care should be taken in its preparation and handling (see ref 10). Aspartate transcarbamylase was the generous gift of Dr. G. A. O'Donovan; the enzyme activity was measured colorimetrically.[11]

Benzyl Hydrogen *N*-Chloroacetylphosphoramidate (10). A solution of *N*-chloroacetyl azide (6) (1.35 M in chloroform) was prepared from hydrazoic acid[10] and chloroacetyl chloride in the presence of triethylamine.[5] The acyl azide solution, 34.3 ml (46 mmol), was allowed to react with 15.9 g (46 mmol) of tribenzyl phosphite (7) according to a method for the preparation of triethyl *N*-chloroacetylphosphorimidate.[5] The reaction evolved 78% of the theoretical amount of nitrogen. The triethylamine hydrochloride was removed by evaporating the chloroform in vacuo and distributing the oily residue between water and carbon tetrachloride. The organic layer was washed with one portion of water and with 5% sodium bicarbonate solution and dried over anhydrous sodium sulfate. The solution was cooled to 0 °C and saturated with anhydrous hydrogen chloride and a small amount of thick oil formed in a few minutes, followed by a white precipitate. After 3.5 h the small amount of oil was skimmed off and the precipitate was collected by filtration. Two recrystallizations from acetonitrile yielded 1.92 g (24% based on the yield of nitrogen): mp 132–133 °C dec; IR (Nujol) 1687 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 4.30 (2 H, s, $COCH_2Cl$), 5.15 (2 H, d, J_{HP} = 4 Hz, benzylic), 7.55 (5 H, s, Ph). Anal. ($C_9H_{11}ClNO_4P$) C, H, N.

Dilithium Salt of *N*-Chloroacetylphosphoramidate (5). To 0.74 g (2.8 mmol) of **10** was added 3 ml of trifluoroacetic acid. After several minutes at 25 °C, the trifluoroacetic acid was removed in vacuo and the residue dissolved in 12 ml of 95% ethanol. Two equivalents of a solution of lithium hydroxide in 90% ethanol (1.32 M) was added; the fine white precipitate was centrifuged, washed with absolute ethanol, and dried in vacuo to yield 0.4 g (77%) of the desired salt: IR (Nujol) 1630, 1476 cm^{-1}; NMR (D_2O) δ 4.40 (s). Anal. Calcd for $Li_2(C_2H_3ClNO_4P)$: C, 12.9; H, 1.6; N, 7.55. Found: C, 12.34; H, 1.94; N, 7.28.

Acknowledgment. These compounds were prepared in the course of work sponsored by the Research Corporation, the Robert A. Welch Foundation, and the National Science Foundation.

References and Notes

(1) S. M. D'Ambrosio, G. I. Glover, S. O. Nelson, and R. A. Jensen, *J. Bacteriol.*, **115**, 673 (1973).
(2) E. Shaw and J. Ruscica, *Arch. Biochem. Biophys.*, **145**, 484 (1971).
(3) P. L. Birch, H. A. El-Obeid, and M. Akhtar, *Arch. Biochem. Biophys.*, **148**, 447 (1972).
(4) E. Shaw and G. Glover, *Arch. Biochem. Biophys.*, **139**, 298 (1970).
(5) M. I. Kabachnik, V. A. Gilyarov, C. Cheng-tieh, and E. I. Matrosov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1504 (1962).
(6) Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen, Drug Evaluation Branch, Drug Research and Development, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. 20014.
(7) Y. H. Hui, K. B. DeOme, and G. M. Briggs, *J. Natl. Cancer Inst.*, **46**, 929 (1971).
(8) W. J. Stith, D. S. Hodgins, and C. W. Abell, *Cancer Res.*, **33**, 966 (1973).
(9) D. Paul, *Biochem. Biophys. Res. Commun.*, **53**, 745 (1973).
(10) H. Wolf, *Org. React.*, **3**, 307 (1947).
(11) J. C. Gerhart and A. B. Pardee, *J. Biol. Chem.*, **237**, 891 (1962).

