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Pentazocine.[1] Strong Analgesics and Analgesic Antagonists in the Benzomorphan Series[2]

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A series of N-substituted 5-alkyl-2′-hydroxy-9-methyl-6,7-benzomorphans were synthesized and evaluated as analgesic antagonists in rodents in the hope of obtaining drugs which would be potent analgesics in man. The rationale for using this approach to the problem of separating strong analgesia from addiction liability is discussed.

Many attempts to find an analgesic comparable to morphine in clinical acceptability and potency without the ability to produce addiction have resulted in failure. Within the past decade the outlook was so discouraging that Schaumann[3] was prompted to state that it would be impossible to separate strong analgesia from addiction liability.

It is generally accepted that the most reliable laboratory procedures for evaluating analgesics are the rat tail-flick method of D'Amour and Smith[4] as modified by Bass and VanderBrook[5] and a mouse hot-plate technique such as that of Eddy and Leimbach.[6] The former method is the more specific for strong analgesics since other pharmacodynamically active drugs, such as the phenothiazine tranquilizers and mephenesin-like muscle relaxants which are positive in the hot-plate procedures, are negative in the rat assay. However, all drugs which are positive in the tail-flick test are also positive in the mouse hot-plate test and, furthermore, those that were tested clinically were found to be active.

There was a growing conviction in the minds of some investigators that the failure to achieve any significant separation of addiction-producing effects from strong clinical analgesia was due in a large measure to the fact that the laboratory rodent tests which were so successful in predicting analgesic potency in man were equally successful, if not more so, in foretelling addiction liability. Spearman rank-order correlation coefficients were all 0.9 or greater when seven well known analgesics[7] were used for the following parameters: analgesic potency in rats, analgesic potency in mice, analgesic potency in man, and potency in a morphine-substitution test (a measure of addiction liability). Similar calculations, using a longer list of analgesics but without the rat values, gave slightly lower, but still highly significant interparameter correlation coefficients.[8]

It became clear, that, in order to achieve the desired separation of analgesic potency from addiction liability the classical approach to the problem had to be abandoned. This notion was strongly supported by the highly important but generally neglected case of nalorphine. Not only is this drug negative in the usual analgesic assays, but it actually antagonizes the effects of morphine and its congeners. Yet Keats and Telford[9] were able to confirm the observations of Lasagna and Beecher[10] that this drug was a potent analgesic in man, approximately equivalent in milligram-potency to morphine. Isbell[11] was unable to produce addiction with this drug. Thus a strong analgesic, free of addiction liability, was finally at hand. The high incidence of side effects, particularly of a psychotomimetic nature, precluded the use of this drug as a substitute for morphine. In pursuing this line of attack, Keats[12] studied a varied and heterogeneous collection of analgesic antagonists for their analgesic effects in man. For one reason or another, none was considered to be an acceptable drug.[12b]

Chemistry.—Replacement of the methyl group of

(1) Approved generic name for 2-dimethylallyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan, also known as NIH 7958 and Win 20,228.

(2) Previous papers (a) L. S. Harris and A. K. Pierson, Addendum 1, Minutes of Twenty-fourth Meeting, Committee on Drug Addiction and Narcotics, National Research Council, Jan. 29-30, 1962; (b) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, J. G. Bird, A. S. Keats, J. Telford, and C. Papadopoulos, *Science*, **137**, 541 (1962).

(3) O. Schaumann, *Brit. Med. J.*, 1091 (1956).

(4) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1944).

(5) W. B. Bass and N. J. VanderBrook, *J. Am. Pharm. Assoc.* (Sci. Ed.), **41**, 569 (1952).

(6) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(7) The analgesics for which adequate data were available were morphine, codeine, methadone, isomethadone, meperidine, ketobemidone, and *d*-propoxyphene.

(8) The analgesics used were listed in Table III in N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Organ.*, **14**, 382 (1956).

