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Alfred Burger Award Address

A Half Century in Medicinal Chemistry with Major Emphasis on Pain-Relieving Drugs and Their Antagonists†

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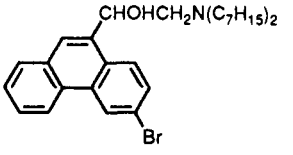
I am highly honored and thrilled to be the 1992 recipient of the Alfred Burger Award in Medicinal Chemistry sponsored by SmithKline Beecham and administered by the Division of Medicinal Chemistry, American Chemical Society. I had the good fortune to be geographically associated with Dr. Burger from 1935–1939 while obtaining my Ph.D. degree at the University of Virginia and to have been the beneficiary of his wise counsel ever since. I also had the honor and pleasure of being his assistant editor (Journal of Medicinal Chemistry) from 1964–1968. It is appropriate to state, also, that about 1955, Drs. Glen Ullyot and Maxwell Gordon of the (then) Smith Kline & French Laboratories initiated and promoted for several years a close and effective collaboration with our laboratory at the National Institutes of Health.

Most of my scientific career has centered on organic compounds that act on the central nervous system with major emphasis on narcotic analgesics and their antagonists. However, during World War II, our efforts at the National Institute (later to become Institutes) of Health (NIH) were diverted to the synthesis of potential antimalarial agents, substitutes for quinine, atabrine, and plasmochine. From this 5-year effort came two phenanthrene amino alcohols which reached the clincial stage of testing. The original designer of these alcohols as potential analgesics was Erich Mosettig, like Dr. Burger, a transplanted Austrian, from Ernst Spaeth's laboratory, University of Vienna. Dr. Mosettig was my Ph.D. advisor and research director at NIH until 1950. The second, of

Chart I



antimalarial

these compounds[1] (chronologically) shown in Chart I was resurrected by Drs. David Jacobus and Thomas Sweeney, then at the Walter Reed Army Institute of Research early in the Vietnam war. It proved to be curative for resistant strains of the deadly falciparum and vivax malarias and was used frequently throughout the war.

Following this World War II hiatus during which time the totally synthetic analgesics pethidine, methadone, isomethadone, and 3-hydroxy-*N*-methylmorphinan had been developed in Germany and Switzerland, attention was again directed to the opioid scene. Our mission still was to provide analgesics that would relieve moderate to severe pain at safe doses and would cause minimal or no dependence and tolerance development.

Because methadone and isomethadone, developed in Germany, resembled morphine pharmacologically, operations on these molecules seemed like a worthy project. Accordingly, reduction of the carbonyl group of these isomeric compounds, with one chiral center, was effected in ways that produced both possible diastereomers of each antipode and of each racemate (Scheme I). The alcohols

† This is taken in part from the text of the Alfred Burger—SmithKline Beecham Award Address delivered on April 9, 1992 at the 203rd American Chemical Society National Meeting, April 5–10, San Francisco, CA.

(1) May, E. L.; Mosettig, E. Attempts to Find New Antimalarials. XVII. Amino Alcohols of the Type -CHOHCH$_2$NR$_2$ Derived from 3-Chloro-10-Acetylphenanthrene. *J. Org. Chem.* **1946**, *11*, 441–443.

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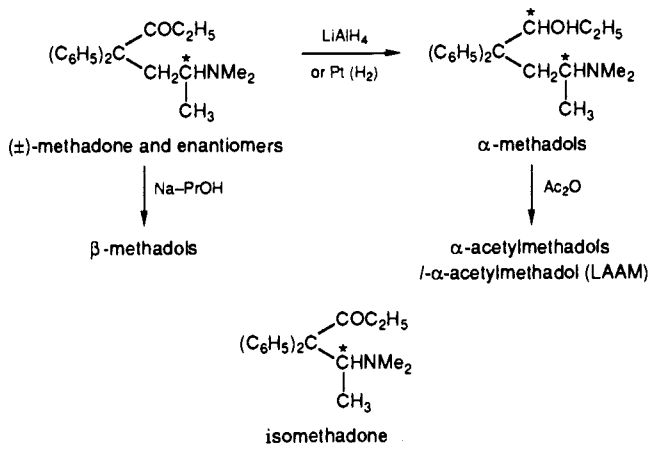
Scheme I

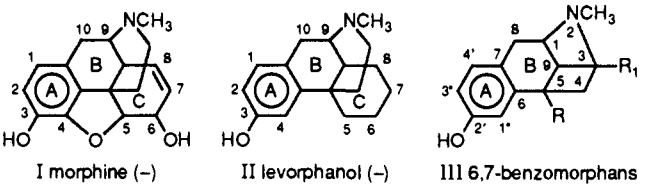


so obtained were invariably of lower antinociceptive potency than the parent ketones. However, O-acetylation restored, in every instance, activity to a level equal to or greater than that of the ketone from which it was derived. In all, 24 compounds, methadols[2] and isomethadols[3] and their *O*-acetyl derivatives, were prepared and tested in the CPDD program. One of these, α-acetylmethadol (LAAM) has, for many years, been under investigation as a substitute for methadone in maintenance therapy. It is about 3 times more potent than methadone and has a longer duration of action.[4]

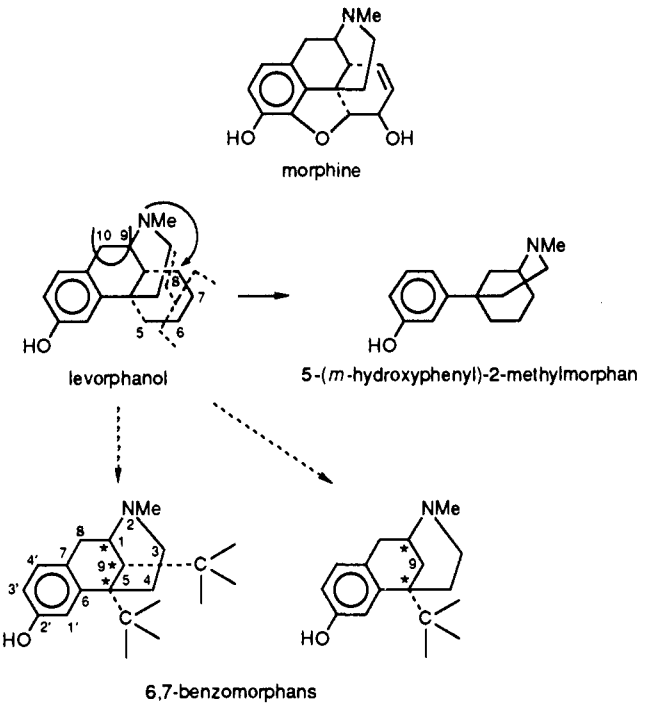
For those of you not familiar with CPDD, it is now a membership organization called College on Problems of Drug Dependence. It evolved from a National Academy of Sciences endeavor begun in 1929, as the Committee on Drug Addiction, changing to the Committee on Drug Addiction and Narcotics in 1947, and to the Committe on Problems of Drug Dependence in 1965. During some 60 years, this group has evaluated over 2000 compounds, principally, those that act centrally, and has severed in an advisory capacity to the World Health Organization, the United Nations Narcotics Laboratory, the Food and Drug Administration, the Drug Enforcement Administration, the Department of Defense, and the National Institute on Drug Abuse, which now financially supports a good portion of CPDD's operations.

