Chemistry and Pharmacology of Homologs of 6-Acetyl- and 3,6-Diacetylmorphine

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Abstract □ 3,6-Diformyl- and 3,6-dipropanoylmorphine and 6-formyl- and 6-propanoylmorphine were prepared to obtain longer acting, heroin-like compounds. The 6-acylated compounds were more potent than heroin subcutaneously and were orally effective, and their duration of action was at least two to three times greater than that of heroin in monkey species.

Keyphrases □ Morphine derivatives, various—synthesized, analgesic activity evaluated, monkeys □ Analgesic activity—various morphine derivatives, monkeys □ Structure–activity relationships—various morphine derivatives, analgesic activity evaluated, monkeys

For some time, there has been an interest in heroin-like compounds whose duration of action would be greater than that of heroin (3,6-diacetylmorphine, I). Goldstein (1), for example, recently suggested a provocative procedure for rehabilitating "hard-core" addicts who resist contemporary methods of treatment. One early step that might lead to the complete withdrawal of narcotics would entail the use of a longer acting heroin. As potential agents for this phase of treatment, higher and lower homologs of I, the 3,6-diformyl (II), 3,6-dipropanoyl (III), 6-formyl (V), and 6-propanoyl (VI) derivatives were prepared. The chemistry and pharmacology of I–VI and 3-acetylmorphine (VII) are described here and some stability data are presented.

3,6-Diformylmorphine (II) was prepared from morphine hydrate and excess formic–acetic anhydride (2) at 15–25°. If pyridine was used as a solvent, 6-formylmorphine (V) resulted. Excess propanoic anhydride and morphine at 100° gave 3,6-dipropanoylmorphine (III) (3). Anhydrous morphine, potassium carbonate, and 1.2 *M* equivalents of propanoic anhydride (reflux temperature) produced 6-propanoylmorphine (VI). Finally, 3-acetylmorphine (VII) was synthesized by the method of Welsh (4) for pharmacology and stability comparisons.

EXPERIMENTAL[1]

3,6-Diformylmorphine (II)—To 60 ml of acetic anhydride (ice cooled and stirred) was added dropwise (5–10 min) 25 ml of 97% formic acid (5). The mixture was warmed slowly to 50–55°, where it was kept for 15–20 min. To 25 ml of this solution was added (ice cooling) 5.0 g of morphine monohydrate so that the temperature did not rise above 15°. The solution was then treated with an additional 5 ml of the acetic anhydride–acetic acid mixture.

Stirring was continued at room temperature (21–24°) for 24 hr, after which another 25-ml portion of the formylating mixture was added during 5 min. The solution was left at 21–24° for an additional 70 hr and then evaporated to dryness *in vacuo*. The residue was dissolved in ice water; after 20 min, methylene chloride and then 10% Na_2CO_3 were added to pH 9 (at 10–12°). The dried (sodium sulfate) methylene chloride layer was evaporated to dryness *in vacuo*. The residue was dissolved in 50–70 ml of boiling acetone, from which II crystallized on cooling to 0°, yielding 4.5 g, mp 170° (gas evolution) and 212–215° dec.

Anal.—Calc. for $C_{19}H_{19}NO_5$: C, 66.84; H, 5.61; N, 4.00. Found: C, 66.64; H, 5.58; N, 4.10.

The hydrochloride salt (from acetone–hydrogen chloride gas) was dried at 65°, mp 210–211° (froth).

Anal.—Calc. for $C_{19}H_{20}ClNO_4 \cdot 0.5H_2O$: C, 58.98; H, 5.47; Cl, 9.16; N, 3.62. Found: C, 58.93; H, 5.53; Cl, 9.04; N, 3.40.

6-Formylmorphine (V)—Formic acid (90 ml) and 40 ml of acetic anhydride (5) were mixed at 0° and then kept at 50–55° for 15 min. The solution was cooled to 0° (stirring) and treated dropwise (at 0°) with 7.4 g of morphine monohydrate in 50 ml of pyridine. The mixture was kept at 25° for 65–70 hr, poured into ice water, and treated with 100 ml of methylene chloride and 20% Na_2CO_3 to pH 9. The organic layer and one methylene chloride extract of the aqueous layer were combined, dried (magnesium sulfate), and evaporated to dryness *in vacuo*. Trituration of the 9.1 g of residue in acetone gave, after cooling to 0°, 5.4 g of V, mp 208–215° dec.