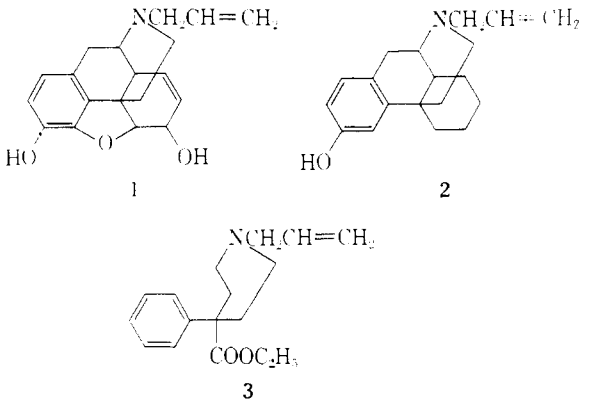
(9) A. S. Keats and J. Telford, *J. Pharmacol. Exptl. Therap.*, **117**, 190 (1956).

(10) L. Lasagna and H. K. Beecher, *ibid.*, **112**, 356 (1954).

(11) H. Isbell, *Federation Proc.*, **15**, 442 (1956).

(12) (a) J. Telford, C. N. Papadopoulos, and A. S. Keats, *J. Pharmacol. Exptl. Therap.*, **133**, 106 (1961); (b) For a detailed and elegant review of the subject, see N. B. Eddy, *Public Health Rept.* (U. S.), **78**, 673 (1963).

morphine by an allyl radical furnishes nalorphine (**1**),[13] a potent narcotic antagonist.[14] A similar manipulation in the morphinan series gives levallorphan (**2**), a more potent narcotic antagonist.[15] However, N-allylnormeperidine (**3**) is an analgesic, not an antagonist.[16]

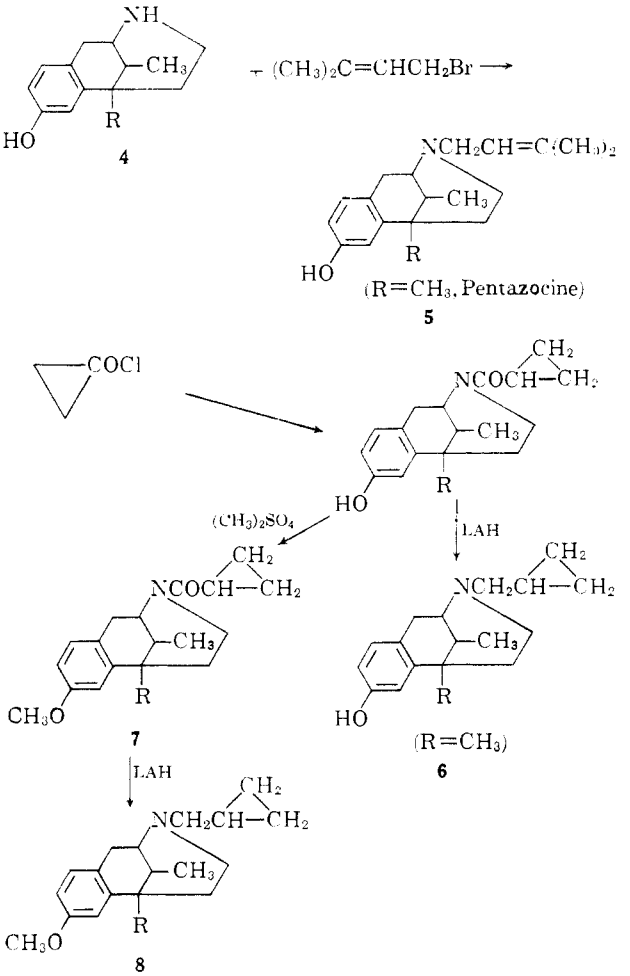


The pharmacological properties of these drugs may be correlated with any of the following structural features: (a) the number of rings in the molecule—**1** is pentacyclic, **2** is tetracyclic, while **3** is only bicyclic; (b) the presence of a phenethylamine fragment in **1** and **2** which is not present in **3**; (c) the nonplanarity of **1** and **2** as compared with **3**. The synthesis and biological evaluation of a tricyclic derivative, such as a benzomorphan[12b] would be of interest because, if such a drug were inactive as an antagonist, then the important structural feature correlating with biological activity would be the number of rings in the molecule. Another reason for studying the benzomorphan series was the high clinical interest shown in phenazocine[17] at the inception of this work.

