10.05, and 7.09 μ) and with PtO_2, was completely hydrogenated in 100 sec. to the 4-ethylpiperidine XIV, which was converted to the hydrochloride and found to be identical with authentic material prepared by the Wolff-Kishner reduction of XII followed by formaldehyde–formic acid methylation.

Acknowledgment. Microanalyses were performed by Byron Baer, Paula Parisius, and Evelyn Peake of the Institutes' Microanalytical Laboratory, under the direction of William C. Alford. Some of the infrared determinations[10] were made by William Jones, of the same laboratory.

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Morphinone*

HENRY RAPOPORT, DON R. BAKER, AND HELEN N. REIST

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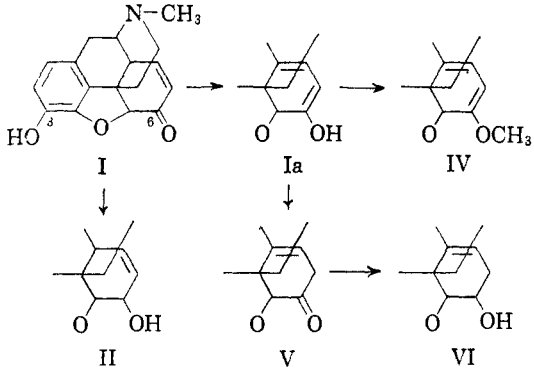
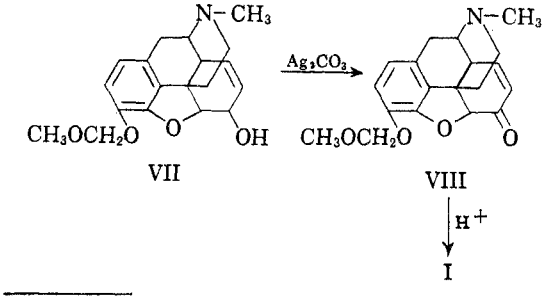
Morphinone, a compound which conceivably might serve as a common precursor for the other morphine alkaloids, has been prepared by silver carbonate oxidation of methoxymethylmorphine to methoxymethylmorphinone, followed by acid hydrolysis. With methyllithium, methoxymethylmorphinone gives the 1,2-adduct which is easily cleaved to 6-methylmorphine. Both monoacetyl derivatives and the diacetyl derivatives of 6-methylmorphine have been prepared. It appears that reactivity at the phenolic hydroxyl group may be influenced by groups at the 6-position.

In recent years there has been considerable interest in morphinone (I) since, as has been pointed out by Schöpf,[1] it (or its enolic form, Ia) conceivably might be the common parent of the other naturally occurring morphine alkaloids. For example, reduction of the carbonyl group would lead to morphine (II), and reduction to the alcohol and methylation of the phenolic hydroxyl would give codeine (III). Conversion to thebaine (IV) might be accomplished by both enol and phenol etherification, while isomerization to the β,γ-unsaturated ketone (IV), either before or after methylation of the phenol, followed by reduction to the alcohol gives neopine (VI).



Further interest in morphinone resides in the fact that it has remained one of the very few ketones still unknown in this series of alkaloids. Codeinone, dihydrocodeinone, and dihydromorphinone are well known compounds.[2] Also neopinone (V, O[3]-methyl ether) recently has been prepared from thebaine.[3] The preparation of morphinone, however, by methods such as employed for the previous ketones, has been precluded by the extreme sensitivity of the molecule. The possibility of overcoming this difficulty was offered by the recent procedure for converting codeine to codeinone[4] in excellent yield by oxidation in benzene with silver carbonate, and it is the application of this method to the preparation of morphinone which is the subject of the present report.

Although the silver carbonate-in-benzene procedure offered the mild, neutral oxidant desired, it was still necessary to protect the phenolic group, and formation of the methoxymethyl ether appeared to be a suitable method, since the protecting group could be removed by mild acid hydrolysis. The oxidation procedure, therefore was applied to the readily prepared methoxymethylmorphine (VII)[5]



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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) C. Schöpf, *Naturwissenschaften*, **39**, 241 (1952).

(2) L. F. Small, *Chemistry of the Opium Alkaloids*, U. S. Government Printing Office, Washington, D. C., 1932; K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, The Clarendon Press, Oxford, 1954.

(3) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).

(4) H. Rapoport and H. N. Reist, *J. Am. Chem. Soc.*, **77**, 490 (1955).