While the chemistry of the methadols and isomethadols was being completed, the Korean war erupted and our charge in the Laboratory of Chemistry was altered somewhat. We were now exhorted to discover adequate, totally synthetic substitutes for morphine and codeine because of the threat to opium supply lines. Accordingly, our "sights" were leveled at 3-hydroxy-*N*-methylmorphinan, an indirect result of one of the earliest attempts at the total synthesis of morphine by a German chemist, Rudolph Grewe. This compound (the racemate called racemorphan, the *levo*-isomer levorphanol) was synthesized by Grewe and about simultaneously by Swiss Hoffman-LaRoche chemists, Schnider and associates.[5]

Chart II



Scheme II



Although it lacks the allylic alcohol system and the oxygen bridge of morphine, levorphanol is 3–5 times more potent than morphine, analgesically, with no greater and perhaps less side effects at equivalent analgesic doses. My simplistic reasoning was that still simpler, smaller molecules might elicit similar or improved pharmacologic action if structural features believed at that time to be essential for strong, central, pain-relieving properties were retained. Stated tersely, these features are a phenyl group and a tertiary aminoethyl system attached to the same quaternary carbon, the phenyl nucleus probably needing a *m*-hydroxy group. The structure at the right in Chart II, generically called a 6,7-benzomorphan by Barltrop[6] meets these criteria.

Three (mental) dissections of levorphanol that leave inviolate the just-stated concepts are in Scheme II. The first, elimination of the 9,10-carbon bridge of the octahydrophenanthrene system and relocation of nitrogen attachment from what had been position 9 to 8, generated the so-called phenylmorphans to be discussed shortly. The other two involve excision of two (6 and 7) or three (6, 7, and 8) carbons of hydroaromatic ring C. The resulting carbon vestiges may become methyl or higher alkyl by satisfying the unsaturation left with H or C_nH_{2n+1}, respectively.

Returning to the phenylmorphans, a relatively simple synthesis is shown in brief in Scheme III. The resulting

(2) Eddy, N. B.; May, E. L.; Mosettig, E. Chemistry and Pharmacology of the Methadols and Acetylmethadols. *J. Org. Chem.* **1952**, *17*, 321–326.

(3) May, E. L.; Eddy, N. B. The Isomethadols and Their Acetyl Derivatives **1952**, *17*, 1210–1215

(4) For a key reference see Hough, G.; Washton, A. M.; Resnick, R. B. Addressing the Diversion of Take-Home Methadone: LAAM as the Sole Treatment Choice for Patients Seeking Maintenance Therapy. NIDA Research Monograph Series 43. Proceedings of the 44th Annual Scientific Meeting of The Committee on Problems of Drug Dependence, Inc., 1982; pp 302–5.

(5) Hellerbach, J.; Schnider, O.; Besendorf, H.; Pellmout, B. *Synthetic Analgesics Part II (A). Morphinans, International Series of Monographs in Organic Chemistry*; Pergamon Press: Oxford, 1966, Vol. 8, pp. 3–112.

(6) Barltrop, J. A. Synthesis in the Morphine Series. Part I. Derivatives of Bicyclo[3:3:1]-2-Azanonane. *J. Chem. Soc.* **1947**, 399–401.

Scheme III

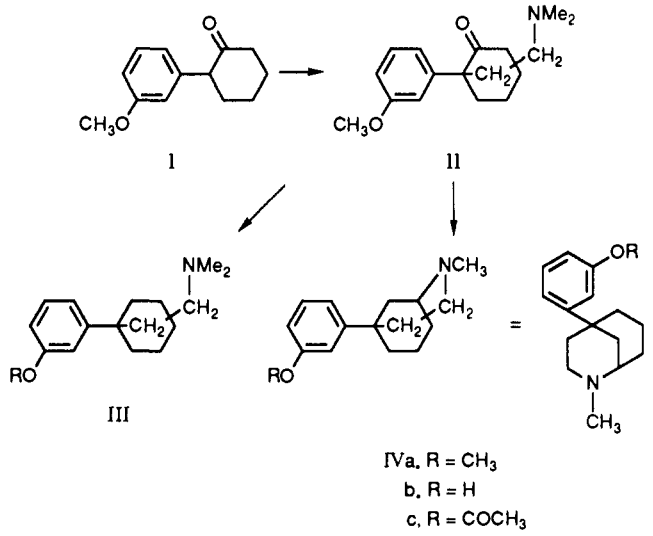
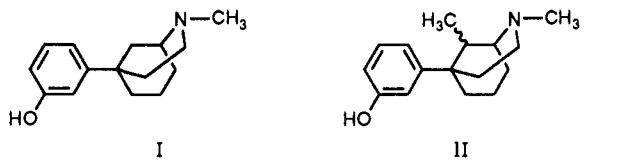


Chart III



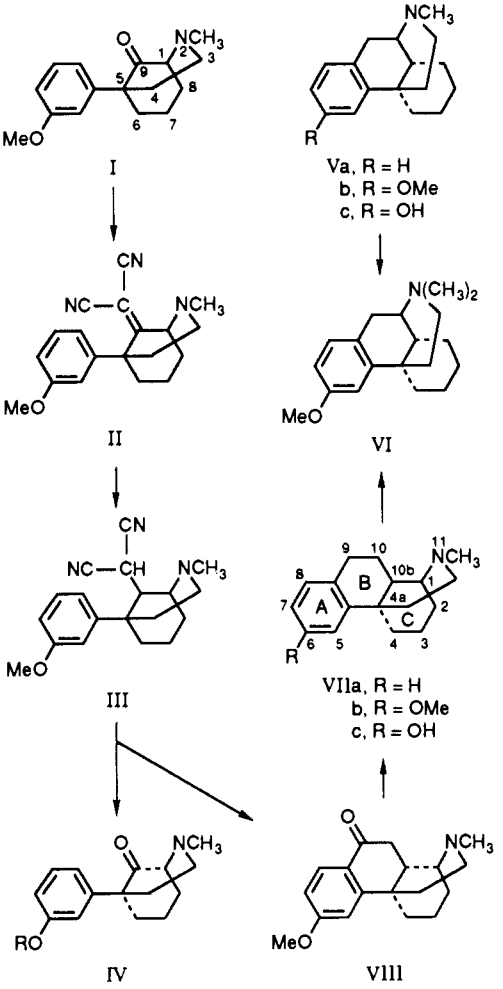
(−)-I: Morphine-like in potency in HP, PPQ and TF antinociceptive tests. Will not support morphine dependence in monkeys or rats. Exacerbates monkey abstinence symptoms.