It was our aim to prepare a series of analgesic antagonists of varying potency by suitable substitution on a benzomorphan nucleus such as **4**. If activity were found, then, on the basis of appropriate pharmacological and toxicological studies in animals, a few members of the series of differing biological profiles would be selected for analgesic assay in man. A major pharmacological requirement was that all the putative drugs must be negative in the D'Amour–Smith test.

The synthesis of **4** (R = CH_3), the *cis* or α-isomer, was previously reported by May and his associates[18] and our task consisted of preparing the requisite derivatives by either alkylation with the appropriate halide such as dimethylallyl bromide to furnish pentazocine (**5**)[1] or by acylation with an acid halide such as cyclopropylcarbonyl chloride followed by lithium aluminum hydride reduction to give the desired **6**. The methoxy analog (**8**) was prepared as shown in the accompanying equations.

A series of derivatives of **4** (R = CH_3 and C_2H_5), together with their analgesic–antagonist potencies, are collected in Table I. While our work was in progress, Gordon, *et al.*,[19] reported the preparation and antagonist–potency of compound **9**. Our data are in essential agreement with theirs.



Biological Results.—The method of assay for analgesic–antagonist potency[2a] is outlined in the Experimental part. Reversal of analgesia is only one manifestation of antagonist action. It can be carried out rapidly in small animals, lending itself readily to quantitation, thus allowing comparisons among drugs to be made. For the purposes of this work, a substance will be classified as an analgesic antagonist if it can reverse meperidine analgesia in rats. A more complete description of the pharmacology of some of these agents will be published elsewhere.[20]

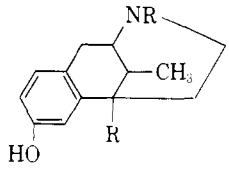
The alkyl derivative (**9**) was more potent than nalorphine (**1**) and equal to levallorphan (**2**). Alkyl substitution on the allyl group reduced potency (*cf.* **5** and **14**). The 2-chloroallyl compound (**11**) was considerably weaker than **12** but the *cis*-3-chloroallyl derivative (**12**) was the most potent allyl derivative encountered.

It should be kept in mind that we are dealing with racemic substances here, and if it may be assumed that most, if not all, of the activity resides in one isomer, then the benzomorphan nucleus furnishes the most

(13) J. Weijlard and A. E. Erikson, *J. Am. Chem. Soc.*, **64**, 869 (1942).
(14) C. A. Winter, P. D. Orahovats, and E. G. Lehman, *Arch. Intern. Pharmacodyn.*, **110**, 186 (1957).
(15) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **34**, 2211 (1951).
(16) P. J. Costa and D. D. Bonnycastle, *J. Pharmacol. Exptl. Therap.*, **113**, 310 (1955).
(17) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).
(18) E. M. Fry and E. L. May, *ibid.*, **24**, 116 (1959); E. L. May and J. H. Ager, *ibid.*, **24**, 1432 (1959); S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).
(19) M. Gordon, J. J. Lafferty, D. H. Tedeschi, N. B. Eddy, and E. L. May, *Nature*, **192**, 1089 (1962).
(20) L. S. Harris and A. Pierson, *J. Pharmacol. Exptl. Therap.*, in press.

