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THIRD SMISSMAN AWARD ADDRESS:

Reminiscences and Musings of a Classical Medicinal Chemist

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I am thrilled and highly honored to be the third recipient of the E. E. Smissman Award sponsored by Bristol Laboratories and administered by the Division of Medicinal Chemistry of the American Chemical Society. It is an honor, too, to be following the very large scientific footsteps of the two previous awardees, Corwin Hansch and Alfred Burger. I fear my tracks are much smaller.

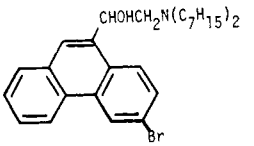
This moment gives me the opportunity to say a few words about the man in whose memory the award was established. As many of you here know, Professor Smissman was not only an outstanding scientist, scholar, educator, and administrator, he was also a warm, considerate, genteel person. It has been my good fortune to have known him well and to be the beneficiary of three talented postdoctoral students expertly trained by Professors Mertes, Grunewald, and Borchardt in the outstanding department Professor Smissman so prudently fashioned and directed.

So, may I express my deep gratitude to the Awards Committee, Bristol Laboratories, the Division of Medicinal Chemistry of the American Chemical Society, and to my many advisors and colleagues, past and present, all of whom have made this memorable occasion possible for me.

In pondering a topic and contents for this address, my first thoughts were to summarize the highlights of my research as an organic chemist. But on further reflection, I realized that there were few, if any, highlights, mainly plodding efforts. Furthermore, it was a fairly safe assumption that many of you would already have suffered through one or more such summaries, and it would be inconsiderate of me to subject you to this again. Nevertheless, I have, for various reasons, decided on only a minor compromise. With your indulgence, I should like to present a little history and then a brief account of what I consider to be some of the more interesting aspects of my research career while including some personal reflections. I apologize to those of you who had the patience to listen before and hope I can add a little that is new and different.

I am not certain that the adjective in the title is appropriate, but I decided to give myself the benefit of a good deal of doubt, using "classical" rather that the less attractive empirical, traditional, or perhaps even prosaic. In any event, I cannot claim sophisticated rationale as the basis for the research to be described but have relied simply on conventional structure–activity information and trial and error tactics with perchance a sprinkling of intuition and a hope that serendipity would "bail me out" from time to time. This is not to discourage or disparage the young superbly trained medicinal chemists being graduated today. It is my belief that they are utilizing well the up-to-date trends and present-day sophistication of chemistry, biochemistry, pharmacology, and allied disciplines to improve their chances for success in this keenly competitive world.

Chart I



Antimalarial

Since the beginning of my predoctoral training at the University of Virginia related to the development of improved morphine and codeine substitutes, compounds that affect the central nervous system have been my main interest. However, there was a hiatus of 9 years, nearly 3 of which were spent in an industrial setting when vitamins of the B complex and textile assistants were the focus of attention. During the remaining 6 years of this hiatus, after I managed to rejoin at the National Institutes of Health, my former advisors at Virginia, Drs. Lyndon, Small, and Erich Mosettig, malaria and tuburculosis were the principal research themes. This switch from centrally acting analgesics was occasioned by World War II. From the research on malaria came, among other new compounds, a series of phenanthrene alcohols, several of which were essentially quinine-like toward malaria parasites, one in clinical trials. However, nothing of practical importance came of this until scientists at the Walter Reed Army Institute of Research (WRAIR), among them my good friends Drs. Thomas Sweeney and David Jacobus, in their intensive and intelligent program to help combat resistant strains of vivax and the deadly falciparum malaria, during our involvement in Vietnam, resurrected and reinvestigated one of these compounds (Chart I). They found it to be among their most effective agents in curing stubborn

(1) E. E. Smissman Award address presented to the Division of Medicinal Chemistry on Sept 12, 1979, at the 178th National Meeting of the American Chemical Society.

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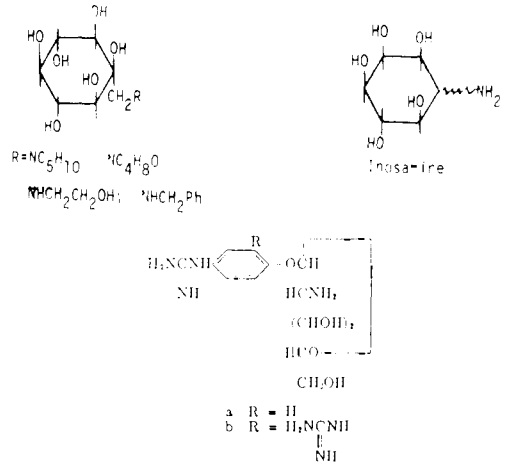
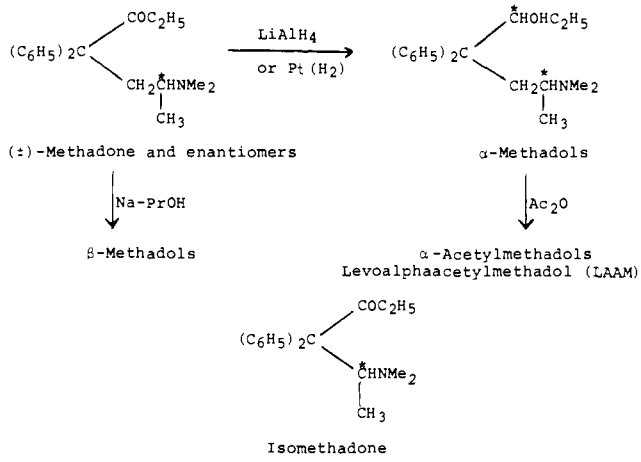
Chart II



