Narcotic Antagonists. 4. Carbon-6 Derivatives of N-Substituted Noroxymorphones as Narcotic Antagonists

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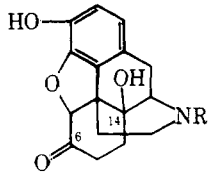
A series of new narcotic antagonists has been synthesized by modifying the C-6 carbonyl group in naloxone (Ia) and naltrexone (Ib). New functional units were introduced by reaction with various phosphorus and sulfur ylides and alkyllithium reagents. The activity of the new compounds was measured by the hot-plate and tail-clip tests after oral administration to mice. The majority of the new narcotic antagonists exhibited oral potencies considerably superior to the parent compounds, with 6-methylene derivatives IIa and IIb showing the most impressive increases.

Narcotic agonists such as morphine and its synthetic equivalents are currently used to provide effective analgesia in cases of severe pain. However, the development of tolerance and physical dependence and the resulting problems of narcotic addiction and abuse are associated with their use. Significant effort has therefore been directed to the development of narcotic antagonists, drugs with the capacity to reverse or block the agonist effects of narcotics. They are presently used to reverse the respiratory depression that accompanies narcotic usage in clinical practice and are being tested as prophylactic agents in combating narcotic drug abuse. For this latter purpose a narcotic antagonist is required which exhibits little or no agonist properties, has an extended duration of action, and is preferably orally effective. This paper reports on the synthesis of a number of new narcotic antagonists which, from initial pharmacological testing in rodents, appear to possess the desired properties to a greater degree than any heretofore available.

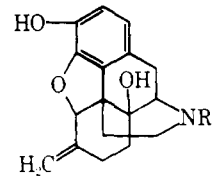
The vast majority of narcotic antagonists synthesized to date have varying degrees of agonist activity,[1-3] and it remains a formidable challenge to obtain antagonists devoid of such properties. Virtually the only "pure" antagonists known today are naloxone (Ia) and naltrexone (Ib), with the latter retaining somewhat greater agonist activity but exhibiting greater potency and a longer duration of action.[4,5] The two drugs are structurally closely related, and in an effort to retain their desirable qualitative pharmacological profile we directed our initial synthetic efforts toward compounds retaining the basic structural features of these narcotic antagonists.



Ia, R = $CH_2CH{=}CH_2$

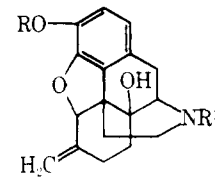
b, R = CH_2—cyclopropyl

Chemistry. The C-6 carbonyl group in structure I lends itself readily to modification. It appeared reasonable to us that the structure–activity correlation derived at this position for narcotic agonists might also translate to the antagonists. Replacement of the C-6 carbonyl by a methylene group has resulted in morphine and codeine analogs up to 75 times more potent than the parent compound.[6-8] This increase in potency was accompanied by a decrease in the duration of action,[7] except for the 14-hydroxy series where the length of activity was unaffected.[8] There was therefore some expectation that a similar increase in potency, without a decrease in duration of action, might be attainable for 14-hydroxy antagonists Ia and Ib. A Wittig reaction, using Corey's modified reagent[9,10] when carried out on Ia and Ib, gave the 6-methylene derivatives IIa and IIb. Selective esterification of the phenolic group in each compound with acetic anhydride yielded the respective monoacetates IIIa and IIIb. Reaction of IIb with cinnamoyl chloride under controlled conditions similarly yielded 3-cinnamate IIIc.



