solution was heated to boiling and filtered, and the filtrate was chilled. The crystals that separated were collected and washed with MeOH. An analytical sample was prepared by recrystallization from MeCN: IR 2940, 2910, 2870, 2084 (SCN^-), 1601, 1495, 1460, 1437, 1300, 1274, 1202, 877, 778, 771 cm^{-1}.

Method B. A solution of 500 mg (1.25 mmol) of **7** in 75 mL of refluxing propionitrile was treated with a solution of 122 mg (1.25 mmol) of KSCN in 20 mL of propionitrile. The solution was heated under reflux for 15 min and chilled, and the crystals that separated were collected. Recrystallization was effected from MeCN to give 235 mg (44%) of **11**. Infrared spectra of the products obtained by methods A and B were identical.

Thiocyanato[*N*,*N*-3-azabicyclo[3.2.2]nonane-3-thiocarbohydrazonato][1-(2-pyridyl)ethylidene]nickel(II) (12). A suspension of 800 mg (2.02 mmol) of chloro[3-azabicyclo-[3.2.2]nonane-3-thiocarboxylic acid 2-[1-(2-pyridyl)ethylidene]-hydrazinato]nickel(II) (**9**) in 70 mL of acetonitrile was treated with 250 mg (2.57 mmol) of KCNS and heated at reflux for 5 min. The reaction mixture was chilled, and the product was collected by filtration and washed well with H_2O to remove KCl. An analytical sample was prepared by recrystallization from MeCN: IR 2935, 2910, 2860, 2090, 1600, 1500, 1465, 1448, 1437, 1305, 1195, 777 cm^{-1}.

Biological Methods. The compounds described in this paper were tested for antimalarial activity at the Dr. Leo Rane Laboratory, University of Miami, Miami, FL, against a drug-sensitive strain of *Plasmodium berghei* (strain KBG 173) in ICR/HA Swiss mice. Five mice per dose level are infected by the intraperitoneal administration of parasitized erythrocytes. Untreated infected animals, which serve as controls, die, on the average, after 6.2 days. A candidate drug is given 72 h after the mice are infected and is judged to be "toxic" if they die before the 6th day, "inactive" if they die between the 6th and 12th day, "active" if the mean survival time is at least doubled, and "curative" if the mice survive at least 60 days postinfection. Compounds that are "active" or "curative" at a dose of 40 mg/kg are retested at several lower dose levels, but results are not reported unless extension of mouse survival time is observed. Details of the test procedure were given in the first paper of this series and by Osdene, Russell, and Rane.[14]

The antitumor activity of the thiosemicarbazones and their metal complexes was determined at the National Cancer Institute (NIH), Bethesda, MD, by the standard screening procedure (cf. Instruction 14) in the P388 lymphocytic leukemic test system. The tumor inoculum of 10^6 ascites cells was implanted on day 0 ip in CD_2F_2 (CDF_1) mice. The drugs were administered daily ip in accordance with the treatment schedule indicated in Table III. A compound is considered active when T/C (test/control) survival times produce a percentage >125.

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Synthesis and Pharmacology of Metabolically Stable *tert*-Butyl Ethers of Morphine and Levorphanol

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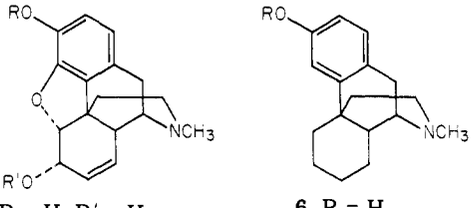
3-*O*-*tert*-Butylmorphine (**5**) was prepared from 6-*O*-acetylmorphine (**3**) via alkylation with *N*,*N*-dimethylformamide di-*tert*-butyl acetal, followed by hydrolytic removal of the 3-(dimethylamino)-2-propenoate group. The same process was used to prepare the *tert*-butyl ether of levorphanol (**6**), (−)-3-*tert*-butoxy-*N*-methylmorphinan (**8**). Both **5** and **8** exhibited in vitro affinity for the opiate receptor comparable to codeine and had analgesic properties in the writhing test. Only **5** exhibited activity in the tail-flick procedure and neither compound showed significant antitussive activity.

