Table II. Fractional Atomic Coordinates for MeCCNU[a]

	x	y	z
Cl	7477 (1)	1179 (1)	9182 (1)
O(1)	6593 (2)	592 (3)	4778 (2)
O(2)	4314 (2)	3004 (2)	6390 (2)
N(1)	5567 (2)	1868 (3)	5567 (3)
N(2)	5723 (3)	1159 (3)	4555 (3)
N(3)	3940 (2)	2542 (3)	4169 (2)
C(1)	6328 (4)	1011 (5)	7721 (5)
C(2)	6430 (4)	2012 (4)	6816 (4)
C(3)	4543 (3)	2522 (3)	5412 (3)
C(4)	2813 (3)	3031 (4)	3829 (3)
C(5)	2022 (3)	2031 (4)	3190 (5)
C(6)	844 (3)	2516 (4)	2784 (5)
C(7)	754 (3)	3615 (4)	1869 (4)
C(8)	1546 (3)	4608 (4)	2514 (4)
C(9)	2724 (3)	4132 (4)	2912 (4)
C(10)	−440 (4)	4071 (5)	1472 (5)
H(N)	418 (2)	224 (3)	358 (3)
H(1, 1)	561 (3)	99 (3)	804 (3)
H(1, 2)	635 (3)	23 (3)	726 (3)
H(2, 1)	720 (3)	204 (3)	679 (3)
H(2, 2)	640 (2)	282 (3)	730 (3)
H(4)	261 (2)	330 (3)	464 (3)
H(5, 1)	227 (3)	174 (3)	241 (3)
H(5, 2)	206 (3)	141 (3)	378 (3)
H(6, 1)	62 (3)	288 (3)	369 (3)
H(6, 2)	45 (3)	193 (3)	237 (3)
H(7)	98 (2)	332 (3)	108 (3)
H(8, 1)	128 (2)	483 (3)	337 (3)
H(8, 2)	150 (2)	530 (3)	190 (3)
H(9, 1)	319 (2)	478 (3)	338 (3)
H(9, 2)	302 (2)	387 (3)	213 (3)
H(10, 1)	−68 (3)	427 (3)	236 (3)
H(10, 2)	−47 (3)	480 (3)	91 (3)
H(10, 3)	−93 (3)	341 (3)	98 (3)

[a] The fractional coordinates have been multiplied by 10^4 for "heavy" atoms and 10^3 for hydrogen atoms.

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Supplementary Material Available: A listing of structure-factor amplitudes and of atomic thermal parameters (11 pages). Ordering information is given on any current masthead page.

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Benzomorphans. Structure of a Position Isomer

N. F. Albertson,* W. F. Michne, and B. F. Tullar

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received June 27, 1977*

May's benzomorphan synthesis leads not only to the α or cis isomer and the β or trans isomer but also to a position isomer hereinafter called the γ isomer. The structure and synthesis of this isomer are described. Biological activities of the α and γ isomers are compared.

In the benzomorphan synthesis developed by May and co-workers, a benzyl Grignard reagent is added to a pyridinium salt and the resulting dihydropyridine reduced and cyclized to give a benzomorphan.[1]

In their initial work May and Fry cyclized about 0.02 mol of tetrahydropyridine to obtain **1a** as the sole isolated

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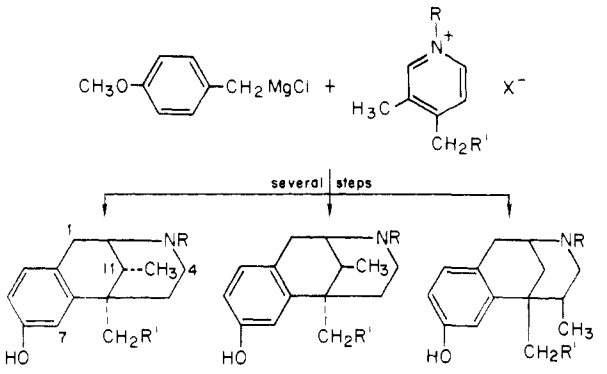


product.[2] Work on a scale about ten times as large enabled May and Ager to isolate a second isomer, **2a**, in about 1% yield[3] and to show that **1** and **2** differed in the configuration of the 11-methyl group. The cis configuration was subsequently established for **1** and trans for **2**.[4]

