Analgesics and Narcotic Antagonists in the Benzomorphan and 8-Oxamorphinan Series. 5

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3-Methoxy-8-oxamorphinans **9** have been prepared from the corresponding 5-allyl-9α-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphans **7**. The former compounds were transformed to the 3-hydroxy-8-oxamorphinans **6**, a class of potent analgesics and analgesic-antagonists. In ring C of the morphinan nucleus substitution of 8-CH_2 with oxygen enhanced both analgesic and antagonist activities, while replacement of hydrogen with a methyl group at C-14 in these compounds enhanced antagonist activity and decreased analgesic activity. Tetrahydrofuranobenzomorphans **3** and 3-hydroxy-8-oxaisomorphinans **4** displayed lower levels of activity. Structural requirements for antagonist activity are discussed.

In paper 4 of this series[1] we have reported on the selective transformations of 5-allyl-2′-methoxy-2-methyl-9-oxo-6,7-benzomorphan[2] to the corresponding 9α-hydroxybenzomorphans **2** (Chart I) and tetrahydrofuranobenzomorphans **3**, derived from **2**. Also described were a number of 3-hydroxy-8-oxaisomorphinans **4** derived from 9β-hydroxybenzomorphans **1**.[3]

We now report on the pharmacological properties of compounds **2–4** as well as on the synthesis and pharmacological properties of 3-hydroxy-8-oxamorphinans **6**. Structure–activity relationships in the 3-hydroxymorphinan related series **5** and structural requirements for antagonist activity are also discussed.

Chemistry. The synthesis of the 8-oxamorphinan compounds **9** is outlined in Scheme I. The hydroboration–oxidation of 5-allyl-9α-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphans **7a,b**, followed by mesylation of the resulting alcohols **8a,b** and treatment with sodium hydride in DMF, gave the 3-methoxy-17-methyl-8-oxamorphinans **9a,b**, respectively, in high yields. Transformations of **9** via von Braun demethylation, acylation–reduction, or alkylation followed by demethylation gave a number of the 3-hydroxy-8-oxamorphinans **6** shown in Table I. Resolution of **9k** by treatment with dibenzoyl-L- and -D-tartaric acids in methanol gave (+)- and (−)-**9k**, which were demethylated to (+)- and (−)-**6c**, respectively. Similar treatment of **6d** with the same resolving reagents gave the optical isomers (−)- and (+)-**6d**.

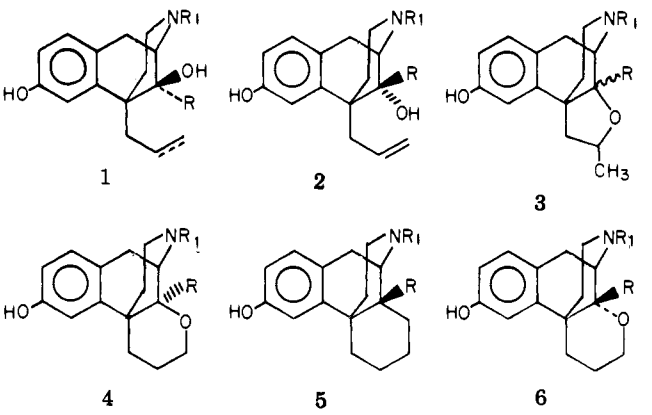
Pharmacological Results. Compounds **2–4** and **6** were tested for analgesic and narcotic antagonist activities according to the methods previously described.[3] The results are summarized and presented in Table I. Both the analgesic and narcotic antagonist activities of compounds **2** bearing a cyclopropylmethyl side chain (**2b,d**) are decreased (three to seven times) in comparison with the corresponding 9β-hydroxyl isomers **1**.[3] These findings are consistent with earlier reported results in the 14-hydroxymorphinan and -isomorphinan series[4] and the 9β- and 9α-hydroxybenzomorphan series.[5]

Cyclization of **2d** to the tetrahydrofuranobenzomorphan **3c** resulted in a sixfold decrease in antagonist activity, following the pattern observed in the 9β-hydroxyl series.[3] In contrast to this result, cyclization of **2b** and **2d** to the 8-oxamorphinans **6c** and **6d**, respectively, resulted in a dramatic enhancement of analgesic potency, whereas antagonist activity was only marginally increased in the case of **6d** and more significantly in the case of **6c**. Resolution of **6c** and **6d** showed that all the activity resided with *l* isomers, while *d* isomers were inactive.

