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Synthesis and Pharmacology of 6-Methylenedihydrodesoxymorphine[1]

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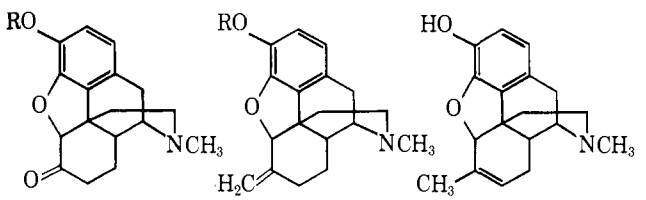
An improved synthesis of 6-methylenedihydrodesoxymorphine (6-MDDM) from dihydromorphinone in an over-all yield of 53% is described. In rats, 6-MDDM is a more potent analgesic than morphine with a more rapid onset but similar duration of action. The analgesia as measured by the tail-flick response to heat is antagonized by nalorphine. Tolerance to the analgesic and sedative effects of 6-MDDM develops more slowly and to a lesser degree than is the case for morphine. Effects on arterial pressure and intestinal motility are less for 6-MDDM than for morphine, but the two have about the same respiratory depressant and antidiuretic actions. Limited human trial indicates that 6-MDDM has analgesic, sedative, and respiratory depressant actions.

Initial pharmacological evaluation of 6-methylenedihydrodesoxymorphine (6-MDDM) (IIa) and related compounds[2] revealed that in mice and dogs, 6-MDDM is a potent analgesic with less side effects than morphine. Minimal effects of analgesic doses on the propulsive activity of the gastrointestinal tract were particularly interesting and called for detailed pharmacologic study. However, the original method of preparation[3] was not adequate to provide the quantities of pure material needed for extensive testing, so a new synthesis was devised. The previous procedure resulted in only a 20% yield of impure 6-MDDM (IIa) from dihydrocodeinone (Ib). The contaminant was probably the *endo* isomer (III) or material in which the oxide ring, now allylic, had been cleaved. On the basis of the specific optical rotations of −115° for pure IIa and −240° for III, and assuming III was the impurity in the original IIa, the −140° rotation found for that sample indicates it was 80% IIa and 20% III. Pure 6-MDDM could be obtained from this product by chromatographic separation and recrystallization but the yield then was less than 5%.[4]



Ia, R = H
b, R = CH_3
c, R = CH_3OCH_2

IIa, R = H
b, R = CH_3
c, R = CH_3OCH_2

III

Consideration of the previous method of preparation indicated that the step probably responsible for introducing impurities was the final cleavage of the methoxyl group in 6-methylenedihydroxydesoxycodeine (IIb) (pyridine hydrochloride, 220°) to the phenolic IIa. Such high temperature and acidity could easily cause isomerization of the *exo* to the *endo* double bond isomer, as well as oxide ring opening. This suggested that milder conditions might be used to generate the phenolic group at C-3.

In an attempt to avoid the necessity of ether cleavage, dihydromorphinone (Ia) methylenetriphenylphosphorane was treated directly. However, even when using a large excess of Wittig reagent, starting ketone was the only substance isolated.

An alternative was to apply a more easily removable blocking group such as a methoxymethyl ether. These ethers are easily prepared, stable to the anticipated reaction conditions, and removed by relatively mild acid hydrolysis. It was possible to prepare the O^3-methoxymethyl ether of dihydromorphinone (Ic) by treating the sodium salt of Ia with chloromethyl methyl ether. This, when treated with methylenetriphenylphosphorane, gave IIc which on hydrolysis in acetic acid yielded 6-MDDM (IIa). The reactions were straightforward and the over-all yield (Ia → Ic → IIc → IIa) was 53%.

Purity of the product was established in three ways. First, a sample of IIa was converted in practically 100% yield to its methyl ether, IIb, by treatment with diazomethane. The product was identical with IIb as prepared by the original method[3] in which IIb is considered free of the *endo* isomer, since no acid was used

(1) This investigation was supported in part by research Grant NB-00570 from the National Institutes of Health.

(2) R. Okun and H. W. Elliott, *J. Pharmacol. Exptl. Therap.*, **124**, 255 (1958).

(3) M. S. Chada and H. Rapoport, *J. Am. Chem. Soc.*, **79**, 5730 (1957).

(4) P. E. Wiegert, G. Dela Mater, G. C. McElheny, and L. A. Patterson, *J. Org. Chem.*, **26**, 5249 (1961).

in its preparation. Second, no C-methyl group could be detected in IIa by appropriate analyses (Kuhn-Roth and n.m.r.). Third, we demonstrated that the acid conditions to which IIa had been exposed in its preparation (0.1 *M* H_3PO_4 at room temperature and 2 *M* acetic acid at 90°) were nonisomerizing and nonequilibrating by repeating this exposure in the presence of tritium oxide. Since the recovered 6-MDDM was nonradioactive, we can set 0.1% as the upper limit of isomerization or equilibration.