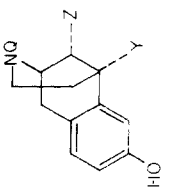
From the mother liquors of an 85-mol cyclization of 1-benzyl-2-(*p*-methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine oxalate, in 62% HBr,[5] we have obtained a third compound isomeric with the expected **1b** and **2b**. Similar results were obtained when a 1-benzyl-4-ethyl-3-methylpyridinium salt was employed; **4b**, **5b**, and **6b** were obtained.

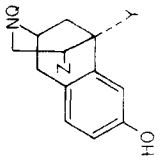
Both **3b** and **6b** hydrobromides were recovered unchanged upon further treatment with hydrobromic acid and were debenzylated upon catalytic hydrogenation to give a nor base which could be N-methylated with formaldehyde and hydrogen. Both **3a,b** and **6a,b**, as well as the nor bases, were very sensitive to UV light. It had previously been observed in this laboratory that hydroxybenzomorphans unsubstituted in position 11 undergo photochemical oxidation very readily, whereas substitution of either the axial or equatorial hydrogen by OH or alkyl groups leads to light-stable compounds. These facts suggested that **3** and **6** were the most probable structure for the γ isomers. The NMR data (see the Experimental Section) were in agreement and further suggested that in **3** the alkyls in the 5 position were oriented toward the benzene ring. This isomer arises as a result of attack of the Grignard reagent at the 6 position of the pyridinium intermediate.

Final proof of structure, by synthesis, was achieved only after Fry published a method of synthesis of 6-substituted 1,3,4-trialkyltetrahydropyridines.[6,7] Reduction of 3,4-lutidine methiodide with $NaBH_4$ in the presence of cyanide ion afforded 6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine.[6,7] This reacted with *p*-anisylmagnesium chloride to form 6-*p*-methoxybenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine which cyclized with HBr to **3a**. This did not depress the melting point of the compound obtained by replacing the *N*-benzyl group of the isolated γ isomer by the *N*-methyl group, and the infrared spectra were identical for the two samples.

Pharmacology. The data summarized in Table I show that, in the case of compounds having the typical N–Me agonist side chain, the α isomer shows a fivefold greater activity as agonist over the γ isomer in the dimethyl series, **2**, and an 18-fold greater activity in the methyl ethyl series, **6**. The same sort of agonist ratio—13-fold for the dimethylallyl side chain **3** and 40-fold for the allyl side chain

Table I. Comparison of Agonist and Antagonist Activities of Some α- and γ-Benzomorphans





Compd	Q	Y	Z	α: AD_{50},[d] mg/kg sc	α: ED_{50},[e] mg/kg sc	γ: AD_{50},[d] mg/kg sc	γ: ED_{50},[e] mg/kg sc
1	$CH_2C_6H_5$	Me	Me	Inact at 10[a]	8.5 (6.1–12)	1.3 flat	23 (15–33)
2	CH_3	Me	Me		2.9 (2.0–3.9)	N.D.R.[b]	0.54 (0.39–0.91)
3	$CH_2CH{=}C(CH_3)_2$	Me	Me	2.8 (1.4–5.3)	29 (20–42)	3.9 (2.1–7.4)[c]	2.2 (1.7–2.7)[c]
4	$CH_2CH{=}CH_2$	Et	Me	0.037 (0.023–0.059)	10 (7.5–13)	0.064 (0.041–0.099)	0.23 (0.048–0.61)
5	$CH_2CH{=}C(CH_3)_2$	Et	Me	>40		10.9 (7.8–15.3)	2.1 (1.6–2.8)
6	CH_3	Me	Et	9 (5.6–14)	20 (12–35)	Inact at 80	1.1 (0.91–1.4)
	Morphine			Inact	0.47 (0.38–0.56)	Inact	0.47 (0.38–0.56)

[a] Toxic at 80 mg/kg sc. [b] No dose response. [c] This is pentazocine. [d] See ref 8. [e] See ref 9.