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

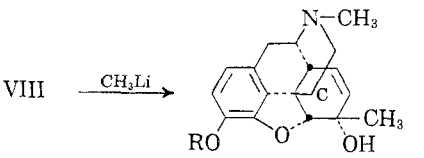
and methoxymethylmorphinone (VIII) was formed in good yield. Acid hydrolysis of the methoxymethyl ether proceeded readily in acid solution or on a sulfonic acid ion-exchange resin, and the morphinone appeared to be reasonably stable to these hydrolytic conditions.

However, attempts to liberate the free base clearly showed that morphinone was extremely sensitive to alkali, and only by keeping contact with alkali to a minimum could pure, crystalline material be isolated. This was achieved by eluting the alkaloid from the column with potassium chloride solution, adding chloroform and cooling before adjusting the *p*H to 8.7, and extracting as rapidly as possible. In this way morphinone exhibiting a strong α,β unsaturated carbonyl absorption at 5.98 μ as the only carbonyl peak could be obtained. If stronger alkali or longer times were used, or if cooling was omitted, a product with a weak additional carbonyl absorption at 5.80 μ resulted, and this impurity could not be removed.

Reduction of morphinone with sodium borohydride gave morphine, and dihydromorphinone was formed on catalytic hydrogenation. Numerous attempts were made to duplicate some of the postulated biogenetic conversions, but these met only with failure. The appearance of a carbonyl absorption at 5.80 μ when morphinone was exposed to alkali looked promising for a possible conversion to the β,γ-unsaturated ketone (V) and thence to neopine (VI). Although longer exposure to alkali increased the intensity of this absorption it also led to polymeric material. The reaction with diazomethane was investigated as a possible route to codeinone and thebaine, but again the reaction was complex and no crystalline product could be isolated.

A reaction of interest was that with methyllithium, since this should lead to a nuclear methylated morphine derivative of possible pharmacological interest. For this purpose, methoxymethylmorphinone (VIII) was the starting material and it was treated with ethereal methyl lithium in the cold. This gave 6-methylmethoxymethylmorphine (IX) which was directly hydrolyzed to 6-methylmorphine (X). The assigned structure as the 1,2-addition product is based on the analogous reaction with codeinone,[6] methylation to 6-methylcodeine,[6] and hydrogenation to 6-methyldihydromorphine.[7]

Both monoacetyl derivatives and the diacetyl derivative of 6-methylmorphine were prepared. The O^3-monoacetyl compound was readily formed on shaking 6-methylmorphine with chloroform, aqueous sodium hydroxide, and acetic anhydride. That it was the phenolic group which was acetylated and not the tertiary hydroxyl was established by its ultraviolet absorption. The compound showed absorption at 282 mμ, typical of morphine alkaloids



IX, R = CH_3OCH_2
X, R = H
XI, R = CH_3

(4)

and due to the guaiacol moiety. However, on addition of alkali, the absorption peak shifted gradually to 300 mμ and the extinction coefficient increased, indicating the progressive hydrolysis of the ester and formation of the phenolate ion. To prepare the O^6-monoacetyl derivative, the methyllithium-methoxymethylmorphinone reaction mixture was treated with acetic anhydride and mild acid hydrolysis removed the O^3-methoxymethyl ether, leaving the O^6-acetyl intact. On addition of alkali to an ethanolic solution of the O^6-acetyl-6-methylmorphine, the shift in absorption maximum from 287 mμ to 300 mμ took place immediately as is characteristic of free phenols.

In order to prepare the O^3, O^6-diacetyl derivative it was necessary to heat the O^6-monoacetyl compound with acetic anhydride and pyridine. The very mild conditions used previously to acetylate the phenolic group of 6-methylmorphine resulted only in unchanged starting material when applied to O^6-acetyl-6-methylmorphine. Apparently the O^6-acetyl group was exerting a slight hindering effect on reactions of the phenol. Considering the stereochemistry of the morphine molecule with the benzene ring on the underside of the piperidine-ring C fused ring system, addition of methyllithium to the carbonyl group of VIII would be expected to occur from above to give the tertiary alcohol with the hydroxyl group on the same side as the benzene ring, as shown in IX. This would allow the O^6-acetyl group to approach fairly close to the phenol and might explain the decreased reactivity.

