mole) was stirred in 95% ethanol (200 ml) while a solution of $NaHSO_3$ (18 g, 0.17 mole) in water (30 ml) was added dropwise over a period of 10 min. The reaction mixture was stirred at room temperature for 0.5 hr then in an ice bath for 1 hr. The crystals were collected, washed with a small amount of cold methanol and then ether, and dried, giving 45 g (95%) of **sodium 9-amino-9-fluorenesulfonate** which was mixed with water (750 ml) and cooled in ice. To the stirred mixture a solution of KCN (21 g) in water (100 ml) was added dropwise over a period of 25 min. The mixture was stirred in the ice bath for 1 more hr and at room temperature for several hours and the 9-amino-9-cyano derivative was isolated giving 23 g (70%). Recrystallization from ether–petroleum ether (bp 30–60°) gave a pure product, mp 95–96.5° (lit.[10] mp 95–96°).

N-Acetyl derivative, mp 237.5–238°.

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.19; H, 4.76; N, 11.48.

N-9-(9-Cyanofluorenyl)urea.—9-Cyanofluoren-9-amine (1.1 g, 5 mmoles) was dissolved in AcOH (30 ml) containing concentrated HCl (0.5 ml). To the stirred solution KCNO (0.4 g, 5 mmoles) was added. The mixture was then heated at 65–75° for 1 hr and diluted with water. The product was isolated and recrystallized from methanol–benzene giving lustrous crystals (0.5 g), mp 270° dec (with a preheated bath).

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.56; H, 4.55; N, 17.01.

9,9′-Difluorenyl Disulfide.—Fluorenone (9 g), CS_2 (25 ml), methanol (200 ml), water (100 ml), KCN (13 g), and NH_4Cl (10.8 g) were mixed and stirred in a Parr apparatus at 115–125° for 2 hr and the solvent evaporated. The residual gummy solid was triturated in water and boiled in 95% ethanol (200 ml). The crystalline material was collected on a filter giving 4.6 g (23%), mp 165–167°. Recrystallization from benzene–methanol gave silky crystals, mp 168–169° (lit.[5] mp 170–171°).

Anal. Calcd for $C_{26}H_{18}S_2$: S, 16.26. Found: S, 16.20.

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Drug Latentiation. II.[1] Labile Ether Derivatives of Phenolic Analgesics

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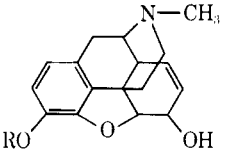
The main metabolic pathway for the elimination from the body of analgesics bearing phenolic hydroxyl groups is conjugation with glucuronic acid; the main site of conjugation is the phenolic hydroxyl group.[3]

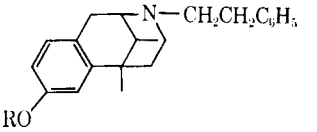
Interference with this mechanism by masking the site may well have a profound effect upon the nature and duration of activity of such analgesics. Etherification is a better means of achieving such masking than is acylation since acylated phenols, such as diacetylmorphine (heroin), are rapidly hydrolyzed *in vivo*.[3] Although the potency of phenolic analgesics is considerably reduced when they are alkylated (*e.g.*, morphine → codeine), it was considered of interest to examine ethers that are much less stable chemically than simple alkyl ethers, *e.g.*, methoxymethyl ethers. The *in vivo* rate of breakdown of methoxymethyl ethers of phenolic analgesics may be such that the speed of conjugation is reduced while allowing sufficient free phenol to be liberated at the site of action to produce a potent analgesic response.

The phenolic analgesics selected for this study were morphine (I) and phenazocine (II). Methoxymethylmorphine (III) was first reported by Mannich[4] and later used by Rapoport, Baker, and Reist,[5] in a synthesis of morphinone, as a derivative in which the phenolic moiety is stable to oxidizing agents. No reports of pharmacological studies have been found. The procedure of Mannich was repeated and gave the desired derivative in 50% yield; isopropyl ether–ethanol was found to be far superior to the described solvent, dilute alcohol, as a crystallization solvent for the product.

Difficulties were encountered in applying the same process to phenazocine. The sodio derivative of morphine, prepared by dissolving the base in sodium ethoxide–ethanol–water, precipitated when its solution was diluted with ether and was readily collected, washed, and dried. In contrast, the sodium salt of phenazocine did not precipitate and needed to be dried by azeotropic distillation with benzene followed by storage in a vacuum desiccator over concentrated sulfuric acid. The dry product was soluble in $CHCl_3$ (in contrast to sodium morphinate) and after reaction with chloromethyl methyl ether gave an oil (insoluble in aqueous NaOH), that could not be induced to solidify. This was chromatographed on neutral alumina. Benzene eluates yielded the desired ether (IV) as an oil, characterized as the crystalline acid succinate (salts with strong acids were avoided due to the lability of the ether group). Elution with 1% methanol in benzene gave unchanged starting material. The latter should normally have been removed by the isolation procedure, but it was observed that phenazocine base was sparingly soluble in aqueous NaOH, in contrast to morphine; furthermore, the hydroxyl stretching band of the phenol was not apparent in the infrared spectrum of phenazocine either as the free base or hydrobromide salt. A better yield of the methoxymethyl ether of phenazocine (IV) was obtained by treating the phenolic base with sodium naphthyl followed by the halide, conditions previously found suitable for forming sodio derivatives of secondary alicyclic alcohols.[1a] The product from this reaction was further characterized as a methiodide.



I, R = H
III, R = CH_3OCH_2



II, R = H
IV, R = CH_3OCH_2

Pharmacological Evaluation.—In the mouse hot plate test for analgesic activity, 3-methoxymethylmorphine (III) showed a mouse ED_{50} of 28.0 mg/kg (25.0–33.2) with a duration of 168 min[6] (*cf.* morphine

(1) (a) Part I: S. M. Kupchan, A. F. Casy, and J. V. Swintosky, *J. Pharm. Sci.*, **54**, 514 (1965). (b) This investigation was supported, in part, by a grant from Smith Kline and French Laboratories.

(2) This author thanks the Wellcome Trust for a travel grant.

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

(4) C. Mannich, *Arch. Pharm.*, **254**, 349 (1916).

(5) H. Rapoport, D. R. Baker, and H. N. Reist, *J. Org. Chem.*, **22**, 1489 (1957).

(6) 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).

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 $C_{25}H_{34}INO_5$: 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 Berkman 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. Clouet, *Federation Proc.*, **21**, 326 (1962).