N-Ethoxy-4-ethylamino-3-methyl-2-phenyl-2-propionoxy-1-α-pyridylbutane. An Analog of the Analgesic Propoxyphene

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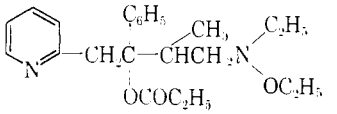
Propoxyphene hydrochloride, α-*d*-4-Dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane hydrochloride, is an analgesic that is orally effective and relatively nonaddicting.[1]

It has been found that the hydroxylamine derivative, 1-methoxy-3-methyl-4-phenyl-4-propionyloxypiperidine, is an active analgesic as is the related amine, α-prodine or 1,3-dimethyl-4-phenyl-4-propionoxypiperidine.[2]

It seemed quite possible that a hydroxylamine analog of propoxyphene might prove to be an analgesic also. However, since hydroxylamine derivatives are generally weaker bases than the corresponding amines,[3] it was decided that the new molecule should contain another basic group in addition to the substituted hydroxylamine group. For the present study, N-ethoxy-4-ethylamino-3-methyl-2-phenyl-2-propionoxy-1-(2-pyridyl)butane (I) has been synthesized.



I

As an intermediate in the preparation of this compound, N-ethoxy-β-ethylaminoisobutyrophenone (II), $C_6H_5COCH(CH_3)CH_2N(C_2H_5)OC_2H_5$, was made by a Mannich-type reaction between propiophenone, paraformaldehyde, and N-ethoxyethylammonium chloride. Two diastereoisomeric alcohols were obtained by the interaction of II with α-picolyllithium. These alcohols were separated and purified by chromatography followed by fractional crystallization of the picrates. Further purification of one of the new diastereoisomeric alcohols, α-N-ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (α-III), was achieved by fractional vacuum distillation of the base or by column chromatography. Since the diastereoisomeric alcohols III were tertiary and relatively unstable, a modification of the mild method of esterification described by Spassow was adopted for the preparation of propionates.[4] The β-isomer of the alcohol III, prepared from the β-picrate was treated with propionyl chloride in the presence of magnesium dust in dry ether. The hydrochloride of this basic ester which formed was converted into its base with sodium carbonate and then extracted with ether and dried. The propionate β-I was purified by means of column chromatography over Florisil followed by vacuum distillation.

In view of the difficulty of preparing the individual diastereoisomeric alcohols, α- or β-N-ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (α-III or β-III), and their propionates for biological testing, a larger quantity of a mixture of the diastereoisomeric alcohols was propionated for the biological assays. The mixture of diastereoisomeric alcohols was purified by chromatography, followed by vacuum distillation. Care was taken to discard fractions for analysis and further use which showed a carbonyl band at about 5.9 μ in the infrared.

The propionate of the α,β-alcohol (α,β-I) was made essentially by the same method as described for the preparation of the β-ester, except that tetrahydrofuran was used in place of ether.

It has not yet proved possible to synthesize the corresponding compound, N-methoxy-4-methylamino-3-methyl-2-phenyl-2-propionoxy-1-α-pyridylbutane (IV) in a state of purity, although a mixture which undoubtedly contains it has been made. However, the intermediates, N-methoxy-β-methylaminoisobutyrophenone (V) and N-methoxy-1-methylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (VI), have been prepared by analogous methods to those used with the corresponding ethyl homologs described above.

Pharmacological Activity.—Dr. C. A. Stone of the Merck Institute for Therapeutic Research, West Point, Pennsylvania, has kindly informed us that he and his associates have examined the effect of α,β-N-ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol and its propionate ester on mice. A general mouse screening test showed no signs of activity at doses of either compound up to 324 mg./kg. i.p. Lethal effects were likewise not observed. Dr. C. A. Winter of the same laboratory has kindly informed us that he had tested the effect of α,β-N-ethoxy-4-ethylamino-3-methyl-2-phenyl-2-propionoxy-1-α-pyridylbutane on rats as an analgesic. Oral doses of 128 mg./kg. were essentially inactive in the tail-pinch squeak threshold method. In comparison, *d*-propoxyphene exhibited activity in doses within the range of 10-50 mg./kg. *p.o.*