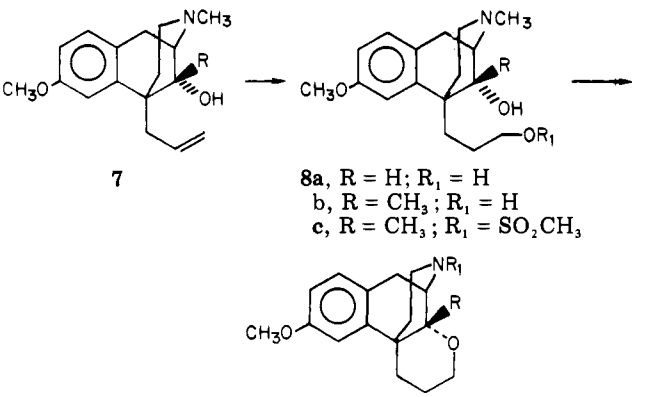
Similar cyclization in the 9β-hydroxyl series to **4** resulted in a 50-fold decrease of antagonist activity, while analgesic activity was only slightly affected.

Several test methods were used to compare the analgesic and antagonist activities of (−)-**6c** and (−)-**6d** with reference agents in the morphinan series **5** (cyclorphan,[6] R_1 = CH_2-c-C_3H_5, R = H; oxilorphan,[4] R_1 = CH_2-c-C_3H_5, R = OH; and butorphanol,[4] R_1 = CH_2-c-C_4H_7, R = OH) as shown in Table II.

Chart I



Scheme I



	R	R_1		R	R_1
9a	H	CH_3	**9i**	H	CO-c-C_4H_7
b	CH_3	CH_3	**j**	CH_3	CO-c-C_4H_7
c	H	CN	**k**	H	CH_2-c-C_3H_5
d	CH_3	CN	**l**	CH_3	CH_2-c-C_3H_5
e	H	H	**m**	H	CH_2-c-C_4H_7
f	CH_3	H	**n**	CH_3	CH_2-c-C_4H_7
g	H	CO-c-C_3H_5	**o**	CH_3	$CH_2CH{=}CH_2$
h	CH_3	CO-c-C_3H_5	**p**	CH_3	$CH_2CH{=}C(CH_3)_2$

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Table I. Analgesic and Narcotic Antagonist Activities of Compounds 2-4 and 6

Compd[a]	R_1	R	ED_{50}, mg/kg (95% confidence limits) Analgesic act. (mouse writhing)	Antagonist act. (oxymorphone-induced Straub tail)
2a	CH_3	H	>40	>40
2b	CH_2-c-C_3H_5	H	0.23 (0.17-0.30)	1.9 (1.3-3.7)
2c	CH_2-c-C_4H_7	H	11 (5.9-18.7)	4.5[b]
2d	CH_2-c-C_3H_5	CH_3	>40	0.8 (0.49-1.20)
2e	CH_2-c-C_4H_7	CH_3	1.3 (0.6-2.3)	10[b]
3a	CH_3	H	1.8[b]	>40
3b	CH_3	CH_3	0.4 (0.21-0.63)	>40
3c	CH_2-c-C_3H_5	CH_3	>40	5[b]
4a	CH_3	H	30[b]	>40
4b	CH_2-c-C_3H_5	H	8.4 (6.1-10.6)	20[b]
4c	CH_3	CH_3	>40	>40
4d	CH_2-c-C_3H_5	CH_3	35[b]	6[b]
4e	CH_2-c-C_4H_7	CH_3	16 (14.3-17.7)	5[b]
6a	CH_3	H	0.60 (0.07-1.68)	>40
6b	CH_3	CH_3	0.03[b]	>40
6c	CH_2-c-C_3H_5	H	0.03 (0.021-0.037)	0.3[b]
(-)-6c	CH_2-c-C_3H_5	H	0.013 (0.009-0.017)	0.26 (0.12-0.41)
(+)-6c	CH_2-c-C_3H_5	H	>40	>40
6d	CH_2-c-C_3H_5	CH_3	0.19 (0.10-0.34)	0.61 (0.46-0.83)
(-)-6d	CH_2-c-C_3H_5	CH_3	0.105 (0.083-0.12)	0.2[b]
(+)-6d	CH_2-c-C_3H_5	CH_3	>40	>40
6e	CH_2-c-C_4H_7	H	0.15 (0.13-0.17)	10 (5-20)
6f	CH_2-c-C_4H_7	CH_3	0.068 (0.057-0.079)	23[b]
6g	$CH_2CH=CH_2$	CH_3	28[b]	1.0[b]
6h	$CH_2CH=C(CH_3)_2$	CH_3	0.18 (0.11-0.28)	>40

[a] Tested subcutaneously as 0.4% solutions in saline starting with 40 mg/kg; free bases were dissolved in 0.1 N HCl and the concentration was adjusted to 0.4% with saline. [b] The 95% confidence limits could not be calculated due to a lack of a significant slope of the regression line relating log dose to effect of the drug.