Narcotic Antagonists. Synthesis and Evaluation of Some Substituted 1,2,3,4,5,6-Hexahydro-1,4:2,6-dimethano-3-benzazocines

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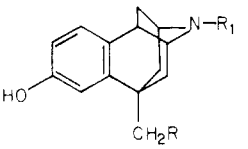
A series of (±)-N-substituted 6-ethyl- or -methyl-8-hydroxy-1,2,3,4,5,6-hexahydro-1,4:2,6-dimethano-3-benzazocines has been prepared from 6-hydroxytropinone. The *N*-cyclopropylmethyl compounds **10a** and **10b** were found to be strong narcotic antagonists approximately equivalent to nalorphine. Only slight analgetic activity was found in any of these compounds including the two *N*-methyl analogues.

Synthetic investigations on the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines[1] have produced many compounds possessing interesting profiles with respect to narcotic antagonist and analgetic activities.[2] The structure–activity effects of altering the substituents at positions 3, 6, 8, and 11 have been intensively studied, because of their close structural resemblance to morphine and the morphinans. Only recently has attention been directed toward modification of other positions on the ring system. Ziering et al.[3] have introduced methyl groups into the 1α and 9 positions and phenyl into the 1α position on the 3-benzazocine nucleus. Equatorial methyl groups have been introduced into the 4 and 5 positions,[4] and these modifications have produced compounds with interesting analgetic properties, although the 8 position lacks a phenolic hydroxyl substituent. Another interesting series has been prepared by benzylic oxidation to give 1-keto derivatives possessing mixed analgetic and narcotic antagonist activities.[5] Both isomeric 3-benzazocin-1-ols have also been prepared.[6]

In order to investigate further the structure–activity relationships in the 3-benzazocine series at positions which have attracted only limited attention, we chose to introduce a methylene group connecting the 1 and 4 positions. This modification creates a very rigid bridged [5,6,7] tricyclic ring system and should affect the steric environment around the nitrogen and above the aromatic ring. Lewis[7] has proposed that this area may be important for binding on the receptor site. The synthesis of several (±)-1,2,3,4,5,6-hexahydro-1,4:2,6-dimethano-3-benzazocines and their activities are reported in this paper.

Chemistry. The synthesis of the title compounds from 6-hydroxytropinone (1) is outlined in Scheme I. Treatment of **1** with ethylene glycol in the presence of *p*-toluenesulfonic acid gave the ketal **2** in high yield. Pfitzner–Moffit[8] oxidation smoothly converted **2** into the 6-keto derivative **3**. It is worthy of note that the use of the Collins reagent[9] for this conversion was not satisfactory because of extensive oxidation of the *N*-methyl group to *N*-formyl. Treatment of **3** with *p*-methoxyphenylmagnesium bromide gave the endo alcohol **4** in good yield. The stereochemical assignment of **4** is based on steric and electronic factors as they strongly favor exo addition of the organometallic reagent. The highly hindered nature of the

Table I. (±)-1,2,3,4,5,6-Hexahydro-1,4:2,6-dimethano-3-benzazocines



No.	R	R_1	Method[a]	Mp, °C	Recrystn solvent	% yield	Formula[b]
8a	H	$-CH_3$	A	>280	EtOH-H_2O	68[c]	$C_{15}H_{19}NO\cdot HBr$
8b	CH_3	$-CH_3$	A	>250	1-PrOH-H_2O	46[c]	$C_{16}H_{21}NO\cdot HBr$
9a	H	-H	B	>250	2-PrOH-H_2O	76	$C_{14}H_{17}NO\cdot HBr$[d]
9b	CH_3	-H	B	>250	EtOH	79	$C_{15}H_{19}NO\cdot HBr$
10a	H	$-CH_2$-c-C_3H_5	C	>250	1-PrOH-H_2O	71	$C_{18}H_{23}NO\cdot 0.5\text{-}C_4H_4O_4$
10b	CH_3	$-CH_2$-c-C_3H_5	C	230-232	EtOH	85	$C_{19}H_{25}NO\cdot HBr$
10c	H	$-CH_2$-c-C_4H_7	C	223-226	EtOH	80	$C_{19}H_{25}NO\cdot HBr$
10d	CH_3	$-CH_2$-c-C_4H_7	C	233-235	EtOH	81	$C_{20}H_{27}NO\cdot HBr$
10e	H	$-CH_2CH_2$-c-C_3H_5	C	225-227	EtOH	70	$C_{19}H_{25}NO\cdot HBr$
10f	CH_3	$-CH_2CH_2$-c-C_3H_5	C	155-169	EtOH-Me_2CO	69	$C_{20}H_{27}NO\cdot HBr$
10g	CH_3	$-CH_2CH{=}CH_2$	D	208-211	EtOH	36	$C_{18}H_{23}NO\cdot HBr$