The pure 6-MDDM obtained by this method was converted to the acetate salt by addition of 1 mole of acetic acid to 1 mole of base and was used as such in the following pharmacological studies with morphine as the control drug. These were determination of (a) the ED_{50} for analgesia, LD_{50}, and therapeutic index in rats; (b) the rate of development in rats of tolerance to analgesic and sedative effects; (c) the action on the respiration of rats; (d) the effect of single doses on the blood pressure of rats; (e) the antidiuretic action in rats and the influence of cortisone thereon; and (f) the effects on the gastrointestinal tract of rats and rabbits. Results of administration of 6-MDDM to four human subjects will also be reported.

Experimental Section

Synthesis.[5] **O^3-Methoxymethyldihydromorphinone (Ic).**—To 100 ml. of 1.07 *N* sodium ethoxide in ethanol was added 31.4 g. (0.11 mole) of dihydromorphinone (Ia).[6] The resulting solution was evaporated, and the residue was dissolved in 100 ml. of benzene which was also evaporated to leave the sodium salt of dihydromorphinone as a frothy residue. This in 100 ml. of anhydrous $CHCl_3$ was cooled in an ice bath and treated dropwise with 8.0 g. (0.1 mole) of chloromethyl methyl ether. The reaction mixture, after standing at room temperature for 12 hr., was diluted with 200 ml. of $CHCl_3$, extracted four times with 50-ml. portions of 1 *N* NaOH, washed with water, and dried. Evaporation left a residue (30.2 g.) which was crystallized from ethyl acetate–hexane to give 25.1 g. (70%) of Ic, m.p. 102–103°, $[\alpha]^{30}D$ −164°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0; OCH_3, 9.4. Found: C, 69.5; H, 7.1; OCH_3, 9.4.

O^3-Methoxymethyl-6-methylenedihydrodesoxymorphine (IIc).—A solution of 12.0 g. (36 mmoles) of Ic in 150 ml. of tetrahydrofuran was added dropwise to a standardized solution[3] of methylenetriphenylphosphorane prepared from 15 g. of methyltriphenylphosphonium bromide. The mixture was stirred for 3 hr. at room temperature and for 60 hr. at reflux after which time the solvent was evaporated, and the residue was dissolved in 200 ml. of $CHCl_3$. This was washed with four 100-ml. portions of 0.1 *M* H_3PO_4, the combined aqueous extracts were adjusted to pH 10 with NaOH, the aqueous phase was extracted with two 100-ml. portions of CH_2Cl_2, and the CH_2Cl_2 was evaporated to leave 9.1 g. of residue. The original $CHCl_3$ solution was now shaken four times with 50-ml. portions of 4 *N* NaOH and then extracted with H_3PO_4 and CH_2Cl_2 as described above to give another 5.5 g. of crude residue. The combined residues were digested with 400 ml. of benzene. Washing the benzene solution with pH 7 bisulfite–sulfite buffer removed ketonic material which was then recovered by adjusting the pH to 12 and extracting with CH_2Cl_2. Evaporation of the CH_2Cl_2 left 2.0 g. (17%) of recovered Ic. The residue from evaporation of the benzene solution was chromatographed on alumina (Merck, alkaline), using benzene to elute the IIc as a colorless glass; yield, 7.8 g. (65% conversion or 78% allowing for recovered ketone).

The **picrate**, prepared from ethanolic picric acid, was recrystallized from ethanol; m.p. 188–189°.

Anal. Calcd. for $C_{26}H_{28}N_4O_{16}$: C, 56.1; H, 5.1; N, 10.1. Found: C, 56.2; H, 5.1; N, 9.8.

6-Methylenedihydrodesoxymorphine (IIa).—The O^3-methoxymethyl ether IIc (1.1 g., 3.4 mmoles) was dissolved in 50 ml. of 2 *N* acetic acid and heated at 90° for 40 hr. Chloroform (200 ml.) was added after the aqueous solution was evaporated to dryness, and the $CHCl_3$ phase was extracted with two 100-ml. portions of 2 *N* NaOH. After adjusting the combined aqueous extracts to pH 9, they were extracted with 200 ml. of CH_2Cl_2. Evaporation of the CH_2Cl_2 left a residue which was twice crystallized from methanol–water and sublimed (180°, 10 μ) to give 0.94 g. (97%) of 6-methylenedihydrodesoxymorphine, m.p. 207–209°, $[\alpha]^{22}D$ −115° (lit. m.p. 196–198°,[3] 208.5–210.5°,[6] $[\alpha]^{21}D$ −140°,[3] $[\alpha]^{25}D$ −117°[7]).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5; N, 4.9; CCH_3, 0. Found: C, 76.2; H, 7.4; N, 4.8; CCH_3, 0.