IIa, R = $CH_2CH{=}CH_2$

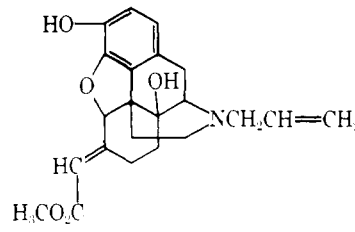
b, R = CH_2—cyclopropyl



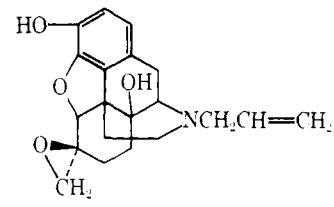
IIIa, R = Ac; R¹ = $CH_2CH{=}CH_2$

b, R = Ac; R¹ = CH_2—cyclopropyl

c, R = $O_2CCH{=}CHPh$; R¹ = CH_2—cyclopropyl



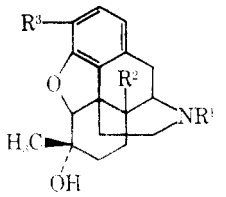
V



VI

Reaction of naloxone (Ia) with carbomethoxymethylenetriphenylphosphorane[11] (IV) yielded the Wittig product V as a 3:1 mixture of cis–trans isomers. Although the isomers were separable by preparative thin-layer chromatography, the spectral data obtained were not sufficient to allow for definite structural assignments. Since the pharmacology of the compounds proved to be unexceptional, no further effort was devoted to the structural elucidation of the isomers.

In another modification of the C-6 ketone in naloxone, Ia was allowed to react with dimethyloxosulfonium methylide[12] to give the oxirane VI in good yield. The α stereochemistry of the oxirane ring was assigned on the basis of



VIIa, $R^1 = CH_2CH{=}CH_2$; $R^2 = R^3 = OH$

b, $R^1 = CH_2$—⟨▷⟩; $R^2 = R^3 = OH$

c, $R^1 = CH_2CH{=}CH_2$; $R^2 = OAc$; $R^3 = OH$

d, $R^1 = CH_2CH{=}CH_2$; $R^2 = OH$; $R^3 = OAc$

analogy to a similar reaction in the codeine series.[13]

The C-6 ketone in the morphinone structure is notoriously resistant to Grignard reagents, but it can be alkylated by means of lithium alkyls.[14] The 14-hydroxy group apparently does not interfere with this addition since reaction of Ia or Ib with methyllithium yielded the respective 6-methyl derivatives VIIa and VIIb. When the 3,14-diacetate of naloxone was used as the starting material, the product was the 6-methyl-14-monoacetate VIIc, the result of concomitant hydrolysis of the 3-acetate. The isomeric 3-monoacetate VIId could be obtained by selective acetylation of VIIa. The orientation of the newly introduced methyl group in the above compounds was assigned as β on the basis of nmr evidence.[15] This confirmed that the presence of the 14β-hydroxyl group does not serve to reverse the usual stereochemistry of reactions at C-6. The above-mentioned studies[15] required the preparation of the mono-, di-, and triacetates (VIIIa–c) of the $NaBH_4$ reduction product of naloxone,[16] and these were also included in the present pharmacological evaluation.

Results and Discussion

The oral potency of the new narcotic antagonists in the mouse is compared with that of naloxone and naltrexone in Table I. The agreement between the tail-clip and hot-plate end points is generally good with the only significant divergence appearing in the case of compounds IIIb and IIIc which were considerably more potent in the hot-plate test. Introduction of a methylene function instead of the 6-ketone results in impressive increases in oral potency. Thus the 6-methylene-*N*-cyclopropyl derivative IIb and its 3-acetate and cinnamate esters IIIb and IIIc are 2–7 times more active than the corresponding 6-ketone Ib. The 6-methylene-*N*-allyl derivative IIa and its 3-acetate ester IIIa are also more potent than the parent ketone Ia, although the difference is not as pronounced as in the *N*-cyclopropylmethyl series. Extending the methylene group to a carbomethoxymethylene substituent as in V results in a reduction in potency while introduction of an oxirane at C-6 as exemplified in VI fails to produce any improvement over the parent ketone.

The generation of a 6-methyl-6-hydroxy function *via* alkyl addition produces a considerable increase in activity in the *N*-allyl series as in compound VIIa which exhibits four times greater potency than the 6-ketone, but similar modification in the *N*-cyclopropyl series as in VIIb actually induces a decrease in oral antagonist activity. The increased potency of compound VIIa is abolished in its 3- or 14-monoacetate esters VIId and VIIc.

The sodium borohydride reduction product of naloxone has been reported to have lesser activity (sc) than the parent ketone.[16] The possibility that this decrease in potency may be modified by selective or total acetylation has not been borne out by the results obtained for compounds VIIIa–c, none of which demonstrate impressive activity by the oral route.