Scheme I



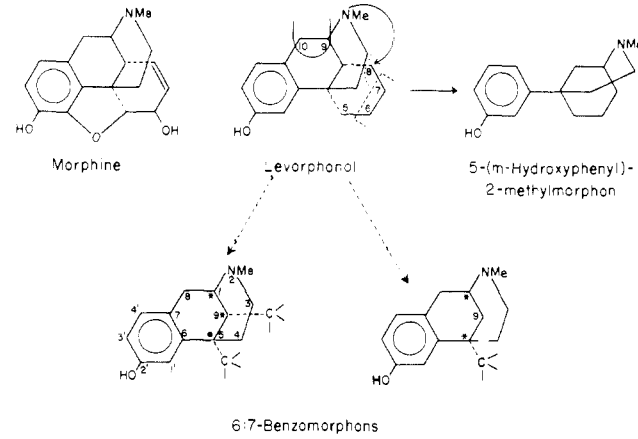
human malarias. This was also to provide the stimulus for further WRAIR-sponsored research and for the development of still more effective antimalarial agents.

Perhaps the lesson to be learned from this is that very simple structures can be effective therapies for medical problems other than those for which they are initially designed. In this instance, the prototypes were intended as potential analgesics.

Our research on synthetic antitubercular agents proved to be nothing more than an interesting chemical excursion in which many amino- and guanidinophenyl glucosides and glucosaminides and amino cyclitols (Chart II) were synthesized as distantly related analogues of the potent antitubercular agent streptomycin. This antibiotic had been discovered by Dr. Selman Waxman at Princeton a few years before. None of our compounds had useful activity against the tubercle bacillus.

By this time we were eager to resume research on pain-relieving agents when the major emphasis was that of improving upon morphine and codeine, particularly with respect to abuse potential, tolerance, and respiratory depression. The synthetic agent methadone developed in Germany in the early 1940's had just "hit" the American scene. It proved to have a morphine-like profile with some advantages and some disadvantages. Our manipulations with methadone (Scheme I) included reduction of the carbonyl group to carbinol, to generate a second asymmetric carbon, and then O-acetylation. If the reduction was effected with $LiAlH_4$ or platinum-catalyzed hydrogen, so-called α-methadols were formed exclusive of β diastereoisomers. O-Acetylation gave very potent, long-acting analgesics. The acetylmethadol resulting from *l*-methadone, levoalphacetylmethadol (LAAM), has been under study for several years as a "maintenance drug" (a substitute for methadone) in formerly heroin-dependent individuals. If the reduction was accomplished with sodium and propanol, the β-alcohols were formed principally, but not to the exclusion, of the α isomers. I hasten to add that almost simultaneously the α compounds were prepared at the Merck and Lilly laboratories. Only we, I believe, prepared and tested the β-methadols and their *O*-acetyl derivatives, which are similar to the α isomers in pharmacologic behavior.[2] These β compounds were never extensively studied. We also synthesized and tested the corresponding alcohols and *O*-acetyl alcohols of the isomethadone series.[3] They were less interesting than those compounds derived from the position isomer, methadone. The complete stereochemistry of the α- and β-methadols and isomethadols has since been determined.[4]

Chart III

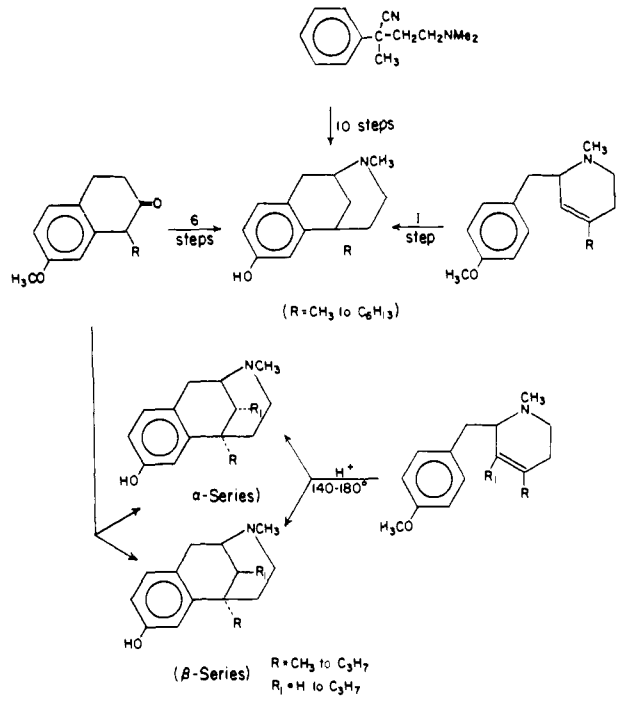


The Korean Conflict erupted about this time (1950), causing a philosophical change in emphasis because of the threat to opium supplies. Opium, as you no doubt know, is the sole commercial source of morphine and codeine. Our charge at NIH now became simply to develop adequate, not necessarily improved, substitutes for morphine and codeine.