The results indicate that substitution of 14-H in (-)-**6c** with methyl, to give (-)-**6d**, decreased analgesic and increased antagonist potencies by about factors of 5 and 3, respectively. The antagonist activity was similarly enhanced by substitution of 14-H in cyclorphan with hydroxyl to give oxilorphan, while analgesic activity was reduced over 400 times.

In the cyclobutylmethyl series, DL-**6f** was equally potent as an analgesic and 15 times less potent as an antagonist when compared with butorphanol.

In conclusion, for the cyclopropylmethyl substituent on nitrogen, present and previous results can be summarized as follows. (a) Introduction of 14-OH in morphinans and 9-OH in benzomorphans, regardless of the stereochemistry of the hydroxyl group, decreases analgesic activity relative to the parent compounds, while antagonist activity is enhanced in both series with β orientation of OH. (b) Substitution of 14-H with CH_3 in 8-oxamorphinan enhances antagonist and decreases analgesic activity. (c) Formation of the tetrahydrofuran ring adversely affects analgesic and narcotic antagonist potency levels. (d) Formation of the tetrahydropyran ring gives a reverse effect, i.e., the more potent 9β-hydroxybenzomorphans **1** give less potent oxaisomorphinans **4**, whereas the less potent 9α isomers **2** give more potent oxamorphinans **6**.

Discussion

In recent years a number of structural series have been evaluated for agonist and narcotic antagonist activities.[7]

Unfortunately, structure–activity relationships are far too complex to be understood on the basis of available data. Any attempt to single out one structural parameter or even a group of parameters as a structural requirement for antagonist activity breaks down with a change of a structural system. Thus, previously generally accepted assumptions that N-CH_3 is typical and essential for agonist activity and N-allyl or N-CH_2-c-C_3H_5 is essential and typical for antagonist activity are invalidated by the findings that antagonist activity is not limited to the above substituents or even to tertiary amines and morphine-related structures.[7] In addition, agonist activity can even be associated with a quaternary nitrogen system.[8] It appears that the only required, although not necessarily sufficient, structural feature for production of antagonist activity is a certain degree of nitrogen crowding, above or below of which agonist activity prevails. For a given structural series, such as morphine-related compounds, the optimal structural requirements are characterized by the 14β-OH group and the antagonist substituent on the nitrogen atom, which in turn is characterized by frozen rotation between C-2′ and C-3′ by virtue of small rings or multiple bonds. Nevertheless, that the overall structure and geometry of a particular compound has an overiding effect concerning the ratio of agonist to antagonist activity is best exemplified by work of Bentley et al.[7k] in the oripavine series, where homologization of an alkyl substituent at a center remote from the nitrogen atom drastically changes the ratio of agonist to antagonist activity.

Experimental Section

Melting points are uncorrected; microanalyses were provided by Micro-Tech Laboratories, Skokie, Ill.; and results are indicated by symbols of the element and are within 0.4% of theory. The NMR and IR spectra are consistent with assigned structures.

5-Allyl-2-cyclobutylmethyl-2′,9α-dihydroxy-6,7-benzomorphan (2c) was prepared in three steps from 5-allyl-9α-hydroxy-2′-methoxy-6,7-benzomorphan and cyclobutanecarboxylic acid chloride in 68% overall yield by the procedure given previously for the preparation of **2b**.[1] The product distilled at 165 °C (0.02 mm). Anal. ($C_{20}H_{27}NO_2$) C, H, N.

5-Allyl-2-cyclobutylmethyl-2′,9α-dihydroxy-9β-methyl-6,7-benzomorphan (2e) was similarly prepared from 5-allyl-9α-hydroxy-2′-methoxy-9β-methyl-6,7-benzomorphan in 37% overall yield as the HCl salt: mp 235–237 °C (MeOH–Et_2O). Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N.

