hydrochloride, 1.17 mg/kg, and codeine hydrochloride, 7.50 mg/kg[7]). The route of administration was subcutaneous and the figures in parentheses are the limits of error in probit analysis. The physical dependence capacity, which is the capacity of a substance to suppress abstinence symptoms in morphine-dependent monkeys, was very low. Doses of 2.0–48.0 mg/kg sc produced no suppression. A dose of 60.0 mg/kg produced slight suppression in one monkey and convulsions in another monkey.[8]

O-Methoxymethylphenazocine (IV) showed an analgesic ED_{50} of 3.35 mg/kg (2.94–3.81) with a duration of 203 min, given subcutaneously in the mouse hot plate test[6] (*cf.* phenazocine hydrobromide, 0.25 mg/kg, and phenazocine O-methyl ether hydrobromide, 6.5 mg/kg[9]). No physical dependence capacity or toxic effects were noted at doses of 2.0–32.0 mg/kg.[7] The effects of O-methoxymethylation upon the analgesic properties of morphine and phenazocine thus resemble those of O-methylation in regard to potency. The interest in the phenazocine ether IV lies in its reasonably high potency order with no physical dependence capacity, in the range of doses tested.

Experimental Section[10]

3-Methoxymethylmorphine (III).—Morphine (4.74 g, 0.016 mole) was dissolved in a solution of sodium (0.38 g, 0.016 g-atom) in an ethanol–water (9:4.5 ml) mixture. Ether (50 ml) was added and the solid which separated was collected, washed with ethanol–ether, and dried in a vacuum desiccator. Freshly distilled chloromethyl methyl ether (1.27 g, 0.016 mole) in $CHCl_3$ was added to a suspension of the sodio derivative in the same solvent (20 ml); the reaction flask was stoppered and shaken well. The next morning the mixture was washed with aqueous NaOH, and the $CHCl_3$ was dried (K_2CO_3) and evaporated. The residual oil (3.56 g) solidified on storage in a vacuum desiccator and was crystallized from isopropyl ether–ethanol to give **III** (2.69 g), mp 98° (lit.[4] mp 94–96°).

O-Methoxymethylphenazocine (IV). A.—Phenazocine base (3.2 g, 0.01 mole), mp 183–185° (lit.[9] 181–182°), obtained from the hydrobromide salt (prinadol hydrobromide, SK and F) was dissolved in a warm solution of 50% NaH dispersion (0.48 g, 0.01 mole) in a 2:1 ethanol–water mixture (11 ml). Benzene was added and the solution evaporated; this process was repeated several times and the residue was stored for several days in a vacuum desiccator (concentrated H_2SO_4). Freshly distilled chloromethyl methyl ether (0.75 g, 0.009 mole) was added to a solution of the sodio derivative in $CHCl_3$ (20 ml); the reaction flask was stoppered and shaken well. The next morning the mixture was washed with alkali and dried, and the solvent was evaporated as above. The residue (3.35 g) was chromatographed on Merck alumina (100 g); benzene eluates yielded crude IV (1.55 g) that gave a crystalline **acid succinate,** mp 131–133°, after recrystallization from isopropyl ether–methanol.

Anal. Calcd for $C_{28}H_{37}NO_8$: C, 69.6; H, 7.7; N, 2.9. Found: C, 69.6; H, 7.5; N, 2.95.

Elution with 1% methanol in benzene gave starting material (1.2 g), mp 185–186°, from benzene–Skellysolve B. The melting point was not depressed by admixture with authentic phenazocine.

B.—Phenazocine (1.07 g, 0.0033 mole) in 1,2-dimethoxyethane was added dropwise to sodium naphthyl in the same solvent (20 ml), prepared from Na (0.1 g, 0.004 g-atom) and naphthalene (0.58 g, 0.004 mole); the dark green color disappeared at the end of the addition. Freshly distilled chloromethyl methyl ether (0.35 g, 0.004 mole) in 1,2-dimethoxyethane was then added. After stirring for 2 hr, the mixture was shaken with aqueous $NaHCO_3$, and the organic phase was dried (K_2CO_3) and evaporated. The residue was chromatographed on Merck alumina (30 g); naphthalene was eluted with Skellysolve B, while 25 and 50% benzene in Skellysolve B eluates gave crude IV (1.1 g) which was converted to the acid succinate as above. The crystalline **methiodide** showed mp 182–183°, after crystallization from acetone.

Anal. Calcd for $C_{25}H_{34}INO_4$: C, 59.2; H, 6.7; N, 2.8. Found: C, 59.1; H, 6.5; N, 2.9.

(7) G. A. Deneau and M. H. Seevers, Addendum to the Minutes of the Committee on Drug Addiction and Narcotics, National Academy of Sciences–National Research Council, 1965.

(8) G. A. Deneau and M. H. Seevers, Addendum to the Minutes of the Committee on Drug Addiction and Narcotics, National Academy of Sciences–National Research Council, 1964.