The most interesting compounds in the present series are the 6-methylene derivatives IIa and IIb, with the latter showing much greater oral activity. Indeed IIb and its esters IIIb and IIIc are the most potent "pure" oral narcotic antagonists known to date. What makes these compounds particularly significant is that other pharmacological data now being accumulated reveal that, compared to their parent ketones, the 6-methylene derivatives exhibit longer durations of action in mice[17] and retain less agonist character.[18] Furthermore, by the parenteral route early trials have shown that up to 25-fold increases in potency are induced by the methylene group introduction.[18] Should these findings be confirmed in higher species and eventually in man, they would constitute the narcotic antagonist of choice from those presently available.

Biological Data. Methods. a. Hot Plate. Male mice, ten per group, were administered the test compounds orally in water + 10% Tween 80. After 15 min, an analgesic ED_{95} of morphine sulfate was administered sc. Thirty minutes after morphine, the mice were placed individually under a glass evaporating dish onto a hot plate heated with circulating water to 58°. The ED_{50} was calculated as that dose of standard or derivative narcotic antagonist that resulted in foot licking within 30 sec in 50% of the mice placed on the hot plate. This procedure is a modification of the method of Eddy and Leimbach.[19]

b. Tail Clip. Male mice, ten per group, were administered the antagonist orally in water + Tween 80. After 15 min an analgesic ED_{95} of morphine sulfate was administered sc. Mice were tested for antagonism of the morphine-induced analgesic effect 30 min after the dose of morphine. An ED_{50} was that dose of antagonist that caused 50% of the mice to bite at an artery clamp that was applied to the base of the tail. This procedure is a modification of the method of Haffner.[20]

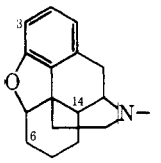
Experimental Section[21]

6-Desoxy-6-methylenenaloxone (IIa). A solution of methylenetriphenylphosphorane was prepared from NaH (576 mg, 53% in oil, 12 mmol) and methyltriphenylphosphonium bromide (4.3 g, 12 mmol) in dimethyl sulfoxide (5 ml).[10] The ylide was stirred for 15 min at room temperature before use. Naloxone (200 mg, 0.6 mmol) dissolved in DMSO (5 ml) was added and the reaction was stirred at 55–60° under a positive pressure of nitrogen for 18 hr. The cooled reaction was neutralized with a saturated solution of ammonium chloride and then extracted with ether. The organic extracts were backwashed with a saturated solution of sodium chloride and then dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was mixed with a 5% hydrochloric acid solution and stirred at room temperature for 30 min. The mixture was extracted with ether, and the aqueous phase was adjusted to pH 8 with 5% sodium hydroxide solution. The aqueous phase was extracted with chloroform (three times) and the combined organic extracts were dried as above, filtered, and evaporated *in vacuo*. The crude product was purified *via* preparative tlc on silica gel using ethyl acetate–ethanol–ammonia (90:10:3) as the solvent system. The yield was 155 mg (79%): mp 185–186° (EtOAc); ir (KBr) λ max 3300 (broad), 1650, 1620, 1450, 1230, 990, 930 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.8 (2 H, arom), 4.9–5.5 (m, 5 H, allyl and 6-methylene), 4.82 (s, 1 H, H^5), 1.3–3.2 (m).

6-Desoxy-6-methylenenaltrexone (IIb). The procedure used in the synthesis of IIa was followed using naltrexone (105 mg, 0.3 mmol), methyltriphenylphosphonium bromide (6.4 g, 18 mmol), and sodium hydride (846 mg, 53% in oil). The yield of product was 83%: mp 188–190° (EtOAc); ir (KBr) λ max 3300 (broad), 1650, 1620, 1460, 1120, 990, 930 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.8 (2 H), 4.82–5.43 (4 H, on addition of D_2O one peak disappears, 6-methylene, H^5 and hydroxyl), 0.5–0.9 (5 H, cyclopropyl).

