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# *N*-Alkylnorketobemidones with Strong Agonist and Weak Antagonist Properties

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Replacement of the *N*-methyl group of ketobemidone (1) with propyl, cyclopropylmethyl, or allyl (*cf.* 6, 11, and 13) does not produce antagonists but weak to medium strength analgesics with high physical dependence capacity (Rhesus monkeys). When the N-substituent is amyl (8) strong analgesic and atypical properties of antagonism are exhibited. *N*-Hexyl- and -heptylnorketobemidones (9 and 10) are between morphine and pethidine in analgesic potency, and both are weak, long-acting, nalorphine-like antagonists in monkey and guinea-pig ileum experiments. *N*-Ethylnorketobemidone (5) is a weak agonist, but the *N*-butyl homolog 7 is as potent as morphine with low physical dependence capacity.

It is well known that strong analgesics of fused tricyclic to hexacyclic systems (benzomorphans to *endo*-ethenooripavines) can be converted to potent antagonists by replacement of methyl on the nitrogen with allyl, propyl, or cyclopropylmethyl. More recently it was demonstrated that the strong analgesic, 5-*m*-hydroxyphenyl-2-methylmorphan,[1] bicyclic in character, gave only weak antagonists by this simple change despite a favorable location of the phenolic hydroxyl. We now wish to report complete failure to obtain antagonists from the powerful analgesic, ketobemidone (monocyclic), with these three N-substitutions and the preparation of strong analgesics containing properties of antagonism by higher *N*-alkyl substitution.

**Chemistry.** The starting material, 2, for the preparations described herein was obtained in double the yield and one-fifteenth the time reported by Avison, *et al.*,[2] in the reaction of EtMgI with 4-cyano-4-*m*-methoxyphenyl-1-methylpiperidine, simply by very efficient stirring. Conversion of 2 to 3 was effected by the ethyl chloroformate method.[3]

Reaction of 3·HCl with alkyl bromides or iodides in boiling 2-butanone or DMF at 90° ($K_2CO_3$) followed by treatment of the resultant *N*-alkyl methyl ethers with boiling 48% HBr gave phenols 5–10. Compound 11 was similarly obtained using allyl bromide.

The cyclopropylmethyl analog, 13, was synthesized by a less direct route. Phenol 4, prepared from 3 with boiling 48% HBr, and cyclopropylcarbonyl chloride gave the *O,N*-diacyl derivative which was reduced to carbinol 12 with $LiAlH_4$. Oxidation of 12 to 13 was effected with DMSO-$Ac_2O$[4] or by the Oppenauer method.

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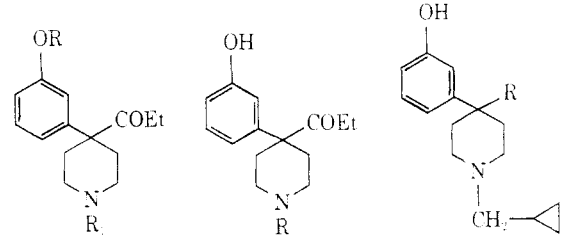

1, R = H; $R_1$ = Me
2, R = $R_1$ = Me
3, R = Me; $R_1$ = H



4, R = H
5, R = Et
6, R = Pr
7, R = Bu
8, R = Am
9, R = Hex
10, R = Hept
11, R = allyl



12, R = CHOHEt
13, R = COEt

**Pharmacology.** In Table I are given analgesic activities (hot-plate and Nilsen),[5] physical dependence capacities (PDC),[6] and properties of narcotic antagonism for ketobemidone (1) and pentazocine (standards) and analogs of 1. Predictably, a change from methyl to ethyl with respect to the N-substituent (1 *vs.* 5) nearly abolishes the CNS effects seen in the strongly active 1, partially restored in the *N*-propyl homolog 6 and its *O*-acetyl derivative. *N*-Butyl homolog 4 is half as potent (as an analgesic) as 1 but is more toxic and has little PDC. The *N*-amyl derivative 8 is nearly three times stronger than 1 but will not sustain morphine dependence in monkeys; in fact, it displays some (atypical) properties of antagonism. The hexyl and heptyl homologs 9 and 10 are typical nalorphine-like antagonists with a longer duration of action, a steeper