4—holds for the antagonist side chains.

The *N*-benzyl compound 1 reverses the trend and shows greater agonist activity in the γ series.

Changing either **3** α (pentazocine) or **4** α to the γ isomers resulted in, at best, a slight increase in antagonist activity. Unexpectedly, the replacement of the methyl of the quaternary carbon by ethyl (series **5**) resulted in a lowering of antagonist activity, especially in the γ series.

Interestingly, the γ-*N*-methyl isomer having a 5-ethyl group (6 γ) showed some antagonist activity albeit weak.

Experimental Section

Unless otherwise indicated, melting points are not corrected for emergent stem errors. Analyses are within ±0.4% of the theoretical values. The antagonist sc dose in mg/kg was determined vs. meperidine in rats by the method of Harris and Pierson.[8] Agonist activity was measured by the acetylcholine writhing test by the procedure of Collier.[9] Compounds were delivered sc in distilled water and 95% confidence limits are given. Bases were dissolved by addition of lactic acid.

(2α,5β,6α)-3-Benzyl-1,2,3,4,5,6,-hexahydro-5,6-dimethyl-2,6-methano-3-benzazocin-8-ol (3b). After removal of the α and β isomers (**1b** and **2b**) from the cyclization liquors (originating from 35 kg of the tetrahydropyridine oxalate[5,10]) as completely as possible, the liquor remaining (*i*-PrOH) was returned to the cold room for 15 months. A crop of 230 g of a mixture of α and β isomers was removed by filtration and the filtrate again refrigerated. After 6 months, an additional crop of 105 g, mp 140–160 °C, was recovered. This was converted to the base and dissolved in 50 mL of Et_2O and 50 mL of hexane. Storage at 5 °C for several days gave a 14-g crop of α base. The filtrate was freed of solvent, the residue dissolved in 100 mL of *i*-PrOH, and the solution acidified with 62% HBr. There was immediate crystallization of an HBr salt. This (45 g) was recrystallized from 300 mL of AcOH to give a 30-g crop at 25 °C, mp 245 °C. The melting point was depressed to 220–230 °C on admixture with the α-hydrobromide.

Conversion of 5 g of this HBr salt to the base with NH_4OH and recrystallization from 10 mL of 1:1 C_6H_6–hexane gave 2.6 g (66%) of base, mp 125–126 °C. Anal. ($C_{21}H_{25}NO$) C, H, N.

1,2,5,6-Tetrahydro-6-(*p*-hydroxybenzyl)-1,3,4-trimethylpyridine. The Grignard from 52 g (0.33 mol) of anisyl chloride was reacted with 24.2 g (0.161 mol) of 6-cyano-1,2,5,6-tetrahydro-1,3,4-trimethylpyridine[6,7] to give 27.8 g (70%) of 1,2,5,6-tetrahydro-1,3,4-trimethyl-6-(*p*-methoxybenzyl)pyridine. Refluxing 25.6 g (0.104 mol) of this with 25 mL of 48% HBr for 24 h and cooling gave 16.4 g (51%) of the product HBr, mp 190–192 °C. The base melted at 201–204 °C from MeOH. Anal. ($C_{15}H_{21}NO$·HBr) C, H.