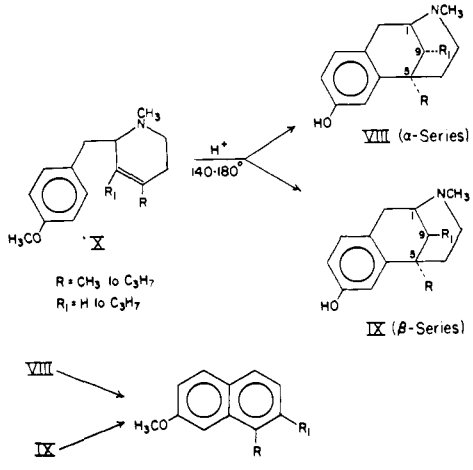
This new charge provided the stimulus for the discovery of the 6,7-benzomorphans, of which levorphanol was our model. This orally and parenterally powerful analgesic was developed by Hoffman-La Roche, Basle,[5] in the mid to late 1940's and was an indirect result of one of the earlier attempts at the total synthesis of morphine by the German chemist Rudolph Grewe.[6] How levorphanol was mentally dissected to give birth to the benzomorphans is shown in Chart III. As you can see, for the former, parts of hydroaromatic ring C (either 2 or 3 carbons) were deleted in such a way as to preserve the integrity of the quaternary carbon and the $N\text{-}CH_3$, two chemical features considered at that time essential for strong analgesic activity. The vestiges of ring C may become methyl or higher alkyl depending on whether the unsaturation left by excision is satisfied with H or C_nH_{2n+1}. Time will not permit a discussion of the stereochemistry of the 6,7-benzomorphans[7]

(2) N. B. Eddy, E. L. May, and E. Masettig, *J. Org. Chem.*, 17, 321 (1952).
(3) E. L. May and N. B. Eddy, *J. Org. Chem.*, 17, 1210 (1952).
(4) P. S. Portoghese and D. A. Williams, *J. Med. Chem.*, 12, 839 (1969); *ibid.*, 13, 626 (1970).
(5) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, 32, 821 (1949).
(6) R. Grewe, *Naturavissinschaften*, 33, 333 (1946).
(7) For an excellent review on benzomorphans including stereochemistry, see D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 77, 1 (1977).

Scheme II



Scheme III



or the various methods of synthesis shown in Scheme II. Suffice it to say that the sequence outlined briefly at the right-center and bottom of Scheme II patterned after Grewe's morphinan synthesis proved to be the most versatile and satisfactory.[7] Later, for special structures, other more complex methods had to be devised.

By the Grewe sequence, shown a little more clearly in Scheme III, a representative number of 2′-hydroxy-5-monoalkyl- and -5,9-dialkyl-α(and β)-6,7-benzomorphans were synthesized and found to elicit (Table I) moderate to strong analgesic activity in the mouse and low or no physical dependence capacity as determined in rhesus monkeys, clearly a separation of morphine-like effects for these two animal species. Many other examples have been added since this table was made several years ago. The α and β designations refer to the stereochemistry of the 9-alkyl substituent, determined initially by NMR and reaction-rate data.

Now, as implied earlier, methyl on nitrogen was for a long time considered sacred for strong antinociceptive activity in morphine-like compounds. In fact, in the early 1940's scientists at Merck had demonstrated that replacement of this methyl with allyl gave a substance, nalorphine, which would antagonize most of the pharmacologic effects of morphine-like analgesics.[8] Some 10–12 years later another group of investigators, also at Merck, in a systematic study of N-substituted normorphines found that phenethyl for methyl markedly increased analgesic potency.[9] A similar substitution of one of our simplest α compounds, normetazocine, gave a product phenazocine, 5–10 times more powerful than the parent metazocine (Chart IV) which for animal species and, to a lesser extent man, had somewhat reduced abuse liability and circulatory depression compared to morphine.[10] It was marketed for

Table I. Pharmacology of (±)-5-Alkyl- and (±)-5,9-Dialkyl-2-methyl-6,7-benzomorphans

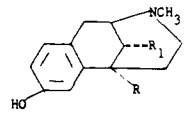
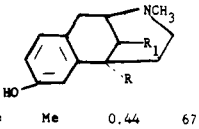
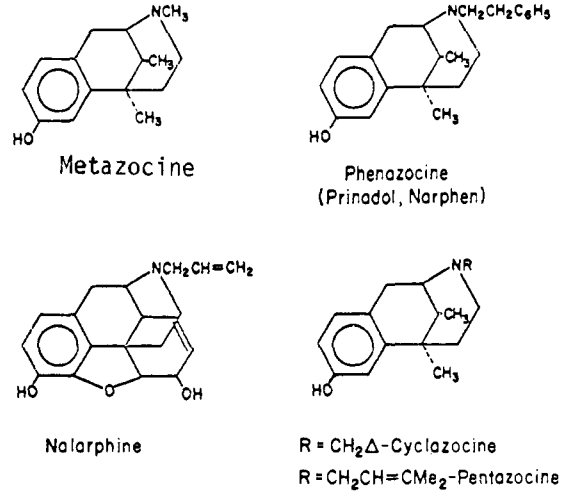
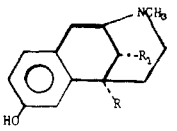
No.	R	R_1	ED_{50}	LD_{50}	Abstinence suppressant dose, mg./kg.	Physical dependence capacity
					-5-Monoalkyl and α-5,9-dialkyl compounds	
1	Me	H	10.4	175	2-60, No suppression	None
2	Et	H	2.3	170	1-16, No suppression	Low
3	Pr	H	2.1	130	3-30, No suppression	None
4	Bu	H	2.0	130		
5	Am	H	3.4	93		
6	Hex	H	10.8			
7	Me	Me	3.0	175	24	Low
8	Me	Et	1.5	134	2-12, No suppression	None
9	Et	Me	4.9	309	>40	Low
10	Et	Et	4.2	425	2-60, No suppression	None
11	Pr	Me	2.9	>300		
12	Pr	Pr	71.2	>400	3-48. No suppression	None
					β-5,9-Dialkyl compounds	
13	Me	Me	0.44	67	>18	Low
14	Me	Et	0.47	100		
15	Et	Me	0.07	75	1.0	Intermediate
16	Et	Et	0.28	120	0.5-12, No suppression	None
17	Pr	Pr	0.87	55	.....	
	Morphine		2.1	550	3	High