With ethereal diazomethane, a methanolic solution of IIa gave a quantitative yield of 6-methylenedihydrodesoxycodeine (IIb), identical (melting point, specific rotation, ultraviolet, and infrared) with the previous material prepared from Ib.[3]

6-Methyl-Δ^6-desoxymorphine (III) was liberated from a sample of the hydrochloride[7] and after two crystallizations from ethanol–water and sublimation (170°, 10 μ) melted at 232–233°, $[\alpha]^{25}D$ −240° (lit.[8] m.p. 225–229°, $[\alpha]^{25}D$ −215°; m.p. 235–237°[3]).

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5; N, 4.9; CCH_3, 5.5. Found: C, 76.3; H, 7.7; N, 5.1; CCH_3, 5.1.

6-Methylenedihydrodesoxymorphine hydrochloride was prepared by adding a slight excess of concentrated aqueous HCl to a warm solution of 6-methylenedihydrodesoxymorphine in absolute ethanol. The crystals formed on cooling were recrystallized from ethanol: m.p. 314–315°. The n.m.r. absorption showed the absence of a $CH_3C=C$ group and the presence of a $H_2C=C$ group.

Anal. Calcd. for $C_{18}H_{22}NO_2 \cdot HCl$: C, 67.6; H, 6.9; N, 4.4. Found: C, 67.6; H, 7.1; N, 4.4.

Isomerization and Equilibration Studies with 6-Methylenedihydrodesoxymorphine (IIa).—Solutions of 55 mg. of IIa in 5 ml. of (a) 0.1 *M* H_3PO_4 and (b) 2 *N* acetic acid were prepared, each containing 5-μc. of radioactivity as tritium oxide. The H_3PO_4 solution stood at room temperature for 4 days, and the acetic acid solution was heated at 90° for 40 hr. Alkalization in each case gave practically a quantitative recovery of completely inactive IIa, as determined by scintillation counting.

Estimation of Analgesia, Acute Toxicity, and Development of Drug Tolerance.—Young adult male Sprague–Dawley rats weighing 80–170 g. were used for drug potency studies. 6-MDDM and morphine sulfate or various drug combinations were administered subcutaneously and doses were expressed in terms of the free bases. At least 20 rats were used at each dose level. The tail-flick response to a thermal stimulus (analgesia) was determined by the method of D'Amour and Smith.[9] Lethality was measured at 24 hr. with all rats in groups of not more than 5 animals in similar wire mesh cages. The ED_{50} (analgesia) and the LD_{50} and their confidence limits were established by the method of Litchfield and Wilcoxon.[10] The tail-flick response was quantified by the method of Winter and Flataker[11] in which the total analgesic effect is expressed as "minute-seconds," *i.e.*, the product of the prolongation of reaction time and the duration of this prolongation. In determination of tolerance to analgesia, equipotent doses of morphine (8.0 mg./kg.) and 6-MDDM (0.35 mg./kg.) were administered subcutaneously once daily, and the tail-flick response was measured weekly or once every 2 weeks. Development of tolerance to the sedative effects of 6-MDDM and morphine was studied in the same rats by measuring the period of sedation or inactivity time following drug injection. For this purpose, after their daily drug injection, the rats were placed in simple activity cages made from wire baskets suspended from Grass force-displacement transducers (FT 03) which recorded cage movement on a polygraph. Pendulum motion was kept to a minimum by suspending the cages 1–2 cm. above wooden bases provided with 4 nails that fit the corners of the cages. The

(5) All melting points are corrected and those above 200° were taken in evacuated capillaries; analyses were performed by the Microchemical Laboratory, University of California, Berkeley; all evaporations were made *in vacuo* from rotary evaporators; optical rotations were observed with the sodium D line on 1% solutions in 95% ethanol.

(6) Generously supplied by Dr. A. Homeyer of the Mallinckrodt Chemical Works, St. Louis, Mo.

(7) We are indebted to Dr. K. Pfister of Merck Sharp and Dohme, Railway, N. J., for this sample.

(8) H. D. Brown, I. M. Rasmussen, G. B. Payne, and K. Pfister, 3rd., *J. Am. Chem. Soc.*, **75**, 6238 (1953).

(9) F. E. D'Amour and D. M. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(10) J. T. Litchfield, Jr., and F. Wilcoxon, *ibid.*, **96**, 99 (1949).

(11) C. A. Winter and L. Flataker, *ibid.*, **98**, 305 (1950).

end of the period of sedation was clearly marked by the recording of continuous or near-continuous activity. Inactivity time was measured 6 days a week and on the 7th day the response to tail flick was determined.

