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Notes

Effect of 9-Hydroxylation on Benzomorphan Antagonist Activity

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In a benzomorphan bearing an antagonist side chain, introduction on the methano bridge of a hydroxyl oriented away from nitrogen has little effect on antagonist activity whereas a hydroxyl oriented toward nitrogen enhances this activity. Hydroxylation tends to decrease analgesic activity.

In a series of pioneering papers,[1-4] May and coworkers demonstrated the effects on analgesic activity of introducing an OH group on the methano bridge of benzomorphans.[5]

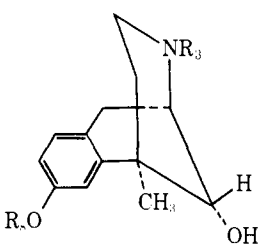
In more recent years morphine derivatives having antagonist side chains of varying degrees of potency have been oxygenated in the analogous position to give naloxone, naltrexone, nalmexone, and nalbuphine, and this oxygenation has been extended to the morphinan series to give oxilorphan and butorphanol.

The present note provides some data on the effect of this hydroxy group on antagonist activity in the benzomorphan series. Workers at Bristol-Myers have described some 9-hydroxybenzomorphans[6] but apparently have not prepared the compounds listed in Table I.

Chemistry. May's procedures were used in the synthesis of **1a**, **2a**, and **3a**.

Treatment of **1a** with CNBr proceeded uneventfully as noted by Kugita and May.[3] However, treatment of **2a** or **3a** with CNBr gave considerable by-product which proved to be **4**.

Elemental analysis, the strong band in the ir at 1750 cm^{-1}, and the lack of a CN band were the most conclusive evidence for structure **4a**, but uv, NMR, and MS were confirmatory. The structure of **4b** was inferred by analogy and by the ir spectrum.



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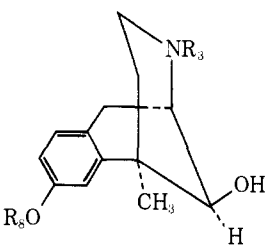

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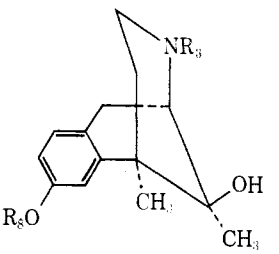
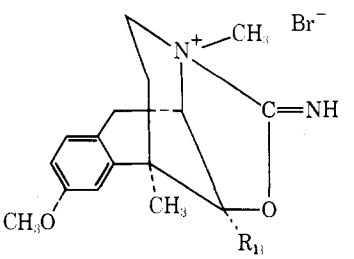


3

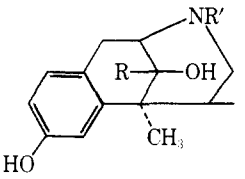
a, $R_3 = R_8 = CH_3$
b, $R_3 = CN$; $R_8 = CH_3$
c, $R_3 = H$; $R_8 = CH_3$
d, $R_3 = R_8 = H$

Recently Vaughan, Hill, and Mitchard[7] published a method using mass spectrometry for distinguishing the configuration of the hydroxy group at C_{11} when only one isomer is available. The determination depended upon the relative peak heights of the mass ion, $M^+ - C_{11}CO$, and the



4a, $R_{11} = H$
b, $R_{11} = CH_3$

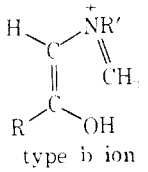
Table I. Antagonist Activity of Some 2,6-Methano-3-benzazocine-8,11-diols



R′	R	C_{11} confign	AD_{50} sc[a]	vs.
$CH_2CH{=}CMe_2$	H	*RS*	6.8 (4.6–10.1)	Meperidine
$CH_2CH{=}CH_2$	H	*RS*	0.115, very flat curve	Meperidine
CH_2-c-C_3H_5	H	*RS*	0.056, very flat curve	Meperidine
$CH_2CH{=}CMe_2$	CH_3	*SR*	0.62 (0.33–1.2)	Meperidine
CH_2-c-C_3H_5	CH_3	*SR*	0.0026 (0.001–0.004)	Phenazocine

[a] The antagonist dose was determined in rats by the method of L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, 143, 141 (1964).