Table II. Analgesic and Narcotic Antagonist Activities of Compounds (−)-6c and (−)-6d Compared with Cyclorphan, Oxilorphan, and Butorphanol

	ED_{50}, mg/kg[a] (95% confidence limits)				
	Analgesic act.		Antagonist act.		
Test compd	Phenylquinone writhing in mice	Phenylquinone writhing in rats	Oxymorphone-induced Straub tail	Oxymorphone-induced narcosis	Antagonism of morphine analgesia (rat tail flick)
(−)-6c	0.013 (0.009–0.017)	0.009 (0.003–0.019)	0.26 (0.12–0.41)	0.04 (0.01–0.07)	0.097 (0.063–0.141)
(−)-6d	0.105 (0.083–0.127)	0.020 (0.088–0.057)	0.2[b]	0.014 (0.011–0.019)	0.021 (0.008–0.056)
Cyclorphan	0.031 (0.022–0.044)	0.028 (0.014–0.055)	0.32 (0.21–0.43)	0.1 (0.05–0.16)	0.032 (0.016–0.064)
Oxilorphan	12.8 (5.1–32.5)	8.0 (5.1–12.7)	0.19 (0.23–0.39)	0.03 (0.02–0.04)	0.012 (0.007–0.020)
Butorphanol	0.051 (0.039–0.066)	0.040 (0.023–0.070)	0.98 (0.73–1.30)	0.27 (0.19–0.39)	0.43 (0.27–0.68)

[a] Subcutaneous administration. [b] See footnote *b* in Table I.

9α-Hydroxy-2′-methoxy-2-methyl-5-(3-hydroxypropyl)-6,7-benzomorphan (8a). To a cooled (ice bath), stirred solution of 5-allyl-9α-hydroxy-2′-methoxy-2-methyl-6,7-benzomorphan (**7a**)[1] (250 g, 0.914 mol) in dry THF (1.5 L) was added, over a period of 1 h, 2 mol of 1 M borane solution in THF, and the mixture was allowed to stand at 0 °C for 1 h. This was cautiously treated with 20% NaOH (170 mL, 1.01 mol), followed by 30% H_2O_2 (92 mL, 0.903 mol), and the mixture was left at room temperature for 1 h. To this was added 25% aqueous $(CH_3)_3N$ (450 mL) and the mixture stirred for 18 h, followed by concentration in vacuo. The concentrate was partitioned between water and CH_2Cl_2. The organic phase was washed with water, dried, and evaporated to dryness. The solid residue was washed with ether to give 20.5 g (77%) of **8a**, mp 147–154 °C. Recrystallization from benzene gave a sample, mp 158–159 °C. Anal. ($C_{17}H_{25}NO_3$) C, H, N.

9-Hydroxy-2′-methoxy-2,9β-dimethyl-5-(3-hydroxypropyl)-6,7-benzomorphan (8b). To a cooled (ice–salt), stirred solution of 1 M borane in THF (1.56 mol) was added a solution of **7b**[1] (102 g, 0.355 mol) in THF (400 mL) over a period of 1.5 h. The mixture was allowed to stand for 3.5 h at −10 °C, and then it was treated cautiously with water (238 mL), followed by 20% NaOH (382 mL) and 30% H_2O_2 (177 mL). The mixture was stirred 18 h, treated with another 20 mL of H_2O_2, and stirred for 1 h. After concentration in vacuo, the product was collected by filtration and washed with ether to give 107 g (98.6%) of **8b**. Recrystallization from THF–petroleum ether gave a sample, mp 152–154 °C. Anal. ($C_{18}H_{27}NO_3$) C, H, N.

9α-Hydroxy-2′-methoxy-2,9-dimethyl-5-[3-(mesyloxy)-propyl]-6,7-benzomorphan (8c). To a cooled (ice bath), stirred solution of **8b** (95.7 g, 0.328 mol) in dry THF (900 mL) and pyridine (900 mL) was added dropwise CH_3SO_2Cl (71 g, 0.633 mol), and the mixture was stirred for 45 min at room temperature, followed by concentration in vacuo. The concentrate was partitioned between aqueous ammonia and CH_2Cl_2. The organic phase was dried and evaporated to dryness to give 116 g (95%) of **8c** as an oil. The HCl salt was crystallized from MeOH–Et_2O to give a sample, mp 143–145 °C. Anal. ($C_{19}H_{29}NO_5S$·HCl) C, H, N.

3-Methoxy-17-methyl-8-oxamorphinan (9a). To a stirred solution of **8a** (207.5 g, 0.712 mol) in THF (1 L) and triethylamine (1 L) was added dropwise a solution of CH_3SO_2Cl (90 g, 0.786 mol) in THF (100 mL). The mixture was stirred for 1 h, treated with KO-*t*-Bu (207 g, 1.84 mol), and stirred for another 2 h. Water (500 mL) was added and the mixture concentrated in vacuo. The residue was extracted with petroleum ether, and the extract was dried and concentrated in vacuo to give 165 g (84%) of solid **9a**, mp 76–79 °C. A sample was sublimed at 80 °C (0.02 mm). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

3-Methoxy-14,17-dimethyl-8-oxamorphinan (9b). An oil was obtained in 73% yield from **3c** by treatment with excess NaH in DMF (18 h at room temperature) and standard workup. The HCl salt crystallized from MeOH–Et_2O to give a sample, mp 242–244 °C. Anal. ($C_{18}H_{25}NO_2$) C, H, N.

