Synthesis and Analgetic Activity of Some 5-Aryl-2-azabicyclo[3.2.1]octanes

Helen H. Ong,* V. B. Anderson,

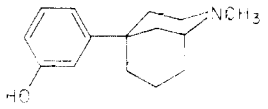
Chemical Research Department

and Jeffrey C. Wilker

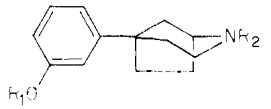
Department of Biological Sciences, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey 08876.
Received February 2, 1978

A series of 5-aryl-2-azabicyclo[3.2.1]octanes II has been synthesized and evaluated for analgetic agonist–antagonist activity. These compounds can be regarded as five-membered, conformationally more rigid analogues of the potent agonist–antagonist (−)-5-(3-hydroxyphenyl)-2-methylmorphan (I). Several of these compounds have demonstrated marked analgesic potency comparable to morphine in the mouse writhing assay. Structure–activity correlations, generated by varying N-substitution and O-acetylation of the phenolic function, seem to indicate that optimum activity is associated with an arylethyl side chain attached to the basic nitrogen. Among the most interesting compounds in this series are the phenethyl analogue **31** and its *O*-acetate **39**; the former shows the profile of a well-balanced analgetic–antagonist virtually devoid of physical dependence liability as demonstrated in the rat infusion test.

The discovery of (−)-5-(3-hydroxyphenyl)-2-methylmorphan (I) as an analgesic agonist–antagonist of clinical



I

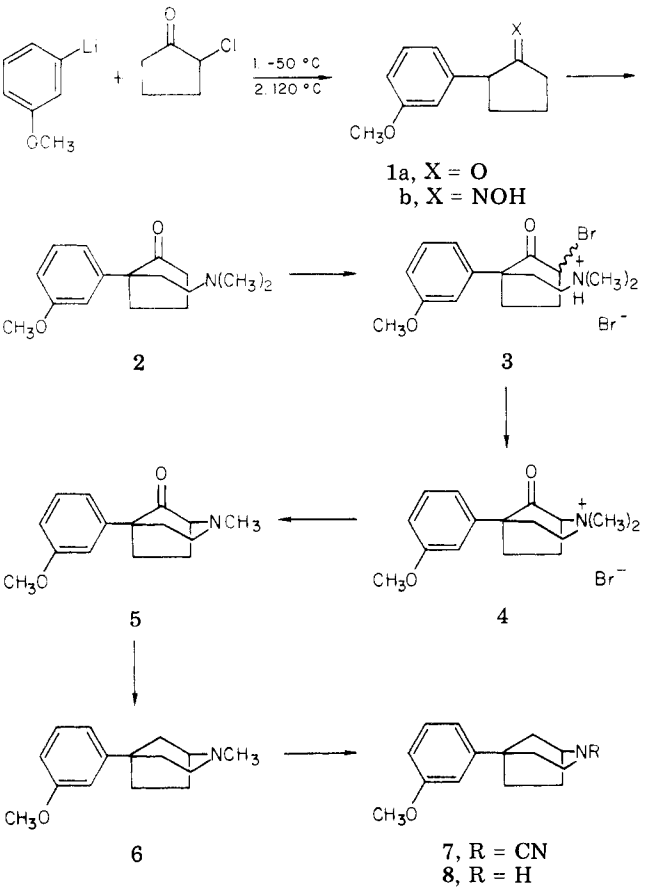


II, R_1 = H, CH_3, $CH_3C(=O)$–; R_2 = alkyl, cycloalkyl, aralkyl

potential[1] has stimulated considerable research interest in strong analgesics of fused bicyclic structures. This interest was further enhanced by demonstration[2] that potent antagonists of the phenylmorphan type, having equatorial phenyl rings in a nonrigid orientation, could not necessarily be fashioned from corresponding potent analgesics by mere substitution of the *N*-methyl with an allyl or cyclopropylmethyl radical, despite ample documentation of such conversions in tricyclic to hexacyclic systems (benzomorphans to *endo*-ethenooripavins).[3] The absolute configuration of (−)-I[4] was established by X-ray crystallography to be 1*R*,5*S*, corresponding to the 4*R* enantiomers of α- and β-prodines,[5] and because of steric interactions between C_3 and C_7, both rings of the 2-azabicyclo[3.3.1]nonane system exist in chair–chair conformation with distorted interplanar angles. Thus it appeared to us that replacement of the six-membered carbocycle in I with a five-membered cyclopentyl ring could result in "phenylnormorphans"[6] of increased molecular rigidity and, possibly, a modified torsion angle between piperidine and the aromatic plane; conformational effects such as these might be expected to induce significant variations in drug–receptor binding and, hence, biological actions. In this paper we wish to describe the synthesis and pharmacological activity of a series of racemic 5-aryl-2-azabicyclo[3.2.1]octanes as represented by the general formula II. After this work had been completed, compound **22**, the *N*-methyl congener of II, was reported to be analgetically inactive while displaying weak narcotic antagonist activity comparable to pentazocine.[7] Our results, based upon the study of a sizable number of such analogues, differ somewhat from those of Takeda[7] and permit a more discerning view of the structure–activity relationships existing among the 2-azabicyclo[3.2.1]octanes. Thus, the diminution of agonist activity associated with a change in the alicyclic ring size, as typified by compound **22**, could be effectively reversed by proper manipulation of the N-substituent.