6-Desoxy-6-methylenenaloxone 3-Acetate (IIIa). Compound IIa (25 mg, 0.08 mmol) was dissolved in a minimum amount of pyridine and acetic anhydride (7.5 μl, 0.08 mmol) was added. The reaction was stirred at room temperature for 15 hr after which time the solvent was removed *in vacuo*. The residue was purified by preparative tlc using the conditions described for IIa to give a

Table I. A Comparison of the Potency of Narcotic Antagonists in the Hot-Plate and Tail-Clip Analgesia Tests in Mice



	ED_{50}, mg/kg[a]		Structural substitution				Rel potency	
Compd	TC	HP[b]	3	6	14	N–	TC	HP
Ia	5.0 (3.4–7.4)[c]	3.1 (1.8–5.4)	–OH	=O	–OH	$-CH_2CH=CH_2$	1.0	1.0
Ib	0.21 (0.13–0.34)	0.19 (0.12–0.29)	–OH	=O	–OH	$-CH_2$-c-C_3H_5	23.8	16.4
IIa	3.0 (1.07–8.4)	3.0 (1.1–8.4)	–OH	$=CH_2$	–OH	$-CH_2CH=CH_2$	1.7	1
IIb	0.106 (0.06–0.19)	0.053 (0.016–0.17)	–OH	$=CH_2$	–OH	$-CH_2$-c-C_3H_5	47.6	58.8
IIIa	2.1 (0.95–4.62)	1.8 (1.06–3.42)	–OAc	$=CH_2$	–OH	$-CH_2CH=CH_2$	2.4	1.7
IIIb	0.11 (0.041–0.248)	0.27 (0.105–0.473)	–OAc	$=CH_2$	–OH	$-CH_2$-c-C_3H_5	48.5	11.5
IIIc	0.21[d]	0.08 (0.04–0.14)	$-O_2CCH=CHPh$	$=CH_2$	–OH	$-CH_2$-c-C_3H_5	23.8	38.5
V	11.0 (8.02–15.07)	12.0 (8.28–17.40)	–OH	$=CHCO_2CH_3$	–OH	$-CH_2CH=CH_2$	0.4	0.2
VI	4.5 (2.14–9.45)	4.9 (3.12–7.69)	–OH	-c-C_2H_4O	–OH	$-CH_2CH=CH_2$	1.1	0.6
VIIa	1.3 (0.58–2.86)	1.1 (0.65–1.87)	–OH	–OH, $-CH_3$	–OH	$-CH_2CH=CH_2$	3.8	2.8
VIIb	0.32 (0.16–0.64)	0.43 (0.23–0.82)	–OH	–OH, $-CH_3$	–OH	$-CH_2$-c-C_3H_5	15.6	7.2
VIIc	5.8 (3.31–10.15)	6.5 (3.61–11.70)	–OH	–OH	–OAc	$-CH_2CH=CH_2$	0.9	0.5
VIId	~2–6[e]						1.2	0.8
VIIIa	5.7 (3.4–9.6)	6.0 (4.1–8.8)	–OH	–OH	–OAc	$-CH_2CH=CH_2$	0.9	0.5
VIIIb	~5[e]						~1	0.6
VIIIc	~10[e]						~0.5	0.3

[a]Morphine sulfate, used ED_{85}. Dose-response curves for morphine were determined separately for hot-plate test and tail-clip test at 30 min after a sc injection of morphine. The ED_{85} for the tail clip was 7.5 mg/kg and for the hot plate, 9.0 mg/kg. Dose-response curves were determined according to the method of J. P. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949). [b]The hot plate was maintained at 58° according to the method of Goldstein and Sheehan, *J. Pharmacol. Exp. Ther.*, **169**, 175 (1969). See also the paper by S. I. Ankier, *Eur. J. Pharmacol.*, **27**, 1 (1974). [c]95% confidence limits calculated according to the method of Litchfield and Wilcoxon (1949). [d]Dose-response too flat to obtain confidence limits. [e]Insufficient drug for third point on dose-response curve.

quantitative yield of IIIa as an amorphous solid: ir (KBr) similar to IIa, with a peak at 1770 cm^{-1} (3-OAc); nmr ($CDCl_3$) δ 6.4–6.8 (2 H, arom), 4.9–5.8 (m, 1 H disappears on addition of D_2O), 4.82 (s, 1 H), 2.31 (s, 3 H, acetate).

6-Desoxy-6-methylenenaltrexone 3-Acetate (IIIb). The procedure used in the synthesis of IIIa was followed using IIb. A quantitative yield of IIIb was isolated after purification: ir (KBr) similar to IIb with a peak at 1775 cm^{-1} (3-OAc); nmr ($CDCl_3$) δ 6.4–6.8 (2 H, arom), 4.8–5.4 (3 H), 2.30 (s, 3 H, acetate), 0.5–0.9 (5 H, cyclopropyl).