Experimental

N-Alkoxy-β-ethylaminoisobutyrophenone (VII).—One-half mole of propiophenone, 0.65 mole of N-alkoxyalkylammonium chloride, and 0.22 mole of paraformaldehyde were placed in a 1-l. flask. After 1 ml. of concentrated HCl in 80 ml. of 95% ethanol had been added, the mixture was refluxed on a water bath for 2 hr. To the clear yellowish solution which was obtained was added 200 ml. of water; the mixture was then extracted twice with ether. The aqueous layer was then made alkaline with 2 *N* NaOH and extracted with ether. The extract was dried (Na_2SO_4), evaporated, and the residual oil was distilled *in vacuo*. The picrate was prepared from the redistilled oil in an ether solution. It was recrystallized to constant melting point from methanol.

N-Ethoxy-β-ethylaminoisobutyrophenone (I) was collected in 65% yield, b.p. 105–108° (0.15 mm.).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.09; H, 9.08.

The **picrate** had m.p. 128°.

Anal. Calcd. for $C_{20}H_{24}N_4O_9$: C, 51.72; H, 5.21; N, 12.06. Found: C, 51.65; H, 5.21; N, 11.98.

N-Methoxy-β-methylaminoisobutyrophenone (IV) was collected in 68% yield, b.p. 88–92° (0.16 mm.).

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.50; H, 8.00.

The **picrate** had m.p. 141–143°.

(1) "Merck Index," 7th Ed., Merck and Co., Inc., Rahway, N. J., 1960, p. 862.

(2) R. T. Major and F. Dürsch, *J. Org. Chem.*, **26**, 1867 (1961).

(3) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Am. Chem. Soc.*, **79**, 796 (1957).

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Anal. Calcd. for $C_{18}H_{20}N_4O_2$: C, 49.54; H, 4.62; N, 12.84. Found: C, 49.54; H, 4.44; N, 12.52.

N-Alkoxy-1-alkylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (VIII).—To 100 ml. of absolute ether and 2.07 g. (0.298 g.-atom) of lithium metal under a nitrogen atmosphere, 32.1 g. (0.205 mole) of bromobenzene in 70 ml. of absolute ether was added in portions. First 20 ml. of the solution was added to the lithium in the ether; after the reaction had started, the rest was added dropwise. The mixture was stirred for 3 hr., then 10.51 g. (0.113 mole) of α-picoline was added dropwise. After the addition was complete, the mixture was stirred for 30 min. Then 0.1 mole of VII in 60 ml. of absolute ether was added dropwise, the mixture was stirred for 6 hr., then refluxed for 30 min. After the mixture had cooled, 250 ml. of moist ether was added in order to decompose the lithium complex. The reaction mixture was washed with ice water and then the ether solution was dried (K_2CO_3). After the ether was evaporated, an orange-red oil containing VIII remained.

N-Methoxy-1-methylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (VI).—The residual orange-red oil described above was fractionated *in vacuo* at 0.2 mm. pressure into five fractions boiling from under 37° to 158°. Fractions boiling at temperatures over 37° showed a strong carbonyl absorption band at about 5.95 μ in the infrared. Then the undistilled oil (14.8 g.) was chromatographed on 255 g. of Woelm alumina. Elution of the chromatograph with petroleum ether (fractions 1–13) gave 1.2 g. of residue, with benzene (fractions 14–28) gave 3.5 g. of residue, with methylene chloride (fractions 29–44) gave 1.8 g. of residue, with ether (fractions 45–57) gave 1.0 g of residue, and with chloroform (fractions 58–91) gave 5.5 g. of residue. The infrared spectrum of none of these fractions showed much absorption at 5.95 μ, but did absorb at 3.05 (OH) and at 9.55 μ (methoxyamines).

A sample of the chloroform eluate was distilled in a Kugelrohr, b.p. 180° (0.2 mm.). Characteristic infrared absorption occurred at 3.05 and 9.05 μ and only very little at 5.95 μ.