Chemistry. The synthetic route employed for the preparation of the 5-aryl-2-azabicyclo[3.2.1]octane ring system was patterned after the original synthesis of I by May and Murphy,[1a] as shown in Scheme I. Although Takeda and co-workers[7] described a similar approach which corresponded closely to ours, the reaction conditions, however, were usually different and for a number of key steps, our procedures appear to provide somewhat better yields. 2-(3-Methoxyphenyl)cyclopentanone (Ia)[8] was prepared in 90% purity by condensing 3-methoxyphenyllithium with 2-chlorocyclopentanone at −50 °C, followed by thermal rearrangement. A similar reaction sequence using 3-methoxyphenylmagnesium bromide, as described by Mislow and Hamermesh,[9] afforded **1a** in less than 20% yield and lower purity. Alkylation of **1a** with β-dimethylaminoethyl chloride and potassium *tert*-butoxide in glyme gave predominantly the desired product, **2**, with some O-alkylated isomer which was readily hy-

Scheme I



0022-2623/78/1821-0758$01.00/0

drolyzed to **1a**. Bromination of **2**·HBr in an aprotic solvent led to bromo ketone **3**, isolable only as the hydrobromide salt, whereas in acetic acid, a dibromo compound was also obtained along with **3** and some unreacted ketone. Neutralization of **3** with a mild base liberated a highly reactive bromoamine which underwent facile cyclization to give quaternary compound **4**. The degradation of **4** to tertiary amine **5** was effected thermally, with concomitant extrusion of CH_3Br, and **5** was converted to deoxy compound **6** by Wolff–Kishner reduction. N-Demethylation of **6** by a modified von Braun procedure[10] gave, as an intermediate, a crystalline cyanamide **7**, which was readily hydrolyzed to secondary amine **8**. Conversion of **8** to the various target compounds described in Table I proceeded by diverse routes, depending on the nature of the N-substituent. Compounds **9–13**, bearing open-chained alkyl or benzoylalkyl groups, were prepared by direct alkylation of **8** (method A) with an appropriate halide, followed by O-demethylation with 48% hydrobromic acid (method B). Compounds **27** and **28**, carrying acid-sensitive cyclopropylmethyl and dimethylallyl groups, respectively, were prepared by a reversal of the above reaction sequence: first, O-demethylation of **8** to **21**, and, then, selective N-alkylation of the phenolic amine (method C). The 2-aralkyl congeners, compounds **14–20**, were synthesized via acylation of **8** and lithium aluminum hydride reduction of the resulting amides (method D). The subsequent O-demethylation of these amines generally proceeded smoothly with the exception of the 2-furylmethyl analogue **29**, the formation of which was usually accompanied by extensive polymerization. A preferred method for preparing **29** was to bis-acylate **21** with 2-furoyl chloride and to reduce the intermediate amido ester with lithium aluminum hydride (method E).

An additional structural variation included in this study was the acetylation (method F) of phenolic hydroxyl functions in **31** and **37**. This attempt was prompted by expectations that the *O*-acetyl derivatives, **39** and **40**, respectively, would have enhanced oral analgesic potency.[18]

Pharmacology and Discussion of Results. As shown in Table II, analgesic activities for target compounds **22–40** were determined by measuring the inhibition of phenylquinone (PQW) induced writhing and the delay in response to noxious heat stimuli in mice (D'Amour–Smith tail-flick method). Comparative data for morphine, pentazocine, and some selected 5-(3-methoxy)phenyl analogues are also given. In general, compounds showing marked analgesic activity were further screened for antagonistic potency using the inhibition of morphine-induced mania as the primary index. Results of narcotic antagonism are also included in Table II.

It can be seen that compounds having straight-chain alkyl substituents on the nitrogen displayed only weak analgesic action in the PQW screen with relative potencies ranging from $^1/_{20}$ to $^1/_{10}$ of that possessed by morphine.[11] The frequently noted potentiating effect of a metaphenolic hydroxyl group was not observed in this homologous series; in fact, the precursory methoxy compounds, **6** and **9–12**, were found to be slightly more potent in the PQW assay, and results obtained with the tail-flick method, though showing only marginal activity in some cases, generally conformed to this pattern with only one exception.

Replacement of the *N*-methyl group with a cyclopropylmethyl or dimethylallyl radical (**27** and **28**, respectively) resulted in little increase in either analgesic or antagonist activity, thus paralleling May's earlier findings in the phenylmorphan[2] and ketobemidone[12] series. N-Furylmethylation, on the other hand, led to a good antagonist without much improvement on the analgesic property. The pronounced PQW activities shown by **13** and **30** could conceivably be attributed, at least in part, to a CNS depressant component associated with the butyrophenone moiety; the significance of this CNS effect was amply demonstrated by ptosis, ataxia, and decreased motor activity when given parenterally at low doses. A similar line of reasoning could be extended to the interpretation of antagonistic results for these two compounds.

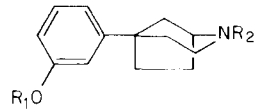
It was somewhat surprising that optimum analgesic effect was conferred by substitution of *N*-methyl with a phenethyl radical, in view of opposite findings in the phenylmorphan series that such chemical transformation reduced activity by a factor of 3. Compound **31** was found to be equipotent to morphine in the PQW assay (a tenfold increase in potency) and half as active in the tail-flick test; equally unexpected was the discovery that **31** also displayed a high level of nalorphine-like activity in two screening procedures used for narcotic antagonism.[13] This duality of action, brought on by a typical agonist "analgesiophore" such as the *N*-phenethyl group,[14] constitutes, in our views, a second major deviation of the present system from those classical (fused), polycyclic analgetics.