17-Cyano-3-methoxy-8-oxamorphinan (9c). A solution of **9a** (100 g, 0.366 mol) in dry benzene (750 mL) was treated with a solution of BrCN (77 g, 0.73 mol) in dry benzene (250 mL) for 3 h at room temperature. This was washed with 1 N HCl (200 mL), followed by brine, dried, and concentrated in vacuo to give 97 g (93%) of a fawn-colored solid **9c**, mp 92–98 °C. A sample which distilled at 160 °C (0.02 mm) had mp 100–102 °C. Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

17-Cyano-3-methoxy-14-methyl-8-oxamorphinan (9d) was similarly prepared in 88% yield from **9b** by reaction at reflux temperature for 2.5 h: mp 157–158 °C (MeOH). Anal. ($C_{18}H_{22}N_2O_2$) C, H, N.

3-Methoxy-8-oxamorphinan (9e). A solution of **9c** (132 g, 0.464 mol) in dry THF (650 mL) was added dropwise to a refluxing solution of $LiAlH_4$ (43.6 g, 1.15 mol) in THF (1.25 L), and the mixture was heated under reflux for 2 h. After cooling, the excess hydride was decomposed (H_2O and NaOH), and inorganic salts were removed by filtration. The filtrate was concentrated in vacuo to give 111 g (92.5) of a viscous oil, **9c**. The HCl salt crystallized from MeOH–Et_2O with $1H_2O$: mp 253–254 °C. Anal. ($C_{16}H_{21}NO_2$·HCl·H_2O) C, H, N.

3-Methoxy-14-methyl-8-oxamorphinan (9f), an oil, was similarly prepared in 98% yield from **9d**. The reduction was conducted in dioxane under reflux for 1 h. A sample was crystallized as the HCl salt from MeOH–Et_2O: mp 270 °C. Anal. ($C_{17}H_{23}NO_2$·HCl) C, H, N.

The following compounds were prepared by treatment of the corresponding secondary amines with cycloalkanecarboxylic acid chlorides and triethylamine in CH_2Cl_2. **9g**: viscous oil (98% yield); bp 165–170 °C (0.002 mm). Anal. ($C_{20}H_{25}NO_3$) C, H, N. **9h** (96.5%): mp 141–143 °C (Et_2O–petroleum ether). Anal. ($C_{21}G_{27}NO_3$) C, H, N. **9i**: viscous oil (100%); bp 170–175 °C (0.002 mm). Anal. ($C_{21}H_{27}NO_3$) C, H, N. **9j** (93%): mp 156–157 °C (Et_2O). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

The following tertiary bases were prepared from the corresponding amides by the procedure given for the preparation of **9e**. **9k**: viscous oil (89% yield); HCl salt mp 250–252 °C (MeOH–Et_2O). Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N. **9l**: viscous oil (97%); HCl salt mp 246–247 °C (MeOH–Et_2O). Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N. **9m**: viscous oil (92.5%); HCl salt mp 232–234 °C (MeOH–Et_2O). Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N. **9n**: white solid (86%); mp 105–107 °C (EtOH). Anal. ($C_{22}H_{31}NO_2$) C, H, N.

Resolution of 9k. A solution of **9k** (133.5 g, 0.427 mol) in MeOH (250 mL) was treated with a solution of (–)-dibenzoyl-L-tartaric acid (160.3 g, 0.426 mol) in warm MeOH (300 mL), and the mixture was allowed to crystallize for 3 days to give 166 g of the salt, $[\alpha]_D$ –37.8° (*c* 0.396, MeOH). This was recrystallized twice from MeOH to give 91 g of (+)-**9k** (–)-dibenzoyltartrate, $[\alpha]_D$ –36.8° (*c* 0.31, MeOH), mp 154–156 °C; the free base was an oil, $[\alpha]_D$ +67° (*c* 0.29, MeOH).

The mother liquid after the first crystallization was made basic with NH_4OH, concentrated in vacuo, and extracted with CH_2Cl_2 to give 64 g of **9k**, $[\alpha]_D$ –59° (*c* 0.36, MeOH). This was similarly treated with (+)-dibenzoyl-D-tartaric acid to give, after two recrystallizations from MeOH, 94 g of the salt, $[\alpha]_D$ +36.9° (*c* 0.25, MeOH), mp 154–156 °C; the free base had $[\alpha]_D$ –66° (*c* 0.207, MeOH). The oxalate salt was recrystallized from MeOH–Et_2O: $[\alpha]_D$ –42° (*c* 0.30, MeOH); mp 187–189 °C. Anal. ($C_{20}H_{27}NO_2$·$C_2H_2O_4$) C, H, N.