Our interest in *tert*-butyl analogues of codeine (**2**) and levomethorphan (**7**) was prompted by the expectation that replacement of the methyl group on the phenolic oxygen by a *tert*-butyl group would prevent the in vivo metabolic conversions to morphine (**1**) and levorphanol (**6**), respectively, with their attendant undesirable side effects. Disregarding the controversial hypothesis[1] that the analgesic activity of codeine (**2**) in man may be due to its metabolic conversion to morphine,[2] we envisaged the possibility that compounds **5** and **8** would retain the analgesic properties of the corresponding methyl ethers. We also speculated that (−)-3-*tert*-butoxy-*N*-methylmorphinan (**8**), the *tert*-butyl ether of levorphanol (**6**), might exhibit enhanced analgesic potency in comparison to **5**, since **6** is analgetically more potent than morphine (**1**).[3]

Chemistry. Conventional methods[4] for the preparation of *tert*-butyl ethers require strong acid catalysis and were precluded for the synthesis of **5**, since such conditions readily rearrange morphine (**1**).[5] However, based on the observation that *N*,*N*-dimethylformamide acetals[6] alkylate phenols, treatment of certain phenols with excess *N*,*N*-dimethylformamide di-*tert*-butyl acetal[7,8] at elevated temperature furnished the corresponding *tert*-butyl ethers.[9]

Chart I



1, R = H; R′ = H
2, R = CH_3; R′ = H
3, R = H; R′ = $C(=O)CH_3$
4, R = $C(CH_3)_3$; R′ = $C(=O)CH{=}CH_2N(CH_3)_2$
5, R = $C(CH_3)_3$; R′ = H

6, R = H
7, R = CH_3
8, R = $C(CH_3)_3$

[†] Chemistry Department.
[§] Deceased July 8, 1981.
[‡] Pharmacology Department.

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Table I. Analgesic Activities and Opiate Receptor Affinities

compd	analgesic act.:[a] ED_{50}, mg/kg sc		binding affinities:[h,i] [^{3}H]naltrexone (10^{-9} M) $IC_{50} \times 10^6$ (Tris buffer)
	writhing	tail flick	
1[b]	0.46 (0.26-0.83)[f]	4.06 (3.78-4.41)	0.027
2[c]	2.3 (1.21-3.91)	38.97 (35.31-42.79)	10.0
5[d]	26.8 (13.40-53.60)	inactive[g]	20.0
6[d]	0.1 (0.06-0.18)	1.30 (1.21-1.40)	0.004
7[e]	0.64 (0.34-1.22)	6.78 (6.23-7.42)	2.0
8[d]	5.0 (3.13-8.00)	5.81 (4.89-6.83)	3.0

[a] The compounds were administered to the mice subcutaneously in distilled water for the writhing tests and in normal saline solution for the tail-flick tests. [b] Sulfate. [c] Phosphate. [d] Tartrate. [e] Hydrobromide. [f] Numbers in parentheses are the 95% confidence limits obtained by the probit analysis.[16] [g] Inactive up to 200 mg/kg. [h] Binding was performed with rat brain homogenate. [i] Expressed as the concentration of compound required to inhibit stereospecific [^{3}H]naltrexone binding by 50%. The IC_{50} values are the means of results from three closely similar experiments.

For the conversion of morphine (1) into the desired 3-*O*-*tert*-butylmorphine (5), the allylic alcohol group was protected to form the acetyl derivative 3, since it is known[10] that allylic alcohols undergo a sigmatropic rearrangement in the presence of *N,N*-dimethylformamide acetal.