The effect of aromatic substitution on the phenethyl moiety was also investigated; while the number of analogues precluded any rigorous Hansch-type correlations, it seems apparent that substituents with $+\pi$ values, such as 4-Cl, 3-Cl, and 4-CH_3[15] (compounds **32**, **33**, and **35**, respectively), resulted in enhancement of activity in the PQW assay, and the failure of 3,4-dichloro substituents to show potency increases (**34** was equipotent to **31** and, hence, less active than **32** and **33**) indicated, perhaps, the optimum value for lipophilicity had been exceeded. The much lessened activity shown by **36** could be ascribed to a $-\pi$ effect, a $-\sigma$ effect, or to a combination of $-\pi$, $-\sigma$ rather than an unfavorable steric contribution ($-E_s$) from the *p*-OH substituent. It should be pointed out that, among the nuclear-substituted *N*-phenethyl analogues studied (**31–36**), some discrepancies exist between their relative analgesic potencies as assessed by the PQW assay and those determined by the tail-flick response. One possible explanation for this is that the tail-flick method, like the hot-plate test, has not proven useful in predicting the new, mixed agonist–antagonist type of analgesics. In the absence of antagonist activity, as exemplified by compound **34**, a better correlation of data from the two assays seems more feasible. It is also noteworthy that nuclear substituents, on the whole, exerted a negative effect on the antagonistic activity of *N*-phenethyl analogues, regardless of their electronic and steric properties.

Other structural variations studied included the 2-(2-thienyl)ethyl analogue **37**, which was equipotent to **31** in the PQW assay but weaker as an antagonist. O-Acetylation of **31** and **37** yielded orally effective analogues (**39** and **40**, respectively) with somewhat lowered subcutaneous activity; compound **39** also compared unfavorably with **31** in the test for narcotic antagonism. *O*-Methyl ethers **15–20** were deleted from detailed pharmacological studies because of the comparatively weak analgesic activity demonstrated by the lead compound **14**.

In summary, the 5-aryl-2-azabicyclo[3.2.1]octanes represent a novel class of analgetic agents, some with significant potency and unique profiles. Several compounds in this series were chosen for further studies in species other than rodents and two of these, compound **31** and **39**, were selected as the most promising candidates

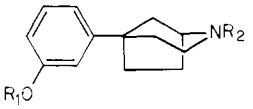
Table I. 5-Aryl-2-azabicyclo[3.2.1]octanes[a]



compd	R_1	R_2	starting material	method	mp, °C	yield,[b] %	recrystn[c] solvent	formula	analyses
6	CH_3	CH_3	5	*d*	175-177[f]	75	A-D	$C_{15}H_{21}NO\cdot HBr$	C, H, Br, N
8	CH_3	H	7	*d*	137.5-138.5	90	A-C	$C_{14}H_{19}NO\cdot HBr$	C, H, Br, N
9	CH_3	C_2H_5	8	A	148-149	58	A-D-E	$C_{16}H_{23}NO\cdot HBr$	C, H, Br, N
10	CH_3	*n*-C_3H_7	8	A	223-224	80	D-E	$C_{17}H_{25}NO\cdot HBr$	C, H, Br, N
11	CH_3	*n*-C_4H_9	8	A	216-217	86	D-E	$C_{18}H_{27}NO\cdot HBr$	C, H, Br, N
12	CH_3	*n*-C_5H_{11}	8	A	144-146.5	75	A-D	$C_{19}H_{29}NO\cdot HBr$	C, H, Br, N
13	CH_3	$(CH_2)_3C(=O)C_6H_4$-4-F	8	A	194-196	90	D-E	$C_{24}H_{28}FNO_2\cdot HBr$	C, H, Br, F, N
14	CH_3	$(CH_2)_2C_6H_5$	8	D	188-189	77	A-D-E	$C_{22}H_{27}NO\cdot HBr$	C, H, N
15	CH_3	$(CH_2)_2C_6H_4$-4-Cl	8	D	204-206	64	A-D-E	$C_{22}H_{26}ClNO\cdot HBr$	C, H, Br, Cl, N
16	CH_3	$(CH_2)_2C_6H_4$-3-Cl	8	D	225-227	74	A-D-E	$C_{22}H_{26}ClNO\cdot HBr$	C, H, Br, Cl, N
17	CH_3	$(CH_2)_2C_6H_3$-3,4-Cl_2	8	D	239-240	64	A-D-E	$C_{22}H_{25}Cl_2NO\cdot HBr$	C, H, Br, Cl, N
18	CH_3	$(CH_2)_2C_6H_4$-4-CH_3	8	D	203.5-205.5	48	A-D-E	$C_{23}H_{29}NO\cdot HBr$	C, H, Br, N
19	CH_3	$(CH_2)_2C_6H_4$-4-OCH_3	8	D	201-202	73	A-D-E	$C_{23}H_{29}NO_2\cdot HBr$	C, H, Br, N
20	CH_3	2-(2-thienyl)ethyl	8	D	173-175	59	A-D-E	$C_{20}H_{25}NOS\cdot HBr$	C, H, Br, N
21	H	H	8	B	259-260	91	A-B	$C_{13}H_{17}NO\cdot HBr$	C, H, N
22	H	CH_3	6	B	254-255[g]	88	D-E	$C_{14}H_{19}NO\cdot HBr$	C, H, Br, N
23	H	C_2H_5	9	B	249-250	77	A-D-E	$C_{15}H_{21}NO\cdot HBr$	C, H, Br, N
24	H	*n*-C_3H_7	10	B	251-253	93	D-E	$C_{16}H_{23}NO\cdot HBr$	C, H, Br, N
25	H	*n*-C_4H_9	11	B	>260	96	D-E	$C_{17}H_{25}NO\cdot HBr$	C, H, Br, N
26	H	*n*-C_5H_{11}	12	B	235-236.5	91	D-E	$C_{18}H_{27}NO\cdot HBr$	C, H, Br, N
27	H	CH_2-*c*-C_3H_5	21	C, E	251-253	38	D-E	$C_{17}H_{23}NO\cdot HBr$	C, H, Br, N
28	H	$CH_2CH=C(CH_3)_2$	21	C	215-216	72	B-D	$C_{18}H_{25}NO\cdot HBr$	C, H, Br, N
29	H	2-furylmethyl	21	E	226-228	50	D-E	$C_{18}H_{21}NO_2\cdot HBr$	C, H, N
30	H	$(CH_2)_3C(=O)C_6H_4$-4-F	13	B	207-208	70	A-D-E	$C_{23}H_{26}FNO_2\cdot HBr$	C, H, Br, N
31[e]	H	$(CH_2)_2C_6H_5$	14	B	212-213	94	A-D-E	$C_{21}H_{25}NO\cdot HBr$	C, H, Br, N
32	H	$(CH_2)_2C_6H_4$-4-Cl	15	B	266-267	84	D-E	$C_{21}H_{24}ClNO\cdot HBr$	C, H, Br, Cl, N
33	H	$(CH_2)_2C_6H_4$-3-Cl	16	B	217-219	93	A-D-E	$C_{21}H_{24}ClNO\cdot HBr$	C, H, Br, Cl, N
34	H	$(CH_2)_2C_6H_3$-3,4-Cl_2	17	B	237-239	82	A-D-E	$C_{21}H_{23}Cl_2NO\cdot HBr$	C, H, Br, Cl, N
35	H	$(CH_2)_2C_6H_4$-4-CH_3	18	B	231-233	70	A-D-E	$C_{22}H_{27}NO\cdot HBr$	C, H, Br, N
36	H	$(CH_2)_2C_6H_4$-4-OH	19	B	278-279	88	A-D-E	$C_{21}H_{25}NO_2\cdot HBr$	C, H, Br, N
37	H	2-(2-thienyl)ethyl	20	B	195-197	74	D-E	$C_{19}H_{23}NOS\cdot HBr$	C, H, Br, N, S
38	$CH_3C(=O)$-	CH_3	22	F	152-153	80	A-C	$C_{16}H_{21}NO_2\cdot HBr$	C, H, Br, N
39	$CH_3C(=O)$-	$(CH_2)_2C_6H_5$	31	F	160-162	85	A-D	$C_{23}H_{27}NO_2\cdot HBr$	C, H, Br, N
40	$CH_3C(=O)$-	2-(2-thienyl)ethyl	37	F	175-177	74	A-D-E	$C_{21}H_{25}NO_2S\cdot HBr$	C, H, Br, N