Effect of 6-MDDM and Morphine on Respiration of Rats.—The effects of 6-MDDM and morphine on respiration were determined in rats using the body plethysmograph–metabolism chamber described by Kokka, Elliott, and Way.[12] With this apparatus, respiratory rate, tidal and minute volumes, and oxygen consumption can be measured before and after drug administration. In essence, a rat sealed in a body plethysmograph by means of a latex collar is placed in a metabolism chamber with connections for administering drugs and recording pressure changes within the chamber. A schematic drawing of the apparatus is shown in Figure 1. After the rat has adjusted to its surroundings, control recordings of rate, tidal volume, and oxygen consumption are made at 15-min. intervals for 1 hr. and a drug is then administered *via* a previously implanted no. 50 polyethylene catheter. Measurement of respiratory parameters is then continued for the duration of drug action. In these studies the original method of recording was slightly modified. Instead of determining tidal volume from pressure changes within the plethysmograph, that chamber was opened to the atmosphere during recording and tidal volume was recorded as pressure changes within the metabolism chamber. This minimized errors from leakage of air around the collar and made the fit of the collar less critical. Equianalgesic doses (ED_{95}) of 6-MDDM (0.19 mg./kg.) and morphine (4.0 mg./kg.) were given in these studies. Five animals weighing 133–172 g. were used for each drug with each animal serving as its own control. Measurements were made until values returned to control levels. The time involved was less than 8 hr., a period during which respiratory rate, tidal volume, and oxygen consumption of untreated rats did not change.

Effect of 6-MDDM and Morphine on Blood Pressure of Rats.—Male Sprague–Dawley rats weighing 265–300 g. were anesthetized with urethan (1.5 mg./kg.) and given 10 mg./kg. of heparin intravenously. The trachea and a carotid artery were cannulated and the arterial catheter was connected to a Statham transducer (Model P23AC) for recording blood pressure on a Grass polygraph. Equianalgesic doses of 6-MDDM (4.5 μg./kg.) and morphine (100 μg./kg.) were given to two groups of three rats each in a volume of 1.0 ml./kg. of body weight.

Evaluation of the Antidiuretic Effect of 6-MDDM and Morphine.—Essentially the method of Winter, *et al.*,[13] was used to determine the antidiuretic effect of the two drugs in male Sprague–Dawley rats weighing 88–124 g. The rats were fasted overnight but had free access to water. Just before drug administration, 50 ml./kg. of tepid tap water was administered by intragastric tube. The treated rats were then placed in groups of 6 or 7 in a metabolic cage, the floor of which was covered with paraffin. Urine volume was measured every 15 min. for 120 min.

In determining the effect of chronic cortisone treatment on the narcotic antidiuretic action 12 rats per drug plus 12 controls were given 2.5 mg. of cortisone (Cortone acetate, Merck) subcutaneously, daily for 9 days. Narcotic injection and urine collection were done 90–120 min. after the last injection of cortisone.

Effects of 6-MDDM and Morphine on Gastrointestinal Motility.—The method of Van Arsdel[14] was used to determine the effect of the ED_{50} (analgesia) of 6-MDDM and morphine on the passage of a charcoal meal through the gastrointestinal tract of rats. The drugs were given subcutaneously to rats fasted for 36 hr. Thirty minutes later 0.6 ml. of a slurry composed of 5% charcoal and 5% tragacanth in distilled water was administered by intragastric tube. After another 30 min., the rats were killed by ether, and the stomach and small intestine were removed, suspended from the stomach, and stretched with a 5-g. weight. The percentage of the length of the small intestine traversed by the slurry was computed.

Other studies on intestinal mobility utilized 6 unanesthetized male, New Zealand, white rabbits (2.7–3.7 kg.). Under ether anesthesia a no. 10 rubber catheter was introduced into the jejunum and secured by a purse string suture. The catheter was brought through a stab wound, sutured to the skin at the point of exit, filled with saline, and clamped. Several days were allowed for recovery before the animals were used for drug studies. To determine the effects of 6-MDDM and morphine on jejunal motility the animals were confined in rabbit holders, and the catheters were filled with saline and connected to a Statham pressure transducer for recording pressure changes on a polygraph. After a control record was obtained, drugs were given *via* a marginal ear vein and recordings were made during the duration of drug action. Each animal was used several times with 1–2 days rest between recordings.

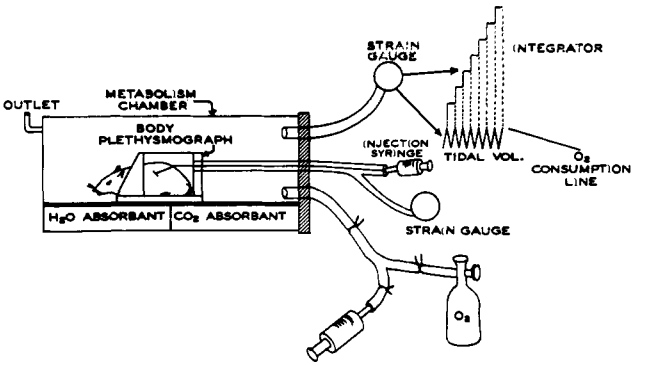


Figure 1.—Schematic drawing of apparatus for studying respiration in unanesthetized rats.