**Table I.** Pharmacology of Ketobemidone Analogs

| Compound[a] | $ED_{50}$, mg/kg sc | | PDC[c] | Antag act.[d] |
|---|---|---|---|---|
| | Hot-plate | Nilsen[b] | | |
| Ketobemidone (**1**) | 0.8 (0.7–0.9) | | High[e] | No |
| **5** | 23.0 (17.8–29.8) | 44.7 (35.7–56.0) | No | No |
| **6** | 5.7 (4.7–6.8) | 4.2 (2.7–6.5) | Intermediate[f] | No |
| **6**-OAc | 4.5 (3.7–5.5) | | Intermediate[f] | No |
| **7** | 1.7 (1.4–2.2) | | Low[g] | No |
| **8** | 0.3 (0.2–0.4) | 0.4 (0.3–0.6) | No[h] | Yes[h] |
| **9** | 3.0 (2.2–4.1) | 2.4 (1.8–3.4) | No | Yes[i] |
| **10** | 3.7 (2.9–4.8) | 3.5 (2.4–5.0) | No | Yes[i] |
| **11**[j] | 2.9 (2.7–3.1) | 2.3 (1.6–3.2) | High | No |
| **12** | Inactive to 100 | Inactive to 40 | No | No |
| **13** | 24.8 (18.8–32.6) | 24.0 (15.9–36.2) | Probably high | No |
| Pentazocine | 12.3 (9.3–16.3) | 4.7 (2.9–5.1) | No | Yes[k] |

[a] Administered as HBr or HCl salts. [b] See ref 5. [c] Physical dependence capacity (in Rhesus monkeys, ref 6). [d] Capacity to antagonize morphine dependence in Rhesus monkeys (ref 6). [e] R. G. Hardy, Jr., and M. G. Howell in "Medicinal Chemistry," Vol. 5, G. DeStevens, Ed., Academic Press, New York, N. Y., 1965, Chapter V. [f] Slight suppression of morphine abstinence at 4.0, partial at 8.0 mg/kg; at 16.0 mg/kg there was almost complete suppression plus signs of CNS depression after recovery from complete loss of muscle strength which lasted 1 hr. [g] No effect or very mild suppression at 8.0 mg/kg (toxic at 16 mg/kg). [h] No suppression of abstinence at 0.2–3.2 mg/kg and exacerbation at 6.4 mg/kg. In nonwithdrawn monkeys there were long-lasting abstinence-like effects at 6.4–25.6 mg/kg. When these effects have disappeared, injections of morphine do not restore the animals to normal. [i] Longer acting than nalorphine; $^1/_{20}$ as potent with a steeper dose–response curve. [j] A. Langbein, H. Merz, K. Stockhaus, and H. Wick, First International Conference on Narcotic Antagonists, Airlie House, Warrenton, Va., 1972. [k] See ref 5, 6, and 8.

dose–response curve, and the potency of pentazocine. They are, however, more potent than pentazocine as analgesics. The results described above with **8**, **9**, and **10** were essentially corroborated in guinea-pig ileum studies (private communication from Professor H. W. Kosterlitz, University of Aberdeen, Scotland[7]).

A change from methyl to allyl or cyclopropylmethyl (*cf.* **11** and **13**) did not produce properties of antagonism. Rather, **11** and **13**, like **6**, have narcotic properties, **6** and **11** being much stronger than **13**. Alcohol **12** is inert.

Thus, it is clear that below the tricyclic (benzomorphan)[8] system, strong antagonists cannot be obtained from strong agonists simply by replacement of the nitrogen methyl with the (now) classical allyl, cyclopropylmethyl, or propyl radicals.[1a,8] However, the demonstration of long-lasting properties of antagonism and medium to strong analgesic activity in higher (amyl to heptyl) *N*-alkylnorketobemidones adds a new dimension to this area of research.