TABLE I

BENZOMORPHAN ANALGESIC ANTAGONISTS



No.	R	R′	Method (% yield)	M.p., °C.	—% Carbon— Calcd.	Found	% Hydrogen Calcd.	Found	—% Nitrogen— Calcd.	Found	Antagonist activity, mg./kg.
1	Nalorphine										0.13
2	Levallorphan										0.052
3	N-Allylnormeperidine										Analgesic
4	CH_3	H	Ref. 18								
5	CH_3	$CH_2CH{=}C(CH_3)_2$	See text	145.4–148.6	79.95	79.84	9.34	9.28	4.91	5.23	3.9
6	CH_3	$CH_2CH(CH_2)CH_2$	See text	200.8–203.8	79.65	79.34	9.29	9.02	5.16	5.15	0.019
7	CH_3	$COCH(CH_2)CH_2$	See text	180.9–183.0	75.75	75.49	8.12	7.94	4.91	4.97	
8	CH_3[a]	$CH_2CH(CH_2)CH_2$	See text	215.8–218.8[b]	70.89	71.19	8.77	8.65	11.01[c]	11.05	0.146
9	CH_3[d]	$CH_2CH{=}CH_2$	A (65)	141.2–143.8	79.32	78.99	9.01	9.04	5.44	5.38	0.047
10	CH_3	$CH_2C{\equiv}CH$	A (55)	169.2–170.0	79.94	79.95	8.29	8.20	5.48	5.23	0.78
11	CH_3	$CH_2C(Cl){=}CH_2$	A (78)	261.8–265[b]	62.21	62.53	7.06	7.02	4.27	4.10	4.2
12	CH_3	*cis*-$CHCl{=}CHCl$	A (50)	186.2–189.0	69.97	69.89	7.60	7.30	4.80	4.67	0.018
13	CH_3	$CH_2CH{=}CCl_2$	A (62)	145.2–147.2[b]			21.73[c]	21.47	4.29	4.34	5.1
14	CH_3	$CH_2C(CH_3){=}CH_2$	A (59)	260.0–261.0[b]	70.21	70.44	8.51	8.54	4.55	4.45	0.094
15	CH_3	$CH_2CH_2CH(CH_2)CH_2$	See text	203–206	79.96	79.94	9.54	9.47	4.91	4.90	0.092
16	CH_3	$COCH(CH_2CH_2)CH_2$	B (72)	181–184	76.22	75.56	8.42	8.16			
17	CH_3	$CH_2CH(CH_2CH_2)CH_2$	B (48)	167.6–169.2	79.96	79.85	9.54	9.73	4.91	5.13	0.37
18	CH_3	$CH_2CH(CH_2CH_2CH_2)CH_2$	B (86)	230.4–233.2[b]	71.53	71.27	9.01	9.03	4.17	4.01	0.28
19	CH_3	$CH_2CH(CH_2CH_2)CH_2$	B (68)	Glass[e]	80.46	80.28	9.97	10.07	4.47	4.44	14.5
20	C_2H_5	$CH_2CH{=}CH_2$	See text	166.4–168.2	79.65	79.39	9.29	8.95	5.16	5.06	0.049
21	C_2H_5	$CH_2CH{=}C(CH_3)_2$	C (78)	161.6–164.2	80.23	80.41	9.76	9.82	4.68	4.79	10.9
22	C_2H_5	$CH_2CH(CH_2)CH_2$	See text	180.8–183.2	79.96	80.11	9.54	9.36	4.91	5.03	0.024
23	C_2H_5	$CH_2CH(CH_2CH_2)CH_2$	D (50)	195.2–197.2	80.23	80.21	9.76	9.66	4.68	4.89	14.6
24	CH_3	$CH_2CH_2CH_3$	Ref. 21								0.019

[a] This is the 2′-methoxy compound. [b] Hydrochloride. [c] Chlorine analysis. [d] See ref. 19. [e] Trituration with methanol gave a crystalline methanolate, m.p. 81.5–85.0°.

potent series of antagonists now known.[21] This is borne out by a comparison of **9** and **2** and the fact that **5** is a definite but weak antagonist while the corresponding derivative in the morphinan series is an analgesic in man and animals.[12]

May[22] prepared a series of homologs derived from **4** (R′ = CH_3) and reported that the *n*-propyl derivative (**24**) was devoid of analgesic activity. Since *n*-propylnormorphine was reported to be an antagonist[14] it occurred to us that **24** should be too. As can be seen from Table I this is indeed the case. Historically then, **24** was the first benzomorphan antagonist reported in the literature, but it was not recognized as such.