Results and Discussion

ED_{50} and LD_{50}.—Values for the ED_{50} and LD_{50} of 6-MDDM and morphine administered subcutaneously to rats are shown in Table I. In the rat, 6-MDDM is more than 22 times as potent as morphine and its therapeutic index is about 7 times that of morphine. A favorable ratio has also been reported for the mouse.[2] When equipotent doses (ED_{95}) of morphine and 6-MDDM were quantified by the method of Winter and Flataker,[11] the two drugs produced approximately the same minute-seconds of analgesia (Figure 2). Significant analgesia was produced 7 min. after administration of 6-MDDM with maximum response at 15 min., in contrast to morphine for which at least 15 min. was required for development of analgesia. The drugs summate, since a mixture of half of the ED_{95} of both drugs produced the same minute-seconds of analgesia as the ED_{95} of either drug (Figure 2).

TABLE I

ANALGESIC POTENCY AND TOXICITY OF MORPHINE AND 6-MDDM IN RATS

Drug	ED_{50}, mg./kg. (95% confidence limits)	LD_{50}, mg./kg. (95% confidence limits)	Therapeutic index (LD_{50}/ED_{50})
Morphine	1.020 (0.76–1.35)	270.0 (207–351.0)	265.0
6-MDDM	0.045 (0.033–0.062)	82.0 (45.0–148.0)	1822.0

Analgesia, as measured by the tail-flick response to heat, is reversed when either 6-MDDM- or morphine-treated rats are given nalorphine. Figure 2 shows that 2.0 mg./kg. of nalorphine decreased the response to the ED_{95} doses to about one-third of control values. No attempt was made to determine the optimum narcotic/nalorphine ratios for antagonism of analgesia, but a 6-MDDM/nalorphine ratio of 1/10.5 had about the same effect as a morphine/nalorphine ratio of 1/0.5. Analgesia was practically abolished at a 6-MDDM/nalorphine ratio of 1/21. Since nalorphine antagonizes equipotent doses of both drugs equally, they probably cause analgesia by the same mechanism. The ratios

(12) N. Kokka, H. W. Elliott, and E. L. Way, *J. Pharmacol. Exptl. Therap.*, **148**, 386 (1965).

(13) C. A. Winter, *ibid.*, **111**, 360 (1954).

(14) W. C. Van Arsdel and N. David, *Federation Proc.*, **12**, 375 (1953).

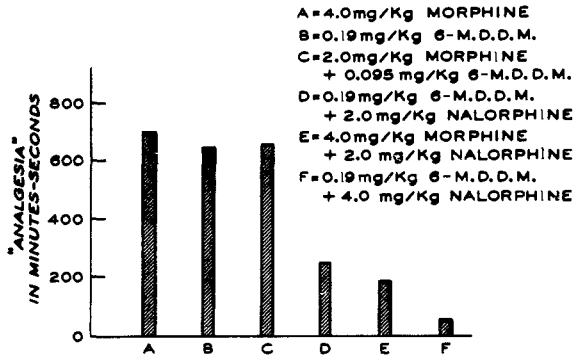


Figure 2.—Analgesic response in minute-seconds of ED_{95} values of individual drugs and of drug combinations in rats.

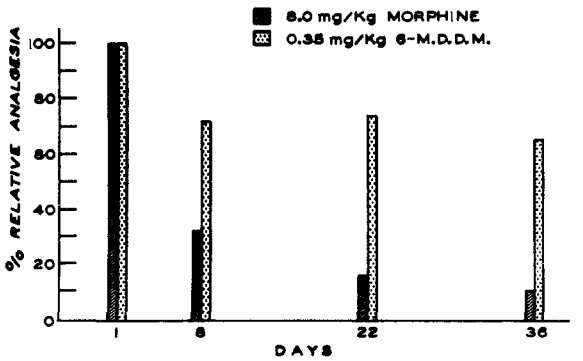


Figure 3.—Development of tolerance to analgesic effects of 6-MDDM and morphine by rats.

do not necessarily mean that nalorphine is a more effective antagonist of morphine than of 6-MDDM, since the latter may penetrate to the ultimate site of action more quickly than does morphine.

The increased potency and more rapid onset of action of 6-MDDM, as compared to morphine, might be taken as another example of increased activity following masking of the alcoholic hydroxyl on the C ring of morphine. In addition, substitution of a lipophilic (methylene) group for a hydrophilic (hydroxyl) group may contribute by either making the molecule more lipid soluble, thus enhancing penetration to hypothetical receptors in the brain or by permitting formation of a more stable hydrophobic bond with the receptor.

Tolerance Studies.—With two groups of 5 rats each, given the ED_{95} doses (6-MDDM 0.19 mg./kg., morphine 4.0 mg./kg.), analgesia was measured on the 1st, 8th, and 15th days of treatment. On the 8th and 15th days, 6-MDDM retained 87 and 68%, respectively, of its original effectiveness, whereas comparable figures for morphine were 24 and 7%. Another two groups of 5 rats each were given the ED_{99} doses (6-MDDM 0.35 mg./kg. s.c. and morphine 8.0 mg./kg. s.c.) and tested weekly for 3 weeks. On the 22nd day 6-MDDM retained 80% of its original effectiveness; morphine fell to 27%. Another two groups of rats each were given daily ED_{99} doses and followed for 5 weeks. The contrast between the rapid development of tolerance to morphine and minimal tolerance to 6-MDDM is shown graphically in Figure 3. Since the duration of analgesia is the same following comparable doses of 6-MDDM and morphine, opportunity for tolerance development should be the same for both drugs. However, the more rapid onset of action of 6-MDDM suggests that the half-life of the drug in the body may be shorter than is the case for morphine. The gradual