## Experimental Section

Melting points were taken in a Hershberg apparatus (total immersion, Anschutz thermometers). Elemental analyses (indicated by C, H, Br, and N when within ±0.4% of the theoretical values) and mass data are due to the Section on Analytical Services and Instrumentation of this laboratory.

**4-*m*-Methoxyphenyl-1-methyl-4-propionoxypiperidine (2).** To the Grignard reagent prepared (in $Et_2O$) from 23.4 g (0.96 mol) of Mg and 150 g (0.96 mol) of EtI was added (efficient stirring) 55 g (0.24 mol) of 4-cyano-4-*m*-methoxyphenyl-1-methylpiperidine[2] (supplied by Ciba-Geigy, Basel) in 400 ml of $C_6H_6$. The $Et_2O$ was distilled and the mixture was refluxed for 1 hr. After cooling, 80 g of $NH_4Cl$ in $H_2O$ was added. The separated organic layer was washed with dilute $NH_4Cl$ and refluxed for 30 min with 600 ml of 2 *N* HCl. The aqueous layer was separated, washed with $C_6H_6$, made alkaline with KOH pellets, and extracted with $C_6H_6$. The extract was dried‡ and evaporated to give an oil (46 g): bp 160–161° (2 mm); yield 40.5 g (65%); $\nu$ 1710 $cm^{-1}$.

Avison, *et al.*,[2] obtained **2**, bp 130–134° (0.3 mm), in 33% yield, reaction time 15 hr.

**4-*m*-Methoxyphenyl-4-propionylpiperidine (3) Hydrochloride.** To a stirred solution of 25 g (0.24 mol) of ethyl chloroformate in 80 ml of $C_6H_6$ was added 20.5 g (0.08 mol) of **2** in 100 ml of $C_6H_6$ during 30 min. The mixture was refluxed for 2 hr, washed with $H_2O$ and then 10% HCl, dried,‡ and evaporated to dryness to give 23 g (90%) of oily carbamate: $\nu$ 1710–1705, 1250 $cm^{-1}$. From the $H_2O$ and acid washings 2 g (10%) of **2** was recovered.

The 23 g of carbamate and 300 ml of 23% HCl were refluxed together for 12.5 hr, washed with $C_6H_6$, made alkaline with NaOH pellets, and extracted with $C_6H_6$. Drying‡ and evaporation of the $C_6H_6$ gave 11.6 g of an oil which was converted to the hydrochloride. Recrystallization from EtOH gave 11.5 g (52%) of plates: mp 205–207°; $\nu^{Nujol}$ 1700 $cm^{-1}$. *Anal.* ($C_{15}H_{22}ClNO_2$) C, H, Cl, N.

Compound **3** was prepared in 10–15% overall yield by reaction of **2** and cyclopropylcarbonyl chloride in refluxing toluene, followed by hydrolysis of the resultant *N*-cyclopropylcarbonyl derivative (obtained in 64% yield)§ with 20% HCl. Similar reaction of **2** with benzoyl, acryloyl, cyclohexanecarbonyl, or propionyl chloride gave no displacement of the nitrogen methyl by acyl. Principally, **2** was recovered.

**1-Ethyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (5) Hydrobromide.** EtI (1.2 g), 2.0 g of **3**·HCl, 3.0 g of $K_2CO_3$, and 50 ml of 2-butanone were refluxed (stirring) for 5 hr and evaporated to dryness. The residue was treated with $CHCl_3$ and $H_2O$. The $CHCl_3$ layer was washed with $H_2O$, dried,‡ and evaporated to give an oil (2.3 g). This and 6 ml of 48% HBr were refluxed for 30 min and evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave 1.9 g (77%) of **5**·HBr, mp 243–244°. *Anal.* ($C_{16}H_{24}BrNO_2$) C, H, Br, N.