The pharmacological properties of the cycloalkylmethyl derivative of **4** proved to be of great interest. The cyclopropylmethyl derivative (**6**), in addition to being a potent meperidine antagonist, is capable of blocking polysynaptic reflexes and also shows a trace of D'Amour–Smith positivity.[20] The cyclobutyl homolog (**17**) is a moderately potent antagonist (about 0.33 nalorphine), but is also about 0.5 as active as meperidine in the D'Amour–Smith test. The cyclopentyl compound (**18**) is also a moderately potent antagonist, but the next higher homolog (**19**) is almost inactive. The interesting pharmacology of the cyclopropylmethyl group is not confined to the benzo-

(21) A description of the optically active and *trans* isomers will be reported at a later date by B. F. Tullar, N. F. Albertson, L. S. Harris, and S. Archer.

(22) J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960).

morphan series but is also true for the corresponding morphinan and morphine derivatives.[23]

In general, the analgesic-antagonist potency of derivatives of **4** (R = CH_3) is greater than **4** (R = C_2H_5) (*cf.* **5** *vs.* **21**, **6** *vs.* **22**, **17** *vs.* **23**). However, the allyl derivatives (**9**, **20**) are equipotent as antagonists.

On the basis of interesting pharmacological and favorable toxicological studies, compounds **20**, a strong antagonist, **5**, a weak antagonist, and **6**, the cyclopropylmethyl derivative, were chosen for the first clinical studies.

Lasagna and DeKornfeld[24] compared **6** with morphine in post-operative patients. They found that 0.25 mg. of the drug was equivalent to 10 mg. of morphine. Although excessive sedation and dysphoria were noted at higher doses, particularly by the oral route in subjects who were ambulatory, at lower, effective dose levels, the drug appeared to be fairly well tolerated.

The two other benzomorphans (**20** and **5**, pentazocine) were evaluated by Keats according to his usual method of assay in post-operative pain.[2b,12] The strong antagonist (**20**) was found to be about twice as potent as morphine as an analgesic (5 mg. equivalent to 10 mg. of morphine), but the psychotomimetic effects were similar to those produced by nalorphine. Accordingly, no further clinical studies were carried out.

In contrast, the weak antagonist, pentazocine (**5**), appeared to be at least as well tolerated as morphine at equiactive dose levels. No disturbing mental effects were noted even at very high doses. Careful comparison with morphine indicated that about 20–30 mg. of pentazocine is approximately equivalent to 10 mg. of morphine in controlling post-operative pain.[25] The addiction liability of pentazocine was determined to be sufficiently low, if present at all,[26] to obviate narcotics control of the agent.

On the basis of these and other clinical studies now in progress it appears that pentazocine is the *first clinically acceptable, strong analgesic that is free of any significant addiction liability.*

Experimental[27]

Assay for Analgesic Antagonist Activity.—A modification of the rat tail-flick method of D'Amour–Smith[4] and Bass–VanderBrook[5] was used. Groups of rats were medicated with a dose of meperidine that produced an 80% effect. A 20-sec. cutoff time was used, *i.e.*, if a rat did not flick its tail within 20 sec. the animal was removed from the heat source. In order to employ probit analysis, 20 sec. minus the animal's normal reaction time was arbitrarily considered to be the 100% effect. The heat source was adjusted to give a normal reaction time of 2–4 sec.

Groups of rats were medicated with logarithmically increasing doses of the potential antagonist 10 min. prior to receiving the standard dose of meperidine, and the rats were then exposed to the heat source. Antagonism was measured as a per cent reduction of the maximum effect and quantitatively expressed as the dose which would reduce the effect 50% (AD_{50}).