Thus, treatment of the morphine monoacetate 3[11] with excess *N,N*-dimethylformamide di-*tert*-butyl acetal at 110 °C led to simultaneous alkylation and condensation to afford the *tert*-butyl ether 4 (Chart I). Hydrolytic removal of the 3-(dimethylamino)-2-propenoate group was achieved with sodium hydroxide in ethanol to give the target compound 5, whose spectral properties were in full agreement with the assigned structure. Confirmation of structure was provided by the mild acid hydrolysis of 5 to morphine (1).

Preparation of 8 was achieved by treatment of 6 with an excess of *N,N*-dimethylformamide di-*tert*-butyl acetal (Chart I).

Pharmacological Results

Analgesic potencies were determined by both the tail-flick[12] and phenylquinone writhing methods.[13] The results are presented in Table I.

Antitussive activities were tested in the dog by the method of Stefko and Benson.[14] No significant antitussive activity was observed for 5 or 8 at the subcutanous dose of 8 mg/kg, whereas codeine (phosphate) at a dose of 2 mg/kg produced a maximum of 76% reduction in the number of coughs.

Binding assays were performed in rat brain homogenates as previously described.[15] The concentration of test compound necessary to displace one-half of the stereospecific [^{3}H]naltrexone binding (IC_{50}) is shown in Table I.

Conclusions

Data shown in Table I confirm the known observation that conversion of morphine (1) to codeine (2) and levorphanol (6) to levomethorphan (7) results in a marked reduction in receptor-binding affinity and a moderate reduction in analgesic potency. The same trend in reduction of binding affinity and analgesic activity is observed with the *tert*-butyl ethers 5 and 8. 3-*O*-*tert*-Butylmorphine (5) is inactive in the tail-flick test but not in the writhing test, whereas (−)-3-*tert*-butoxy-*N*-methylmorphinan (8) is active by both in vivo tests employed.

Metabolic studies in the rat have shown[17] that these compounds (5 and 8), in contrast to codeine (2) and levomethorphan (7), are not transformed to morphine (1) and levorphanol (6), respectively. These studies demonstrate, not unexpectedly, that the presence of a *tert*-butyl group eliminates O-dealkylation as a major metabolic pathway. Surprisingly, the extraordinary bulk of this substituent does not preclude the interaction of these substrates with the analgesic receptor.

In summary, *tert*-butyl ether compounds 5 and 8 are unable to metabolize to morphine (1) and levorphanol (6), respectively, yet are analgetically active and interact with the opiate receptor with an affinity comparable to the methyl ethers 2 and 7.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are not corrected. All new compounds were characterized by IR (Beckman IR-9 spectrophotometer), NMR (Varian Associates A-60 and HA-100 spectrometers, Me_4Si internal standard), UV (Cary 14 spectrophotometer), and MS (CEC 110-21B spectrometer) and were in agreement with their assigned structures. Analyses are indicated only by the symbols of the elements; analytical results obtained for the elements were within ±0.4% of the theoretical values.

3-*O*-*tert*-Butyl-6-*O*-[3-(dimethylamino)-1-oxo-2-propenyl]morphine (4). A mixture of 23.0 g (70 mmol) of 6-*O*-acetylmorphine (3) and 32.0 g (158 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was heated at 100–110 °C for 30 min under nitrogen. Then an additional two 16.0-g (79 mmol) portions of *N,N*-dimethylformamide di-*tert*-butyl acetal were added successively in 2-h intervals, and the heating was continued for an additional 6 h. The excess reagent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (500 mL) and washed successively with 5 N sodium hydroxide (75 mL) and water (70 mL). The ethyl acetate solution was dried and concentrated to give a residue, which was distilled to afford 15.5 g (50%) of 4: bp 220–225 °C (0.1 mm); IR ($CHCl_3$)