Chart IV



(8) J. Weijlard and A. E. Erickson, *J. Am. Chem. Soc.*, **64**, 869 (1942); K. Unna, *J. Pharmacol. Exp. Ther.*, **64**, 869 (1943).
(9) J. Weijlard, P. D. Orahovats, A. P. Sullivan, Jr., G. Purdue, F. K. Heath, and K. Pfister III *J. Am. Chem. Soc.*, **78**, 2342 (1956).
(10) N. B. Eddy and E. L. May, "Synthetic Analgesics", Part II (B), Pergamon Press, New York, 1966, pp 115–192.

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



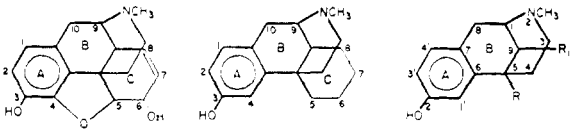
R	R_1	Enantiomer	ED_{50} mg/kg	PDC	Antagonistic Potency
Me	Me	(-)	0.6	No	1/50-1/30 nalorphine
		(+)	Inactive	No	No
Et	Et	(-)	1.2	No	1/10 Nalorphine
		(+)	7.5	Intermediate	No
Pr	Me	(-)	0.8	No	1/5 Nalorphine
		(+)	12.3	High	No
Et	H	(-)	0.6	No	1/40-1/20 Nalorphine
		(+)	21.8	Low	No
Me	H	(-)	1.8	No	1/50 Nalorphine
		(+)	22.9	Very low	No
Morphine			1.2	High	No
Codeine			7.5	Intermediate	No

several years by the Smith-Kline Corp. as Prinadol and is still being prescribed as Narphen by Smith and Nephew, Ltd., England, for both oral and parenteral use.

Although the first benzomorphan antagonist, *N*-allylnormetazocine (SKF 10, 047),[11] was prepared by Dr. Maxwell Gardon and his associates at the Smith Kline & French Laboratories, it remained for a team at Sterling-Winthrop headed by Drs. Louis Harris and Sydney Archer to make a thorough, scholarly study of the effect of substitution at the nitrogen in the benzomorphan series.[12] They, more than any other group, developed and promoted the agonist–antagonist concept of antinociception, which is very prominent in present-day, analgesic-research rationale. This concept was given birth, but not fully appreciated, some 10 years earlier when it was discovered serendipitously that the narcotic antagonist nalorphine also elicited analgesic activity. Practical results of the Sterling-Winthrop research were the weak antagonist, moderately strong agonist pentazocine and the powerful antagonist with equally powerful pain-relieving qualities, cyclazocine. The latter has proved to be a good research tool and may yet find application as an oral analgesic or in narcotic deterrence. About the same time, Professor Marshall Gates, who, at Rochester University, had effected the first total synthesis of morphine, synthesized the counterparts of pentazocine and cyclazocine with 3-hydroxymorphinan.[13]

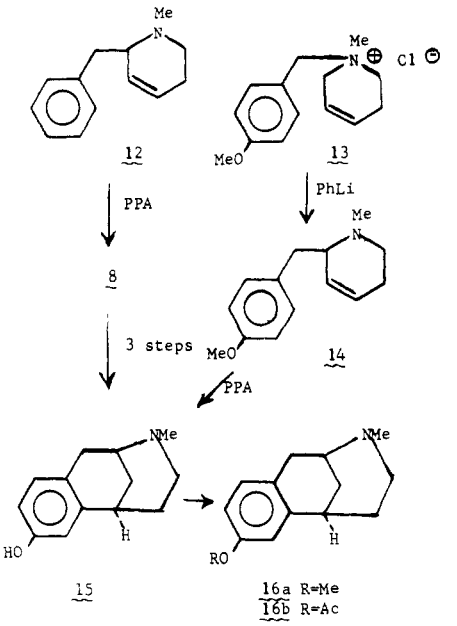
Until now we have said nothing about optical isomerism. Let me remind you that morphine, levorphanol, and nalorphine are all *levorotatory* in the usual laboratory solvents and that their enantiomers are essentially inert in vivo and in vitro. So, in no great stroke of genius, we decided to separate into their enantiomers several of our more interesting racemates. As expected the levo isomers were twice as potent as the correspondence racemates (Table II)[14] and like the racemates would not sustain morphine dependence in rhesus monkeys. Still better, they actually showed nalorphine-like properties in precipitating the morphine abstinence syndrome in these morphine-dependent animals, which was unique for *N*-methyl com-