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Isolated yields; no efforts were made to optimize these yields. [c] A = acetone; B = ethanol; C = ethyl acetate; D = ethyl ether; E = methanol. [d] Refer to the Experimental Section. [e] The free base crystallized from acetone-hexane: mp 176-177 °C. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.19; N, 4.55. Found: C, 82.08; H, 8.33; N, 4.38. [f] Lit.[7] mp 178.5-180 °C. [g] Lit.[7] mp 245.5-247 °C.

Table II. Pharmacology of 5-Aryl-2-azabicyclo[3.2.1]octanes



compd[a,k]	R_1	R_2	analgesic act.,[b] ED_{50}, mg/kg: phenylquinone writhing	analgesic act.,[b] ED_{50}, mg/kg: tail flick	antagonistic act.,[b] AD_{50}, mg/kg, inhibn of morphine-induced mania
6	CH_3	CH_3	6.96 (6.34-7.54)	10% at 25 mg/kg	~50[c]
9	CH_3	C_2H_5	11.87 (8.91-17.89)	17.74 (6.30-18.89)	10% at 10 mg/kg
10	CH_3	n-C_3H_7	7.4 (7.01-8.66)	40% at 25 mg/kg	8.30 (3.24-22.55)
11	CH_3	n-C_4H_9	4.87 (4.70-5.03)	9.71 (5.94-16.19)	*d*
12	CH_3	n-C_5H_{11}	5.77 (5.18-6.38)	40% at 25 mg/kg	*d*
13	CH_3	$(CH_2)_3COC_6H_4$-4-F	0.85 (0.80-0.92)	10% at 2 mg/kg[h]	3.7 (2.5-6.1)
14	CH_3	$(CH_2)_2C_6H_5$	5.99 (5.58-6.41)	~13[c]	*e*
22	H	CH_3	10.03 (8.52-11.57)	40% at 25 mg/kg	*f*
23	H	C_2H_5	41% at 10 mg/kg	30% at 25 mg/kg	*d*
24	H	n-C_3H_7	8.79 (8.09-9.49)	20% at 25 mg/kg	*d*
25	H	n-C_4H_9	8.66 (7.32-10.32)	30% at 25 mg/kg	40% at 10 mg
26	H	n-C_5H_{11}	8.34 (7.41-9.41)	20% at 25 mg/kg	4.31 (2.63-10.44)
27	H	CH_2-c-C_3H_5	5.44 (5.02-5.86)	30% at 25 mg/kg	20% at 10 mg/kg
28	H	$CH_2CH{=}C(CH_3)_2$	~25[c]	20% at 25 mg/kg	*d*
29	H	2-furylmethyl	22.73 (16.10-39.90)	10.00 (9.98-10.02)	3.7 (1.8-7.5)
30	H	$(CH_2)_3COC_6H_4$-4-F	0.35 (0.32-0.38)	40% at 2 mg/kg[h]	2.01 (0.74-3.58)
31[j]	H	$(CH_2)_2C_6H_5$	60.89 (55.76-67.78)[g] 0.68 (0.59-0.78)	6.45 (9.32-3.21)	1.06 (0.93-3.01)
32	H	$(CH_2)_2C_6H_4$-4-Cl	0.42 (0.41-0.44)	7.32 (5.58-17.14)	50% at 10 mg/kg
33	H	$(CH_2)_2C_6H_4$-3-Cl	0.46 (0.33-0.57)	5.46 (5.45-16.65)	20% at 10 mg/kg
34	H	$(CH_2)_2C_6H_3$-3,4-Cl	0.75 (0.73-0.79)	2.73 (2.73-8.33)	*d*
35	H	$(CH_2)_2C_6H_4$-4-CH_3	0.58 (0.55-0.62)	8.54 (5.64-17.34)	≤10[e]
36	H	$(CH_2)_2C_6H_4$-4-OH	2.081 (1.93-2.23)[i]	~25.00	20% at 10 mg/kg
37	H	2-(2-thienyl)ethyl	0.72 (0.63-0.81)	11.02 (9.58-15.86)	~10[c]
38	CH_3CO	CH_3	14.14 (13.87-14.42)	14% at 25 mg/kg	16.04 (8.56-25.10)
39	CH_3CO	$(CH_2)_2C_6H_5$	1.00 (0.90-1.10) 15.25 (3.26-17.86)[g]	2.82 (2.65-7.94) 35.00 (27.42-67.20)[g]	*d*
40	CH_3CO	2-(2-thienyl)ethyl	0.95 (0.88-1.04) 64.00 (60.50-67.90)[g]	≤3.8[e]	*f*
morphine			0.68 (0.65-0.72)	3.80 (1.72-9.51)	
pentazocine			2.40 (2.10-2.90)	14.6 (7.4-24.4)	13.8 (9.8-24.7)
nalorphine					0.43 (0.28-1.35)