6-Desoxy-6-methylenenaltrexone 3-Cinnamate (IIIc). Compound IIb (20 mg, 0.06 mmol) was dissolved in chloroform (5 ml) and triethylamine (0.03 ml, 0.2 mmol) was added. The solution was cooled to 0°. Cinnamoyl chloride (30 mg, 0.18 mmol) in chloroform (3 ml) was added over a 5-min period. The solution was allowed to warm to room temperature and was then stirred for 12 hr. After this period chloroform (25 ml) was added, and the solution was extracted with water. The organic phase was dried, filtered, and evaporated *in vacuo*. The residue was purified by preparative tlc using the solvent system employed for IIa to give a quantitative yield of IIIc: ir (KBr) λ max 3280 (broad), 1735, 1630, 1620 (shoulder), 1490, 1450, 1200, 1155, 990, 910 cm^{-1}; nmr ($CDCl_3$) δ 7.3–7.8 (m, 5 H, arom), 6.4–7.0 (m, 4 H, vinyl and H^1H^2), 4.8–5.4 (3 H), 0.5–0.9 (5 H, cyclopropyl).

6-Desoxy-6-carbomethoxymethylenenaloxone (V). Naloxone (510 mg, 1.5 mmol) and carbomethoxymethylenetriphenylphosphorane[11] (2.36 g, 7.5 mmol) were dissolved in methanol (200 ml) and heated under reflux for 18 hr with a positive pressure of nitrogen being maintained. The reaction was cooled and the solvent was removed *in vacuo*. The residue was mixed with 5% hydrochloric acid solution and stirred for 30 min. The solution was filtered to remove insoluble salts, and the pH of the filtrate was adjusted to about 8 with 5% sodium hydroxide solution. The aqueous phase was extracted with chloroform (twice), and the combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 550 mg of product which could be crystallized from ether–petroleum ether (bp 30–40°) to give a compound of mp 132–134°: ir (KBr) λ max 3300 (broad), 1730, 1645, 1635, 1610, 1500, 1435, 1260, 980 cm^{-1}; nmr ($CDCl_3$) 6.5 (s, 2 H, arom), 4.9–5.5 (m, 4 H), 4.6 (s, 1 H, H^5), 3.85 (s, 3 H, methyl), 1.3–3.2 (m).

6β-Methyleneoxynaloxone (VI). Sodium hydride (120 mg, 2.5 mmol) was placed in a 100-ml three-neck round-bottom flask which was fitted with a condenser, addition funnel, and a gas inlet and outlet tube. A stream of nitrogen was maintained while trimethyloxosulfonium chloride[12] (320 mg, 2.5 mmol) and dioxane (25 ml) were introduced. The mixture was heated to reflux, and heating was continued for 2 hr. The reaction was cooled to about 75° and then naloxone (300 mg, 0.9 mmol) in dioxane (20 ml) was

added dropwise. Heating was continued for a total of 18 hr after which time the cooled reaction mixture was adjusted to pH 7.5 with a saturated solution of ammonium chloride. The aqueous phase was extracted with chloroform (three times) and the combined organic extracts were dried, filtered, and evaporated *in vacuo*. The residue was washed with petroleum ether, and 350 mg of crude product was isolated. This was purified by preparative thin-layer chromatography on silica gel (ethyl acetate–ethanol–ammonia 90:10:3). The product was crystallized from ether–petroleum ether (bp 30–40°): mp 96–98°; ir (KBr) λ max 3400 (broad), 3080, 1640, 1610, 1505, 1445, 1280, 1260, 1050, 920 cm^{-1}; nmr ($CDCl_3$) δ 6.6 (s, 2 H), 4.9–5.5 (m, 3 H), 4.65 (s, 1 H), 3.85 (s, 2 H, methyleneoxy), 1.3–3.2 (m).