17-Allyl-3-methoxy-14-methyl-8-oxamorphinan (9o). To a solution of **9f** (2.66 g, 9.74 mmol) and triethylamine (3 g) in anhydrous ethanol (25 mL) was added allyl bromide (1.8 g, 15 mmol), and the mixture was heated under reflux for 2 h, followed by concentration in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous ammonia. The organic layer was dried and evaporated to dryness, and the residue was chromatographed on a silica gel column (eluent Et_2O) to give 3.05 g (72%) of **9o** as a viscous oil. The HCl salt crystallized from MeOH–Et_2O: mp 244–246 °C. Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

17-Dimethylallyl-3-methoxy-14-methyl-8-oxamorphinan (9p) was similarly prepared from **9f** and dimethylallyl bromide in 78% yield as a viscous oil. The oxalate salt crystallized from MeOH–Et_2O with 0.5MeOH: mp 218–219 °C. Anal. ($C_{22}H_{31}NO_2$·$C_2H_2O_4$·0.5MeOH) C, H, N.

3-Hydroxy-17-methyl-8-oxamorphinan (6a). To a solution of **9a** (760 mg, 2.78 mmol) in dry THF (5 mL) was added a 0.78 N solution of $(C_6H_5)_2PLi$ in THF (20 mL, 15.6 mol), and the mixture was heated under reflux for 6 h, followed by addition of H_2O (3 mL) and concentration in vacuo. The residue was taken in 0.5 N HCl (50 mL) and extracted with Et_2O (2 × 50 mL). The acidic layer was made basic (NH_4OH) and extracted with CH_2Cl_2 to give, after drying, concentration, and crystallization first from Et_2O and then from C_6H_6, 400 mg (57%) of **6a**: mp 226–229 °C. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

3-Hydroxy-14,17-dimethyl-8-oxamorphinan (6b). To a cooled (0 °C) solution of **9b** (0.5 g, 1.67 mmol) in CH_2Cl_2 (10 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (3.5 mL), and the mixture was allowed to stand at room temperature for 2 h. This was carefully treated with water, made basic with NH_4OH, and extracted with CH_2Cl_2. The product was isolated by chromatography (Al_2O_3, $CHCl_3$–5% MeOH) and purified as the HCl salt to give 0.32 g (59%): mp 258–260 °C (MeOH–Et_2O). Anal. ($C_{17}H_{23}NO_2$·HCl·0.5MeOH) C, H, N.

17-Cyclopropylmethyl-3-hydroxy-8-oxamorphinan (6c). To a cooled (ice), stirred suspension of NaH (25.2 g of a 50% suspension in oil, washed with C_6H_6, 0.525 mol) in DMF (500 mL) was added at a moderate rate EtSH (40 mL, 0.525 mol). To this was added a solution of **9k** (29.9 g, 95.4 mmol) in DMF (200 mL), and the mixture was heated under reflux for 5 h, followed by cooling and partitioning between a mixture of ice, H_2O, NH_4Cl, and C_6H_5. The organic layer was washed with H_2O, dried, and concentrated in vacuo to give crude oily **8c**. This was purified as the HCl salt to give 27.9 g (87.2%) of the hydrochloride: mp 256–267 °C (MeOH–Et_2O). Anal. ($C_{19}H_{25}NO_2$·HCl) C, H, N.

The optically active isomers were similarly prepared from (–)- and (+)-**9k**, respectively. (–)-**6c**: colorless solid, mp 190–192 °C (sublimed), $[\alpha]_D$ –73.6° (*c* 0.265, MeOH); the HCl salt had mp 264–266 °C (MeOH–Et_2O), $[\alpha]_D$ –55.5° (*c* 0.256, MeOH). Anal. ($C_{19}H_{25}NO_2$·HCl) C, H, N. (+)-**6c**: mp 190–192 °C, $[\alpha]_D$ +74° (*c* 0.32, MeOH).

17-Cyclopropylmethyl-3-hydroxy-14-methyl-8-oxamorphinan (6d) was similarly prepared from **9l** in 86% yield: mp 268–270 °C (MeOH–Et_2O). Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

17-Cyclobutylmethyl-3-hydroxy-8-oxamorphinan (6e) was similarly prepared from **9m**. The crude product was purified by chromatography (silica gel, Et_2O), followed by sublimation at 170–180 °C (0.002 mm): mp 177–178 °C. Anal. ($C_{20}H_{27}NO_2$) C, H, N.