[a] All compounds were tested as racemic hydrobromides. [b] Determined by subcutaneous administration unless otherwise specified. [c] Approximate values obtained graphically from dose-response data. [d] No effect with doses up to 10 mg/kg. [e] Poor dose-response effect. [f] Not determined. [g] Determined by oral administration. [h] CNS effects required a lower initial screening dose. [i] Marked overt effects were observed. [j] The lack of physical dependence liability of compound 31 was ascertained by the rat infusion test. At 50 and 100 mg/kg/day, 31 failed to substitute for morphine in rats infused with the latter by the usual schedule (50, 100, 4 × 200 mg/kg/day). [k] The vehicle control used in all three biological tests consists of distilled water and a few drops of Tween 80.

based on their mixed agonist–antagonist properties, potency, and a minimum of side effects; the former was found to be devoid of physical dependence liability in the rat infusion test. Optical resolution of **31** and **39** is currently in progress and the results, including comparative pharmacological data for the enantiomers, will be the subject of a future paper.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (Jeolco C60HL) (tetramethylsilane) spectra. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. GC–mass spectral data were determined with Finnigan Model 4000 spectrophotometer at 70-eV ionization voltage. Where analyses were indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Labs., Skokie, Ill.) were within 0.4% of theoretical values.

2-(3-Methoxyphenyl)cyclopentanone (1a). To a cold (−50 °C) stirred solution of 41.1 g (0.2 mol) of *m*-bromoanisole in 150 mL of anhydrous THF was added dropwise 114 mL of 2.2 M *n*-butyllithium in hexane (Alfa Chemical Co.) under nitrogen. After 2 h, a solution of 23.7 g (0.2 mol) of 2-chlorocyclopentanone in 15 mL of THF was slowly added during 10 min, and the mixture was stirred for 1 h at −50 °C overnight at room temperature. Xylene (500 mL) was added and THF was distilled off until the internal temperature reached 120 °C. After 2 h at reflux, the cooled reaction mixture was treated with ice-cold 1 N HCl, filtered, and separated. The organic layer was washed with aqueous $NaHCO_3$ and dried ($MgSO_4$). Fractionation of the crude product in vacuo yielded, as the main fraction, 19 g (50%) of **1a**: bp 116–117 °C (0.1 mm) [lit.[8a] bp 155–159 °C (0.9 mm)]; IR ($CHCl_3$) 1750 cm^{-1}; mass spectrum *m/e* 190 (M^+). Anal. ($C_{12}H_{14}O_2$) H; C: calcd, 75.75; found, 75.17.

2-(3-Methoxyphenyl)cyclopentanone Oxime (1b). A solution of 1.52 g (0.008 mol) of **1a**, 1.2 g of hydroxylamine hydrochloride, and 1.2 g of sodium acetate in 15 mL of 80% aqueous ethanol (v/v) was refluxed overnight. The cooled reaction mixture was extracted with ether and the ether solution was washed, dried ($MgSO_4$), and concentrated to an oily residue. Trituration with warm hexane afforded 1.3 g (78%) of **1b** which was recrystallized to give an analytically pure sample, mp 112–113 °C (see ref 8a). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