**4-*m*-Hydroxyphenyl-4-propionyl-1-propylpiperidine (6) Hydrobromide.** PrI (1.4 g), 2.0 g of **3**·HCl, 2.9 g of $K_2CO_3$, and 50 ml of 2-butanone gave, as described for **5**, 2.0 g (69%) of **6**·HBr, mp 195–197°. *Anal.* ($C_{17}H_{26}BrNO_2$) C, H, N, Br.

The *O*-acetyl derivative, prepared in 90% yield from **6** (0.6 g), 10 ml of $Ac_2O$, and 2 ml of pyridine (4 hr, reflux), was characterized as the HCl salt, mp 190–191° ($Me_2CO$). *Anal.* ($C_{19}H_{28}ClNO_3$) C, H, Cl, N.

**1-Butyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (7) hydrobromide,** mp 217–218°, was prepared in 89% yield (using BuI) similarly to **5** and **6**. *Anal.* ($C_{18}H_{28}BrNO_2$) C, H, Br, N.

**1-Amyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (8) Hydrobromide.** AmBr (0.6 g), 1 g of **3**·HCl, 1.5 g of $K_2CO_3$, and 25 ml of DMF were kept at 90° for 6 hr and evaporated to dryness *in vacuo*; the residue was treated with $CHCl_3$ and $H_2O$. Evaporation of the $CHCl_3$ layer gave 1.1 g of oil which was demethylated with 5 ml of 48% HBr (30 min, reflux). Distillation to dryness *in vacuo* and recrystallization of the residue from *i*-PrOH gave 1.1 g (83%) of **8**·HBr, mp 189.5–190°. *Anal.* ($C_{18}H_{30}BrN$).

This compound was similarly prepared in slightly lower yield from **4**.=

**1-Hexyl-4-*m*-hydroxyphenyl-4-propionylpiperidine (9) Hydrobromide.** As described in the preparation of **8**, the hydro-

‡ With $Na_2SO_4$.

§ We are indebted to Drs. E. Mohacsi and W. Leimgruber, Hoffmann-La Roche, Inc., Nutley, N. J., for this suggestion (see ref 9).

= Compound **4** was generously supplied by Dr. H. Merz, Boehringer Sohn, Ingelheim, Germany. We prepared **4** from **3** (boiling 48% HBr).

bromide was obtained in 85% yield from hexyl bromide and 3·HCl (15 hr, 80°), mp 179–181°. *Anal.* ($C_{20}H_{32}BrNO_2$) C, H, N, Br.

1-Heptyl-4-*m*-**hydroxyphenyl-4-propionylpiperidine (10) Hydrobromide.** This was obtained in 78% yield as described for 9 using heptyl bromide: plates, mp 147–149°, from $Me_2CO$. *Anal.* ($C_{21}H_{34}BrNO_2$) C, H, N, Br.

1-Allyl-4-*m*-**hydroxyphenyl-4-propionylpiperidine (11) Hydrobromide.** The yield of 11·HBr (allyl bromide, 7 hr) was 74%; plates, mp 192–193° (from EtOH). *Anal.* ($C_{17}H_{24}BrNO_2$) C, H, Br, N.

1-Cyclopropylmethyl-4-*m*-**hydroxyphenyl-4-(1-hydroxypropyl)piperidine (12).** A mixture of 2.4 g of 4, 3.8 g of cyclopropylcarbonyl chloride, 12 ml of $Et_3N$, and 70 ml of $CH_2Cl_2$ was refluxed for 3 hr and evaporated to dryness. The residue was dissolved in $C_6H_6$ and $H_2O$. The $C_6H_6$ layer was washed with 10% HCl, saturated $NaHCO_3$, and $H_2O$, successively, dried,‡ and evaporated to give 4.2 g of the *N,O*-dicarbonyl compound: $\nu$ 1750, 1705, 1640 $cm^{-1}$. This was reduced with 3.6 g of $LiAlH_4$ in 100 ml of refluxing THF (24 hr) giving, after the usual work-up, 2.7 g (87%) of **12**: mp 180–182° (from EtOH); M$^+$ 289. *Anal.* ($C_{18}H_{27}NO_2$) C, H, N.