(+)-I: Morphine-like in all respects.

(+)-II: Pure antagonist, $^1/_{80}$ as potent as naloxone when Me is α for the cyclohexane ring.

(−)-II: Mixed agonist–antagonist, half as potent as nalorphine.

Scheme IV



racemate, 5-(*m*-hydroxyphenyl)-2-methylmorphan (IVb)[7] was indeed morphine-like in almost every respect. Optical resoluton resulted in a favorable separation of deleterious from desired effects (Chart III). The (1*S*,5*R*)-(+)-enantiomer (I) (absolute configuration determined by Cochran[8]) is a typical μ agonist in vivo and in vitro, slightly more potent than morphine antinociceptively (mice) and somewhat less potent in dependence liability (monkeys and rats) and in vitro. The (1*R*,5*S*)-(−)-antipode is comparable to morphine antinociceptively (mice) but will not support morphine dependence in monkeys or rats; in fact, it exacerbates abstinence symptoms in monkeys.[9] It has relatively weak, μ-binding properties and would be an interesting study in man.

Attempts to prepare antagonists from racemic or (+)-I by replacing methyl with the standard groups—allyl, propyl, cyclopropylmethyl—gave only weaker agonists with no more than a hint of antagonist property.[10] Introduction of a 9-methyl substituent did, however, produce a mild agonist–antagonist, (−)-II, a little less potent than nalorphine, and one relatively pure antagonist, (+)-II, when the radical on N was 9α-methyl.[9]

Recent researches by Froimowitz et al.[11] have demonstrated that these phenylmorphans have greatest affinity for μ1 and μ2 receptors excepting the antagonist (+)-II, the 9α-methyl analog, a relatively pure antagonist which binds slightly better to κ1 receptors. They further found that both (−)- and (+)-I have antinociceptive activity after intrathecal administration indicative of μ2 action. The potency ratio was 1:4 again favoring (+)-I.

Before leaving the phenylmorphans you may be interested in what happens when the octahydrophenanthrene moiety is restored (Scheme IV). The resulting isomeric morphinan (VIIc), with nitrogen closure at position 8 rather than 9 as in racemorphan, is almost devoid of antinociceptive activity. The sequence for its synthesis is shown in Scheme IV as is its degradation to the same octahydrophenanthrene (VI) as that obtained from 3-hydroxy-*N*-methylmorphinan (Vc) proving identical stereochemistry at the concerned chiral centers.[12]

As for structures resulting from deletion of carbons 6 and 7 of racemorphan, several 5,9-dialkyl-2′-hydroxy-2-methyl-6,7-benzomorphans were obtained from appropriate 3,4-dialkylpyridines converted to precursors as

(7) May, E. L.; Murphy, J. G. Structures Related to Morphine IV. m-Substituted Phencyclohexane Derivatives *J. Org. Chem.* **1955**, *20*, 1197–1201; Rogers, M. E.; May, E. L. Improved Synthesis and Additional Pharmacology of the Potent Analgesic, (−)-5-*m*-Hydroxyphenyl-2-methylmorphan. *J. Med. Chem.* **1974**, *17*, 1328–30.

(8) Cochran, T. G. Stereochemistry and Absolute Configuration of the Analgesic Agonist–Antagonist (−)-5-*m*-Hydroxyphenyl-2-methylmorphan. *J. Med. Chem.* **1974**, *17*, 987–9.

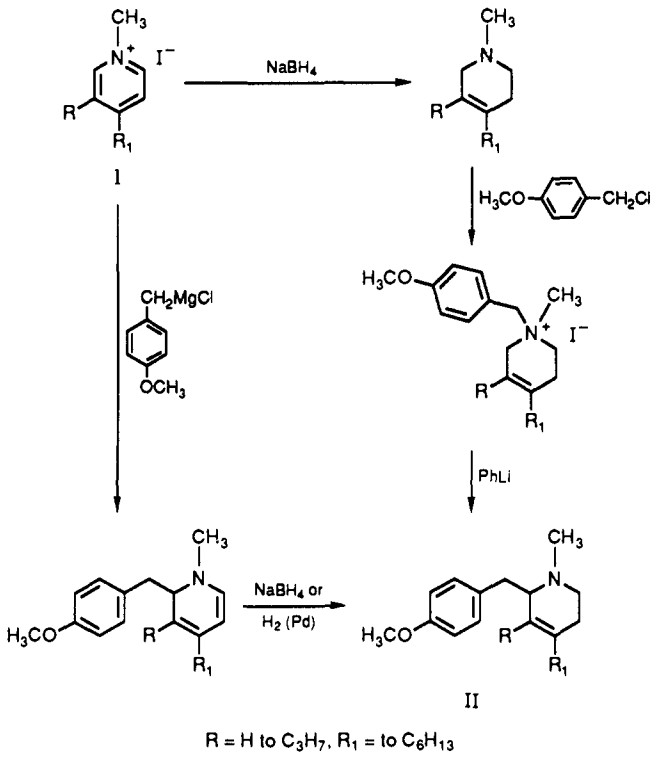
(9) Awaya, H.; May, E. L.; Aceto, M. D.; Merz, H.; Rogers, M. E.; Harris, L. S. Racemic and Optically Active 2,9-Dimethyl-5-(*m*-Hydroxyphenyl) morphans and Pharmacological Comparison with the 9-Demethyl Homologues. *J. Med. Chem.* **1984**, *27*, 536–9.

(10) Ong, H. H.; Oh-ishi, T.; May, E. L. Phenylmorphan Agonist-Antagonists. *J. Med. Chem.* **1974**, *17*, 133–4.

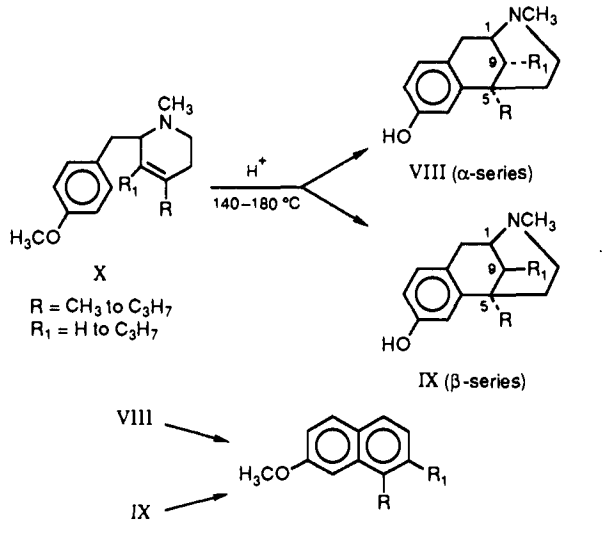
(11) Froimowitz, M.; Pick, C. G.; Pasternak, G. W. Phenylmorphan and Analogues: Opioid Receptor Subtype Selectivity and Effect of Conformation on Activity. *J. Med. Chem.* **1992**, *35*, 1521–5.