Anal. Calcd., for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05. Found: C, 72.52; H, 8.36.

A sample of the benzene eluate was also distilled in a Kugelrohr, b.p. 180° (0.2 mm). The infrared absorption spectrum was very similar to that obtained from the distillate of the chloroform eluate.

Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05. Found: C, 72.51; H, 8.40.

Dipicrate.—The calculated amount of a saturated solution of picric acid in ethyl acetate was added to a soluion of VI in ethyl acetate. The precipitate which formed was recrystallized from methanol, m.p. 155°.

Anal. Calcd. for $C_{30}H_{36}N_8O_{16}$: C, 47.49; H, 3.99; N, 14.78. Found: C, 47.50; H, 4.13; N, 14.82.

N-Ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (III) Picrates.—Most of the orange oil described above, containing α,β-N-ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (34.0 g.), was chromatographed on a column (470 × 26 mm.) of alumina (alumina for adsorption, Fisher Scientific Co., Catalog No. A-540). The following fractions were collected using 100 ml./fraction of the solvent indicated: 1–10, petroleum ether, 22.5 g.; 11–18, benzene, 7.4 g.; 19–20, ether, 2 g.

Inspection of the infrared spectra of the individual fractions showed that fraction 1 contained some starting ketone whereas all the others consisted only of alcoholic material. Fractions 2–6 were combined (18.8 g.) and 1.5 g. of the oily material was converted in ether solution to 2 g. of a crystalline picrate mixture, m.p. 103–133° (sintering at 80°). One recrystallization from ethanol gave 0.8 g. of picrate of m.p. 142–147°. A second recrystallization raised the m.p. to 147–148.5° which was not altered by further recrystallizations.

Anal. Calcd. for $C_{32}H_{34}N_8O_{16}$: C, 48.80; H, 4.36. Found: C, 48.87; H, 4.62.

Fractions 12–14 (5.9 g.) were combined also. A sample (1 g.) of this material afforded 1.1 g. of a crude picrate, m.p. 136–144° (ethanol); a single recrystallization raised the m.p. to 146–147°, which was unchanged on subsequent crystallizations. The mixture melting point of these two picrates gave no depression. The different melting point ranges of the crude picrates suggested, however, that the benzene fraction contained more of the tertiary alcohol whose picrate was isolated.

For further separation of the alcohol mixture, 15 g. of the combined petroleum ether–benzene fractions were chromatographed on a column of alumina (28 × 500 mm.). The following fractions were collected using 250 ml. of solvent each for elution of fractions 1–3; 630 ml. for fraction 4; 750 ml. for fraction 5; 1000 ml. each for fractions 6 and 7; and 800 ml. for fraction 8. The solvents used and yields obtained were: petroleum ether–benzene (7:3), fractions 1–4, 8.3 g.; petroleum ether–benzene (3:2), fractions 5–6, 1.9 g.; benzene, fraction 7, 2.2 g.; ether, fraction 8, none. Fractions 2–6 (4.5 g.) were pooled and converted to 8.7 g. of a picrate having m.p. 134.5–138°. Recrystallization from ethanol raised the m.p. to 136–138.5°; this was not changed on subsequent recrystallizations.

Anal. Calcd. for $C_{32}H_{34}N_8O_{16}$: C, 48.80; H, 4.36. Found: C, 48.97; H, 4.39.

The benzene fraction (12 g., from combined runs) was chromatographed also (column 405 × 28 mm.) and the following fractions were collected: fractions 1–3, using 250 ml. of solvent each for elution; fractions 4–6, 500 ml. each; fraction 7, 1000 ml.; and fraction 8, 750 ml. The solvents used and yields obtained were: petroleum ether–benzene (1:1), fractions 1–5, 8.1 g.; benzene, fractions 6–7, 1.8 g.; and ether, fraction 8, 1.5 g. Fractions 6–8 (3.3 g. combined) yielded 4 g. of a picrate, m.p. 135° (sintering at 118°). Recrystallization from ethanol furnished 2.8 g. of a picrate, m.p. 145–148°; another recrystallization yielded 2.4 g. of material, m.p. 146–149°.