Another example of this effect was found in a comparison of the rates of hydrolysis of the O^3-acetyl groups of O^3-acetyl-6-methylmorphine and O^3,O^6-diacetyl-6-methylmorphine. Using the appearance of phenolate ion absorption in the ultraviolet to follow the reaction, the half-time for hydrolysis was 40 seconds for the former and 120 seconds for the latter. This result also is consistent with a close approach of the O^6-acetyl group to the phenol.

EXPERIMENTAL[8]

Methoxymethylmorphinone (VIII). Methoxymethylmorphine was prepared by the reaction of sodium morphinate

(6) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **72**, 3249 (1950).

(7) L. F. Small and H. Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(8) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

and chloromethyl ether[9] following the procedure of Mannich,[5] m.p. 92–94° (reported[5] m.p. 94–96°). A 16.5 g. (0.05 mole) portion of this methoxymethylmorphine was dissolved in 330 ml. of benzene and 69 g. (0.25 mole) of silver carbonate[4] was added after 30 ml. of benzene had been distilled from the solution. The mixture was heated under reflux in a nitrogen atmosphere with vigorous stirring for 1 hr. during which 20 ml. of benzene was distilled from the reaction mixture. It was then cooled sufficiently to permit the addition of another 69 g. portion of silver carbonate and the process was repeated. The mixture then was filtered, the insoluble material was digested with three 70 ml. portions of benzene, and the combined filtrate and digests were washed with two 100-ml. portions of 1*N* sodium hydroxide. Four 110-ml. portions of *p*H 7 sulfite-bisulfite solution were then used to wash the benzene solution, and these aqueous solutions then were combined, adjusted to *p*H 10 with potassium carbonate, and extracted with benzene. The original benzene solution and the benzene extracts of the *p*H 10 aqueous sulfite solution, on drying and evaporation, yielded 6.1 g. (37%) of recovered methoxymethylmorphine.

To the *p*H 10 sulfite solution was added 15 ml. of 15*N* sodium hydroxide, and this strongly alkaline solution was shaken mechanically with 500 ml. of chloroform for 2 hr. after which the chloroform was removed and a fresh portion added. In all, four such portions were used. Washing with water, drying over magnesium sulfate, and evaporating the chloroform left 6.2 g. (60% yield) of methoxymethylmorphinone, m.p. 121–125°. Crystallization from benzene-hexane gave pure ketone, m.p. 129–130°; $[\alpha]_D^{25}$ −176° (c, 0.98, ethanol).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.5. Found: C, 69.7; H, 6.4.

With sodium borohydride in methanol at room temperature, methoxymethylmorphinone was reduced to methoxymethylmorphine, m.p. 94–96°.

Morphinone (I). A solution of 502 mg. (1.5 mmoles) of methoxymethylmorphinone (VIII) in 20 ml. of 0.1*N* hydrochloric acid was added to a Dowex 50 × 1 ion exchange column (50–100 mesh) in the acid form. Distilled water (800 ml.) was washed through the column during 5 hr., after which the morphinone was eluted with four 100-ml. portions of 10% potassium chloride solution. The solutions were cooled, chloroform was added, and the aqueous phase was adjusted to *p*H 8.7 with sodium bicarbonate solution. Separation of the phases and extraction with three additional 50-ml. portions of cold chloroform during three minutes led, after evaporation of the chloroform extracts, to 270 mg. (62% yield) of crude morphinone.

Hydrolysis could also be effected by allowing 1.04 g. (3.2 mmoles) of methoxymethylmorphinone in 20 ml. of 1*N* hydrochloric acid solution to stand at room temperature for 5 hr. Isolation in the same manner as above led to an 85% yield (763 mg.) of crude morphinone. Crystallization of 500 mg. from 5 ml. of absolute ethanol gave 450 mg. of pure morphinone, strongly decomposing at 148° and melting at 230° (evac. cap.); $[\alpha]_D^{25}$ −194° (c, 0.87, methanol); λ_{max} 280 mμ (ε 1420), in ethanol; 297 mμ (ε 2710) in ethanol, 0.01*N* in sodium hydroxide.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1. Found: C, 71.9; H, 6.4.

The *perchlorate* was prepared by dissolving 52 mg. of morphinone in 3 ml. of methanol and adding 1.9 ml. of 0.1*N* ethanolic perchloric acid. Recrystallization from methanol-ether and drying gave hygroscopic material of m.p. 151–155°; $[\alpha]_D^{25}$ −124° (c, 0.75, methanol).