[a] Method refers to Experimental Section. [b] All compounds except 9a were analyzed for C, H, and N and were within ±0.4% of theoretical values. [c] Overall yield from 5. [d] Although 9a was not analyzed for C, H, and N, IR and NMR spectra were obtained and are consistent with the assigned structure.

alcohol 4 was indicated by its inertness to treatment with acetyl chloride, acetic anhydride, and mesyl chloride under normal reaction conditions.

Conversion of 4 into the 6-*endo*-*p*-methoxyphenyltropinone 5 was effected by treatment with a mixture of 6 N HCl-HOAc to eliminate the tertiary alcohol and remove the ketal followed by catalytic reduction of the styrene system with $Pd(OH)_2$ in 52–59% yield. The stereochemical outcome of this reaction was predicted on the basis of the expected addition of hydrogen from the least hindered side of the olefin. This was confirmed later by successful cyclization to the 3-benzazocines as the exo isomer is incapable of this cyclization.

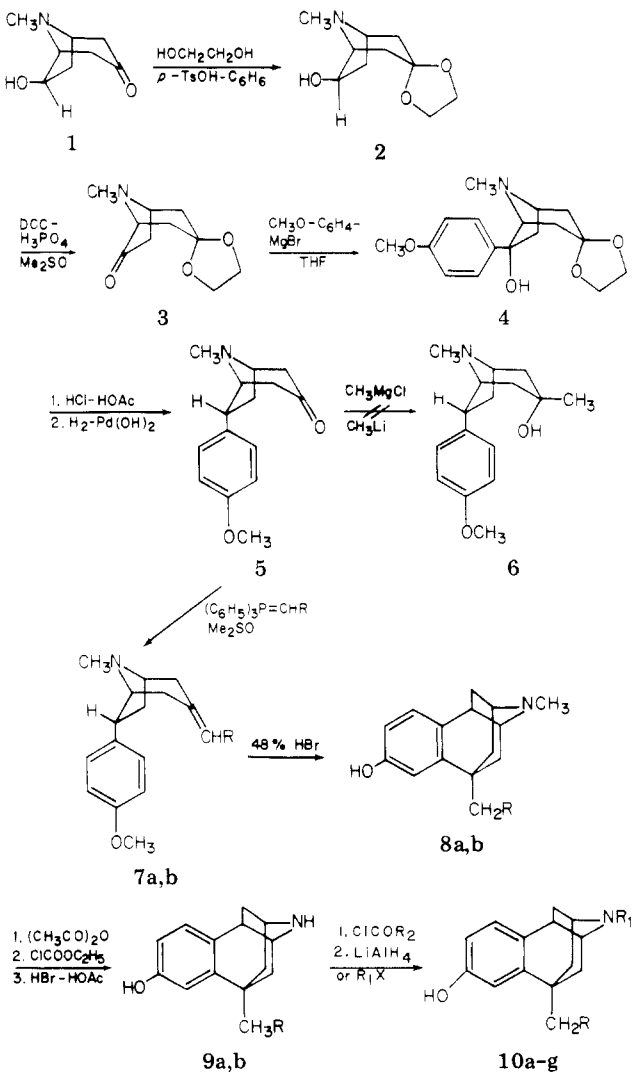
Treatment of 5 with either methyllithium or methylmagnesium chloride failed to give the tertiary carbinol 6, and 5 was recovered almost quantitatively in both instances. The exocyclic olefins **7a** and **7b**, however, could be readily prepared by treatment of 5 with methylidene and ethylidene triphenylphosphorane. These underwent cyclization to the (±)-1,4:2,6-dimethano-3-benzazocines **8a** and **8b** upon heating with 48% HBr.