Chart V



I Morphine (-) II Levorphanol (-) III 6,7-Benzomorphans

Scheme IV



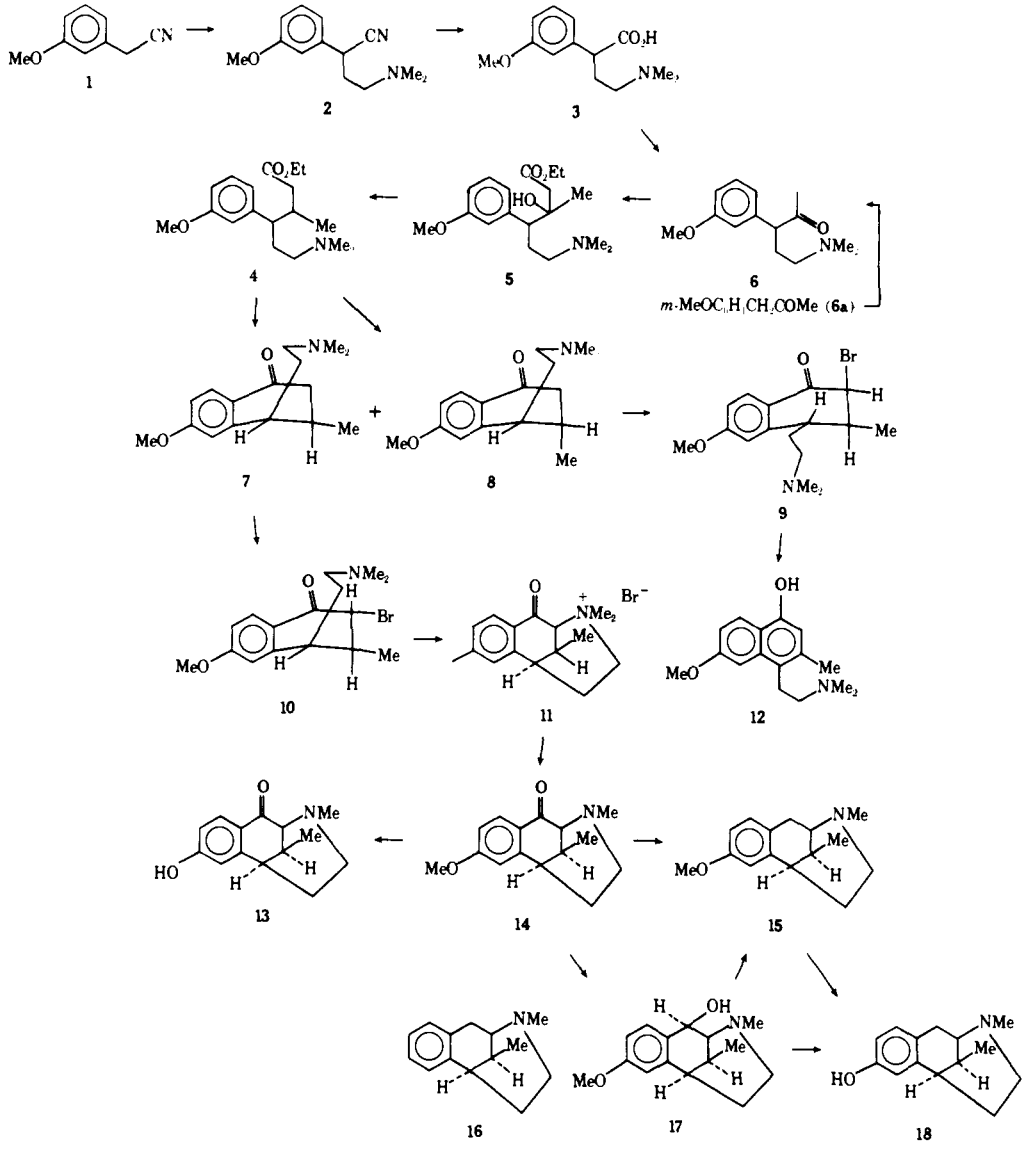
12 13 8 14 15 16a R=Me 16b R=Ac

pounds. The most effective levo isomer in this respect was the 5-methyl-9α-propyl compound, which was one-fifth as potent as nalorphine as an antagonist but stronger than morphine as an antinociceptive agent. Just as surprising was the capacity of four of the five dextro isomers (Table II) to substitute for morphine. Two of the levo isomers proved to be excellent pain-relieving agents in man, but with respect to abuse potential they (metazocine and etazocine) were more like morphine than nalorphine. So the carryover to man from animals with these two compounds was at best qualitative and disappointing. Nevertheless, for these animal species, optical resolution effected an even sharper dissociation of analgesic activity from physical dependence capacity. I might just add that this kind of separation was shown by an optical pair from Dr. Frank Clarke's laboratory[15] and by some of our phenylmorphans[16] which are being studied further by Dr. Michael Rogers at the Medical College of Virginia. I should record also that brain-receptor experiments by Drs. Candace Pert and Solomon Snyder supported the agonist–antagonist behavior seen for the levo isomers in vivo.[17] Why, then, these species differences? One can only speculate that different pharmacokinetics and/or modes of metabolism are responsible for such differences.

As has been stated many times, the quaternary carbon and the N-methylated tertiary nitrogen were, for a long time, considered absolutely essential features for strong analgesic activity. The Merck group, followed by others, having exploded the *N*-methyl theory, we set about to ascertain the importance of the quaternary carbon in rigid structures, fully aware that with the more flexible mole-

(11) M. Gordon, J. J. Lafferty, D. H. Tedeschi, N. B. Eddy, and E. L. May, *Nature (London)*, **192** (no. 4087), 1089 (1961).
(12) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).
(13) M. Gates and T. Montzka, *J. Med. Chem.*, **7**, 127 (1964).
(14) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969).
(15) N. Yokoyama, F. B. Block, and F. H. Clarke, *J. Med. Chem.*, **13**, 488 (1970).
(16) E. L. May and M. Takeda, *J. Med. Chem.*, **13**, 805 (1970).
(17) C. Pert, S. Snyder, and E. L. May, *J. Pharmacol. Exp. Ther.*, **196**, 316 (1976).