17-Cyclobutylmethyl-3-hydroxy-14-methyl-8-oxamorphinan (6f) was similarly prepared from **9n**. The crude product was purified as the oxalate to give **6f** in 78% yield: mp 130–132 °C (EtOH). Anal. ($C_{21}H_{29}NO_2$·0.5$C_2H_4O_2$·C_2H_5OH) C, H, N.

17-Allyl-3-hydroxy-14-methyl-8-oxamorphinan (6g) was prepared from **9o** in 55% yield by the procedure given for the preparation of **6b**. It was purified as HCl salt: mp 245–250 °C (MeOH–Et_2O). Anal. ($C_{19}H_{25}NO_2$·HCl) C, H, N.

17-Dimethylallyl-3-hydroxy-14-methyl-8-oxamorphinan (6h) was similarly prepared from **9p**. The crude product was chromatographed (silica gel, $CHCl_3$) and then crystallized as the HCl salt to give **6h** in 36% yield: mp 158–160 °C (MeOH–Me_2CO–Et_2O). Anal. ($C_{21}H_{29}NO_2$·HCl·CH_3OH) C, H, N.

Resolution of 6d. A solution of **6d** (33.7 g, 0.108 mol) in acetone (300 mL) was treated with a solution of (–)-dibenzoyl-L-tartaric acid (40.6 g, 0.109 mol) in hot MeOH (400 mL), and the mixture was allowed to crystallize at room temperature for 3 days. The solid thus obtained was recrystallized three times from *i*-PrOH to give 21.9 g of (–)-**6d** (–)-dibenzoyltartrate, $[\alpha]_D$ –79° (*c* 0.274, *i*-PrOH), mp 159–161 °C; the free base was an amorphous solid, mp 50–60 °C, $[\alpha]_D$ –74° (*c* 0.294, MeOH); the HCl salt had mp 281–283 °C (MeOH–Et_2O), $[\alpha]_D$ –73° (*c* 0.30, MeOH). Anal. ($C_{20}H_{27}NO_2$·HCl) C, H, N.

(+)-**6d** was similarly obtained by isolation of the free base from mother liquors and treatment with (+)-dibenzoyl-D-tartaric acid; the HCl salt had mp 283–285 °C, $[\alpha]_D$ –73.8° (*c* 0.224, MeOH).

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References and Notes

(1) Y. Lambert, J. P. Daris, and I. Monković, *Can. J. Chem.*, **54**, 2523 (1977).
(2) A paper by G. Kavadias and S. Velkof of these laboratories, describing an improved synthesis of this compound, is in preparation.
(3) M. Saucier, J. P. Daris, Y. Lambert, I. Monković, and A. W. Pircio, *J. Med. Chem.*, **20**, 676 (1977).
(4) I. Monković, H. Wong, A. W. Pircio, Y. G. Perron, I. J. Pachter, and B. Belleau, *Can. J. Chem.*, **53**, 3094 (1975).
(5) (a) I. Monković, M. Saucier, Y. Lambert, and T. A. Montzka, U.S. Patent 3966747; (b) N. F. Albertson, *J. Med. Chem.*, **18**, 619 (1975).
(6) M. Gates and T. Montzka, *J. Med. Chem.*, **7**, 127 (1964).
(7) This subject has been reviewed by (a) F. M. Robinson, (b) H. Blumberg and H. B. Dayton, (c) W. Leimgruber, E. Mohacsi, H. Baruth, and L. O. Randall, (d) M. Gates, (e) I. J. Pachter, (f) N. F. Albertson, (g) F. H. Clarke, R. T. Hill, J. K. Saelens, and N. Yokoyama, (h) H. Merz, A. Langbein, K. Stockhaus, G. Walther, and H. Wick, (i) P. A. J. Janssen, (j) M. Takeda, M. Konda, H. Inoue, S. Saito, H. Kugita, and

S. Nurimoto, (k) J. W. Lewis, (l) M. E. Freed, J. R. Potoski, E. H. Freed, M. I. Gluckman, and J. L. Malis, (m) D. A. McCarthy, (n) A. Langbein, H. Merz, K. Stockhaus, and H. Wick, and (o) J. E. Giering, T. A. Davidson, B. V. Shetty, and A. P. Truant in "Narcotic Antagonists: Advances in Biochemical Psychopharmacology", Vol. 8, M. C. Braude et al., Ed., Raven Press, New York, N.Y., 1973, pp 21–187.
(8) K. E. Opheim and B. M. Cox, *J. Med. Chem.*, 19, 857 (1976).