"type b" ion. Only four compounds were available for this study and R and R′ were always CH_3. We have found that the proposed rule applies for R or R′ equal to H, but fails if R′ is CN (neither **1b** nor **2b** has an $M^+ - CHO$ peak more than 8% of the M^+ peak) or if R′ is a relatively unstable group. For example, **3** (R_3 = $CH_2CH{=}CMe_2$; R_8 = H) showed the most intense bands at 233 (loss of



type b ion

$CH_2CH{=}CMe_2$) and 190 (further loss of CH_3CO). The mass ion (81 mm) was more intense than the $M^+ - CH_3CO$ (59 mm). The b ion was 7 mm.

Apparently a relatively stable R′ on nitrogen is necessary to obtain spectral data that will enable structural assignments to be made with confidence at present.

Pharmacology. In the three cases examined, introduction of a hydroxyl group oriented away from the nitrogen (Table I, *RS* compounds) has had essentially no effect on antagonist activity whereas the opposite orientation increased the antagonist activity of pentazocine from 2.2 (1.7–2.7) mg/kg vs. meperidine to 0.62 mg/kg (fourth compound in Table I) and the antagonist activity of cyclazocine from 0.028 (0.018–0.043) mg/kg vs. phenazocine to 0.0026 mg/kg (fifth compound in Table I).

May and coworkers have shown[1-4] that introduction of an 11-hydroxyl decreases agonist activity with *N*-methyl series with the exception of one C_6-ethyl compound.[4] Our results show the same decrease with the *N*-cyclopropylmethyl compounds. The third compound in Table I shows a 400-fold decrease in the acetylcholine writhing ED_{50}[8] upon introduction of the 11-hydroxyl. The last compound shows no significant dose response in this test whereas cyclazocine gave an ED_{50} of 0.15 mg/kg sc. The second, third, and fifth compounds were inactive on the D'Amour–Smith test.

Experimental Section[9]

(2*RS*,6*SR*,11*SR*)-3-Cyano-1,2,3,4,5,6-hexahydro-8-methoxy-6-methyl-2,6-methano-3-benzazocin-11-ol (2b).[10] A solution of 9.4 g of **2a**[3] in 65 ml of $CHCl_3$ was added slowly to 4.3 g of CNBr in 40 ml of $CHCl_3$ and allowed to stand overnight. A precipitate, 5.11 g, was removed by filtration. The filtrate was refluxed for 5 hr, washed with H_2O, concentrated, and recrystallized (Me_2CO) to give 3.8 g: mp 147.5–149.5°; M^+ 258 (89 mm), 243 (10 mm), 229 (8 mm), 217 (7 mm). Anal. ($C_{15}H_{18}N_2O_2$) N.

By-product 4a. The 5.11 g, which was very soluble in water and contained Br^-, was dissolved in 25 ml of EtOH from which it separated while the solution was boiling to give 3.1 g. This was recrystallized (H_2O), washed with hot Me_2CO, and recrystallized (EtOH–Et_2O) to give crystals: mp 148–152°. Anal. ($C_{16}H_{21}BrN_2O_2$) C, H, N, Br.

A solution of 0.16 g in 2 ml of H_2O was basified with 10% NaOH to give a precipitate which was recrystallized (EtOAc–hexane): mp 118.5–121° dec. Anal. ($C_{16}H_{21}N_2O_3$) C, N; H: calcd, 7.53; found, 7.95.

(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-8-methoxy-6-methyl-2,6-methano-3-benzazocin-11-ol (2c). Hydrolysis of 3.00 g of **2b** with 2 *N* HCl gave 2.20 g of crude base: mp 98–128°. Two recrystallizations (Me_2CO) raised the melting point to 136–139°. Anal. ($C_{14}H_{19}NO_2$) C, H.

(2*RS*,6*SR*,11*RS*)-3-Cyano-1,2,3,4,5,6-hexahydro-8-methoxy-6-methyl-2,6-methano-3-benzazocin-11-ol (1b).[11] Treatment of 5.67 g[12] of **1a**[3] with 2.56 g of CNBr in $CHCl_3$ in the usual manner gave 4.47 g of crude product. Recrystallization (EtOH) gave 3.60 g: mp 135–137.5°. A small MS peak at 272 showed that this was not quite pure: M^+ 258 (86 mm), 243 (8 mm), 229 (4 mm), 225 (74 mm). Anal. ($C_{15}H_{18}N_2O_2$) N.

(2*RS*,6*SR*,11*RS*)-1,2,3,4,5,6-Hexahydro-8-methoxy-6-methyl-2,6-methano-3-benzazocin-11-ol (1c).[11] Hydrolysis of 9.7 g of **1b** in 2 *N* HCl gave 7.03 g: mp 137–140°. Recrystallization (Me_2CO) raised the melting point to 140.5–142°. Anal. ($C_{14}H_{19}NO_2$) C, H.