2-(3-Methoxyphenyl)-2-(2-dimethylaminoethyl)cyclopentanone Hydrobromide (2). A solution of 9.5 g (0.05 mol) of **1a** in 10 mL of 1,2-dimethoxyethane (DME) was added dropwise to a well-stirred slurry of 5.7 g (0.05 mol) of potassium *tert*-butoxide (Aldrich Chemical Co.) in 100 mL of DME. The reddish solution was stirred at room temperature for 30 min before 5.4 g (0.05 mol) of freshly distilled 2-dimethylaminoethyl chloride

was added during 5 min. Stirring was continued at reflux under nitrogen for an additional 16 h. The cooled reaction mixture was quenched with water and extracted with ether, and the combined ether solution was shaken with a slight excess of 1 N HCl. The clear acid extract was warmed briefly on a steam bath to give, upon ether extraction, 3.0 g of **1a**, recovered from cleavage of the O-alkylated by-product. The aqueous layer was then basified with ammonia and the precipitated oil was dried (K_2CO_3) in ether. The crude product was distilled at 135–137 °C (0.3 mm) to give 7.2 g of a colorless liquid which was converted to a crystalline hydrobromide **2** with ethereal HBr. Recrystallization from acetone–ether gave 8.9 g (52%) of prisms, mp 158–159 °C (lit.[7] 156.5–157.5 °C). Anal. ($C_{16}H_{24}BrNO_2$) C, H, Br, N.

5-Bromo-2-(2-dimethylaminoethyl)-2-(3-methoxyphenyl)cyclopentanone Hydrobromide (3). A solution of **2** (111 g, 0.324 mol) in 900 mL of anhydrous $CHCl_3$ was cooled to −5 °C, and to it was added, over a period of 3 h, 54.4 g (0.34 mol) of bromine in 900 mL of $CHCl_3$ while the temperature was maintained below 0 °C. After stirring at room temperature overnight, the solution was evaporated in vacuo, leaving an oily residue which slowly crystallized upon standing at 0 °C. Recrystallization from acetone–ether gave 95.5 g (70%) of colorless prisms, mp 103–105 °C. Anal. ($C_{16}H_{23}Br_2NO_2$) C, H, Br, N.

5-(3-Methoxyphenyl)-2-methyl-8-oxo-2-azabicyclo[3.2.1]octane Methobromide (4). A well-stirred solution of 181 g (0.43 mol) of **3** in 700 mL of water was treated dropwise with 40 mL of concentrated ammonia while the temperature of the solution was kept below 10 °C. The liberated oily amine soon solidified to form a crystalline mass which was filtered and air-dried. Recrystallization from methanol–acetone gave 105 g (72%) of colorless granules, mp 248–249 °C (lit.[7] 260–262 °C). Anal. ($C_{16}H_{22}BrNO_2$) C, H, Br, N.

5-(3-Methoxyphenyl)-2-methyl-8-oxo-2-azabicyclo[3.2.1]octane (5). Dry distillation of 27 g (0.08 mol) of **4** at 260 °C (0.2 mm) in the presence of sand afforded 16.5 g (84%) of the tertiary amine **5** which, upon redistillation in vacuo, gave an analytically pure sample, bp 130–132 °C (0.2 mm) [lit.[7] bp 220 °C (0.4 mm)]. Anal. ($C_{15}H_{19}NO_2$) C, H, N.

5-(3-Methoxyphenyl)-2-methyl-2-azabicyclo[3.2.1]octane Hydrobromide (6). A solution of 5.5 g of **5** (0.021 mol), 5.5 mL of 95% hydrazine hydrate, and 5.5 g of 85% KOH in 35 mL of triethylene glycol was stirred at 160–165 °C for 4 h. The reaction temperature was then raised to 190 °C during 30 min and kept there for 1 h as water was slowly distilled off. The cooled mixture was poured onto ice and extracted with ether, and the combined ether solution was washed (four times) with water and dried (K_2CO_3). Treatment of the anhydrous ether solution with ethereal HBr afforded a crystalline hydrobromide which was recrystallized from acetone–ether to give 4.7 g (75%) of **6** in fine needles. Properties of **6** are included in Table I.

2-Cyano-5-(3-methoxyphenyl)-2-azabicyclo[3.2.1]octane (7). To a stirred solution of 2.1 g of cyanogen bromide in 15 mL of anhydrous $CHCl_3$ was added dropwise a solution of the free base of **6** (4.2 g, 0.018 mol) in 35 mL of $CHCl_3$ during 1 h. Following addition, the mixture was stirred at reflux for an additional 3 h and concentrated in vacuo to dryness. Ethanol was added to consume the unreacted reagent and the solution was again concentrated. The viscous residue gradually solidified upon cooling and was recrystallized from ether–hexane to give 4.1 g (94%) of **7** in needles, mp 96–97 °C. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

5-(3-Methoxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (8). A suspension of 3.4 g of **7** (0.014 mol) in 200 mL of 2 N HCl was stirred at reflux (oil bath) for 15 h. The clear solution was extracted with ether to remove any neutral materials and basification of the aqueous solution with 40% NaOH liberated an oily amine. After drying in ether (K_2CO_3) the base was converted to its hydrobromide with ethereal HBr. Recrystallization from acetone–ethyl acetate gave 3.7 g (90%) of colorless prisms. Properties of **8** are included in Table I.

2-Ethyl-5-(3-methoxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (9). Method A. A mixture of 2.17 g of the free base from **8** (0.01 mol), 1.72 g of ethyl iodide (0.011 mol), and 2.0 g of sodium bicarbonate in 30 mL of anhydrous DMF was stirred at 80 °C for 16 h. The reaction mixture was diluted with water and extracted with ether, and the dried (K_2CO_3) ether solution was concentrated to an oily residue. The crude product was purified by passing through an alumina column packed in ether. Elution with ether, followed by treatment with ethereal HBr, afforded 0.94 g of **9**. Properties of **9**, and of **10**–**12**, prepared in a similar manner, are included in Table I.