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.2; H, 4.7. Found: C, 52.8; H, 5.0.

Reduction of morphinone to morphine was achieved by treating 84 mg. of morphinone in methanol with a solution of 270 mg. of sodium borohydride in 2 ml. of water and 3 ml. of methanol. After standing at room temperature for 1.5 hr., the solution was concentrated to remove methanol, water was added, the *p*H was adjusted to 8.7, and the solution was cooled to allow the crystallization of 60 mg. of *morphine*, identical with authentic material in ultraviolet and infrared spectra and melting point.

Catalytic hydrogenation of morphinone in absolute ethanol using a 5% palladized carbon catalyst proceeded rapidly (30 min.) at room temperature with the absorption of one mole of hydrogen, after which hydrogen uptake ceased. The solution was filtered and concentrated, and cooling gave *dihydromorphinone*, identical with an authentic sample in infrared spectrum and m.p.[10]

6-Methylmorphine (X). To 50 ml. of dry ether was added 20 ml. of 0.93*M* ethereal methyllithium. With cooling (ice-salt bath) and stirring and in a nitrogen atmosphere, 2.5 g. of methoxymethylmorphinone (VIII) was added over a 15-min. period. Stirring and cooling was continued for an additional hour after which 60 ml. of ice water was added. The ether layer was separated, the aqueous phase was washed with four 30 ml. portions of ether, and the combined ether solutions were washed with 1*N* hydrochloric acid (four 40 ml. portions). After being allowed to stand at room temperature for 5 hr., the combined acid solutions were adjusted to *p*H 8.7 and were extracted four times with 80 ml. portions of chloroform. Methanol was added to the combined chloroform solutions to prevent precipitation, they were dried and evaporated, and a 97% yield, 2.22 g., of 6-methylmorphine, m.p. 275–276°, was obtained. A sample crystallized from acetone and then from butanone had m.p. 279–280°; $[\alpha]_D^{25}$ −166° (c, 0.82, methanol).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.1; C-CH_3, 5.0. Found: C, 72.0; H, 7.2; C-CH_3, 4.3.

Etherification of 6-methylmorphine in methanol with ethereal diazomethane gave *6-methylcodeine*, identical with an authentic sample.

Hydrogenation of 6-methylmorphine at room temperature in absolute ethanol using a platinum oxide catalyst stopped after 30 min. and the absorption of one mole of hydrogen. *6-Methyldihydromorphine* was isolated by sublimation and was identical with an authentic sample.[7]

O^3*-Acetyl-6-methylmorphine* was prepared by dissolving 350 mg. (1.2 mmoles) of 6-methylmorphine in 25 ml. of chloroform and 1.8 ml. of 1*N* sodium hydroxide. To this cold mixture was added 150 mg. (1.5 mmoles) of acetic anhydride and, after being shaken vigorously for one min., the phases were separated. The aqueous phase, made alkaline with sodium carbonate, was washed with chloroform, and the combined chloroform solutions were washed with 0.5*M* sodium carbonate. Evaporation of the chloroform and crystallization of the residue from ethyl acetate followed by sublimation at 120°/10 μ gave O^3-acetyl-6-methylmorphine, m.p. 167–168°; $[\alpha]_D^{25}$ −198° (c, 0.78, methanol).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; CH_3COO—, 12.6. Found: C, 70.1; H, 6.6; CH_3COO—, 12.5.

O^6*-Acetyl-6-methylmorphine* was prepared by first treating 1.00 g. (3.1 mmoles) of methoxymethylmorphinone (VIII) in 100 ml. of ether with 20 ml. of 0.93*M* ethereal methyllithium in the cold for 1 hr. and then adding 2 ml. of acetic anhydride. This mixture was heated under reflux for 2 hr., after which 100 ml. of 0.1*M* phosphoric acid was added and the ether layer removed. Chloroform was used to wash the aqueous phase (adjusted to *p*H 3), and the water solution then was boiled in a nitrogen atmosphere for 6 hr. After being washed with chloroform, the aqueous layer was adjusted to *p*H 8.7 and was extracted thoroughly with chloroform. Evaporation of the chloroform left 1.0 g. (96% yield) of crude O^6-acetyl-6-methylmorphine which was purified for analysis by crystallization from ethyl acetate

(9) C. S. Marvel and P. K. Porter, *Org. Syntheses*, **Coll. Vol. I**, 377 (1944).