5,9-Dimethyl-2-(3,3-dimethylallyl)-2′-hydroxy-6,7-benzomorphan (5). A.—A stirred mixture of 8.7 g. of 5,9-dimethyl-2′-hydroxy-6,7-benzomorphan, 6.0 g. of 1-bromo-3-methyl-2-butene, 5.0 g. of sodium bicarbonate, and 125 ml. of dimethylformamide was refluxed for 4.5 hr. The reaction mixture was filtered and the filter cake washed with ethanol. The solvent was removed *in vacuo*, and the product was dissolved in ether and filtered from a small amount of insoluble material. The ether layer was extracted with 5 ml. of hydrochloric acid in 20 ml. of water. Addition of dilute ammonium hydroxide to the aqueous phase precipitated 10.6 g. of crude product, m.p. 128–139°. Two recrystallizations from aqueous methanol gave 8.2 g. melting at 145–148°. A second experiment on twice this scale gave 18.2 g. of recrystallized material.

2-Cyclopropylcarbonyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (7).—5,9-Dimethyl-2′-hydroxy-6,7-benzomorphan (8.8 g.) was warmed in 100 ml. of methanol until all had dissolved. Then 15 ml. of water and 10 g. of pulverized potassium carbonate were added, the mixture was cooled to room temperature, and 7.9 g. of cyclopropylcarbonyl chloride was added with stirring. After 3 hr., the solvent was removed *in vacuo* and the residue partitioned between water and benzene–butanol (2:1 v./v.). The organic layer was washed with dilute hydrochloric acid and water. Concentration, after drying, gave 9.1 g. of crude, off-white product showing an amide band at 6.22 μ, but no ester band. Reprecipitation from aqueous sodium hydroxide solution with hydrochloric acid gave 7.9 g. of product melting at 179–181.5°. Recrystallization from aqueous ethanol raised the melting point to 180.9–183.0°.

2-Cyclopropylmethyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (6). B.—A solution of 6.0 g. of 2-cyclopropylcarbonyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan in about 75 ml. of tetrahydrofuran at 35° was added to a stirred suspension of 3.0 g. of lithium aluminum hydride in tetrahydrofuran. The reaction mixture was then refluxed for 3.5 hr. and cooled and 6 ml. of water added dropwise. Filtercel was added[28] and the reaction mixture was filtered through Filtercel. The filter cake was extracted with more tetrahydrofuran. The solvent was removed *in vacuo* from the combined filtrates. The residue was recrystallized from methanol to give 1.9 g. of shiny white crystals melting at 201–204°.

Reduction of 4.0 g. of 2,2′-bis(cyclopropylcarbonyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan with lithium aluminum hydride gave 1.5 g. of the same product melting at 200–202°.

2-Cyclopropylmethyl-5,9-dimethyl-2′-methoxy-6,7-benzomorphan Hydrochloride (8).—To a solution of 5.0 g. of 2-cyclopropylcarbonyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan in 50 ml. of 1 *N* NaOH was added 10 ml. of dimethyl sulfate. The mixture was stirred vigorously for 7 hr. during which time the oily layer became more viscous. The product was extracted into chloroform and the chloroform layer washed with 1 *N* NaOH and dilute hydrochloric acid. After drying, the chloroform was removed *in vacuo* to give 4.7 g. of 2-cyclopropylcarbonyl-5,9-dimethyl-2′-methoxy-6,7-benzomorphan as a yellow sirup. This was reduced with lithium aluminum hydride in tetrahydrofuran in the manner described above. The resulting sirup was taken up in ether and converted to the hydrochloride. It was reprecipitated from ethanol with ether to give 3.7 g. of product.