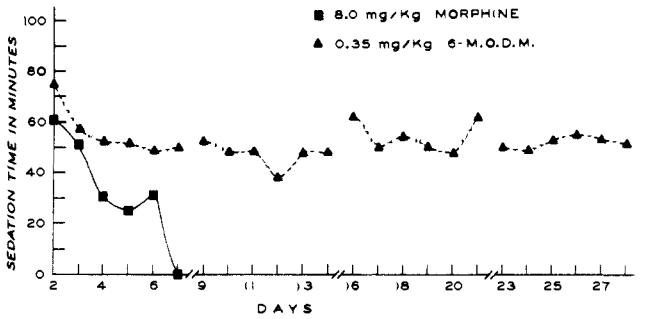


Figure 4.—Development of tolerance to sedative effects of 6-MDDM and morphine by rats.

development of tolerance after morphine differs from the abrupt development of tolerance to the respiratory effects of morphine as reported elsewhere.[12] The response of the third group of rats to the sedative effect produced by ED_{99} doses of the two drugs is shown in Figure 4. The period of sedation following morphine administration decreased rapidly from an average of 60 min. until the 7th day when sedation was replaced by the hyperactivity characteristic of rats tolerant to morphine.

The period of inactivity for the rats given 6-MDDM dropped from an average of 74 min. on day 2, to 50 min. on day 5, and remained there for the next 23 days. Thus, as was the case for analgesia, only minimal tolerance developed to the sedative effects of 6-MDDM. The contrast with morphine was even more striking than was found for analgesia, since, after 7 days, sedation following morphine completely disappeared; after 6-MDDM, tolerance to sedation did not progress beyond the minimal amount seen on day 3. The complete tolerance seen after morphine resembles that produced to the depressant effects on respiratory rate, oxygen consumption, and response to CO_2 after 4–8 days.[12] If the decreased rate of development of tolerance to 6-MDDM, relative to morphine, demonstrated in these studies on rats is valid when 6-MDDM is given in multiple, daily doses as well as in other species, the compound may have an advantage over morphine not shown for other morphine-like agents.

Respiratory Studies.—The effects of ED_{95} doses of 6-MDDM and morphine on respiratory rate, tidal volume, minute volume, and oxygen consumption are presented in Table II. For simplicity, only control, peak-effect, and end-experiment values are included. The peak response occurred 15 min. after injection of 6-MDDM and 45 min. after morphine administration. Maximal depression of minute volume persisted for about 45 min. in both cases, followed by gradual recovery over the next 120 min. In keeping with the early onset of action, recovery was complete 165 min. after 6-MDDM *vs.* 180 min. for morphine. Respiratory rate was not depressed, and hence, decreased tidal volume was responsible for the changes in minute volume. This agrees with the findings of Kokka, *et al.*,[12] for 5 mg./kg. of morphine. The fall in oxygen consumption at the peak effect of 6-MDDM was probably the result of sedation. Further work will be required to determine if the apparent stimulation of oxygen consumption at 165 min. is related to persistence of a stimulant action of 6-MDDM. It is apparent that in equianalgesic doses, 6-MDDM is approximately as depressing as morphine to the respiration of rats

TABLE II

THE EFFECTS OF 6-MDDM AND MORPHINE ON RESPIRATION OF RATS

	Av. control values (Range)	Av. peak effect values, 45.0 min. (Range)	Av. end expt. values, 180.0 min. (Range)
	Morphine, 4.0 mg./kg. (5 animals)		
Respiratory rate	95 (86–105)	91 (78–114)	96 (92–103)
Tidal vol., cc.	0.99 (0.84–1.17)	0.64 (0.51–0.73)	0.99 (0.86–1.2)
Minute vol., cc.	94.2 (85.5–102)	58.3 (45–58.6)	95.2 (80–112)
O_2 consumption[a]	2.73 (2.46–2.97)	2.94 (2.2–3.48)	3.08 (2.47–3.31)
	6-MDDM, 0.19 mg./kg. (5 animals)		
Respiratory rate	94 (75–107)	93 (70–102)	93 (80–110)
Tidal vol., cc.	1.06 (1.0–1.17)	0.55 (0.50–0.63)	1.11 (1.03–1.22)
Minute vol., cc.	100 (88–108)	51.0 (45–58)	101 (86–113)
O_2 consumption[a]	2.77 (2.45–3.73)	2.35 (2.2–2.7)	3.45 (3.2–3.7)

[a] O_2 consumption = cc. of O_2/100 g./min.