(9) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

(10) Melting points, determined on a Fisher-Johns hot stage, are corrected. Infrared spectra were measured in solutions in $CHCl_3$ on a Beckman Model IR5 spectrophotometer. Skellysolve B refers to petroleum ether, bp 60–68°. Microanalyses were carried out by Dr. S. M. Nagy, M.I.T., Boston, Mass.

Drug Latentiation. III.[1] Labile Amide Derivatives of Normeperidine

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The narcotic analgesic meperidine (I) is a widely used therapeutic agent. N-Demethylation of meperidine to normeperidine (II) has been established as an important metabolic pathway by studies in man and the rat.[2] The view that the latter process may have important pharmacologic significance in analgesia was advanced in a provocative hypothesis by Beckett and his collaborators.[3] These authors had proposed earlier that activity of an analgesic compound is due to association with a specific receptor surface in the central nervous system, and that a drug–receptor complex is formed when certain steric requirements for the drug molecule are satisfied. In 1956,[3] they postulated that the formation of the drug–receptor complex does not itself produce analgesia, but that following absorption of the drug on the receptor surface there occurs an oxidative dealkylation with the release of the N-dealkylated moiety. The presence of the nor derivative on the receptor surface was considered to initiate the analgesic response.

In the light of the foregoing considerations, it was deemed desirable to prepare, for evaluation as potential analgesics, several labile amide derivatives of normeperidine. Such nonbasic derivatives may penetrate the blood–brain barrier more readily than basic analogs, and, if readily hydrolyzed once in the central nervous system, will liberate normeperidine near the receptor site. The nor compound could then initiate the analgesic response, either directly or after N-methylation to meperidine.[4]

The amide derivatives selected for this study were the ethyl carbamate III, the monosuccinamide IV, and the pyruvamide V. A study of the kinetics of the alkaline hydrolysis of carbamate esters indicated that, for N,N-dialkylcarbamates, the mechanism of hydrolysis involves hydroxyl ion attack leading to a car-

(1) (a) Part II: S. M. Kupchan and A. F. Casy, *J. Med. Chem.*, **10**, 959 (1967). (b) This investigation was supported by a grant from Smith Kline and French Laboratories.

(2) E. L. Way and T. K. Adler, *Pharmacol. Rev.*, **12**, 383 (1960).

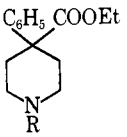
(3) A. H. Beckett, A. F. Casy, and N. J. Harper, *J. Pharm. Pharmacol.*, **8**, 874 (1956).

(4) *Cf.* D. H. Clonet, *Federation Proc.*, **21**, 326 (1962).

bamate ion intermediate.[5] The carbamate ion is unstable and is rapidly decarboxylated to free amine and CO_2. Normeperidine ethyl carbamate (III) was prepared for evaluation in the expectation that hydrolysis of the ethyl ester would be followed *in vivo* by a facile decarboxylation to normeperidine.

Normeperidine monosuccinamide (IV) was prepared for evaluation on the basis of the well-established facilitation of hydrolysis of monoamides of dicarboxylic acids capable of forming cyclic anhydrides.[6,7]

Normeperidine pyruvamide (V) was prepared in the expectation that pyruvamides, like pyruvate esters, would undergo facile hydrolysis. Electron-withdrawing substituents in the acid moiety of esters are known to accelerate the second-order alkaline hydrolysis rates, and the rate of alkaline hydrolysis of ethyl pyruvate was found to be particularly high.[8,9] Furthermore, Sudborough found ethyl pyruvate to undergo substantial hydrolysis even in water.[10]



I, R = CH_3
II, R = H
III, R = COOEt
IV, R = $COCH_2CH_2COOH$
V, R = $COCOCH_3$

Pharmacological Evaluation.—In the mouse hot plate test for analgesic activity, normeperidine ethyl carbamate (III) showed a mouse ED_{50} of 20.15 mg/kg (18.56–21.75) with a duration of 162 min.[11] The route of administration was subcutaneous and the figures in parentheses are the limits of error in probit analysis. In the hot wire tail-withdrawal test in the Wistar rat, III showed a rat ED_{50} of 64.0 mg/kg (33.7–121.6). The route of administration was oral. Meperidine was run side by side on a blind basis, and the two compounds were found to be approximately equipotent by this procedure.[12] The compound showed no toxicity or physical dependence capacity (capacity to suppress abstinence symptoms in morphine-dependent monkeys) at doses ranging from 1.0 to 130.0 mg/kg.[13] The interest in normeperidine ethyl carbamate (III) lies in its reasonably high potency order with no physical dependence capacity, in the range of doses tested.

Normeperidine monosuccinamide (IV) and normeperidine pyruvamide (V) showed no analgesic effect up to 100 mg/kg in the mouse hotplate test.[11] No physical dependence capacity or toxic effects were noted for either compound at doses of 2.0–40.0 mg/kg.[14]

(5) L. W. Dittert and T. Higuchi, *J. Pharm. Sci.*, **52**, 852 (1963).