Anal.—Calc. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.03; H, 6.07; N, 4.29.

The hydrochloride salt (from acetone–hydrogen chloride gas) melted at 265–267° dec.

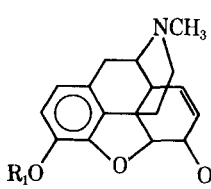
Anal.—Calc. for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; Cl, 10.14; N, 4.00. Found: C, 61.44; H, 5.93; Cl, 10.05; N, 3.84.

3,6-Dipropanoylmorphine (III)—Morphine (2.0 g) and 5.0 ml of propanoic anhydride were kept on the steam bath for 4 hr, cooled to room temperature, and treated with water. After 1 hr, the clear solution was partitioned between ether and 10% KOH (ice cooling). The ether was washed once with water, dried over sodium sulfate, and evaporated. The hydrochloride salt (3) (from ether–hydrogen chloride gas) weighed 2.6 g (87%). After a recrystallization from ethyl acetate, it melted at 150–155° (froth).

In another run, 0.25 g of crude III, obtained as described, was dissolved in acetone and treated with 0.08 g of sulfamic acid in 0.5 ml of water. Further dilution with acetone gave 0.3 g of the sulfamate salt of III, mp 190–191° if the capillary tube was inserted in a bath preheated to 185–188°. Otherwise, the sample became brown at 175° and did not melt even at 200°.

Anal.—Calc. for $C_{23}H_{30}N_2O_8$: C, 55.85; H, 6.11; N, 5.67. Found: C, 56.13; H, 5.91; N, 5.78.

6-Propanoylmorphine (VI) Hydrochloride—Morphine (2.9 g of anhydrous base) and 50 ml of acetone (dried over molecular sieve) were stirred and refluxed together while 1.6 ml (1.2 equivalents) of propanoic anhydride in 10 ml of dry acetone was added during 1 hr. The mixture was refluxed for 4–5 hr and evaporated to dryness *in vacuo*. The residue was treated with cold water, ether, and excess potassium carbonate. The ether was dried (sodium sulfate) to give 3.3 g of base which, as determined by TLC analysis [chloroform–methanol–ammonium hydroxide (85:14:1)] on silica gel, consisted of about 97% of VI and 2–3% of III. It was dissolved in acetone–ether (3:1) and treated (to pH 4–5) with hydrogen chloride gas to give (ice cooling) 2.2 g of VI hydrochloride, which was dissolved in 140 ml of boiling acetone. The solution was concentrated to 45–50 ml



I: $R_1 = R_2 = COCH_3$
II: $R_1 = R_2 = CHO$
III: $R_1 = R_2 = COC_2H_5$
IV: $R_1 = H$, $R_2 = COCH_3$
V: $R_1 = H$, $R_2 = CHO$
VI: $R_1 = H$, $R_2 = COC_2H_5$
VII: $R_1 = COCH_3$, $R_2 = H$

[1] Melting points (uncorrected) were taken on a Fisher-Johns apparatus or by capillary (SGA Melt-Meter). IR (Perkin-Elmer 257), NMR (Varian A60 or HA 100 with tetramethylsilane as internal standard) and mass spectra (Hitachi Perkin-Elmer RMU6E, at 70 ev) were consistent with assigned structures. Analytical results are from the Section on Microanalytical Services and Instrumentation of this Laboratory.

Table I—Pharmacological Properties of *O*-Acylmorphines

Morphine Derivatives[a]	ED_{50}, mg/kg[b]	PDC[c]	Duration of Action, hr (Monkeys)
I	0.5 (0.4–0.6)	High (1.0)[d]	3–4
II	0.6 (0.5–0.8)	—[e]	—
III	0.3 (0.2–0.4)	High (0.8)[d]	3–4
IV	0.5 (0.4–0.6)	High (1.0)[d]	—[f]
V	0.3 (0.2–0.4)	High (1.6)[d]	12
VI	0.3 (0.2–0.4)	Medium high (2.0)[d]	>6
VII[g]	1.3 (1.2–1.5)	High (2.0)[d]	3
Morphine[a]	1.2 (0.9–1.3)	High (3.0)[d]	6

[a] Subcutaneously administered as hydrochloride salts, unless otherwise noted, to mice. [b] Determined by the hot-plate method (6, 7). Numbers in parentheses are the 95% *SE* limits, as obtained by probit analysis. [c] Physical dependence capacity as determined in monkeys (8, 9). [d] Equivalence to 3 mg/kg of morphine sulfate. [e] Too unstable to test in monkeys. [f] Of shorter duration than morphine. [g] Sulfamate salt.