(12) May, E. L. Structure Related to Morphine X. A Position Isomer of (±)-3-Hydroxy-N-meththylmorphinan (Racemorphan). *J. Org. Chem.* **1958**, *23*, 947–9.

Scheme V

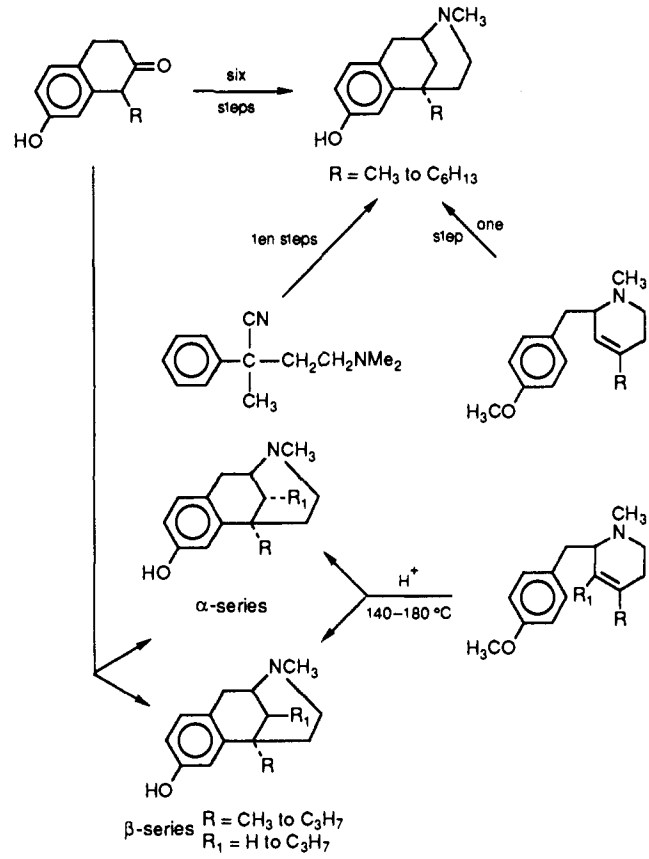


Scheme VI



shown in Scheme V. These precursors (II) shown at the bottom right were prepared from appropriately substituted pyridine methiodides (I) by either of two sequences. The better of the two involved $NaBH_4$ reduction of the pyridine methiodides followed by quaternization with 4-methoxybenzyl chloride and Stevens rearrangement with phenyllithium. The alternative method consisted of a Grignard reaction and subsequent borohydride reduction. Both possible racemates, initially designated α (VIII) and β (IX) were produced from these precursors in a ratio of about 10:1 as shown in Scheme VI. The lesser β-compounds were much more potent as μ agonists. NMR measurements along with reaction rates with methyl iodide proved that the 9-alkyl groups were axial for the predominant α-isomer and equatorial for the β-isomer, with the hydroaromatic ring as reference point.[13] Scheme VII depicts the various routes used to synthesize the 5-monoalkyl as well as the 5,9-dialkyl-6,7-benzomorphans.

Scheme VII



Initially phenylacetonitrile and/or β-tetralone and analogs were used for the 5-alkyl compounds. Later, β-tetralones and the aforementioned 2-benzyltetrahydropyridines served as intermediates for the mono- and dialkyl compounds.

Once again optical resolution effected a favorable separation of pharmacological actions. Invariably, the (−)-isomer of the α-series, whose absolute stereochemistry has been determined in several laboratories to be 1*R*,5*R*,9*R* [identical to that of morphine and the (−)-morphinans at the three common centers of chirality] were 2–3 times more potent than the racemates and morphine and would not support morphine dependence in rhesus monkeys. In fact, *all* shown in Table I,[14] and a few others[15] like nalorphine, exacerbated and/or precipitated withdrawal symptoms. They bind to μ opioid receptors and to the guinea pig ileum, again similar to nalorphine. In humans, the 5,9-dimethyl compound, (−)-metazocine, was at least as good as morphine in pain relief but caused somewhat less tolerance and dependence production.[16] The (+)-isomers, in equal surprise were, in all but one instance [(+)-metazocine], codeine-like antinociceptively and in the morphine-dependent monkey. 5-Monoalkyl compounds were somewhat less potent than corresponding 5,9-dialkyl homologs. Also, brain-receptor experiments

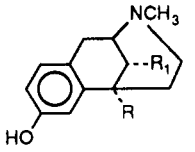
(13) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics. Chemistry and Receptors*; Plenum Press: New York, 1986; pp 196–205.

(14) Ager, J. H.; Jacobson, A. E.; May, E. L. Separation of Morphine-like Effects by Optical Resolution. Levo Isomers as Strong Analgetics and Narcotic Antagonists. *J. Med. Chem.* **1969**, *12*, 288–9.

(15) May, E. L.; Takeda, M. Optical Isomers of Miscellaneous Strong Analgesics. *J. Med. Chem.* **1970**, *13*, 805–7.

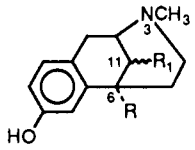
(16) Eddy, N. B.; May, E. L. *Synthetic Analgesics Part II (B). 6,7-Benzomorphans, International Series of Monographs in Organic Chemistry*; Pergamon Press: Oxford, 1966; Vol. 8, pp 153–5.

Table I. Analgesic Activity, Physical Dependence Capacity, and Antagonistic Potency of Some Benzomorphan Enantiomers



R	R_1	enantiomer	ED_{50}, mg/kg	PDC	antagonistic potency
Me	Me	(−)	0.6	no	1/50–1/30 nalorphine
		(+)	inact.	no	no
Et	Et	(−)	1.2	no	1/10 nalorphine
		(+)	7.5	intermed	no
Pr	Me	(−)	0.8	no	1/5 nalorphine
		(+)	12.3	high	no
Et	H	(−)	0.6	no	1/40–1/20 nalorphine
		(+)	21.8	low	no
Me	H	(−)	1.8	no	1/50 nalorphine
		(+)	22.9	very low	no
morphine			1.2	high	no
codeine			7.5	intermed	no

Chart IV



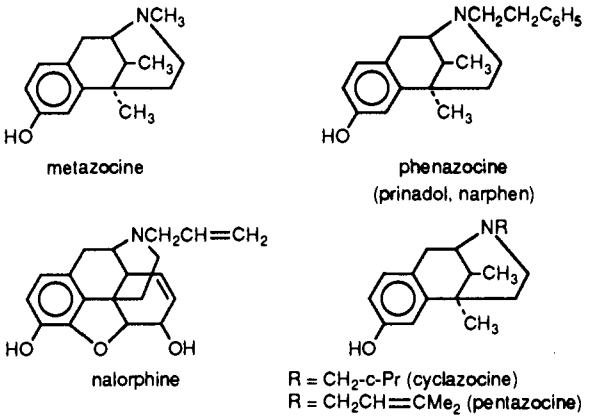
	ED_{50}, mg/kg
1, R = Me, R_1 = H	3.2
2, R = R_1 = H	4.5
3, R = Me, R_1 = 9α-Me	1.2
4, R = H, R_1 = 9α-Me	4.3
5, R = CH_3, R_1 = 9β-Me	0.1
6, R = H, R_1 = 9β-Me	1.1

by Pert and Snyder[17] supported the agonst–antagonist behavior shown by the *levo*-benzomorphans in vivo.