(2α,5β,6α)-1,2,3,4,5,6-Hexahydro-5,6-dimethyl-2,6-methano-3-benzazocin-8-ol (3, R = H). A solution of 21.8 g (0.070 mol) of **3b**·HBr in 200 mL of 95% EtOH with 2 g of 10% Pd/C was hydrogenated at 50 lb of H_2 and 25 °C for 2 h. The residue from 30 mL of *i*-PrOH gave 12.0 g (58%) of the HBr, mp 268–270 °C, which was converted to the base, mp 223–225 °C dec. Anal. ($C_{14}H_{19}NO$) C, H, N.

(2α,5β,6α)-1,2,3,4,5,6-Hexahydro-3,5,6-trimethyl-2,6-methano-3-benzazocin-8-ol (3a). A. From By-product. Reduction of 3 g (0.014 mol) of the above nor base in 100 mL of 38% HCHO with Pd/C at 50 lb and 65 °C took 1 h. The catalyst and solvent were removed, and the residue was slurried with water, filtered, and recrystallized from 20 mL of 95% EtOH to give 1.0 g (31%) of the *N*-methyl base, mp 230–233 °C (depressed on admixture with nor base). Anal. ($C_{15}H_{21}NO$) C, H, N.

B. Via Fry Synthetic Route. Refluxing 1,2,5,6-tetrahydro-6-(*p*-hydroxybenzyl)-1,3,4-trimethylpyridine (vide supra) with 10 vol of 62% HBr for 24 h, followed by conversion to the base with NH_4OH and recrystallization from Me_2CO and then from MeOH, gave a product melting at 230–233 °C, undepressed upon mixing with the above. The IR spectra were identical. Anal. ($C_{15}H_{21}NO$) N.

(2α,5β,6α)-1,2,3,4,5,6-Hexahydro-*trans*-5,6-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol [3, R = $CH_2CH{=}C(CH_3)_2$]. Alkylation of 4.47 g (0.015 mol) of **3**·HBr (R = H) in the usual manner[11] with 1-bromo-3-methyl-2-butene gave 3.53 g (83%) of product. Recrystallization from *i*-PrOAc and then from EtOAc–hexane gave light-sensitive crystals, mp 181.2–185.2 °C cor. Anal. ($C_{19}H_{27}NO$) C, H, N.

(2α,5β,6α)-3-Benzyl-6-ethyl-1,2,3,4,5,6-hexahydro-5-methyl-2,6-methano-3-benzazocin-8-ol (6b). After removal of 26 kg of **4b** and 550 g of **5b** from the cyclization liquors derived from 35 kg of 1-benzyl-4-ethyl-2-(*p*-methoxybenzyl)-3-methyl-1,2,5,6-tetrahydropyridine oxalate (cf. ref 5), the liquors were stored for 2 months in a refrigerator and then stirred at 25 °C to give, after filtration, 500 g of a mixture of α and β and uncyclized hydrobromides, mp 200–210 °C.

One-fifth of the filtrate was concentrated to dryness in vacuo, basified with NH_4OH, and extracted with 2 L of C_6H_6. The C_6H_6 was extracted with 5 × 1 L of 20% AcOH and basified, and the base was extracted into C_6H_6. Solvent removal, solution in 250 mL of *i*-PrOH, and acidification with 62% HBr gave 90 g of the crystalline HBr, mp 255–265 °C. Recrystallization from 200 mL of 95% EtOH gave 48 g, mp 275–278 °C, depressed when mixed with the comparable α or β isomer.

The remaining four-fifths of the liquor, upon standing another year at 5 °C, deposited 120 g of the HBr salt. Upon recrystallization from 95% EtOH, this gave 80 g, mp 272–274 °C.

A sample was converted to the base, to the oxalate (mp 215 °C), and back to the base: mp 90 °C; NMR (base in $CDCl_3$, internal Me_4Si) 0.53 (d, J = 6 Hz, Me) and 0.77 (t, J = 7 Hz, Me). Anal. ($C_{22}H_{27}NO$) C, H, N.