2-(2-Cyclopropyl)ethyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (15).—5,9-Dimethyl-2′-hydroxy-6,7-benzomorphan (4.2 g.) was dissolved in 50 ml. of warm methanol. Potassium carbonate (5 g.) and 7 ml. of water were added, and the mixture was cooled to room temperature. Cyclopropylacetyl chloride (prepared from 4.4 g. of cyclopropylacetic acid and thionyl chloride) was added dropwise. After standing overnight, the reaction was taken up in chloroform and washed with water (which removed some of the color) and hydrochloric acid. Removal of the solvent left 5.1 g. of 2-cyclopropylacetyl-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan as a glassy residue. This was reduced with 2 g. of lithium aluminum hydride in tetrahydrofuran in the usual manner to give 3.8 g. of crude crystalline product. This was dissolved in 200 ml. of methanol, treated with charcoal, filtered, and concentrated to about 50 ml. There was some loss when the solvent boiled over. Cooling afforded 1.9 g. of product.

5-Ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan.—The procedure used by Fry and May[18] for N-demethylation in the di-

(23) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).
(24) L. Lasagna and T. Dekornfeld, *Federation Proc.*, **22**, 248 (1963).
(25) A. S. Keats and J. Telford, *J. Pharmacol. Exptl. Therap.*, in press.
(26) H. F. Fraser, D. E. Rosenberg, and H. Isbell, *ibid.*, in press.
(27) We wish to thank Mr. K. D. Fleischer and his group for performing the analyses.

(28) The work-up of $LiAlH_4$ reductions whereby 2 ml. of water is added per g. of $LiAlH_4$ used has been used in this laboratory since 1950. Almost invariably a very readily filterable precipitate is formed. The present case is one of the rare examples of a very slow filtration.

methyl series was applied to 2,9-dimethyl-5-ethyl-2′-hydroxy-6,7-benzomorphan. Acetylation proceeded in 92–97% yields. The crude sirup or crystalline product was treated with cyanogen bromide in chloroform in the usual manner. A solution of 30.5 g. of the O-acetyl-N-cyano intermediate in 250 ml. of 7% hydrochloric acid was refluxed for 17 hr., concentrated to a small volume, and diluted with water. Ether was added, at which point the nor-base hydrochloride started to precipitate. It was recovered by filtration to give 16.9 g. as a first crop. Cooling the mother liquor gave 4.1 g. more, m.p. 125–128° dec. The first crop was converted to the base by dissolving in approximately 100 ml. of boiling water, treating with charcoal, filtering, and adding excess ammonium hydroxide to give 12.7 g. of off-white nor-base, m.p. 261–265°.

Anal. Calcd. for $C_{15}H_{21}NO$: N, 6.06. Found: N, 5.86.

2-Allyl-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (20). C.—A mixture of 6.2 g. of 5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan, 3.2 g. of allyl bromide, 80 ml. of dimethylformamide, and 3.2 g. of sodium bicarbonate was stirred and refluxed for 4 hr., filtered, the filter cake washed with ethanol, and the combined filtrates concentrated *in vacuo*. The crystalline residue was extracted with chloroform until the remaining residue was all water-soluble. The chloroform solution was concentrated to a small volume, ether was added, and the solution was chilled to give 5.9 g. (81%) of product melting at 165.5–168°. Experiments on a larger scale gave yields of 82–84%.

2-Cyclopropylmethyl-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan (22). D.—A solution of 9.4 g. of 5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan in 235 ml. of hot pyridine was cooled to room temperature and 10.4 g. of cyclopropylcarbonyl chloride added with stirring. After an additional hr. at room temperature, the pyridine was removed *in vacuo* and the residue partitioned between water and ether. The ether layer was washed with dilute hydrochloric acid and water, dried, and concentrated to give 14.0 g. of 2,2′-bis(cyclopropylcarbonyl)-5-ethyl-2′-hydroxy-9-methyl-6,7-benzomorphan as a light orange sirup. This was reduced in tetrahydrofuran with 5 g. of lithium aluminum hydride to give 8.6 g. of crude product, which, when dissolved in ether, gradually deposited crystals of product, m.p. 181–183°. The yield was 55%.