In Chart IV are given data obtained for 6,7-benzomorphans with a tertiary rather than quaternary carbon (position 5). As is evident, these nonquaternary carbon structures (**2**, **4**, and **6**) are about $^1/_2$ to $^1/_{10}$ as potent antinociceptively as their quaternary carbon counterparts (**1**, **3**, **5**). And, even as the racemates, they are nalorphine-like (agonist–antagonists) in the morphine-dependent monkey.[18] Thus, in these rigid structures, antinociceptive activity is not abolished; in fact, it is reduced only 2- to 10-fold in going from a quaternary to a tertiary carbon in contrast to the less rigid molecules such as pethidine, ketobemidone, and methadone. The fairly complex sequences devised for these nonquaternary carbon benzomorphans have been published.[18]

N-Substitution (Chart V) in the racemic α-benzomorphan series produced results similiar, with respect to antinociceptive potency, to those observed with morphine and the morphinans. Phenethyl for methyl increased potency 6–10-fold without, however, a corresponding

Chart V



increase in physical dependence capacity in monkeys where there is a 25–50-fold difference favoring the *N*-phenethylbenzomorphan. Carryover to man was by no means quantitative, although the compound in question, phenazocine, is orally and parenterally effective for deep pain with relatively minimal harmful effects, including abuse liability and those on circulation and respiration.[19] In *N*-alkyl substitution, mixed agonist–antagonists were obtained from *N*-ethyl to *N*-butyl inclusive. However, *N*-pentyl to *N*-octyl-*N*-normetazocines were potent μ agonists. (More about this later.)

The first typical antagonist of the 6,7-benzomorphan series to gain attention was synthesized by Gordon and his associates in 1960.[20] This compound, racemic α-*N*-allyl-*N*-normetazocine (lower right, Chart V, R = allyl), now well-known as SKF 10047, was considered the prototypical σ opioid agonist as a result of the brilliant research of Dr. William Martin at Lexington, KY, on multiple opioid receptors.[21] However, subsequent preparation of its enantiomers at NIH and studies that ensued demonstrated that the (−)-isomer is a strong μ (morphine-like) antagonist, and the (+)-antipode is a non-opioid σ agonist which binds to phencyclidine (PCP) sites. It is similar to PCP in discriminative stimulus properties as determined by Brady and Balster et al.[22] Thus σ is no longer considered a subtype of the opioid receptor. It is now classified as a non-dopaminergic, non-opioid binding site.[23]

In 1964 Archer, Harris, and associates published a scholarly study[24] on N-substitution in the benzomorphan series which heightened interest in agonist–antagonists and led to the development of pentazocine and cyclazocine.[25] This research, no doubt, provided at least part of the stimulus for the ultimate marketing of the strong agonist–antagonists (buprenorphine,[26a] butorphanol,[26b]

(17) Pert, C.; Snyder, S.; May, E. L. Opiate Receptor Interactions of Benzomorphans in Rat Brain Homogenates. *J. Pharmacol. Exp. Ther.* **1976**, *196*, 316–22.

(18) Inoue, H.; Oh-ishi, T.; May, E. L. Synthesis and Pharmacology of 5-Noralkyl-9β-methyl-6,7-benzomorphans and Stereochemistry of Some Intermediates. *J. Med. Chem.* **1975**, *18*, 787–91. Inoue, H.; May, E. L. Synthesis and Pharmacology of 2,9α-2′-hydroxy-6,7-benzomorphan. *J. Med. Chem.* **1976**, *19*, 259–262. Kanematsu, K.; Takeda, M.; Jacobson, A. E.; May, E. L. Synthesis of 6,7-Benzomorphan and Related Nonquaternary Carbon Structures with Marked Analgetic Activity. *J. Med. Chem.* **1969**, *12*, 405–8.

(19) Eddy, N. B.; May, E. L. *Synthetic Analgesics Part II (B). 6,7-Benzomorphans, International Series of Monographs in Organic Chemistry*, Pergamon Press; Oxford, 1966, Vol. 8, pp 142–52.

(20) Gordon, M.; Lafferty, J. J.; Tedeschi, D. H.; Eddy, N. B.; May, E. L. A New Potent Analgetic Antagonist. *Nature* **1961**, *192*, 1089.

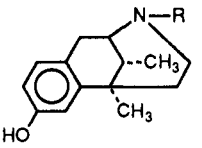
(21) Iwamoto, E. T.; Martin, W. R. Multiple Opioid Receptors. *Med. Res. Rev.* **1981**, *1*, 411–40.

(22) Brady, K. T.; Balster, R. L.; May, E. L. Stereoisomers of N-Allylnormetazocine: Phencyclidine-like Behavioral Effects in Squirrel Monkeys and Rats. *Science* **1982**, *215*, 178–80.

(23) Rothman, R. B.; Reid, A.; Mahboubi, A.; Kim, C.; de Costa, B.; Jacobson, A. E.; Rice, K. C. Labeling by [^{3}H]1,3-Di(2-tolyl)guanidine of Two High Affinity Binding Sites in Guinea Pig Brain: Evidence for Allosteric Regulation by Calcium Channel Antagonists and Pseudoallosteric Modulation by σ Ligands. *Mol. Pharmacol.* **1991**, *39*, 222–32.

(24) Archer, S.; Albertson, N. F.; Harris, L. S.; Pierson, A. K.; Bird, J. G. Pentazocine. Strong Analgesics and Analgesic Antagonists in the Benzomorphan Series. *J. Med. Chem.* **1964**, *7*, 123–7.

Chart VI



(−) and (+), R = H to $C_{10}H_{21}$

σ binding in guinea pig brain (Jacobson–Mattson)
TCP and DAMGO (B.R. Martin et al., MCV)
μ, κ and δ binding, and mouse vas deferens work (Woods, Medzihradsky, Smith)

and nalbuphine[26c]) used for pain relief. Pentazocine, incidentally, was the first agonist–antagonist to be used as an analgesic in clinical practice and is still a schedule IV compound. Cyclazocine is a strong agonist–antagonist and has been a good research tool.[25]

A CPDD program on *N*-alkyl substitution in the benzomorphan series is now in its final stages. It consists of the preparation and extensive testing in vitro and in vivo of 2-H- to 2-decyl(inclusive)-2′-hydroxy-5,9α-dimethyl-6,7-benzmorphans [(−)- and (+)-enantiomers]. Chemical, animal, and some in vitro work is being done at The Medical College of Virginia (MCV) and mostly in vitro studies at NIH and The University of Michigan (Chart VI).