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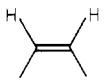
3000, 2975, 2920, 2900, 1670, 1620, 1600, 1100 cm^{-1}; UV (EtOH) λ_{max} 280 (ϵ 31 100); NMR ($CDCl_3$) δ 7.45 (d, 1, J_{trans} = 13 Hz, =CHN), 6.62 and 6.41 (AB, 2, J = 8.5 Hz, Ar H), 5.56 and 5.30 (m, m, 2, J_{cis} = 10 Hz, i), 4.54 (d, 1, J_{trans} = 13 Hz, COCH=), 2.89



i

[s, 6, $N(CH_3)_2$], 1.22 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 438 (M^+), 382, 285, 267, 98. Anal. ($C_{26}H_{34}N_2O_4$) C, H, N.

3-*O*-*tert*-Butylmorphine (5). To a solution of 15.0 g (34 mmol) of 4 in 600 mL of ethanol was added 280 mL of 2 N sodium hydroxide. After this mixture had been heated under reflux for 24 h, the ethanol was removed under reduced pressure, and the resulting suspension was extracted with chloroform (900 mL). The organic layer was washed with 2 N sodium hydroxide (100 mL) and then with water (120 mL) and dried. Removal of the solvent gave a residue, which was distilled to give 10.69 g (92%) of **5**: bp 220–230 °C (0.2 mm); $[\alpha]^{25}_D$ –79.8° (*c* 0.8, MeOH); IR ($CHCl_3$) 3550, 3000, 2975, 2925, 2800, 1730, 1600 cm^{-1}; UV (EtOH) λ_{max} 239 sh (ϵ 4680), 285 (3100); NMR ($CDCl_3$) δ 6.68, 6.50 (AB, 2, J = 8.5 Hz, Ar H), 5.65 and 6.27 (m, m, 2, J_{cis} = 10 Hz, i), 2.45 (s, 3, NCH_3), 1.32 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 341 (M^+), 299, 285, 268, 215, 162, 124, 115, 57. Anal. ($C_{21}H_{27}NO_3$) C, H, N. The tartrate salt of **5** was prepared in ethanol with *d*-tartaric acid. Recrystallization from ethanol gave **5** as the *d*-tartrate diethanolate: mp 105–106 °C dec; $[\alpha]^{25}_D$ –28.2° (*c* 1.18, MeOH); mass spectrum (70 eV), m/e 341 (M^+), 308, 285, 268, 215, 162, 124, 115, 76, 57. Anal. ($C_{21}H_{27}NO_3 \cdot C_4H_6O_6 \cdot 2C_2H_6O$) C, H, N.

Hydrolysis of 3-*O*-*tert*-Butylmorphine (5) to Morphine (1). A solution of 0.12 g (0.35 mmol) of **5** in 1 N hydrochloric acid was stirred at room temperature for 17 h and then neutralized with concentrated ammonium hydroxide. The product, collected by filtration and recrystallization from methanol, gave 0.09 g (90%) of pure morphine (1), mp 254–256 °C (lit.[18] mp 251–256 °C). Its mmp with an authentic sample was undepressed and its spectroscopic properties (UV, IR, and MS) were identical with those of an authentic sample of morphine (1).

(–)-3-*tert*-Butoxy-*N*-methylmorphinan (8). A mixture of 11.3 g (44 mmol) of (–)-3-hydroxy-*N*-methylmorphinan (**6**) and 18.1 g (88 mmol) of *N,N*-dimethylformamide di-*tert*-butyl acetal was heated at 100–110 °C for 2 h under nitrogen. Then an additional two 9.0-g (44 mmol) portions of *N,N*-dimethylformamide di-*tert*-butyl acetal were added successively in 2-h intervals, and the heating was continued for an additional 6 h. The excess reagent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (300 mL). The ethyl acetate solution was washed successively with 2 N sodium hydroxide (2 × 60 mL) and water (50 mL). The organic solution was dried and concentrated to give a residue, which was distilled to give 8.1 g (59%) of (–)-3-*tert*-butoxy-*N*-methylmorphinan (**8**): bp 180–200 °C (0.1 mm); $[\alpha]^{25}_D$ –49.3° (*c* 0.93, MeOH); IR ($CHCl_3$) 3000, 2950, 2875, 2825, 1620, 1505 cm^{-1}; UV (EtOH) λ_{max} 279 (ϵ 2820); NMR ($CDCl_3$) δ 6.9 (m, 3), 2.8 (m, 3, Ar H), 2.4 (s, 3, NCH_3), 1.32 [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV), m/e 313 (M^+), 298, 257, 242, 228, 214, 200, 189, 157, 150, 59. Anal. ($C_{21}H_{31}NO$) C, H, N.