β-N-Ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (β-III).—To 1 g. of the picrate of β-III, m.p. 136–138.5°, was added 20 ml. of 50% alcoholic KOH and 15 ml. of ethyl alcohol. After this mixture had stood for 0.5 hr. it was diluted with water to 100 ml. This was extracted three times with ether. The ether solution was washed with water seven times until the water extract was colorless. Then the ether solution was dried (K_2CO_3). Evaporation of the ether left a yellow oil; this was distilled *in vacuo*, b.p. 192° (0.2 mm.), yield 415 mg. (14%). The infrared absorption spectrum showed no carbonyl band, but characteristic bands at 3.2, 3.55, 6.32, 7.02, 9.59, and 14.2 μ.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.98; H, 8.53; N, 8.50.

α,β-Ethoxy-1-ethylamino-2-methyl-4-α-pyridyl-3-phenylbutan-3-ol (α,β-III).—A mixture of the petroleum ether–benzene (9:1) and benzene extracts of the chromatograms of the orange oil containing α,β-III (except fraction 1 which showed a carbonyl band in the infrared) was distilled, *in vacuo*, in a Kugelrohr; b.p. 200° (0.2 mm.). This oil (5.75 g.) was then dissolved in carbon tetrachloride and poured on a chromatographic column of 171 g. of Woelm aluminum oxide. The eluates were collected in portions of 25 ml. each.

The fractions eluted by the solvent indicated gave the following yields: fractions 1–19, carbon tetrachloride, 311 mg.; 20–25, benzene, 232 mg.; 26–44, methylene chloride, 764 mg.; 45–54, ether, 742 mg.; 55–80, chloroform, 3291 mg.; and 81–88, chloroform–methanol (6:1), 137 mg. Fraction 62 was analyzed without further purification.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 73.13; H, 8.59; N, 8.53. Found: C, 73.07; H, 8.45; N, 8.51.

Fraction 67 showed no carbonyl band in the infrared, but absorption characteristic of an ethoxyamino alcohol was found. This fraction was also analyzed.

Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 72.90; H, 8.42; N, 8.76.

Fractions 61–72 were combined and esterified as described below.

α,β-N-Ethoxy-4-ethylamino-3-methyl-2-phenyl-2-propionoxy-1-α-pyridylbutane (α,β-I).—To 2.5 g. of fractions 61–72 of α,β-III in 1 ml. of dry tetrahydrofuran were added 208 mg. of magnesium and 2.73 g. of propionyl chloride in 1 ml. of dry tetrahydrofuran. After this mixture had stood at room temperature for 1 hr., it was refluxed for 2 hr. Then, after standing at room temperature overnight, it was hydrolyzed with ice, made alkaline with sodium carbonate, and extracted five times with ether. After this ether solution had been dried and the ether had been evaporated, 4.09 g of a brown oil remained. This was fractionated *in vacuo* in a Kugelrohr. A small amount of by-product, b.p. 62° (1 mm.), distilled early in the fractionation, and then the main fraction of 1.91 g. (65.2%) distilled at 195° (0.3 mm.). The infrared spectrum of the ester showed characteristic strong absorptions at 3.4, 5.65, 6.2, 6.72, 6.85, 7.12, 8.32, 9.37, and 13.98 μ.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 72.01; H, 8.25; N, 7.49.

β-N-Ethoxy-4-ethylamino-3-methyl-2-phenyl-2-propionoxy-1-α-pyridylbutane (β-I).—To a solution of 328 mg. of β-III in 1

ml. of dry ether was added 24 mg. of magnesium powder. Then 162 mg. of propionyl chloride in 1 ml. of dry ether was added. The mixture was heated on the water bath for a few seconds and then set aside at room temperature for 1 hr. It was then diluted with 20 ml. of dry ether, refluxed for 30 min., set aside again at room temperature for 1 hr., and then treated with ice-cooled sodium carbonate solution to alkalinity. This mixture was extracted with ether; the ether solution was dried and then the ether was evaporated. The residue was 411 mg. of a yellow oil. This was chromatographed through a column of Florisil. After initial extractions with carbon tetrachloride, benzene, and methylene chloride, the column was extracted with ether. This latter fraction was then distilled in a Kugelrohr *in vacuo*, b.p. 205° (0.2 mm.). The infrared spectrum showed characteristic bands at 3.6, 5.88, 6.4, 7.0, 7.38, 9.6, and 14.2 μ.