That the desired cyclizations had occurred was evident from examination of the NMR spectra (100 MHz, TFA) of **8a** and **8b** hydrobromide. The aromatic protons appear as follows: the C-10 proton δ 7.15 is a doublet ortho coupled ($J_{9,10}$ = 8 Hz) to the C-9 proton δ 6.85 which is further split to a quartet by meta coupling ($J_{7,9}$ = 2 Hz) to the C-7 proton δ 7.05 which is present as a doublet. The signal of the 6-methyl protons of **8a** appears as a singlet δ 1.50, and the 6-ethyl protons of **8b** are present as a triplet δ 1.05 and quartet δ 2.0 (J = 7 Hz) for the methyl and methylene protons, respectively.

Demethylation of **8a** by the von Braun cyanogen bromide procedure went poorly (yield 25–30%) due to extensive ring cleavage.[10] The secondary amino compounds **9a** and **9b** were more conveniently prepared in good yields (70–85%) using a three-step sequence of acetylation, carbamate formation with ethyl chloroformate, and acid hydrolysis. This procedure allows selective demethylation on several ring systems not stable to cyanogen bromide.[11]

The *N*-cyclopropylmethyl, cyclopropylethyl, and cyclobutylmethyl derivatives **10a–f** were prepared from **9a** and **9b** by treatment with an acyl halide followed by reduction with lithium aluminum hydride. Compound **10g** (*N*-allyl) was prepared by treatment of **9b** with allyl bromide (see Table I).

Scheme I



a, R = H; b, R = CH_3

Pharmacology. Analgetic and narcotic antagonist activities of the 1,4:2,6-dimethano-3-benzazocines are given

Table II. Analgetic and Narcotic Antagonist Activities of (±)-1,2,3,4,5,6-Hexahydro-1,4:2,6-dimethano-3-benzazocines

Compd	ED_{50}, mg/kg sc[a] (95% confidence limits)			
	Phenylquinone[b] mouse writhing	Oxymorphone[b] Straub tail	Oxymorphone[b] narcosis	Morphine antagonism[b] rat tail flick
8a	31.8 (26.0-42.5)	Inact. at 40		
8b	24.3 (20.7-28.8)	Inact. at 40		
9a	N.D.[c]	N.D.[c]		
9b	12.9 (7.8-21.1)	Inact. at 40		
10a	Marginally act. at 40	0.96 (0.76-1.20)	~0.63	0.64 (0.35-1.16)
10b	Marginally act. at 40	2.24 (1.64-3.01)	~0.32	0.44 (0.28-0.71)
10c	Inact. at 40	Inact. at 40		
10d	Inact. at 40	~15	~5	~10
10e	Inact. at 40	Inact. at 40		
10f	Marginally act. at 40	>20		>20
10g	~20	8.0 (6.1-10.2)	~1.0	3.3 (1.6-6.7)
Morphine	0.26 (0.18-0.40)			
Pentazocine	3.7 (2.5-5.2)	12.0 (10.0-14.4)	10.1 (6.3-16.2)	12.2 (9.7-15.2)
Nalorphine	0.77 (0.51-1.16)	1.14 (0.90-1.44)	0.58 (0.44-0.76)	0.38 (0.27-0.54)

[a] All compounds were administered subcutaneously as their respective salts in aqueous solution. The weights reported are corrected to read in terms of the free base. The ED_{50} values were calculated from dose-response data (at least three dose levels and a minimum of six animals per dose level) using probit analysis. [b] For a detailed description of the test methods see ref 12 and references cited therein. [c] Not determined.

in Table II. The most active compound in the phenylquinone mouse writhing test is the secondary amino derivative **9b**. The *N*-methyl derivatives **8a** and **8b** are 90–100 times weaker analgetics than morphine. They also are considerably less potent than similar 11-unsubstituted 2,6-methano-3-benzazocines which have been reported to be codeine and morphine like.[13] Substitution of cyclopropylmethyl, cyclobutylmethyl, and cyclopropylethyl for *N*-methyl virtually eliminates analgetic activity.

