 2*H*-3,4-dihydronaphtho[1,2-*b*]pyran (XII)**—To a solution of VII (280 mg, 1.15 mmoles) in 10 ml of $CHCl_3$ at 0° was added triethylamine (1.74 g, 17.2 mmoles), followed by the addition of acetyl chloride (1.35 g, 17.2 mmoles). The reaction mixture was stirred at room temperature for 4 hr and quenched with ice. The chloroform layer was separated, dried (magnesium sulfate), and evaporated to dryness. The residue was purified by column chromatography on 15 g of silica gel. Elution with 80 ml of chloroform gave 70 mg (21%) of XII as a colorless oil. An analytical sample was obtained by rechromatographing on 10 g of silica gel eluting with 40 ml of chloroform; ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, J = 7 Hz, 3, OCH_2CH_3), 1.95 (s, 3, $COCH_3$), 3.77 (q, J = 7 Hz, 2, OCH_2CH_3), 4.20–4.40 (m, 1, $CHOC_2H_5$), 4.40–4.55 (m, 2, OCH_2), 5.26 (q, J = 2 Hz, 1, $CHOCHOCH$), 6.95–8.05 (m, 5, naphthalene H_3, H_4, H_5, H_6, H_7), and 8.25 (dd, J = 6 and 2.5 Hz, 1, naphthalene H_8 proton); partial 300-MHz ^{1}H-NMR spectrum: see Table II; CI-MS: m/z 287 (QM).

Anal.—Calc. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.40; H, 6.52.

REFERENCES

(1) T. F. Blaschke and K. L. Melmon in "The Pharmacological Basis of Therapeutics," 6th ed., A. G. Gilman, L. S. Goodman, and A. Gilman, Eds. MacMillan, New York, N.Y., 1980, p. 739–819.

(2) R. E. Buckingham and T. C. Hamilton, *Gen. Pharmacol.*, **10**, 1 (1979).

(3) F. O. Simpson, *Drugs*, **20**, 69 (1980).

(4) P. A. Bond, *Nature (London)*, **1967**, 721.

(5) J. W. Paterson, M. E. Connolly, C. T. Dollery, A. Hayes, and R. G. Cooper, *Pharmacol. Clin.*, **2**, 127 (1970).

(6) J. F. Pritchard, D. W. Schneck, and A. H. Hayes, Jr., *J. Chromatogr. Biomed. Appl.*, **162**, 47 (1979).

(7) W. L. Nelson and T. R. Burke, Jr., *Res. Commun. Chem. Pathol. Pharmacol.*, **21**, 77 (1978).

(8) T. Walle, T. Ishizaki, and T. E. Gaffney, *J. Pharmacol. Exp. Ther.*, **183**, 508 (1972).

(9) J. L. Tindell, T. Walle, and T. E. Gaffney, *Life Sci.*, Part II, **11**, 1029 (1972).

(10) O. M. Bakke, D. S. Davies, L. Davies, and C. T. Dollery, *Life Sci.*, **13**, 1665 (1973).

(11) M. Schlosses and A. Birch, *Helv. Chem. Acta*, **61**, 1903 (1978).

(12) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 2681.

(13) J. Secta, J. Sandstrom, and T. Drackenberg, *Org. Mag. Reson.*, **11**, 239 (1978).

(14) S. J. Pasaribu and G. C. Brophy, *Aust. J. Chem.*, **31**, 2629 (1978).

(15) J. Runsink, in "Handbook of NMR Spectral Parameters," W. Brügel, Ed., Heyden and Son, London, 1979, Table 68.1.4., p. 541.

(16) B. J. Bolger, A. Hirwe, K. G. Marathe, E. M. Philbin, M. A. Vickers, and C. P. Lillya, *Tetrahedron*, **22**, 621 (1966).

(17) J. W. Clark-Lewis, *Aust. J. Chem.*, **22**, 425 (1968).

(18) B. J. Bolger, K. G. Marathe, E. M. Philbin, T. S. Wheeler, and C. P. Lillya, *Tetrahedron*, **23**, 341 (1967).

(19) W. Brügel, "Handbook of NMR Spectral Parameters," Heyden and Son, London, 1979, Table 24.3.1(b–c), p. 168.

(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon, Oxford, 1969, pp. 334–341.

(21) C.-H. Chen and W. L. Nelson, *Drug Metab. Disp.*, **10**, 277 (1982).

(22) W. L. Nelson and M. J. Bartels, *J. Org. Chem.*, **47**, 1574 (1982).

ACKNOWLEDGMENTS

This work was supported in part by U.S. Public Health Service Grant NIGMS 25373.

The authors thank Mr. James Christie for the ^{13}C-NMR spectra (University of Washington) and Dr. Duane Miller and Mr. John Fowble, (Ohio State University) for the 300-MHz ^{1}H-NMR spectra.