1-Cyclopropylmethyl-4-*m*-**hydroxyphenyl-4-propionylpiperidine (13) Hydrobromide.** $Ac_2O$ (7.5 ml), 1.5 g of 12, and 22.5 ml of DMSO were stirred at room temperature for 65 hr, treated with ice–$H_2O$, made alkaline with 12 *M* $NH_4OH$, and extracted with $CHCl_3$. The $CHCl_3$ was washed with $H_2O$ and evaporated to give an oil which was dissolved in 10% NaOH–EtOH. This solution was refluxed for 3 hr, the EtOH was distilled, $H_2O$ was added to the residue, and the resultant solution was washed with $CHCl_3$ and then made alkaline with 12 *M* $NH_4OH$. The liberated base was dissolved in $CHCl_3$ and dried.‡ Evaporation left 1.0 g of oil which contained some **12**. Column chromatography on 30 g of silica gel (9:1 AcOEt–EtOH as eluent) gave 0.93 g (52%) of 13 whose hydrobromide (from EtOH) melted at 254–255°. *Anal.* ($C_{18}H_{26}BrNO_2$) C, H, Br, N.

Oxidation of 12 by the Oppenauer method (cyclohexanone, aluminum isopropoxide) gave 30% of 13.

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# Anticonvulsants. 4. Metharbital and Phenobarbital Derivatives[1]

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Several metharbital and phenobarbital derivatives were found to possess potent anticonvulsant activity and yet were either devoid of the marked hypnotic effects of the parent compounds or displayed very weak hypnotic activity. Particularly active compounds were the monomethoxymethyl derivative of phenobarbital (3), the 1-methyl-3-butoxymethyl derivative of phenobarbital (12), and the 3-methoxymethyl derivative of metharbital (10).

We reported previously[2] that 1,3-bis(alkoxymethyl) derivatives of phenobarbital possess marked anticonvulsant activity against both maximal electroshock and pentylenetetrazole induced seizures and yet are devoid of the hypnotic effects associated with the parent compound. It was reported[3,4] that the prototype of the 1,3-bis(alkoxymethyl)phenobarbital series, 1,3-bis(methoxymethyl)phenobarbital (DMMP, **16**) is converted to three major metabolites in the rat, which in order of decreasing quantities are: 1-methoxymethylphenobarbital (**3**), phenobarbital (**1**), and 1-methylphenobarbital (**15**). It was also reported[5] that in man, the major metabolites that accumulate in plasma as a result of DMMP administration in order of decreasing quantities are: phenobarbital, 1-methylphenobarbital, and 1-methoxymethylphenobarbital. In addition, smaller amounts of 1,3-dimethylphenobarbital (**7**) and 1-methyl-3-methoxymethylphenobarbital (**14**) have been identified in human plasma.

As a result of these discoveries we became interested in finding out whether the 1-alkyl, 1-alkoxymethyl, 1,3-dialkyl, and 1-alkyl-3-alkoxymethyl derivatives of 5,5-diethylbarbituric acid and 5-ethyl-5-phenylbarbituric acid would display anticonvulsant properties.

**Chemistry.** The synthesis of 1-benzyl-5-ethyl-5-phenylbarbituric acid (**2**) was accomplished from 5-ethyl-5-phenylbarbituric acid (**1**) with benzyl chloride in the presence of sodium hydroxide by a reported procedure.[6] As expected, this procedure yielded a mixture of unsubstituted, monosubstituted, and disubstituted benzyl derivatives of 5-ethyl-5-phenylbarbituric acid, as observed by tlc. Separation of the predominant product, 1-benzyl-5-ethyl-5-phenylbarbituric acid, from the mixture was achieved by column chromatography and crystallization.

The synthesis of 1-alkoxymethyl derivatives of 5-ethyl-5-phenylbarbituric acid, **3** and **4**, was accomplished by an unequivocal method.[7] The dilithium salt of thiophenobar-