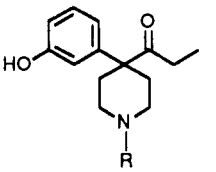
In vivo, in the minus series, *N*-ethyl- to *N*-butyl-*N*-normetazocines are mild agonist–antagonists as stated before and *N*-methyl, -pentyl, -hexyl, -heptyl, and -octyl-*N*-normetazocines are morphine-like (in potency) antincocipetively which (excepting *N*-pentyl) are poor supporters of morphine dependence in monkeys.

The antinociceptive and narcotic antagonist activity of these levo isomers could not be attributed to any single opioid receptor subtype and agonist vs antagonist activity could not be differentiated by opioid receptor subtype. The active agonist or antagonist compounds were those which interacted with both μ and κ receptors. Little selectivity was observed; there was at most a 3-fold difference between displacement at the μ and κ receptors. They were less active at the δ receptors.

As for the (+)-enantiomers, the (+)-*N*-methyl had significant effects on PCP-binding sites and *N*-butyl, -pentyl, -heptyl, and -octyl were exceptionally potent at σ receptors; the heptyl and octyl homologs are among the most potent σ ligands yet discovered. Furthermore, there is a good separation between interaction with σ and PCP sites ranging from about 200-fold for the (+)-*N*-butyl to 900-fold for *N*-pentyl. Thus, these compounds are of potential interest for future in vivo work on the physiological function of σ receptors and the distinction between the σ1 and σ2 subtypes of receptors.[27]

Attempts to prepare antagonists at NIH from the agonist (strong analgesic) ketobemidone [4-(*m*-hydroxyphenyl)-4-(1-oxopropyl)-1-methylpiperidine] by replacement of methyl on nitrogen with allyl, cyclopropylmethyl, ethyl, propyl, or butyl resulted only in producing weak to

Chart VII



R = $-CH_2CH{=}CH_2$, $-CH_2$—◁, -Et, -Bu, -Pent, -Hex, -Hept, -Oct, -Non, -Dec.

compd	R	hot-plate analgesic: ED_{50}, μM	inhibition of [^{3}H]naloxone binding (1 nM): ED_{50}, nM: no sodium	100 mM sodium	ratio of +NaCl/−NaCl
1	methyl	2.1 (1.4–2.8)	7–10	70	7–10
2	ethyl	67.2 (52.0–87.0)	400	1500–2000	3.8–5
3	propyl	16.0 (13.2–19.1)	200	800–1000	4–5
4	butyl	4.6 (3.8–5.9)	50	800–700	12–14
5	pentyl	0.78 (0.62–1.0)	8	30	3.8
6	hexyl	7.5 (5.5–10.3)	20	40	2
7	heptyl	9.0 (7.0–11.6)	20	40–50	2–2.5
8	octyl	26.5 (20.2–34.9)	200	200	1
9	nonyl	inactive	700	700	1
10	decyl	inactive	500	600–700	1.2–1.5

relatively strong μ-like agonists without antagonist effects. However, *N*-pentyl-*N*-norketobemidone is a morphine-like antinociceptive agent in mice with atypical properties of antagonism in the morphine-dependent monkey. *N*-Hexyl- and *N*-heptylnorketobemidones are between ketobemidone and pethidine in antinociceptive potency and are also moderately potent antagonists in monkeys.[28] *N*-Octyl to *N*-decyl are relatively inert.[29] For the homologous *N*-alkyl compounds (*N*-methyl to *N*-decyl), there is a statistically significant correlation of antinociceptive activity (hot plate and Nilsen tests) and capacity to bind to mouse-brain homogenates as determined by Pert and Snyder (Chart VII).[29]

Now, regarding studies in cannabinoid-receptor chemistry, mentioned in the 1991 fall newsletter of the Division of Medicinal Chemistry, my only contribution here came from my having the good sense to listen to and heed the late, great Ed Smissman. He informed me in the early 1970's that he was about to award the Ph.D. degree to Ray Wilson whom he characterized as an excellent postdoctoral candidate. In due course, Ray came to NIH and devised a program of synthesis in the cannabinoid area. It was his thesis (and his reasoning was sound) that the 9-methyl substituent of Δ^8- Δ^9-THC might not be essential for activity. Accordingly, Ray synthesized 9-nor-Δ^8-THC (1, Chart VIII)[30] which was shown by Martin and Dewey and their colleagues to have a profile of biologic activity very similar to that of Δ^8- and Δ^9-THC with nearly equal potency. Ray also synthesized, among other THC analogs, 9-nor-9α- and -9β-hydroxyhexahydrocannabinols (2) intermediates to the 9-nor-Δ^8-THC. The β compound [(−)-isomer] proved to be a potent antinociceptive agent (hot plate and Nilsen tests) in mice while both the α- and β-racemates displayed strong cannabinoid effects in mice and dogs again as demonstrated by Martin and Dewey.[31]

(25) Harris, L. S.; May, E. L. Agonist-Antagonist Analgesics. Historical Introduction and Review of Chemistry. *Drug Alcohol Depend.* **1985**, *14*, 227–32.

(26) (a) Lewis, J. W. Buprenorphine. *Drug Alcohol Depend.* **1985**, *14*, 363–72. (b) Pachter, I. J.; Evans, R. P. Butorphanol. *Drug Alcohol Depend.* **1985**, *14*, 325–38. (c) Schmidt, W. K.; Tam, S. W.; Schotzberger, G. S.; Smith, Jr., D. H.; Clark, R.; Vernier, V. C. Nalbuphine. *Drug Alcohol Depend.* **1985**, *14*, 339–62.

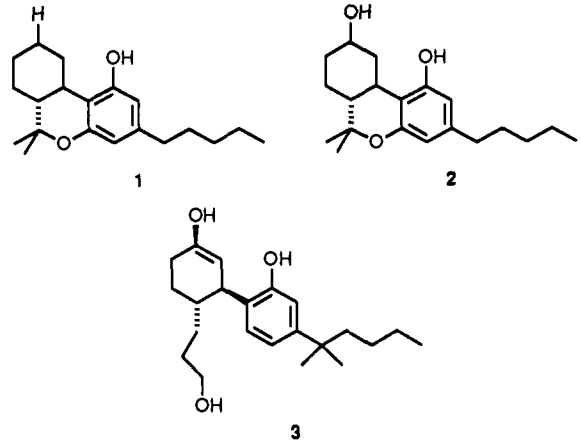
(27) Manuscript on chemical, in vivo, and in vitro data (jointly from MCV, NIH, and The University of Michigan) to be submitted to *J. Med. Chem.* in the near future.

(28) Oh-ishi, T.; May, E. L. N-Alkylnorketobenidones with Strong Agonist and Weak Antagonist Properties. *J. Med. Chem.* **1973**, *16*, 1376–78.

(29) Wilson, R. S.; Rogers, M. E.; Pert, C. B.; Snyder, S. H. Homologous N-alkylnorketobemidones. Correlation of Receptor Binding with Analgesic Potency. *J. Med. Chem.* **1975**, *18*, 240–2.