(2α,5β,6α)-6-Ethyl-1,2,3,4,5,6-hexahyro-5-methyl-2,6-methano-3-benzazocin-8-ol (6, R = H). When 46 g (0.13 mol) of the above oxalate (mp 215 °C) was dissolved in 300 mL of 95% EtOH and hydrogenated with 2 g of 10% Pd/C at 50 lb and 60 °C, the calculated H_2 uptake occurred in 2 h and the nor base oxalate separated massively. After cooling to 5 °C overnight, the mixture was filtered, and the product was dissolved in 400 mL of hot water, filtered from catalyst, and cooled to 5 °C. The nor base oxalate amounted to 29 g (84%), mp 230 °C. Conversion to the base with NH_4OH gave a very light-sensitive material, mp 238–240 °C. It rapidly turned pink on exposure to light. Anal. ($C_{15}H_{21}NO$) C, H, N.

(2α,5β,6α)-6-Ethyl-1,2,3,4,5,6-hexahydro-3,5-dimethyl-2,6-methano-3-benzazocin-8-ol (6a). A solution of 2 g (0.008 mol) of the above nor base in 150 mL of 95% EtOH with 1 g of Pd/C (10%) and 1 mL of 38% HCHO was hydrogenated at 30 lb of H_2 and 60 °C for 1 h to the calculated uptake to give 1.0 g (50%) of the *N*-methyl base, mp 210–211 °C, from 50 mL of Me_2CO. The hydrochloride melted at 279–280 °C. Anal. ($C_{16}H_{23}NO$) C, H, N. The HBr, prepared by reduction of the N–$CH_2C_6H_5$·HBr with Pd/C followed by addition of HCHO and further reduction, melted at 250–252 °C. Anal. ($C_{16}H_{23}NO$·HBr) C, H. The base was also prepared from 4-ethyl-1,3-dimethylpyridinium bromide by the procedure of Fry. IR curves were identical for the bases prepared by both methods.

(2α,5β,6α)-6-Ethyl-1,2,3,4,5,6-hexahydro-5-methyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol [6, R = $CH_2CH{=}C(CH_3)_2$]. Alkylation of the nor base in the usual manner[11] gave a 60% yield: mp 173.0–175.8 °C cor. Anal. ($C_{20}H_{29}NO$) C, H, N.

(2α,5β,6α)-3-Allyl-6-ethyl-1,2,3,4,5,6-hexahydro-5-methyl-2,6-methano-3-benzazocin-8-ol hydrochloride (6, R = $CH_2CH{=}CH_2$) was prepared by alkylation of the nor base: mp 258.8–259.4 °C cor. Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

(2α,5β,6α)-6-Ethyl-1,2,3,4,5,6,hexahydro-8-methoxy-3,5-dimethyl-2,6-methano-3-benzazocine. A suspension of **6a** in MeOH was treated with CH_2N_2. Solution occurred. The product was purified as the oxalate: mp 201–202 °C, from EtOH; NMR (base in $CDCl_3$, external Me_4Si) 0.63 (d, J = 6.5 Hz, Me) and 0.83 (t, J = 7.0 Hz, Me). Anal. ($C_{17}H_{25}NO{\cdot}C_2H_2O_4$) C, H.

(2α,5β,6α)-5-Ethyl-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-8-ol. The Grignard from 57 g (0.36 mol) of anisyl chloride was reacted with 29 g (0.18 mol) of 6-cyano-3-ethyl-1,4-dimethyl-1,2,5,6-tetrahydropyridine and then cyclized with 48% HBr to give the title compound, mp 237–239 °C dec, from butanol. Anal. ($C_{16}H_{23}NO$) C, H, N.

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K. Pierson for pharmacological results.