(2*RS*,6*SR*,11*RS*)-1,2,3,4,5,6-Hexahydro-6-methyl-2,6-methano-3-benzazocine-8,11-diol Hydrobromide (1d). A solution of 7.03 g of **1c** was refluxed for 17 min with 70 ml of 48% HBr and concentrated in vacuo. The residue was stirred with Me_2CO and filtered to give 6.66 g: mp 239–242°. A sample from MeOH–Et_2O melted at 240–242°. The base melted at 256–258°: M^+ 219 (90 mm), 190 (5 mm), 72 (65 mm). Anal. ($C_{13}H_{17}NO_2 \cdot HBr$) C, H, Br.

(2*RS*,6*SR*,11*RS*)-3-Allyl-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-8,11-diol (1, R_3 = allyl; R_8 = H). Alkylation of 2.70 g of **1d** with allyl bromide in DMF gave 1.55 g of product: mp 177–180° (Et_2O); M^+ 259 (75 mm), 244 (33 mm), 232 (21 mm), 230 (5 mm), 112 (20 mm), 27 (94 mm). Anal. ($C_{16}H_{21}NO_2$) H, N; C: calcd, 74.11; found, 74.54.

(2*RS*,6*SR*,11*RS*)-1,2,3,4,5,6-Hexahydro-3-(3-methyl-2-butenyl)-6-methyl-2,6-methano-3-benzazocine-8,11-diol (1, R_3 = dimethylallyl; R_8 = H). Alkylation of 0.659 g of **1d** base with 0.393 g of 3-methyl-2-butenyl bromide in DMF in the presence of $NaHCO_3$ gave 0.67 g of product. Two recrystallizations (*i*-PrOAc) raised the melting point to 180–181°. Anal. ($C_{18}H_{25}NO_2$) C, H, N.

(2*RS*,6*SR*,11*RS*)-3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-8,11-diol Hydrochloride (1, R_3 = cyclopropylmethyl; R_8 = H). A mixture of 3.00 g of **1d** hydrobromide in 20 ml of EtOH, 10 ml of H_2O, and 4.0 g of K_2CO_3 was stirred at room temperature and 2.0 g of cyclopropanecarbonyl chloride added dropwise. After 3 hr, the mixture was concentrated and the residue partitioned between H_2O and benzene–BuOH (1:1). The organic layer was washed with dilute HCl and H_2O and concentrated to give 3.2 g of yellow syrup. Reduction ($LiAlH_4$, THF) gave 1.91 g isolated as the HCl: mp 285–287°. Recrystallization (MeOH) raised the melting point to 289.0–290.4° cor; M^+ 273 (107 mm), 258 (46 mm), 232 (89 mm), 244 (4 mm), 126 (11 mm), 55 (78 mm). Anal. ($C_{17}H_{23}NO_2 \cdot HCl$) C, H, N.

(2*RS*,6*SR*,11*SR*)-3-Cyano-1,2,3,4,5,6-hexahydro-8-methoxy-6,11-dimethyl-2,6-methano-3-benzazocin-11-ol (3b).[11] A solution of 8.55 g[12] of **3a**[1] [M^+ 261 (61 mm), 218 (102 mm), 100 (18 mm)] was added to 3.7 g of CNBr in 35 ml of $CHCl_3$. A precipitate, 4.1 g, was removed by filtration and recrystallized (EtOH): mp 165–170°. This water-soluble by-product **4b** showed a band at 5.66 in the ir but no CN band. The product, 3 g, isolated from the $CHCl_3$ was recrystallized (EtOH) to give 2.69 g, mp 125–126.5°. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-8-methoxy-6,11-dimethyl-2,6-methano-3-benzazocin-11-ol (3c).[11] Hydrolysis of

2.7 g of **3b** with 2 *N* HCl gave 1.7 g: mp 147–150°. Anal. ($C_{15}H_{21}NO_2$) C, H. The hydrochloride melted at 150–153°: M^+ 247 (73 mm), 204 (94 mm), 86 (14 mm). Anal. ($C_{15}H_{21}NO_2 \cdot HCl$) N.

(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-8,11-diol (3d). Demethylation of 4.1 g of **3c** by 15 min of refluxing with 40 ml of 48% HBr gave a 68% yield of **3d**: mp 268.5–270° from MeOH–Et_2O; M^+ 233 (57 mm), 190 (63 mm), 86 (13 mm), 43 (91 mm). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

(2*RS*,6*SR*,11*SR*)-1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine-8,11-diol Hydrochloride (3, R_3 = dimethylallyl; R_8 = H). Alkylation of **3d** with 3-methyl-2-butenyl bromide in DMF gave the product isolated as the hydrochloride: mp 215–218° dec (*i*-PrOH–Me_2CO). Anal. ($C_{19}H_{27}NO_2 \cdot HCl$) C, H, Cl.