This parallelism between analgesic and respiratory-depressant potency also holds for morphinan and benzomorphan narcotic-antagonist analgesics such as pentazocine.[15]

Effects on Blood Pressure.—Small equianalgesic doses of 6-MDDM (4.5 μg./kg.) and morphine (100 μg./kg.) were given intravenously to anesthetized rats prepared for recording blood pressure. The 6-MDDM caused an average drop in mean blood pressure of 13.0 mm. (range 7.0–16.0 mm.). The equivalent dose of morphine produced an average fall of 45 mm. (range 35.0–61.0 mm.). As shown in Figure 5, the duration of hypotension and an increase in pulse pressure were greater after morphine than after 6-MDDM, indicating that in the rat, 6-MDDM produces less vasodilation and/or other cardiovascular depression than morphine.

Antidiuretic Actions.—The antidiuretic effects of 6-MDDM and morphine were determined in normal and cortisone-treated rats. The results are depicted in Figure 6 in terms of percentage of water load excreted in 120 min. In normal rats both drugs had approximately the same antidiuretic activity. However, cortisone pretreatment almost completely negated this action in the case of morphine and partly negated it when 6-MDDM was given. Thus, cortisone has been shown to antagonize the antidiuretic action of morphine-like drugs, as well as the analgesia, hypnosis, and catalepsy in rats, and the hyperactivity and methadone toxicity in mice.[11] It has been shown[16] that methadone concentration in the brain was reduced after cortisone treatment and that at the same time the drug was excreted more rapidly. Thus, the cortisone antagonism could be the result of lower drug concentrations at brain sites of action achieved by alterations in the blood–brain barrier or simply by speeding the passage of the drug through the organism.

Effects on Intestinal Motility.—The findings shown in Table III indicate that, as was true for mice,[2] 6-MDDM has much less effect on gastrointestinal motility of rats than morphine which slows motility to about 40% of control values. The same conclusion is valid for the rabbit. In this species the response of jejunum to approximately equianalgesic doses of 6-MDDM (0.1 mg./kg.) and morphine (2 mg./kg.) was determined from pressure changes transmitted through previously implanted catheters. Both drugs depressed motility without prior stimulation. Depression after 6-MDDM

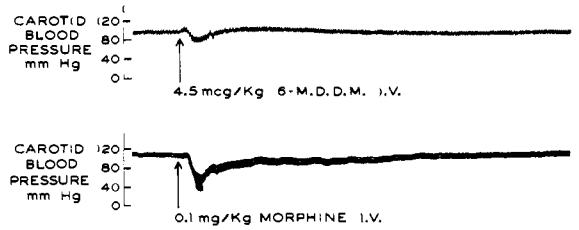


Figure 5.—Blood pressure changes induced by 6-MDDM and morphine in anesthetized rats.

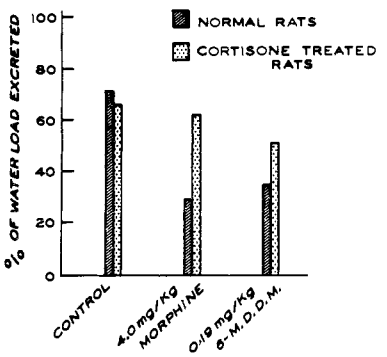


Figure 6.—Excretion of water load of normal and cortisone-treated rats 120 min. after 6-MDDM or morphine administration.

TABLE III

THE EFFECTS OF 6-MDDM AND MORPHINE ON INTESTINAL MOTILITY IN RATS

Treatment	No. of animals	% of small intestine traveled by the slurry Mean ± S.E. (Range)	Comparison to control
Saline, 1 ml./kg.	12	51.4 ± 1.79 (36.4–61.0)	
6-MDDM, 0.045 mg./kg.	13	45.5 ± 2.87 (23.1–59.7)	No significant slowing
Morphine, 1.0 mg./kg.	9	21.0 ± 3.91 (3.8–41.9)	Significant slowing; $p < 0.01$

lasted an average of 20 min. (range 12–27 min.). The comparable value for morphine was 86 min. (range 80–90 min.). Morphine, in a dose of 1.0 mg./kg., caused depression for about 60 min. The mechanism of action of morphine-like drugs on the intestine is uncertain and has been ascribed to effects anywhere between the brain and the intestinal smooth muscle cells. These experiments shed no light on mechanisms but do indicate that 6-MDDM may possess a clear advantage over

(15) J. W. Bellville and J. Green, *Clin. Pharmacol. Therap.*, **6**, 152 (1965).
(16) H. W. Elliott and C. Elison, *J. Pharmacol. Exptl. Therap.*, **131**, 31 (1961).

morphine in that it is analgesic without interfering markedly with intestinal motility.