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Synthesis and Analgesic Activity of Some Long-Acting Piperidinospiro Derivatives of Methadone

James M. Frincke, Gary L. Henderson,*

Department of Pharmacology, University of California, Davis, Davis, California 95616

Paul A. J. Janssen, and Cyriel A. M. Van der Eycken

Research Laboratories, Janssen Pharmaceutica, Beerse, Belgium. *Received September 8, 1977*

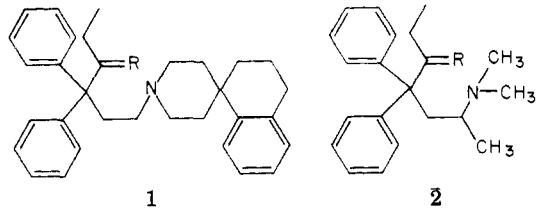
A congener of methadone, in which the metabolically labile C-6 dimethylamino moiety was replaced with a piperidinospiro derivative, was reduced and acetylated. This conversion produced a marked increase in the duration of analgesia, a trend similar to that found for methadone.

Methadone, 4,4-diphenyl-6-(dimethylamino)-3-heptanone (**2a**), is an analgesic currently being used in the maintenance treatment for heroin addiction.

It is known that reduction of the keto moiety of methadone and subsequent acetylation to acetylmethadol results in an increase in the duration of action for analgesia.[1] This transformation also results in an increase in potency.[2]

Compound **1a** is a highly potent, long-acting narcotic analgesic[3] that bears a resemblance to the basic methadone molecule in that this compound is a 4,4-diphenyl-6-amino-3-hexanone derivative. However, the C-6 dimethylamino moiety of methadone, which is the most metabolically labile site,[4] has been replaced by a piperidinospiro derivative. In light of the enhancement in potency and duration of action found for methadone following reduction and acetylation to acetylmethadol, it was of interest to see whether the conversion of the structurally related ketone **1a** to the ester 1c would produce a similar increase in duration of action. We report herein the results of this conversion.

Chemistry. *N*-(3,3-Diphenyl-4-oxohex-1-yl)-7,8-benzo-3-azaspiro[5.5]undecane (R-4066, **1a**), as the oxalate



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1a, **2a**, R = O
1b, **2b**, R = OH, H
1c, **2b**, R = OAc, H

salt, was reduced with sodium borohydride in 2-propanol to give the crystalline racemic alcohol **1b**. The alcohol **1b** was converted to the acetate 1c by treatment with acetic anhydride in pyridine. The oily free amine was converted to its sulfate salt by treating with methanol–sulfuric acid and extracting with methylene chloride. This yielded a light beige crystalline solid. All compounds were characterized by NMR, IR, MS, and elemental analysis, and their physical and chemical properties are summarized in Table I.

Pharmacology. The test compounds were administered to Sprague–Dawley rats by oral intubation, and the analgesic activity was evaluated by determining each compound's ability to inhibit the warm-water tail withdrawal reflex.[5] For each test compound, activity was evaluated at three dose levels. Ten animals were used at each dose. ED_{50} values were determined by probit analysis.[6] Animals were considered analgesic if the tail withdrawal latency was greater than 4 s. Animals were tested every hour until 24 h after drug. The onset, peak, and duration of action were measured from duration–response plots for the highest dose administered for each compound. Mean and standard errors of the mean latency values at each test time were determined using only those animals with tail withdrawal times greater than 4 s. Potency ratios (relative to methadone) were determined according to the method of Litchfield–Wilcoxon.[6] Statistical analysis of the slopes of the dose–response plots showed them to be parallel within experimental error.

The ED_{50} values for these compounds, determined by the results of the warm-water tail withdrawal test and shown in Table II, are 0.07 mg/kg for compound **1a** and 0.14 mg/kg for compounds **1b** and 1c. The ED_{50} value for methadone is in general agreement with the value reported by Smits and Myers (10 mg/kg).[7]

A comparison of the potency ratios (Table II), computed relative to methadone, shows that the racemic mixtures of compounds **1b** and 1c are half as potent (ratio = 106) as compound **1a** (ratio = 212) which possesses to chiral center. This may indicate the existence of only one active stereoisomer as has been shown in the methadone–me-

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