All compounds show toxicity (convulsions) at 80 mg/kg sc in mice. At a dose of 40 mg/kg sc compounds **9b**, **10d** (convulsions), **10f** (depression), and **10g** (tremors) produce significant side effects. Thus introduction of a 1,4-methano bridge has given a series of compounds which is fairly toxic in comparison with its weak analgetic properties.

The two (±)-cyclopropylmethyl derivatives **10** and **10b**, however, possess narcotic antagonist properties at a level considerably greater than pentazocine and approximately equivalent to nalorphine (Table II).[14] This level of antagonist potency was somewhat unexpected, as several reports have indicated that there exists a definite association between the level of analgetic potency of the *N*-methyl compound and the antagonist potency of its *N*-allyl or cyclopropylmethyl counterparts.[2c,15]

It has previously been demonstrated that potent antagonists are not necessarily obtained from the corresponding potent analgetics by modification of the N-substituent.[16] The current results indicate that potent narcotic antagonists can be obtained in a series possessing only weak analgetic properties. Recent reports[17] of potent narcotic antagonists within series of 11β-hydroxy- and 11α-alkoxy-3-benzazocines further support this finding. Thus, contrary to previously indicated correlations, it is not necessary that the *N*-methyl derivative of a series be a potent analgetic agent to give powerful antagonists by substitution of *N*-allyl or cyclopropylmethyl for the *N*-methyl.

Experimental Section

All melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Where analyses are indicated by C, H, and N, the results obtained for these elements were within ±0.4% of the theoretical values. NMR and IR spectra were recorded for all compounds and are consistent with the assigned structures.

3,3-Ethylenedioxy-6β-hydroxy-8-methyltropane (2). A mixture of 6-hydroxytropinone[18] (24.8 g, 0.16 mol), ethylene glycol (99 g, 1.6 mol), and *p*-TsOH (32 g, 0.17 mol) in 750 ml of C_6H_6 was heated at reflux for 4 h using a Dean-Stark trap to remove water. The reaction mixture was cooled, treated with 50 g of Na_2CO_3, and diluted with 1.5 l. of saturated NaCl solution. This was extracted several times with $CHCl_3$ to give after concentration 32 g of crude product. Recrystallization from $Me_2C{=}O$ gave 27.1 g (85%) of pure **2**, mp 95–96 °C. Anal. ($C_{10}H_{17}NO_3$) C, H, N.

3,3-Ethylenedioxy-8-methyltropan-6-one (3). A stirred solution of **2** (25.5 g, 0.128 mol) and dicyclohexylcarbodiimide (79.5 g, 0.38 mol) in 240 ml of Me_2SO under N_2 was treated dropwise with anhydrous H_3PO_4 (18.9 g, 0.19 mol) in 60 ml of Me_2SO. After stirring for 3 h at 25 °C the solids were removed by filtration. The solids were suspended in dilute NH_4OH and extracted with $CHCl_3$. This extract was combined with the Me_2SO filtrate and diluted with 1.8 l. of dilute NH_4OH. This was extracted several times with $CHCl_3$. The extracts were dried ($MgSO_4$) and concentrated to give crude **3** as an oil. Treatment with oxalic acid in absolute EtOH gave 25.0 g (68%) of crystalline material, mp 162–163 °C. An analytical sample was prepared by treatment of **3** with fumaric acid in absolute EtOH, mp 137–139 °C. Anal. ($C_{10}H_{15}NO_3{\cdot}C_4H_4O_4$) C, H, N.

3,3-Ethylenedioxy-6α-hydroxy-6β-*p*-methoxyphenyl-8-methyltropane (4). A solution of **3** (19.7 g, 0.10 mol) in 150 ml of THF was treated with a solution of *p*-methoxyphenylmagnesium bromide (prepared from 5.8 g of Mg and 41.2 g (0.22 mol) of *p*-bromoanisole) in 150 ml of THF and stirred for 3 h under N_2. Treatment of the reaction mixture with an aqueous mixture of NH_4Cl–dilute NH_4OH followed by ether extraction gave after drying ($MgSO_4$) and concentration crude **4** as an oil. Treatment with oxalic acid in absolute EtOH gave 32.9 g (83%) of crystalline product, mp 160–163 °C. Treatment of **4** with fumaric acid in absolute EtOH gave an analytical sample, mp 155–156 °C. Anal. ($C_{17}H_{23}NO_4{\cdot}C_4H_4O_4$) C, H, N.