(6) M. L. Bender, *J. Am. Chem. Soc.*, **79**, 1258 (1957); M. L. Bender, Y. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(7) T. Higuchi and T. Miki, *ibid.*, **83**, 3899 (1961); T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *ibid.*, **85**, 3655 (1963).

(8) C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Bell and Sons, London, 1953.

(9) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

(10) J. J. Sudborough, *J. Chem. Soc.*, **101**, 1227 (1912).

(11) We are indebted to Dr. N. B. Eddy, National Institutes of Health, for these data; *cf.* N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(12) We are indebted to Dr. Maxwell Gordon, Smith Kline and French Laboratories, through whose courtesy these tests were carried out.

(13) We are indebted to Drs. G. A. Deneau and M. H. Seevers, University of Michigan, for these data.

Experimental Section[15]

Normeperidine Ethyl Carbamate (III).—To a stirred, ice-cooled solution of normeperidine hydrochloride (8.07 g, 0.03 mole, Winthrop, mp 134–137°) in $CHCl_3$ (25 ml) were added triethylamine (6.00 g, 0.06 mole) in $CHCl_3$ (15 ml) and (dropwise) ethyl chloroformate (3.24 g, 0.03 mole, Eastman) in $CHCl_3$ (15 ml). The solution was stirred in the cold for 2 hr and then at room temperature overnight. Ether was added to complete precipitation of triethylamine hydrochloride, and the precipitate was filtered. The filtrate was washed twice with water, dried (Na_2SO_4), and evaporated under reduced pressure to a light brown oily residue. The residue was dissolved in Skellysolve A and cooled and rubbed to induce crystallization. The crystalline product was recrystallized four times from Skellysolve A to yield 4.03 g of colorless crystals: mp 37–38°; $\lambda_{max}^{CHCl_3}$ 5.82 (ester C=O), 5.95 (carbamate C=O), 6.25, 14.40 (aryl ring), 8.0 μ (ester C–O–C).

Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.96; H, 7.63; N, 4.79.

Normeperidine Monosuccinamide (IV).—A solution of normeperidine hydrochloride (15 g, 0.055 mole) in water (25 ml) was treated with excess concentrated NH_4OH. The suspension was extracted three times ($CHCl_3$) and the extract was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was treated with succinic anhydride (5.5 g, 0.055 mole) and the mixture was heated on the steam bath for 1 hr. The oily reaction product was rubbed to induce crystallization, and then recrystallized twice from benzene: yield 12.80 g; mp 130–133°; $\lambda_{max}^{CHCl_3}$ 2.85 (OH), 5.82 (broad, ester and acid C=O), 6.10 (amide C=O), 6.25, 14.40 (aryl ring), 8.05 μ (ester C–O–C).

Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.07; H, 7.09; N, 4.44.

Normeperidine Pyruvamide (V).—To a solution of pyruvic acid (3.52 g, 0.04 mole, Eastman, redistilled) in $CHCl_3$ (20 ml) was added $SOCl_2$ (4.76 g, 0.04 mole), and the solution was heated under reflux for 1 hr. To the stirred, refluxing solution, a solution of normeperidine hydrochloride (5.39 g, 0.02 mole) and triethylamine (2.02 g, 0.02 mole) in $CHCl_3$ (25 ml) was added dropwise over the course of 45 min, and refluxing was continued for an additional 75 min. The mixture was extracted three times with water, and the $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Crystallization from Skellysolve B yielded 4.68 g of product, mp 92–94°. Recrystallization from Skellysolve B, with Norit treatment, yielded the analytical sample: mp 94–96°; $\lambda_{max}^{CHCl_3}$ 5.82 (ester and ketone C=O), 6.10 (amide C=O), 6.25, 14.40 (aryl ring), 8.1 μ (ester C–O–C).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.22; H, 7.04; N, 4.79.

(14) G. A. Deneau and M. H. Seevers, Addendum to the Minutes of the Committee on Drug Addiction and Narcotics, National Academy of Sciences–National Research Council, 1965.

(15) Melting points, determined on a Fisher-Johns hot stage, are corrected. Infrared absorption spectra were determined in $CHCl_3$ on a Beckman model IR5A recording spectrophotometer. Microanalyses were carried out by Mr. J. F. Alicino, Metuchen, N. J. Skellysolve A refers to petroleum ether, bp 40–60°.

DL-4,5-Dihydroxy-2-pyridylalanine, an Analog of 3,4-Dihydroxyphenylalanine[1]

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We wish to report the synthesis of DL-4,5-dihydroxy-2-pyridylalanine, a structural analog of 3,4-dihydroxyphenylalanine (DOPA). In previous studies amino acid analogs containing the pyridine ring in place of

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