Anal. Calcd. for $C_{25}H_{32}N_2O_3$: C, 71.84; H, 8.39. Found: C, 71.60; H, 8.68.

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Synthesis and Pharmacological Study of Pyridazines. I. Alkoxypyridazines[1]

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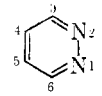
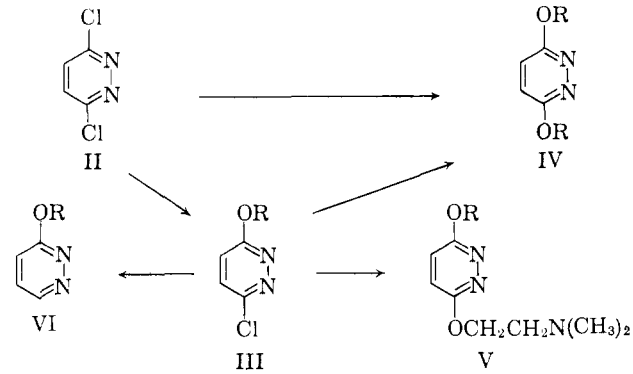
The chemistry of pyridazine (I), though related to pyrimidine, differs sharply in chemical reactivity due to the extreme polar nature of the molecule.[3] The positive nature of C-3 and -6 caused by the adjacent ring nitrogens is demonstrated not only by the ease of nucleophilic substitution at the ring carbons but also by the deshielding effects on the 3 and 6 hydrogen atoms as shown in the n.m.r. spectrum.[3] Because of the similarity of pyridine and pyrimidine, interest in the synthesis and pharmacological study of pyridazine derivatives

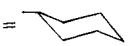


I

as potential medicinal agents has increased markedly in recent years. The pharmacology of many pyridazine derivatives has been studied,[4] including some with regard to CNS activities. A series of alkoxypyridazines, dialkylaminoalkoxypyridazines, and pyridazines containing both alkoxy and dialkylaminoalkoxy substituents was prepared for the purpose of investigating the structure–activity relationships and of evaluating the action on the central nervous system (Tables I–III).

The usual method of producing a 3-alkoxy-6-chloropyridazine has involved the treatment of 3,6-dichloropyridazine (II) with an equivalent amount of sodium alkoxide. We have shown using g.l.c. analysis that the product is invariably contaminated with II and IV. It was found that 3-alkoxy-6-chloropyridazines could be prepared best by heating for longer periods at greatly reduced temperatures.



a, R = CH_3
b, R = n-C_3H_7
c, R = i-C_3H_7
d, R = n-C_4H_9
e, R = n-C_5H_{11}
f, R = i-C_5H_{11}
g, R = 
h, R = $CH_2CH_2N(CH_3)_2$

The 3,6-bisalkoxypyridazines (IV) were prepared from II by treatment with excess sodium alkoxide or by treatment of III with excess sodium alkoxide using a higher temperature. Care had to be taken in preparing 3,6-bis(2-dimethylaminoethoxy)pyridazine (IVh) for it was found that 2-dimethylaminoethanol reacts violently with II on warming, producing copious volumes of smoke.

The 3,6-dialkoxypyridazines (nonbis) were prepared by adding a second mole of the new alkoxide at an appropriate temperature. Special problems were encountered in the process due to a side reaction involving alkoxide exchange, a phenomenon first observed in pyridazines by Coad, *et al.*[5] Conditions were sought to minimize the production of the two different bisalkoxy compounds which would be produced by means of alkoxide exchange. Variables such as the order of entry of the alkoxy groups, the temperature (which had to be sufficiently high to cause halogen displacement but

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