6α-*p*-Methoxyphenyl-8-methyltropan-3-one (5). A solution of **4** (25.3 g, 0.083 mol) in 750 ml of HOAc and 750 ml of 6 N HCl was stirred at 25 °C for 60 h. This solution was concentrated and the residue was neutralized with dilute aqueous K_2CO_3 and extracted with CH_2Cl_2. After drying ($MgSO_4$) and concentration a dark oil was obtained. This was dissolved in 200 ml of absolute EtOH and hydrogenated using 1.0 g of 25% $Pd(OH)_2/C$ as catalyst. Hydrogen uptake was complete within 2.5 h. The catalyst was removed and the filtrate was treated with 7 ml of 12 N HCl. Crystalline HCl salt, 13.9 g (59%), was obtained. Recrystallization from EtOH–H_2O gave an analytical sample, mp 204–209 °C. Anal. ($C_{15}H_{19}NO_2{\cdot}HCl$) C, H, N.

(±)-N-Substituted 6-Methyl- or 6-Ethyl-8-hydroxy-1,2,3,4,5,6-hexahydro-1,4:2,6-dimethano-3-benzazocines. Method A: *N*-Methyl (8a,b). To a stirred solution of the Wittig reagent (prepared from 0.088 mol of 55% NaH–mineral oil and 0.088 mol of triphenylalkylphosphonium bromide in 200 ml of Me_2SO under N_2) was added 0.044 mol of **5** in 25 ml of Me_2SO. The reaction mixture was warmed for 4.5 h at 55 °C under N_2. It was then diluted with 1.5 l. of H_2O and extracted several times with Et_2O.

The Et_2O extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in $CH_3C{\equiv}N$ and washed with *n*-pentane to remove mineral oil. The crude olefins were purified by chromatography on alumina (Woelm neutral, Grade I) and eluted with 3:1 Et_2O–Skellysolve B to give **7a** and **7b** in yields averaging 75–80%.

A stirred solution of 0.035 mol of **7a** or **7b** in 120 ml of 48% HBr was heated at 120 °C for 20 h. Concentration of the reaction mixture gave the crystalline HBr salt. Recrystallization from the appropriate solvent gave analytically pure **8a·HBr** and **8b·HBr**.

Method B: N–H (9a,b). A mixture of 3.8 mmol of **8a** or **8b**, 1 g of NaOAc, and 15 ml of Ac_2O was heated on a steam bath for 3 h. Ac_2O was removed at reduced pressure. The residue was treated with dilute Na_2CO_3 and extracted with $CHCl_3$ to give the phenol acetate in quantitative yield (GC 100%). A refluxing solution of this acetate in 30 ml of benzene was treated with 11.0 mmol of ethyl chloroformate. Heating was continued for 6 h. The reaction mixture was washed with dilute HOAc and dilute $NaHCO_3$, and concentrated to give the carbamate ester (GC 100%). Treatment of this material with 15 ml of 48% HBr, 15 ml of H_2O, and 30 ml of HOAc and 40 h of heating on a steam bath gave after concentration the crystalline HBr salt. Purification was achieved by recrystallization.

Method C: *N*-Cyclopropylmethyl, *N*-Cyclobutylmethyl, *N*-Cyclopropylethyl (10a–f). A stirred solution of 3.0 mmol of **9a** or **9b** in a mixture of CH_2Cl_2 and TEA was treated with 9.0 mmol of acyl chloride. Stirring was continued for 20 h. The reaction mixture was washed with dilute HOAc and dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated to give the amido ester. This was reduced with an excess of $LiAlH_4$ in THF by refluxing for 20 h. After careful treatment with saturated Na_2SO_4 solution, a saturated ammonium tartrate solution was added and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude product. Purification was achieved by salt formation and recrystallization.

Method D: *N*-Allyl (10g). A mixture of 3.0 mmol of **9b**, 3.3 mmol of allyl bromide, and 1.7 g of K_2CO_3 in 20 ml of absolute EtOH was heated at reflux for 20 h. The reaction mixture was filtered and concentrated to dryness. The residue was treated with H_2O and extracted with EtOAc. Evaporation of the solvent gave an oil which was purified by recrystallization of its HBr salt.