2-[3-(*p*-Fluorobenzoyl)propyl]-5-(3-methoxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (13). Method A. A mixture of 1.1 g (0.005 mol) of the free base from **8**, 1.47 g of γ-chloro-*p*-fluorobutyrophenone ethylene glycol ketal, 1.0 g of sodium bicarbonate, and 1.0 g of potassium iodide in 15 mL of DMF was stirred at 70–80 °C for 16 h. The mixture was filtered and the filtrate was concentrated in vacuo to an oily residue. Approximately 20 mL of an ethanolic solution of HCl (prepared by mixing 10 mL of ethanol with 10 mL of 3 N HCl) was added, and the homogeneous solution was stirred at room temperature for 2 h to effect complete hydrolysis of the ketal. Basification of the acidic solution with 40% NaOH liberated an oily amine which was dried (K_2CO_3) in CH_2Cl_2 and purified by column chromatography over alumina as described before. Treatment with ethereal HBr afforded 2.1 g of **13**, whose properties are included in Table I.

5-(3-Hydroxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (21). Method B. A solution of 1.1 g of **8** (0.005 mol) in 15 mL of 48% hydrobromic acid was stirred at 120 °C for 30 min. The excess acid was removed in vacuo, and the solid residue was recrystallized from ethanol–ether to give 1.29 g of **21** as rhombic crystals. Properties of **21**, and of **22**–**26** and **30**–**37**, prepared in similar manners, are included in Table I.

2-Cyclopropylmethyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (27). Method C. A mixture of 0.68 g (0.0024 mol) of **21**, 1.2 g of anhydrous K_2CO_3, 380 mg of cyclopropylmethyl bromide, and a few crystals of KI in 10 mL of DMF was stirred at 80 °C for 24 h. The inorganic salts were removed by filtration and the filtrate was concentrated to an oily residue. The crude alkylation product was purified by passing through a column of activated alumina; elution with 10% methanolic ether gave the pure phenolic tertiary amine which was converted to 320 mg of **27**. Properties of **27**, and of **28**, prepared in a similar manner, are included in Table I.

5-(3-Methoxyphenyl)-2-phenethyl-2-azabicyclo[3.2.1]octane Hydrobromide (14). Method D. A mixture of 1.19 g (0.0055 mol) of **8**, 1.4 g of phenylacetyl chloride, and 2.7 g of sodium bicarbonate in 15 mL of $CHCl_3$ was stirred at reflux for 4 h. The mixture was filtered; the chloroform solution was washed with dilute HCl, dilute $NaHCO_3$, and water. After drying over $MgSO_4$ and removal of solvent, the crude amide (homogeneous by TLC) was reduced with 0.8 g of lithium aluminum hydride in 30 mL of THF for 3 h. Working up in the usual manner led to a pale yellowish oil which was converted to 1.5 g of **14** with ethereal HBr. Properties of **14**, and of **15**–**20**, prepared in a similar manner, are included in Table I.

2-(2-Furylmethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.2.1]octane Hydrobromide (29). Method E. To a stirred suspension of 1.13 g (0.004 mol) of **21**, 5 mL of triethylamine, and 8 mL of $CHCl_3$ was added 670 mg of freshly distilled 2-furoyl chloride. The mixture was stirred at room temperature overnight and concentrated in vacuo to a semicrystalline residue. Trituration with $CHCl_3$, followed by washings with 1 N HCl and 5% $NaHCO_3$ and drying ($MgSO_4$), gave a virtually pure amido ester which was reduced with 1.5 g of lithium aluminum hydride in 50 mL of THF for 3 h. Working up in the usual manner led to a pale yellowish oil which was converted to a crystalline hydrobromide in ether. Recrystallization from methanol–ether afforded 720 mg (50%) of **29** as colorless granules. Properties of **29** are included in Table I. Compound **27**, prepared in a similar manner from **21** and cyclopropylcarbonyl chloride, was identical with that obtained by method C.

5-(3-Acetoxyphenyl)-2-phenethyl-2-azabicyclo[3.2.1]octane Hydrobromide (39). Method F. A suspension of 1.2 g of the free base from **31** (0.004 mol) in 10 mL of acetic anhydride was heated at 100 °C until a clear solution was formed (30 min). The excess anhydride was removed in vacuo, and the residue was dissolved in ether. Treatment of the solution with ethereal HBr gave a gummy precipitate which was crystallized from acetone–ether to give 1.5 g of **39**. Properties of **39**, and of **38** and **40**, prepared in a similar manner, are included in Table I.

Phenylquinone-Induced Writhing in Mice (PQW).[16] The procedure employed was a modification of the method of Siegmund et al. Groups of five male CD-1 Charles River mice weighing 18–24 g were administered the test drug (sc) 15, 30, 60, and 90 min at the initial screening dose of 25 mg/kg prior to the injection of a phenyl-*p*-benzoquinone (Eastman) solution (0.125% in a 5% aqueous ethanol solution). Control mice were treated with an equal volume of vehicle. After phenylquinone injection the mice were placed individually in 1000-mL beakers and 5 min later the number of writhes was recorded for a 10-min period. The peak time of test drug activity was thereby determined. A dose–response study was performed in a similar manner except that ten animals were used at the peak time of activity. Animals were dosed and tested in a randomized manner using four drug doses and one control group. Drug activity is expressed as the percent inhibition of the number of writhes and an estimated ED_{50} is calculated by a computer linear regression analysis.