(to the appearance of crystals) and cooled finally to 0° for 1 hr to give 1.8 g, mp 155–165°.

Anal.—Calc. for $C_{20}H_{24}ClNO_4 \cdot 0.5H_2O$: C, 62.07; H, 6.47; Cl, 9.16; N, 3.62. Found: C, 61.70; H, 6.43; Cl, 9.18; N, 3.29.

RESULTS AND DISCUSSION

As seen in Table I, the 3,6-diformyl (II), 3,6-dipropanoyl (III), and 6-propanoyl (VI) derivatives were comparable to heroin (I) and 6-acetylmorphine (IV) in analgesic potency and were three to four times as potent as morphine (6, 7). 3-Acetylmorphine (VII) sulfamate (4) was nearly identical in potency to morphine. As expected, all had good capacity to sustain morphine dependence in monkeys (8, 9) with a wide variation in duration of action. Superiority in this respect was shown by V (12 hr) and VI (>6 hr), both longer acting than morphine, heroin, or 6-acetylmorphine[2].

The mode of action of the 6-acylated compounds, V and VI, is not known. Like 6-acetylmorphine, they are probably metabolized to morphine (10), albeit less rapidly. Their duration of action for analgesia (mice) was much longer than that for heroin but similar to morphine. Their considerably longer action than heroin and even morphine in higher animals (monkeys) may be more indicative of their behavior in humans.

The oral activity of V and VI (in mice) was relatively good (ED_{50} 11.6 and 7.4 mg/kg, respectively). Thus, V and VI would appear to be the most interesting compounds of this group for further study as possible maintenance drugs or in detoxification therapy. The diformyl compound (II) was too unstable to be tested in monkeys.

Qualitatively, the order of stability of these compounds in the salt form noted in Table I appeared to be: 3,6-diacetyl ≅ 3,6-dipropanoyl > 6-propanoyl ≅ 6-acetyl ≅ 3-acetyl > 6-formyl > 3,6-diformyl derivatives at 25°. This order seems to be at variance with the durations of action in supporting morphine dependence in monkeys. The impression is given by these qualitative studies that the acylmorphines (as salts), except II, are more stable in aqueous solution than is generally believed.

[2] Extracted from Addenda to the Proceedings of several meetings of the Committee on Problems of Drug Dependence in early to mid-1950's.

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Liquid Chromatography in Pharmaceutical Analysis VI: Determination of Dantrolene Sodium in a Dosage Form

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Abstract □ Operating conditions are described for the qualitative and quantitative determination of dantrolene sodium by high-pressure liquid chromatography. A 10-μm porous silica column was employed, using carbon tetrachloride–dimethylformamide (90:10) as the mobile phase. The flow rate was 2.0 ml/min (1800 psig), and the peaks were detected at 375 nm. The analysis of a dosage form can be carried out within 30 min with an accuracy of 3.1%. The results agree favorably with those obtained with a modified spectrophotofluorometric method.

Keyphrases □ Dantrolene sodium—high-pressure liquid chromatographic analysis, commercial dosage forms □ High-pressure liquid chromatography—analysis, dantrolene sodium, commercial dosage forms □ Relaxants, skeletal muscle—dantrolene sodium, high-pressure liquid chromatographic analysis, commercial dosage forms

Dantrolene sodium, 1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin sodium salt hydrate, was first reported by Snyder *et al.* (1) as a representative of a new class of muscle relaxants which apparently acts directly on the skeletal muscle.

Previous reported analyses of dantrolene sodium include spectrophotofluorometry (2, 3), differential pulse polarography (4), and a colorimetric procedure for qualitative