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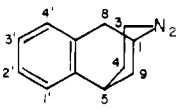
References and Notes

(1) Compounds of this general ring system are also commonly known as 6,7-benzomorphans. For clarity the numbering of the benzomorphan (I), 2,6-methano-3-benzazocine (II), and 1,4:2,6-dimethano-3-benzazocine (III) ring systems is given.



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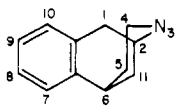

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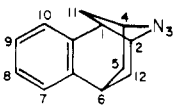

III

(2) (a) E. L. May and L. J. Sargent in "Analgetics", G. de Stevens, Ed., Academic Press, New York, N.Y., 1965, Chapter IV; (b) N. B. Eddy and E. L. May, "Synthetic Analgesics, Part IIB, 6,7-Benzomorphans", Pergamon Press, London, 1966, pp 138 ff; (c) A. F. Casy, *Prog. Med. Chem.*, **7**, 229 (1970).
(3) A. Ziering, N. Malatestinic, T. Williams, and A. Brossi, *J. Med. Chem.*, **13**, 9 (1970).
(4) R. T. Parfitt and S. M. Walters, *J. Med. Chem.*, **14**, 565 (1971).
(5) W. F. Michne and N. F. Albertson, *J. Med. Chem.*, **15**, 1278 (1972).
(6) J. J. Fauley and J. B. LaPidus, *J. Med. Chem.*, **16**, 181 (1973).
(7) J. W. Lewis, P. A. Mayor, and D. I. Haddlesey, *J. Med. Chem.*, **16**, 12 (1973).
(8) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).
(9) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).
(10) H. A. Hageman, *Org. React.*, **7**, 198 (1953).
(11) J. G. Fisher and G. Mikite, *Acta Chim. Acad. Sci. Hung.*, **68**, 253, 261 (1971).
(12) A. W. Pircio, J. A. Gylys, R. L. Cavanaugh, J. P. Buyniski, and M. E. Bierwagen, *Arch. Int. Pharmacodyn. Ther.*, **220**, 231 (1976).
(13) (a) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957); (b) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).
(14) Since narcotic antagonist activity is generally present only in the levo isomer, resolution of compounds **10a** and **10b** would be expected to give antagonists more potent than nalorphine.
(15) (a) S. Archer and L. S. Harris, *Prog. Drug Res.*, **8**, 276 (1965); (b) L. S. Harris, A. K. Pierson, J. R. Dembinski, and W. L. Dewey, *Arch Int. Pharmacodyn. Ther.*, **165**, 112 (1967).
(16) (a) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, 11, 241 (1971); (b) A. F. Casy, A. B. Simmonds, and D. Staniforth, *J. Pharm. Pharmacol.*, **20**, 768 (1968); (c) H. H. Ong, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **17**, 133 (1974).
(17) (a) I. Monkovic, M. Saucier, and T. A. Montzka, U.S. Patent 3 891 657 (1975); (b) N. F. Albertson, *J. Med. Chem.*, **18**, 619 (1975); (c) T. A. Montzka and J. D. Matiskella, U.S. Patent 3 956 336 (1976).
(18) P. Nedenskov and N. Clauson-Kaas, *Acta Chem. Scand.*, 8, 1295 (1954).

Dibenz[*b,e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 2. Dihydro-10-oxofuro- and -thieno[3,2-*c*][1]benzoxepin-8-acetic Acids

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4,10-Dihydro-10-oxofuro[3,2-*c*][1]benzoxepin-8-acetic acid and 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid were evaluated in the carrageenan paw edema assay with the thieno analogue being ten times more active than the furano compound and 1.3 times more active than indomethacin. The therapeutic ratio (antiinflammatory activity/gastric irritation liability) of the thieno analogue was 25 times that of indomethacin.

We have recently reported the synthesis of 6,11-dihydrodibenz[*b,e*]oxepinacetic acids,[1] many of which exhibited good antiinflammatory activity. One of these, 6,11-dihydro-11-oxodibenz[*b,e*]oxepin-2-acetic acid (**10**),