Acknowledgment.—We wish to thank Dr. Leonard Grumbach for carrying out some of the early pharmacological work and Mrs. Hattie Lawyer for technical assistance. It is a pleasure to acknowledge the aid of Dr. Nathan B. Eddy, Executive Secretary, Committee on Drug Addiction and Narcotics, in arranging for some of the trials in man.

Some Potent Morphine Antagonists Possessing High Analgesic Activity[1]

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The synthesis of a number of N-cyclopropylmethylmorphinan and morphine derivatives and one N-cyclobutylmethylmorphinan derivative is described. Very powerful morphine antagonism is exhibited by certain of these, and at least one, 3-hydroxy-N-cyclopropylmethylmorphinan, appears to be a very potent, presumptively nonaddicting analgesic of potential clinical utility.

The highly significant observation of Lasagna and Beecher,[3] confirmed and extended by Keats and coworkers,[4] that nalorphine (N-allylnormorphine), a powerful morphine antagonist which has been shown to be nonaddicting,[5] is a potent analgesic in man even though its analgesic activity is not detectable in the D'Amour–Smith rat tail-flick test suggested that clinically useful potent analgesics devoid of addiction liability might be uncovered among the group of morphine antagonists. Nalorphine itself is not acceptable for clinical use because of a high incidence of undesirable, sometimes bizarre, psychotic effects attending its use.

The relationship between structure and morphine antagonism in substances structurally related to morphine has been studied at length by Clark and coworkers,[6] who found that the substitution of allyl, *n*-propyl, methallyl, or isobutyl for the N-methyl group of morphine or its close relatives produces morphine antagonists. No significant morphine antagonism resulted from the substitution of a number of other groups, both closely and distantly related to these, for the N-methyl group.

We were led to a consideration of the cyclopropylmethyl group as a possible N-substituent which might confer morphine antagonism and analgesic activity at the same time by the well known[7] close similarity of the

(1) Taken in part from a Ph.D. dissertation submitted to the University of Rochester, 1962.

(2) Charles Pfizer Fellow 1959–1960, American Cyanamid Fellow 1960–1961, National Science Foundation Fellow, summer, 1961.

(3) L. Lasagna and H. K. Beecher, *J. Pharmacol. Exptl. Therap.*, **112**, 356 (1954).

(4) A. S. Keats and J. Telford, *ibid.*, **117**, 190 (1956). J. Telford, C. N. Papadopoulos, and A. S. Keats, *ibid.*, **133**, 106 (1961).

(5) H. Isbell, *Federation Proc.*, **15**, 442 (1956); *J. Am. Med. Assoc.*, **161**, 1254 (1956).

(6) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **75**, 4963 (1953).

(7) Although an exhaustive review of these similarities, both theoretical and experimental, would be inappropriate here, the interested reader is referred to A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949); J. E. Kilpatrick and R. Spitzer, *J. Chem. Phys.*, **14**, 463 (1946); and J. F. Music and F. A. Matsen, *J. Am. Chem. Soc.*, **72**, 5256 (1950), for discussions of the theoretical similarities. Diverse physical measurements such as dipole moments (M. T. Rogers and J. D. Roberts, *ibid.*, **68**, 843 (1946); M. T. Rogers, *ibid.*, **69**, 2544 (1947)); ultraviolet absorption spectra (L. I. Smith and E. R. Rogier, *ibid.*, **73**, 3840 (1951); R. H. Eastman and S. K. Freeman, *ibid.*, **77**, 6642 (1955)); and molar refractions (V. A Slabey, *ibid.*, **76**, 3603 (1954)) also suggest the double-bond character and conjugative ability of the cyclopropyl group. There is also much chemical evidence for the unsaturated nature of the cyclopropyl group. Among recent observations may be cited the interesting findings of J. L. von Rosenberg, Jr., J. E. Mahler, and R. Pettit, *ibid.*, **84**, 2842 (1962); J. D. Holmes and R. Pettit, *ibid.*, **85**, 2531 (1963), that both the homotropyl cation and homotropone exhibit aromatic sextet stabilization.