Modified D'Amour–Smith Analgesia (Tail Flick) in Mice.[17] The procedure used was a modification of the test developed by D'Amour and Smith. Groups of ten male Charles River (CD-1) mice were individually placed in a restraining plexiglass compartment and subsequently a noxious stimulus was produced by an intense light beam. The subjects quickly responded by flicking their tails. This reaction time, the intervals between stimulus onset and response, was automatically measured and recorded. Prior to drug administration two control readings of reaction time were measured. Subjects were discarded if their reaction times varied by more than 1 s or if their inclusion would cause the spread of reaction times to exceed 3. For both sets of control readings, a cutoff time was thus determined. Test compounds were administered subcutaneously and control mice received an equal volume (10 mL/kg) of vehicle. For a time response, the animals were tested 15, 30, 45, and 60 min after dosing. Animals which responded after the set cutoff value were called positive, indicative of analgesia. For a dose range, the animals were tested at the peak time with a minimum of three doses in addition to vehicle control. Percent analgesia was calculated for each dose and estimated ED_{50} values were determined using a linear regression analysis.

Inhibition of Morphine-Induced Mania. Groups of male mice weighing 18–30 g were dosed in a random manner and two pairs of mice were used per group. The control mice received morphine sulfate (25 mg/kg sc) and the test group received morphine sulfate plus the compound to be tested for narcotic antagonistic properties. The animals were observed for 15–30 min after dosing, during which time the control mice exhibited a stereotypic behavior manifested by an increase in motor activities. Test compounds which inhibited such morphine-induced behavior were considered positive as narcotic antagonists. For a dose range study, drugs were prepared and administered in the same manner as the screen and ED_{50} values were determined by means of a linear regression analysis.

Acknowledgment. The authors wish to express their appreciation to Marc N. Agnew, Romana H. Fedasiuk, Yorum R. Shatz, and Lee J. O'Donnell for spectral data and to A. Minet, K. R. Malone, M. G. Ma, and R. Matland for performing pharmacological assays. We also gratefully acknowledge Linda Cuiskelly for assistance in preparation of this manuscript.

References and Notes

(1) (a) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955); (b) E. L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970); (c) M. E. Rogers and E. L. May, *ibid.*, **17**, 1328 (1974).
(2) H. H. Ong, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **17**, 133 (1974).
(3) (a) R. L. Clark, A. A. Pessolano, J. Weijlard, and K. Pfister, III, *J. Am. Chem. Soc.*, **75**, 4963 (1953); (b) J. W. Lewis, K. W. Bentley, and A. Cowan, *Annu. Rev. Pharmacol.*, **11**, 241 (1971).
(4) T. G. Cochran, *J. Med. Chem.*, **17**, 987 (1974).
(5) D. L. Larson and P. S. Portoghese, *J. Med. Chem.*, **16**, 195 (1973).
(6) The synthesis and pharmacological activity of an isomeric phenylnormorphan series, the 1-phenyl-6-azabicyclo-[3.2.1]octanes, were recently published: (a) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, and S. Saito, *Chem. Pharm. Bull.*, **24**, 1002 (1976); (b) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, and S. Saito, *ibid.*, **24**, 1514 (1976); (c) M. Takeda, H. Inoue, K. Noguchi, Y. Honma, M. Kawamori, G. Tsukamoto, Y. Yamawaki, S. Saito, K. Aoe, T. Date, S. Nurimoto, and G. Hayashi, *J. Med. Chem.*, **20**, 221 (1977).
(7) K. Noguchi, M. Takeda, and S. Nurimoto, *Chem. Pharm. Bull.*, **25**, 890 (1977).
(8) Takeda and co-workers prepared this compound in 35–40% yield by two multistep sequences starting with *m*-methoxyphenylmagnesium bromide and cyclopentanone (ref 7). Prior to the development of our own procedure, there were two reports in the literature describing the synthesis of this compound; however, the ketone prepared by either of these methods was, at best, only 50% pure. Both methods involved the condensation of a benzyne with the enolate or enamine of cyclopentanone. (a) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, and O. Kusama, *J. Chem. Soc. C*, 1051 (1971); (b) P. Caubere, G. Guillaumet, and M. S. Mourad, *Tetrahedron*, **28**, 95 (1972).
(9) K. Mislow and C. L. Hamermesh, *J. Am. Chem. Soc.*, **77**, 1590 (1955).
(10) H. Rapoport, C. H. Lovell, H. R. Reist, and M. E. Warren, Jr., *J. Am. Chem. Soc.*, **89**, 1942 (1967).
(11) The *N*-methyl congener of this series (see Table II, compound **22**) was found to be $^1/_{20}$ as active as morphine in the PQW assay; this seems to diverge from findings by Takeda et al. that no discernible analgesic activity was exhibited by this compound. However, no valid comparison of results could be made because of the different testing procedures used.
(12) T. Oh-ishi and E. L. May, *J. Med. Chem.*, **16**, 1376 (1973).
(13) In addition to the data shown in Table II, compound **31** was also found to be three times more active than pentazocine in antagonizing morphine-induced analgesia (tail-flick procedure) in mice.
(14) G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, **18**, 656 (1975).
(15) (a) J. G. Topliss, *J. Med. Chem.*, **15**, 1006 (1972); (b) P. N. Craig, *ibid.*, **14**, 680 (1971).
(16) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957).
(17) F. D'Amour and D. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).
(18) N. B. Eddy and E. L. May, "Synthetic Analgesics, Part IIB, 6,7-Benzomorphans", Pergamon Press, Elmsford, N.Y., 1966, pp 131–137.