6β-Methyl-6α-hydroxynaloxone (VIIa). Naloxone (150 mg, 0.45 mmol) was dissolved in dry diethyl ether (30 ml) in a three-neck 100-ml round-bottom flask equipped with a condenser and a rubber septum. The reaction was cooled to 0° and a positive pressure of nitrogen was maintained while methyllithium (1.85 *M*, 3 ml) was added dropwise by a syringe *via* the rubber septum. The milky white reaction mixture was allowed to stir for 18 hr at room temperature after which time the pH was adjusted to 8 by the addition of a saturated ammonium chloride solution. The ether phase was separated and the aqueous phase was extracted with chloroform. The combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 144 mg of a mixture of naloxone and 6-methyl compound VIIa. The desired product was isolated by preparative tlc on silica gel (ethyl acetate–ethanol–ammonia 90:10:3): ir (KBr) λ max 3350 (broad) 1640, 1620, 1505, 1460, 1165, 1100, 950, 790 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.32 (s, 1 H, H^5), 1.27 (s, 3 H, 6-methyl).

6β-Methyl-6α-hydroxynaloxone 14-Acetate (VIIc). Derivative VIIc was prepared using the above procedure on naloxone 3,14-diacetate. The starting diacetate (137 mg) gave 125 mg of a mixture of naloxone, 6-methyl derivative VIIa, and 6-methyl-14-acetate derivative VIIc: ir (KBr) λ max 3560, 3240 (broad), 1745, 1480, 1270, 1245, 1035 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.6 (2 H, arom), 4.9–5.6 (m, 3 H), 4.34 (s, 1 H), 4.18 (d, J = 6 Hz, 1 H, H^9), 2.06 (s, 3 H), 1.30 (s, 3 H).

6β-Methyl-6α-hydroxynaloxone 3-Acetate (VIId). Compound VIIa (25 mg) was dissolved in pyridine (1 ml) and acetic anhydride (1.1 equiv) was added. The solution was allowed to stand overnight at room temperature after which time the solvent was evaporated *in vacuo*. Thin-layer chromatography showed only one compound present in the residue. An ir spectrum of the oil obtained verified the presence of the 3-acetate (1775 cm^{-1}): nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 4.9–5.4 (m, 3 H), 4.35 (s, 1 H), 3.9 and 3.4 (broad, both peaks disappear on addition of D_2O), 2.31 (s, 3 H, acetate), 1.30 (s, 3 H, 6-methyl).

6β-Methyl-6α-hydroxynaltrexone (VIIb). The procedure used in the synthesis of VIIa was followed using naltrexone. After purification VIIb was isolated as an amorphous solid: ir (KBr) λ max 3400 (broad), 1620, 1505, 1460, 1050, 945 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.8 (2 H, arom), 4.32 (s, 1 H), 3.9 and 3.35 (both peaks disappear on addition of D_2O), 1.32 (s, 3 H, 6-methyl), 0.5–0.9 (5 H, cyclopropyl).

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(17) Unpublished results.
(18) At a dose level of 40 μg/kg sc IIa gives protection against a 30 mg/kg morphine challenge administered sc in rats. Naloxone required 1 mg/kg sc to offer the same protection, while compound IIb (40 μg/kg sc) offers protection up to 75 mg/kg morphine challenge sc (personal communication, Dr. F. Foldes and S. Vizi). The method of Woolfe and McDonald [*J. Pharmacol. Exp. Ther.*, **80,** 300 (1944)] was used to evaluate antagonist activity. Compound IIIc (0.1 mg/kg sc) gives 72% protection after 7 days against a 30 mg/kg morphine challenge, while IIb shows 61% protection under similar conditions. Compound IIa (1 mg/kg sc) still retains 25% protection after a 28-day period (personal communication, Dr. W. Dewey). None of these compounds show any significant agonist activity in guinea pig ileum studies (personal communication, Dr. H. Kosterlitz).
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(20) F. Haffner, *Deut. Med. Wochenschr.*, **55,** 731 (1929).
(21) All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ir spectra were obtained on a Beckman IR-9. Nmr spectra were recorded on a Varian EM-360 spectrophotometer, using TMS as the internal standard. Analyses were determined by Spang Microanalytic Laboratory, Ann Arbor, Mich., and are within 0.4% of the theoretical value for all crystalline compounds. Naloxone hydrochloride was obtained from Endo Laboratories. The free base was made by precipitating naloxone from an aqueous solution of its HCl salt by the addition of 10% NH_4OH. The free naloxone was washed with distilled water and dried *in vacuo* at 58° for 24 hr. Methyllithium was purchased from Alfa Inorganics. Silica gel for tlc was obtained from Brinkmann Instruments, Inc. (GF-254, type 60). Drying involved use of anhydrous sodium sulfate.