(2*RS*,6*SR*,11*SR*)-3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-8,11-diol Hydrochloride Sesquihydrate (3, R_3 = cyclopropylmethyl; R_8 = H). A solution of 1.94 g of **3d** in 35 ml of warm pyridine was treated with 1.40 g of cyclopropanecarbonyl chloride. The crude ester (2.8 g) was reduced ($LiAlH_4$, THF) and isolated as the HCl (1.84 g). An analytical sample from MeOH–Et_2O melted at 164–167°: M^+ 287 (52 mm), 246 (83 mm), 244 (54 mm), 140 (9 mm), 55 (73 mm). Anal. ($C_{18}H_{25}NO_2 \cdot HCl \cdot 1.5H_2O$) C, H, N.

The same product was obtained from **3d** and cyclopropylmethyl bromide.

Acknowledgments. We are indebted to Mrs. Anne K. Pierson for pharmacological test results and to Mrs. Susan J. Killeen and Mr. Allan Hlavac of Dr. R. K. Kullnig's laboratory for mass spectral data.

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(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points are not corrected for emergent stem errors.
(10) The 11*SR* compounds correspond to May's α isomers and have the OH oriented toward the nitrogen.
(11) Prepared but not characterized by May and coworkers.
(12) We are indebted to Mr. Stanley Laskowski for the preparation of this starting material.

Quantitative Structure–Activity Relationships in the Δ^6-6-Substituted Progesterone Series. A Reappraisal

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A quantitative structure–activity analysis concerning the progestational activity of a series of Δ^6-6-substituted progesterones is presented which differs from that published recently by other authors. In the current study all compounds in the data set for which parameters are available are included and activity is shown to relate to primarily lipophilic but also steric effects.

A recent article by Wolff and Hansch[1] presented an analysis of quantitative structure–activity relationships in the Δ^6-6-substituted progesterone series. This analysis utilized activity data published by Teutsch et al.[2] The latter authors had discussed structure–activity relationships in this series primarily in terms of steric effects.

Wolff and Hansch presented eq 1 and 2 as those which accounted most satisfactorily for the variation of activity in the series. Of these they were inclined to favor eq 2. A striking feature of the Wolff and Hansch article was that their correlations were derived using a data set from which the most active member of the series, the 6-methyl compound, had been excluded. This exclusion was justified on the grounds that the activity of the 6-methyl compound was very poorly predicted by eq 1 and 2 (off by 4 standard deviations) and it was further stated that the failure of the 6-methyl compound to fit these equations "is a clear indication that the methyl group is acting by a different mechanism from all other substituents". However, no convincing evidence or explanation of why the mechansim should be different was presented.

Wolff and Hansch did not discuss any correlation equations based on the complete data set. In the present study the complete data set (Table I) has been used in a multiple regression analysis in conjunction with the substituent parameters π, representing possible hydrophobic bonding and penetration effects,[3] $\mathcal{F}$ and $\mathcal{R}$ for electronic field and resonance effects,[4] and MR and *C* as alternative measures of substituent size. MR is a crude measure of substituent bulk which contains some electronic contributions.[5] *C* is the circumference of the circle circumscribed by the substituent and was employed by Teutsch et al.[2] for structure–activity correlations in the Δ^6-6-substituted progesterone series.

An examination of single parameter equations reveals π to be the dominant single variable, which alone accounted for 58% of the variance in the data (eq 3). This result is consistent with the findings of Wolff and Hansch. The steric measures *C* and MR also showed some degree of correlation accounting for 37 and 22% of the data variance, respectively. No correlation was observed with the electronic terms.

The best correlation was obtained using the two-parameter eq 4 involving π and the steric term *C*.[6] This equation has high statistical significance, satisfying the *F* test at the 0.005 level, and accounts for 73% of the variance in the data. The π term is significant at the 0.005 level and the *C* term at the 0.05 level. The correlation could not be improved by the addition of other variables. Using the term MR instead of *C* yields eq 5. However, in this case the MR term is significant only at the 0.25 level.

The data fit for eq 4 (r^2 = 0.73, s = 0.54) is only slightly inferior to that for eq 2 proposed by Wolff and Hansch (r^2