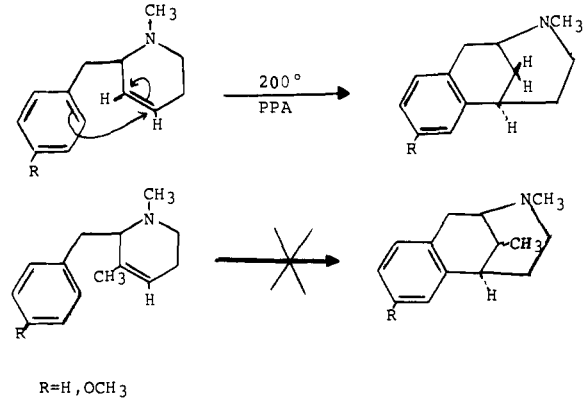
Scheme V



cules (methadone and pethidine) changing the central carbon from quaternary to tertiary does almost completely abolish activity. Of the rigid structures mentioned, only the benzomorphan (Chart V) could be modified in this manner without other major disturbances in structure. Replacement of the alkyl substituent of the 6,7-benzmorphans by H was not as simple a task as predicted. Methods previously described were refractory until Dr. Arthur Jacobson discovered that much higher temperatures and polyphosphoric acid were needed in the cyclization of the precursor α-benyltetrahydropyridines (**12** and **14**) shown in Scheme IV.[18] And even these forcing conditions (PPA, 200 °C) were not effective for producing the 9-methyl compounds with H at position 5 (Chart VI). Apparently, without the inductive and hyperconjugative assistance of the 4-alkyl substituent in the hydrogenated pyridine ring and with apparently counter effects from a 3-methyl substituent, the requisite 4-carbonium ion is not generated.

So, new strategies had to be devised, and it was only through the ingenuity, skill, and patience of two Japanese visiting scientists, Drs. T. Oh-Ishi and H. Inoue, that we were able to obtain the 9α- and 9β-methylbenzomorphans