Human Studies.—A 52-year-old female with metastatic carcinoma of the breast who was extremely tolerant to morphine was given 6-MDDM in doses of 0.5, 1.0, 2.0, and 3.0 mg., subcutaneously. After the 2.0- and 3.0-mg. doses, she was euphoric and less concerned with her pain. The effects occurred sooner (10–15 min.) than with morphine and were accompanied by a mild hypotensive effect (115/60 mm. from 130/75 mm.) and miosis (3.0-mm. pupil diameter from 3.4 mm.). In a single blind study the patient was given a placebo, 15 mg. of morphine, and 2 mg. of 6-MDDM in a 9-hr. period. The placebo was ineffective, and the morphine and 6-MDDM provided a similar degree of analgesia which was distinguishable to the observers by the hypotensive effect of the 6-MDDM. No depression of respiratory rate was noted.

Single 0.5-mg. doses of 6-MDDM were then administered intramuscularly to 3 healthy adult males. These subjects were supine and wore an anesthesia mask for administration of CO_2. All subjects were sedated within 15 min. and remained so for more than 2 hr.; recovery was nearly complete after 3 hr. End tidal CO_2 values were elevated in all subjects from 15–180 min. after drug administration, most markedly at 15 min. Intermittant breathing of 3 and 6% CO_2 produced a ventilatory response to a CO_2 curve which was shifted down and to the right as is typical for narcotic analgesics.[17] No hypotension was noted in the supine position and none of the subjects experienced euphoria, dysphoria, or nausea.

Thus, on the basis of limited trial in man, 6-MDDM appears to be an analgesic, sedative, and respiratory-depressant drug which exhibits partial cross tolerance with morphine and may produce orthostatic hypotension but not nausea or notable euphoria. Addiction liability studies will be done in monkeys and then in humans if the animal evidence is favorable.

(17) C. J. Lambertsen in "Handbook of Physiology," Vol. 1, W. O. Fenn and H. Rahn, Ed., American Physiological Society, Washington, D. C., 1961, p. 545.

Analgesic Antagonists. I. 4-Substituted 1-Acyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepines

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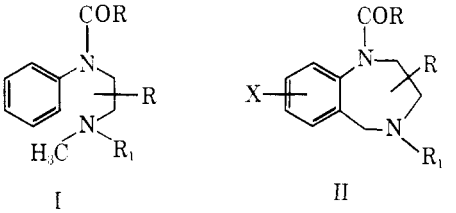
A series of 4-substituted 3H-1,4-benzodiazepine-2,5(1H,4H)-diones has been prepared by two methods. Reductive cyclization of an ethyl N-(*o*-nitrobenzoyl)glycinate gave the seven-membered cyclic diamide in very good yield. Heating an ethyl glycinate with an isatoic anhydride also gave the benzodiazepinedione, but in poor yield. Reduction of the diamides with lithium aluminum hydride followed by acylation gave the title compounds, which are analgesic antagonists.

Anilides of the structural type I have been shown[1] to be strong analgesics. In our search for analgesics and analgesic antagonists, we considered structures of the type II as likely to possess analgesic and/or analgesic antagonist activities, since II may be considered as a cyclized version of I. The structural relationship



I II

between II and Librium[4] was a further spur to our interest in these compounds. The synthetic routes used for obtaining the benzodiazepines II are shown in Scheme I.

Miyatake and Kaga[2] reported the preparation of 3H-1,4-benzodiazepine-2,5(1H,4H)-dione (VI, $R_1 = R_2 = X = H$) by the reduction of *o*-nitrobenzoylglycine using Raney nickel catalyst. Uskokovic and co-workers[3a] have also prepared this compound by heating the piperidide of *o*-aminobenzoylglycine. They reported that heating ethyl *o*-aminobenzoylglycine gave a poor yield of VI ($R_1 = R_2 = X = H$).

We have repeated the preparation of VI ($R_1 = R_2 = X = H$) as described by Miyatake and Kaga[2] and have obtained the aforementioned product in 87% yield. The reduction of *o*-nitrobenzoylglycines[3b] or their ethyl esters was found to be a general method for the preparation of 3H-1,4-benzodiazepine-2,5(1H,4H)-diones. Either Raney nickel or iron–acetic acid was used as the reducing agent, depending on what functional groups were present in the *o*-nitrobenzoylglycine derivatives; the cyclic diamines (VI) were obtained in very good yields by evaporation of the filtered reaction mixture (see Table I).

Another method which was used to prepare compounds of the type VI was heating an isatoic anhydride (X) with a glycine ethyl ester (IX). The poor yields obtained made this method less desirable than the reduction method. However, VI ($R_2 = R_1 = X = H$) and VI ($R_1 = X = H$; $R_2 = CH_2CH{=}CH_2$) prepared by this method were found to be identical with the corresponding products prepared *via* the reduction

(1) W. B. Wright, H. A. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(2) K. Miyatake and S. Kaga, *J. Pharm. Soc. Japan*, **72**, 1160 (1952).

(3) (a) M. Uskokovic, J. Iacobelli, and W. Wenner, *J. Org. Chem.*, **27**, 3606 (1962). (b) After this work had been completed, J. Krapcho, U. S. Patent 3,173,912 (March 16, 1965) was issued, describing a similar method for the preparation of 1,4-benzodiazepinediones.