(30) Wilson, R. S.; May, E. L. 9-Nor-Δ^8-tetrahydrocannabinol, a Cannabinoid of Metabolic Interest. *J. Med. Chem.* **1974**, *17*, 476–7.

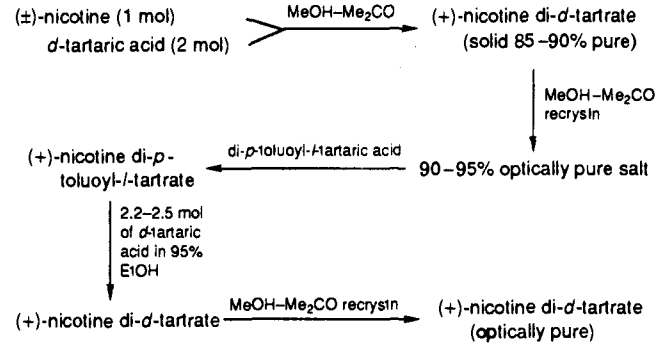
Chart VIII



These findings were brilliantly exploited (in the unselfish and ethical sense, of course) by Johnson, Melvin, and Milne.[32] They developed a large series of bicyclic cannabinoids (with retention of the alicyclic hydroxyl substituent) far more potent as analgesics than morphine. They radiolabeled one of these, designated CP 55,490, which enabled Howlett et al. to characterize, for the first time, a cannabinoid binding site.[33] The localization of this binding site in brain by Herkenham et al.[34] ultimately played a crucial role in the cloning of the cannabinoid receptor by Matsuda et al.[35]

And finally, let me relate a few more of my activities just prior to and after joining the Department of Pharmacology and Toxicology at MCV. About 1975 while I was still at NIH, Drs. Mario Aceto and Lou Harris at MCV asked if we could supply about 1 g each of unnatural, (+)-morphine and -codeine for studies in rodents and morphine-dependent monkeys. We knew that sinomenine, with the opposite stereochemistry of morphine and similar opium alkaloids at all chiral centers had, in the mid-fifties, been converted in low yield and in small quantities to (+)-codeine and (+)-morphine by Goto and Yamamoto.[36] Through a good connection at the Tanabe Laboratories in Japan, namely Dr. Mikio Takeda, a former, brilliant visiting scientist in my laboratory at NIH, we were able to procure 50 g of (−)-sinomenine and put it in the capable hands of Ken Rice. Dr. Rice had, a few years earlier, joined The Section on Medicinal Chemistry, NIH, as a Staff Fellow. He and Dr. I. Iijima, another visiting scientist from Japan, altered and vastly improved Goto's eight-step synthesis and ultimately supplied (+)-codeine and (+)-morphine in sufficient quantities for thorough testing

Scheme VIII



Aceto, Martin, et al. J. Med. Chem. 1979, 22, 174.

in vivo and in vitro.[37] Ken went on from there to devise and implement an elegant and practical total synthesis of (−)-morphine and congeners as well as the important (+)-enantiomers.[38]

Enantioselectivity for morphine, in vivo and in vitro was at least 10 000-fold.[39] This seemed to whet interest at MCV in the unnatural, (+)-isomer of nicotine. One of my first tasks at MCV early in 1977 was to provide optically pure (+)-nicotine, hitherto available in minute quantities only, from naturally occurring but scarce (+)-nornicotine. The (+)-nicotine obtained from optical resolution of racemic nicotine had never been better than 98% optically pure. Thus, pharmacological and biochemical studies to determine enantioselectivity were always in some doubt. Drs. Ted Sanders and Jeff Seeman at Philip Morris in Richmond gave us 5 g of (±)-nicotine (they later supplied 10 g more), which is now readily obtained by an improved racemization procedure.[40]

By use of a combination of resolving agents as shown in Scheme VIII, optically pure (100% ee) (+)-nicotine was obtained. Natural (2*R*,3*R*)-(+)-tartaric acid was used in the first stage and the di-*p*-toluic acid ester of natural tartaric acid in the second. It was important that the nicotinic acid salt of the latter could be converted directly to the di-(+)-tartrate salt of (+)-nicotine, eminently suitable for testing. By the same token, the di-(−)-(2*S*,3*S*)-tartrate salt of (−)-nicotine is a stable, water-soluble salt, suitable for study.[41] With (+)-nicotine in hand in substantial quantitites, researchers at MCV (Martin and Aceto[42] and Rosecrans[43]) were able to demonstrate that enantioselectivity in vivo was not nearly as good as hoped.[42] The natural isomer was 7–100 times more potent than

(31) Wilson, R. S.; May, E. L.; Martin, B. R.; Dewey, W. L. 9-Nor-9-hydroxyhexahydrocannabinols. Synthesis, Some Behavioral and Analgesic Properties and Comparison with the Tetrahydrocannabinols. *J. Med. Chem.* **1976**, *19*, 1165–7.

(32) Howlett, A. C.; Johnson, M. R.; Melvin, L. S.; Milne, G. M. Nonclassical Cannabinoid Analgetics Inhibit Adenylate Cyclase: Development of a Cannabinoid Receptor Model. *Mol. Pharmacol.* **1988**, *33*, 297–302. Johnson, M. R.; Melvin, L. S. The Discovery of Nonclassical Cannabinoid Analgetics. In *Cannabinoids as Therapeutic Agents*; Mechoulam, R.; Ed.; CRC Press: Boca Raton, FL, 1988; pp 121–145.

(33) Devane, W. A.; Dysarz, F. A.; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. Determination and Characterization of a Cannabinoid Receptor in Rat Brains. *Mol. Pharmacol.* **1988**, *34*, 605–13.

(34) Herkenham, M.; Lynn, A. B.; de Costa, B. R.; Richfield, E. K. Neuronal Localization of Cannabinoid Receptors in the Basic Ganglia of the rat. *Brain Res.* **1991**, *547*, 267–74.

(35) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA. *Nature* **1990**, *346*, 561–4.

(36) Goto, K.; Yamamoto, I. See citations in ref 37.

(37) Iijima, I.; Rice, K. C.; Silverton, J. V. Studies in the (+)-Morphinan Series I. An Alternate Conversion of (+)-Dihydrocodeinone into (+)-Codeine. *Heterocycles* **1977**, *6*, 1157–65. Iijima, I.; Minamakawa, J.-I.; Rice, K. C.; Jacobson, A. E.; Brossi, A. Studies in the (+)-Morphinan Series IV. A Markedly Improved Synthesis of (+)-Morphine. *J. Org. Chem.* **1978**, *43*, 1462–3.

(38) Rice, K. C. The Development of a Practical Total Synthesis of Natural and Unnatural Codeine, Morphine and Thebaine. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H., Eds., Springer-Verlag: New York, 1985; pp 191–203.