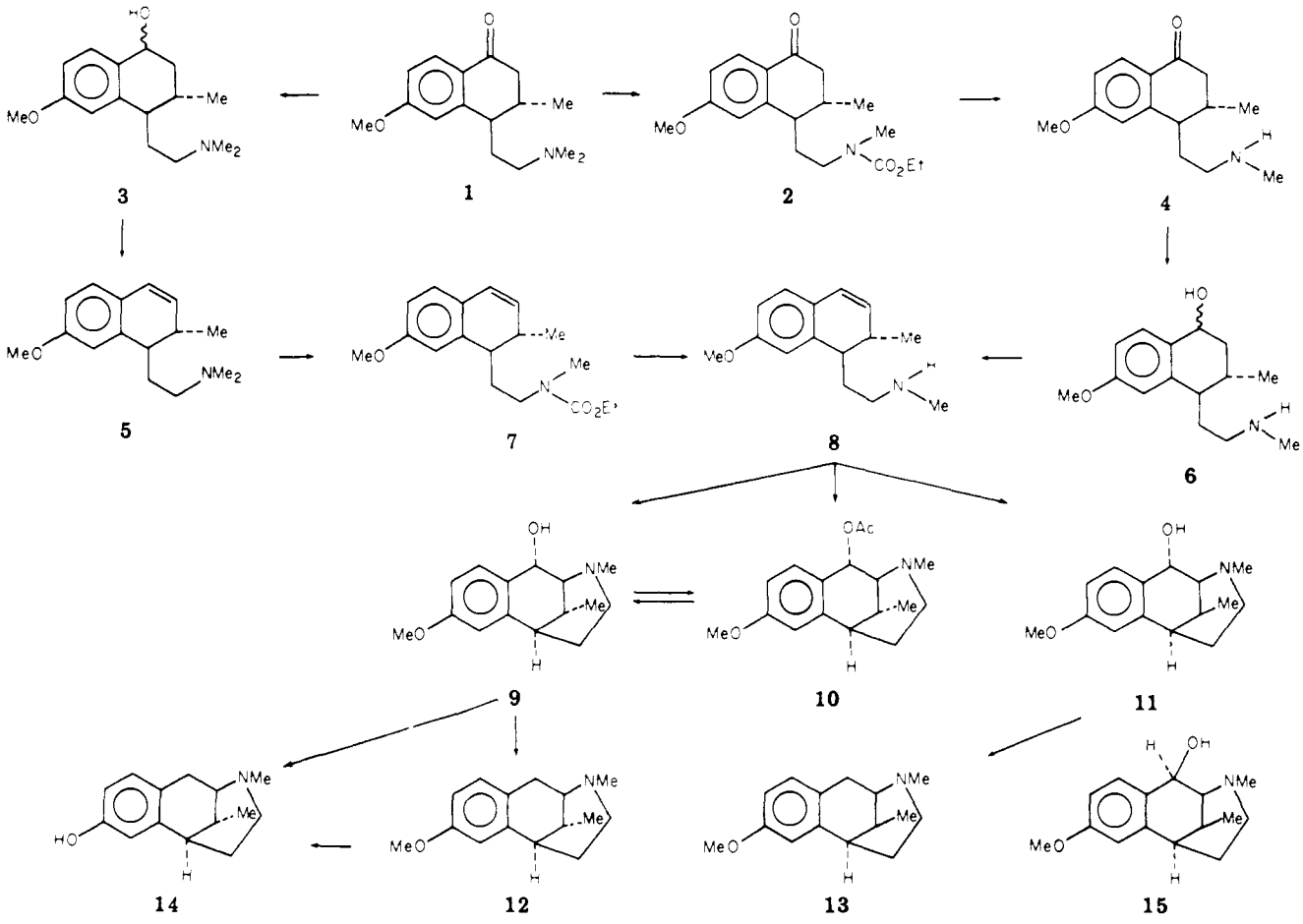
Chart VI



with hydrogen rather than alkyl at position 5. Simple benzene and tetrahydronaphthalene derivatives served as starting materials. For the 9β-methyl compound in the 2′-hydroxy series, the key intermediate is ester **4** (Scheme V), a mixture of diastereoisomers which upon hydrolysis to the corresponding acids and reaction of these acids with polyphosphoric acid gave a mixture of α-tetralones, **7** and **8**. Bromination of **7** to **10** and cyclization of the latter by internal quaternization gave the methobromide **11**, whose conversion to desired compound **18** was routine. NMR and

(18) K. Kanematsu, M. Takeka, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 405 (1970).

Scheme VI

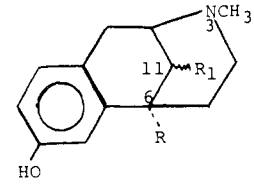


methiodide rate-formation data were adequate to prove the β configuration (for the hydroaromatic ring) of the 9-methyl substituent. Bromination of the isomeric tetralone **8** also proceeded normally to give **9**, which yielded only the naphthalene derivative **12** rather than the expected benzomorphan.

For the 9α diastereoisomer of **18**, compound **14** of Scheme VI,[20] 6-methoxy-α-tetralone, **1**, was the starting point and dihydronaphthalene **8** the key intermediate. Treatment of **8** with $Hg(OAc)_2$ in aqueous THF gave a 41% yield of 9α-hydroxy-9α-methylbenzomorphan (**9**), 13% of the corresponding acetate (**10**), and 5% of the 9α-hydroxy-9β-methyl isomer (**11**). Conversion of **9** to the desired **14** either directly (HI plus P) or in two steps (hydrogenolysis plus O-demethylation) proceeded well.

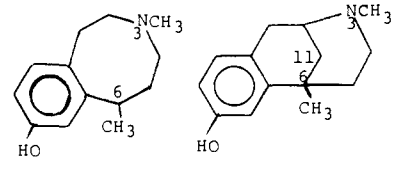
Chart VII gives a comparison of the antinociceptive activity of 6,7-benzomorphans with and without the quaternary carbon. Compounds **2**, **4**, and **6** with H at position 6, although somewhat reduced in potency from the corresponding 6-methyl[19] relatives **1**, **3**, and **5**, respectively, are nevertheless moderately to strongly active. Furthermore, all three *nonquaternary*-carbon compounds as the racemates show mixed agonist–antagonist action in the morphine-dependent monkey, similar to levo isomers (not the racemates) in the 5-alkyl series.[20] These racemates would seem to warrant further study. Since Gless and Rapoport[21] have just published what appears to be more practical syntheses for the 9α- and 9β-methyl compounds, this may be possible.