Synthesis and Antiinflammatory Activity of 6-Oxo-1-(β-D-ribofuranosyl)nicotinic Acid and Related Derivatives

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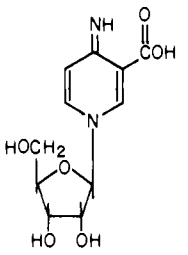
5-Substituted 1-(β-D-ribofuranosyl)pyridin-2-ones (6-oxonicotinic acid nucleosides) were prepared by direct glycosylation of 5-nitro-, 5-carbomethoxy-, 5-carboxamido-, 5-amino-, 5-carbobenzyloxyamino-, and 5-acetamido-2-trimethylsilyloxy or corresponding 2-methoxypyridine derivatives by the Hilbert–Johnson method. The glycosylation products were deblocked by conventional procedures and substituents at the 5 position were modified to give the 5-carboxamide, carboxyhydrazide, and carboxylic acid. Only 1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic acid [1-(β-D-ribofuranosyl)-6-oxonicotinic acid] (12), showed significant activity in treating adjuvant-induced arthritis in rats.

Nicotinamide and related derivatives have shown a variety of interesting biological activities including anti-RNA and DNA virus,[1] antiinflammatory,[2] coronary vasodilator,[3] antifibrillatory,[3] spasmolytic,[3] and hypertensive[3] activity. Niacin derivatives have also been demonstrated to inhibit, among other enzymes, tumor tRNA methylase[4] and glucose-phosphate isomerase.[5] It is possible that nicotinamide derivatives in some cases may act by virtue of their conversion to the corresponding nucleoside or nucleotide (NAD) analogue.

For example, 2-hydroxynicotinic acid, an inhibitor of cholesterol and fatty acid synthesis in the rat,[6] has been shown to be converted to 1-(β-D-ribofuranosyl)-2-oxonicotinic acid by dogs and rats[7] when administered orally. The isolation of labeled 1-(β-D-ribofuranosyl)-2-oxonicotinic acid from the urine accounted for over 75% of the administered 2-hydroxynicotinic acid.[7] The isolation of nicotinic acid ribonucleoside from extracts of *Aspergillus niger* has recently been reported.[8] A new nucleoside, 1-(β-D-ribofuranosyl)-4-iminonicotinic acid, named clitidine, has recently been isolated from the Japanese



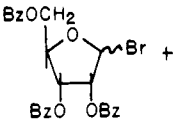
clitidine

mushroom *Clitocybe acromelalga*.[9] Clitidine causes marked hyperemia and hyperesthesia in various parts of the body. Since clitidine, a 4-substituted nicotinic acid, and 1-(β-D-ribofuranosyl)-2-oxonicotinic acid carry no charge on the pyridine nitrogen, it was of interest to synthesize the 6-oxonicotinic acid 12 and other related derivatives to determine their potential biological activity.

A number of *N*-glycosylpyridine derivatives have been reported, including several glycosylpyridin-2-ones[10,11] and pyridine nucleoside analogues[12–14] of the naturally occurring pyrimidine nucleosides. Several methods of glycosylation have been employed in the synthesis of these pyridine nucleosides, most notably the silver salt and the mercury salt methods,[11] rearrangement of the corresponding *O*-glycosides,[15] and the Hilbert–Johnson method.[12] The Hilbert–Johnson method and the silyl modification thereof were selected for this study because of their versatility and the often observed absence of side products.

Discussion

Glycosylation of 2-trimethylsilyloxy-5-nitropyridine (2) in acetonitrile at ambient temperature with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide (1) gave 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitro-2-pyridone (8). Similarly, 1 and 2-trimethylsilyloxy-5-carbomethoxy-



1

	R_1	R_2
2	$-NO_2$	$-Si(CH_3)_3$
3	$-CO_2CH_3$	$-Si(CH_3)_3$
4	$-CONH_2$	$-CH_3$
5	$-NH_2$	$-CH_3$
6	-NHCBz	$-CH_3$
7	-NHAc	$-CH_3$

	R_1	R_3
8	$-NO_2$	-Bz
9	$-NO_2$	-H
10	$-CO_2CH_3$	-Bz
11	$-CO_2CH_3$	-H
12	$-CO_2H$	-H
13	$-CONHNH_2$	-H
14	$-CONH_2$	-Bz
15	$-CONH_2$	-H
16	-NHBz	-H
17	-NHCbz	-H
18	-NHAc	-H

Bz = benzoyl; Ac = acetyl; Cbz = carbobenzyloxy

pyridine (3) gave 10 in excellent yield. A negative Fehling's test demonstrated the absence of any *O*-glycoside in the major nucleoside products isolated. Debenzoylation of 8

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