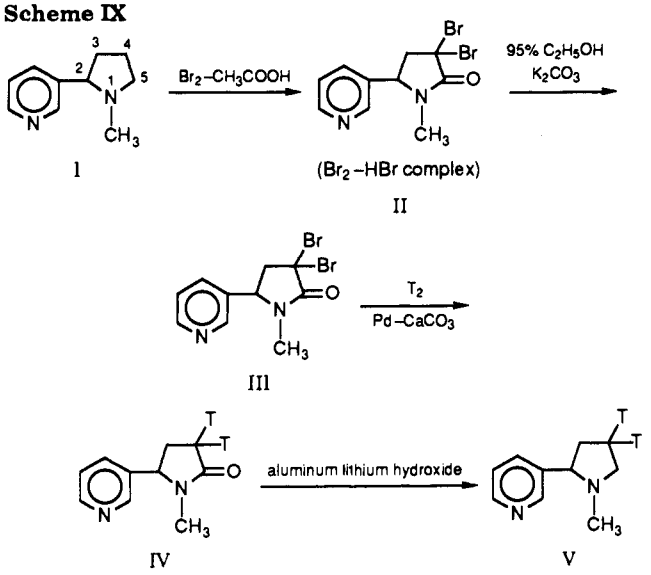
(39) Jacquet, Y. F.; Klee, W.; Rice, K. C.; Iijima, I.; Minamakawa, J.-I. Stereospecific and Nonstereospecific Effects of (+)- and (−)-Morphine: Evidence for a New Class of Receptors? *Science*, *1977*, 198, 842–5.

(40) Bowman, E. R.; Mckennis, Jr., H.; Martin, B. R. A Convenient Method for the Preparation of Racemic Nicotine. *Synth. Commun.* **1982**, *12*, 871–9.

(41) Aceto, M. D.; Martin, B. R.; Uwaydah, I. M.; May, E. L.; Harris, L. S.; Isazola-Conde, C.; Dewey, W. L.; Bradshaw, T. J.; Vincek, W. C. Optically Pure (+)-Nicotine from (±)-Nicotine and Biological Comparisons with (−)-Nicotine. *J. Med. Chem.* **1979**, *22*, 174–7.

(42) Aceto, M. D.; Martin, B. R.; May, E. L. In *Handbook of Stereoisomers: Drugs in Psychpharmacology*; Smith, D. F., Ed.; CRC Press: Boca Raton, FL, 1983; pp 67–78.

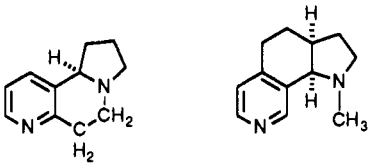
Scheme IX



I II III IV V

α-(−) and β-(+) series (Scheme I)

Chart IX



1 2

(+)-nicotine in a variety of tests, far less than noted for the larger, more rigid morphine types.[39] Actually, Aceto showed with Dreiding models that some conformations of the nicotine enantiomers were close to superposable.[42] Furthermore, binding studies by Martin and co-workers with ditritiated (+)- and (−)-nicotines, prepared as shown in Scheme IX, indicated only a 3-fold difference in affinities.[44]

The foregoing did, however, serve as a stimulus for evaluation of the nicotine pharmacophore. From an agonist point of view Awaya, Suchocki, and Glassco, have synthesized a number of nicotine congeners, most notably two conformationally restrained (bridged) nicotines.

Structure 1 (Chart IX) was first synthesized by Catka and Leete.[45] By a modification of his synthesis, we obtained 1 in low yield and prepared the enantiomers with (+)- and (−)-tartaric acids. In our hands neither the racemate nor the antipodes had substantial nicotinic activity except in the guinea pig ileum where there was, however, a 3–12-fold reduction in activity and less stereoselectivity than that observed with (+) and (−)-nicotine.[46] Compound **2**,[47] on the other hand, as the racemate, is nearly as potent as (−)-nicotine in the tail-flick test for antinociception and reduction of spontaneous activity. Results are not yet available for the enantiomers of **2**. Drug-discrimination studies by Rosecrans at MCV indicated that **2** potentiates, but does not itself produce, a nicotine-like response.[48] We also undertook an assessment of the nicotine antagonist, mecamylamine, and analogs. These studies have largely shown that mecamylamine is most probably acting at a site other than the nicotine receptor. Our current research is designed to characterize the pharmacophore for mecamylamine and active analogs.[49]

Chart X. Foreign Visiting Scientists

Japan	England	India
H. Awaya	C. Chignell	B. C. Joshi
I. Iijima	S. Fullerton	M. F. Rahman
H. Inoue	R. Parfitt	G. Thyagarajan
T. Ishimaru		
K. Kanematsu	Italy	South Africa
H. Kugita		
T. Oh-Ishi	M. Iorio	L. Clingman
S. Saito		
S. Shiotani		
M. Takeda		
Staff Fellows (at NIH)		**Postdoctorals (at MCV)**
L. Getsiv		W. Glassco
M. Mokotoff		J. Suchocki
H. Ong		I. Uwaydah
K. Rice		W. Vincek
M. Rogers		P. Zenk
R. Wilson		

In closing I acknowledge, with many thanks, the strong support and collaboration of several talented visiting scientists, and staff fellows (Chart X) and past and present colleagues and friends at NIH, particularly Arthur Jacobsen, Ken Rice, Marienna Mattson, Werner Klee, and Dick Streaty. I thank heartily also, especially Lou Harris (who provided me, during the last 15 years, a second scientific home at MCV), Bill Dewey, Mario Aceto, Ed Bowman, Billy Martin, Bob Balster, and John Rosecrans along with their effective supporting groups and four postdoctoral fellows, Drs. Uwaydah, Vincek, Awaya, and Zenk. Bill Glassco, at present a postdoctoral fellow, in the Department of Pharmacology and Toxicology, MCV, is also due my gratitude. And last, but far from least, Joyce Pye, Sussie Robinson, and Laura Johnson, Dr. Harris's cooperative, effective office staff, deserve my heartfelt thanks.

(43) Rosecrans, J. A. Nicotine as a Discriminative Stimulus: A Neurobiological Approach to Study Central Cholinergic Mechanisms. *Journal Substance Abuse*, **1989**, *1*, 287–300.

(44) Vincek, W. C.; Martin, B. R.; Aceto, M. D.; Tripathi, H. L.; May, E. L.; Harris, L. S. Synthesis of 4,4-Ditritio-(+)-nicotine: Comparative Binding and Distribution Studies with Natural Enantiomer. *J. Pharm. Sci.* **1981**, *70*, 1292–3.

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(47) Glassco, W.; Suchocki, J.; May, E. L.; Martin, B. R. Chemical and Pharmacological Results to be submitted to *J. Med. Chem.*

(48) Rosecrans, J. A. Personal communication.

(49) Suchocki, J.; May, E. L.; Martin, T. J.; George, C.; Martin, B. R. Synthesis of 2-*exo*- and 2-endo-Mecamylamine Analogues. Structure-Activity Relationships and Nicotinic Antagonism in the Central Nervous System. *J. Med. Chem.* **1991**, *34*, 1003–10.