(10) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

and sublimation (140°/10 μ); m.p. 244–245°; $[\alpha]_D^{25}$ −212° (c, 0.65, methanol).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; CH_3COO—, 12.6. Found: C, 70.3; H, 7.1; CH_3COO—, 13.0.

O^3,O^6-Diacetyl-6-methylmorphine resulted when a solution of 96 mg. of O^6-acetyl-6-methylmorphine, one ml. of acetic anhydride and 2 ml. of pyridine was heated under reflux for 1.5 hr. The reaction mixture was concentrated *in vacuo*, the residue was distributed between chloroform and aqueous phosphate buffer (*p*H 3), and the aqueous phase, after adjustment to *p*H 8.7, was extracted thoroughly with chloroform. The residue from evaporation of the dried chloroform extracts was crystallized from ethyl acetate–hexane to give O^3,O^6-diacetyl-6-methylmorphine, m.p. 166–168°; $[\alpha]_D^{25}$ −200° (c, 0.77, methanol).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.6; C-CH_3, 12.1. Found: C, 69.3; H, 6.4; C-CH_3, 12.3.

Rates of hydrolysis of the O^3-acetyl derivatives prepared above were determined by dissolving 1 mg. of each compound in 10 ml. of 95% ethanol, 0.01*N* in sodium hydroxide. The ultraviolet absorption at 300 mμ, due to the formation of phenolate ion, was followed as a function of time. With O^6-acetyl-6-methylmorphine, the appearance of this peak was instantaneous and did not change with time. With O^3-acetyl-6-methylmorphine and O^3,O^6-diacetyl-6-methylmorphine, this peak appeared as hydrolysis proceeded and the half-time for hydrolysis was 40 sec. for the former and 120 sec. for the latter. Heroin (O^3,O^6-diacetylmorphine), run for comparison, had a half-time for hydrolysis of 100 sec.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Antiparasitic Agents. I. Some New 2,4-Diaminopyrimidines*

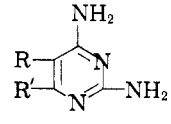
E. F. ROGERS, W. J. LEANZA, AND L. H. SARETT

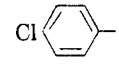
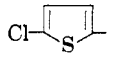
Received July 29, 1957

Six new substituted 2,4-diaminopyrimidines were prepared for chemotherapeutic evaluation. Three of these were found to have activity *vs. S. pyogenes;* one enhances sulfanilamide action *vs. Eimeria spp.*

Various 2,4-diaminopyrimidines and the analogously constituted 2,6-diaminopurines have been found to be folic acid antagonists[1] and, presumably, act in this capacity to inhibit growth of the parasites of malaria[2] and coccidiosis[3] as well as to show antibacterial[4] and antileukemic[5] activity. The most potent of the series in antimalarial activity is pyrimethamine,[2,6] 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (I). In addition to its antimalarial activity it also potentiates sulfaquinoxaline and sulfamezathine.[3] These properties prompted us to prepare some new 2,4-diaminopyrimidines related to pyrimethamine.

The new bases which were made are shown in formulas II–VII. In compounds II–IV, fluoroalkyl or alkoxyalkyl groups replace the 6-ethyl substituent in pyrimethamine; in compounds V–VII the 5-*p*-chlorophenyl is replaced by heterocyclic groups. In each case the bases differ in only one ring substituent.



	R	R′
I		$-C_2H_5$
II	〃	$-CF_3$
III	〃	$-C_2F_5$
IV	〃	$-CH(OCH_3)_2$
V		$-C_2H_5$
VI		$-C_2H_5$
VII		$-C_2H_5$

With the exception of compound VII the syntheses presented no special difficulties. The method is illustrated by the synthesis of 2,4-diamino-5-thienyl-6-ethylpyrimidine. These reactions were exploited most successfully by the Wellcome group in their investigations of 5-aryl-2,4-diaminopyrimi-

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) G. H. Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 467 (1952).

(2) I. M. Rollo, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 474 (1952); L. G. Goodwin, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 485 (1952); G. R. Coatney and W. C. Cooper, *Trans. Roy. Soc. Trop. Med. Hyg.*, **46**, 496 (1952).

(3) R. E. Lux, *Antibiotics and Chemotherapy*, **4**, 971 (1954).

(4) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951); E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

(5) M. L. Murphy, R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *J. Clin. Invest.*, **33**, 1388 (1954).

(6) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).