The tartrate salt of **8** was prepared in 2-propanol with *d*-tartaric acid. Recrystallization from 2-propanol gave **8** as the *d*-tartrate hydrate: mp 105–107 °C dec; $[\alpha]^{25}_D$ –36.3° (*c* 0.99, MeOH). Anal. ($C_{21}H_{31}NO \cdot C_4H_6O_6 \cdot H_2O$) C, H, H.

Acknowledgment. We are indebted to Dr. E. J. Simon, Department of Medicine, New York University Medical Center, for the binding affinity data. We are grateful to the following members of the Research Department, Hoffmann-La Roche Inc: S. Traiman (IR), Dr. V. Toome (UV), Dr. W. Benz (MS), Dr. T. Williams (NMR), and Dr. F. Scheidl (microanalyses).

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Book Reviews

The Molecular Basis of Antibiotic Action. 2nd Edition. By E. F. Gale, E. Cundliffe, P. E. Reynolds, M. H. Richmond, and M. J. Waring. Wiley, New York. 1981. xxiii + 646 pp. 23.5 × 15.5 cm. $83.00.

The current high level of interest in antibiotics makes this volume a timely addition to the literature of medicinal chemistry. Revising their book 9 years after the first edition appeared, the authors have rewritten most of the chapters. The literature cited is up to date for a book published in early 1981. It has an impressive number of references to 1980 publications, but such is the rate of progress in the field of antibiotics that the material on β-lactam antibiotics is already getting dated because of the discovery of the large family of "monobactams" since the publication of the book.

This volume of sizeable dimension does not aim to be compendium of all the antibiotics, but it does deal with a wide spectrum of antibiotics as well as some of their synthetic analogues. A cursory scan of the index shows references to numberous "mycins", penicillins, cephalosporins and many other antibiotics, as well as less well-known substances, e.g., poke-weed antiviral peptide, pederine, and bruceantin. The last-named compound, which is cited along with other inhibitors of eukaryotic protein synthesis, is incorrectly described as an alkaloid, although the compound is devoid of nitrogen.

Synthetic and medicinal chemists trying to devise new antibiotic drugs will find valuable information in the long chapters on "Inhibitors of Bacterial and Fungal Cell Wall Synthesis", "Antibiotics Affecting the Function of the Cytoplasmic Membrane", "Inhibitors of Nucleic Acid Synthesis", and "Antibiotic Inhibitors of Ribosome Function" (128 pages). The chapter on "Bacterial Resistance to Antibiotics" will interest many, especially since it presents a lucid exposition on the genetic basis of resistance.

The last chapter, under the title "Perspectives", discusses the lack of any large-scale success in designing new antibiotics on the basis of "rational chemotherapy". This chapter then provides a brief account of the modification of existing antibiotic nuclei to obtain successful new antibiotic drugs: semisynthetic penicillins and cephalosporins are used as illustrative examples. This volume meets the high standard in production that one has come to expect of Wiley-Interscience. Extensive illustrations and an abundance of structural diagrams aid the reader, as does the extensive index.

Teamwork by five authors with impressive credentials has led to a book with depth of treatment and breadth of coverage. It is, however, not a textbook for beginning graduate students. Unfortunately, the high price of this volume will prevent many professionals from buying a copy for their personal use.

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