Chart VII



1. R=Me, R_1=H	ED_{50}	3.2 Mg/Kg
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

Chart VIII

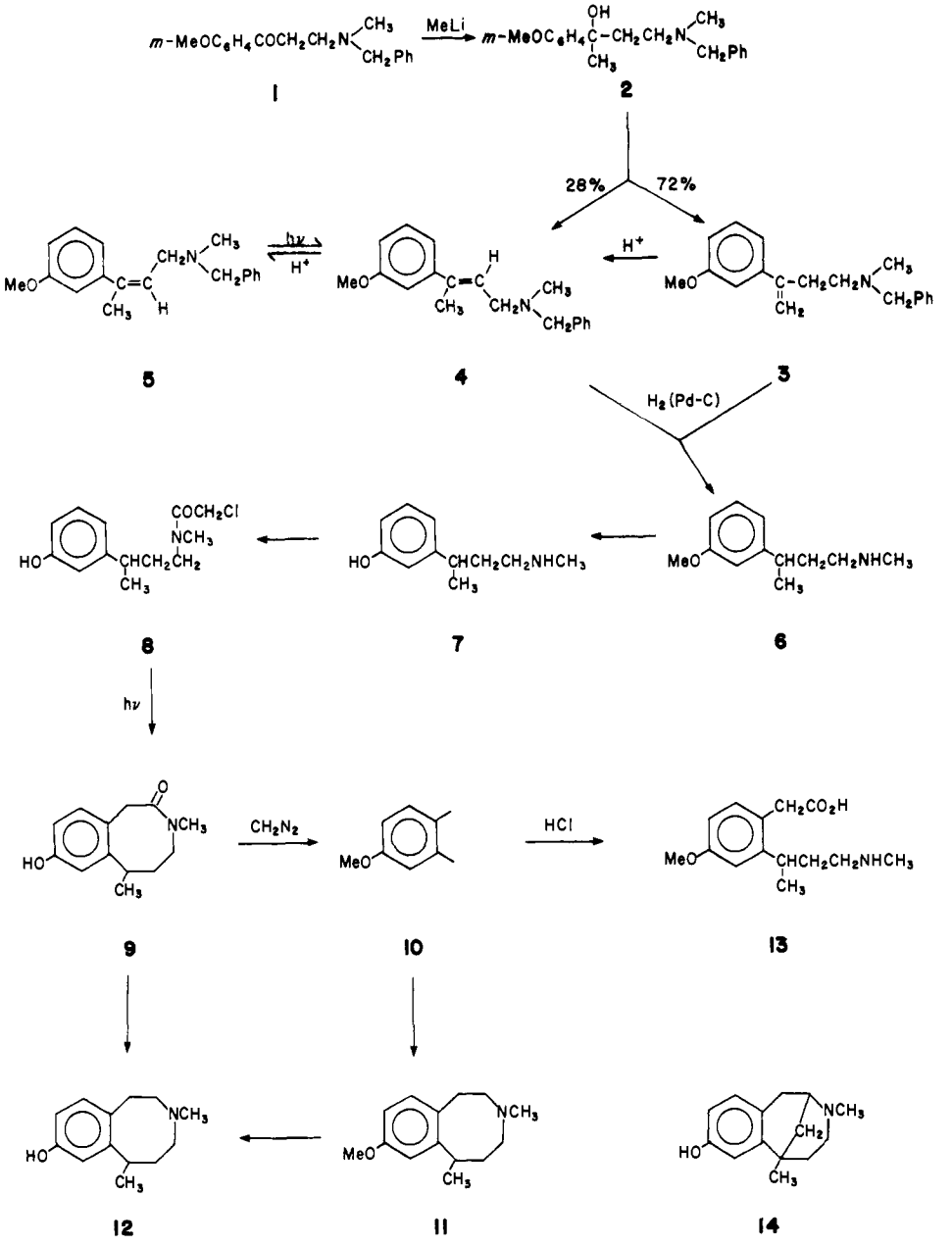


ED_{50} 12.5 ED_{50} 3.2

Finally, let me show you the effect of deleting the methylene bridge, a ploy that not only changes the erstwhile 5 carbon from quaternary to tertiary but also slightly reduces rigidity. Scheme VII[22] depicts the synthesis of

(19) H. Inoue, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, 18, 787 (1975).
(20) H. Inoue and E. L. May, *J. Med. Chem.*, 19, 259 (1976).
(21) R. D. Gless and H. Rapoport, *J. Org. Chem.*, 44, 1324 (1979).
(22) H. H. Ong and E. L. May, *J. Org. Chem.*, **38**, 924 (1973).

Scheme VII



such a compound (**12**), a 3-benzazocine lacking the methano bridge, obtained by photocylization of the benzene intermediate 8 and subsequent $LiAlH_4$ reduction and HBr O-demethylation. The inventor, architect, and builder of **12** was Dr. Helen Ong, then a Staff Fellow at NIH.

Chart VIII shows the reduction in activity resulting from eliminating the methano group. At Hoffman-La Roche, Nutley, Drs. Ben Pecherer and Arnold Brossi and their colleagues[23] made similar 3-benzazocines, with carbon-6 again quaternary (i.e., 6,6-dialkyl-substituted compounds). The antinociceptive potency of these was somewhere between 6-alkyl-3-benzazocines and the 5-alkyl-6,7-benzomorphans.

In this rambling account, I have suggested how World War II and the Korean Conflict affected emphasis and direction of research programs. Vietnam hostilities were also not without influence and, indeed, caused revitalization of antimalarial research, as suggested earlier, and increased awarness of the extensive overuse and abuse of drugs especially in the armed services. This, without a doubt, gave further impetus to narcotic maintenance programs involving methadone. At present, about 75 000 formerly heroin-dependent individuals are being satisfactorily maintained on a 40–100-mg daily oral dose. A derivative, *l*-α-acetylmethadol (LAAM), was mentioned earlier as a possible substitute for methadone because it is somewhat more potent and has a longer duration of action. General toxicity and clinical studies, sponsored by the National Institute of Drug Abuse, were sharply accelerated during the peak of the Vietnam War, and it is now believed that a 20–30-mg oral dose taken three times per week would be just as satisfactory as methadone given every day.

I would not consider these remininscences complete if I did not share with you some of my feelings since retiring from NIH after 35 pleasant years there and joining Dr. Louis Harris' fine Department of Pharmacology at the Medical College of Virginia. Doing a little trouble shooting in chemistry, interacting with faculty and students in

(23) A. Brossi, B. Pecherer, and S. Silbiger, German Patent 2353062, May 9, 1974; *Chem. Abstr.*, 81, 37487*n* (1974).

pharmacology and nearby pharmaceutical chemistry, working directly with one postdoctoral student, and giving an occasional lecture have been gratifying and rewarding experiences. I shall always be grateful to Dr. Harris for enabling me to "wind down" my career so pleasantly.

Finally, I implied at the beginning that I am indebted to many people. At the risk of omitting some I will name several. In addition to Drs. Mosettig and Small (both now deceased) who gave invaluable instruction, aid, and comfort in the early going, there was Dr. Nathan Eddy, premier pharmacologist, wise counselor, and good friend until his death in 1973. Providing valuable, direct collaboration were permanent NIH staff members, Lewis Sargent, Theodore Parrine, James Murphy, Joseph Ager, Edward Fry, and Arthur Jacobson, in addition to several, talented, foreign-visiting scientists from Japan, England, India, and Italy and postdoctoral Staff Fellows Michael Mokotoff, Raymond Wilson, Helen Ong, Michael Rogers, Kenner Rice, Ibrahim Uwaydah, and William Vincek. Addiction studies in monkeys were directed by the late Dr. Maurice Seevers at the University of Michigan, addiction studies in man were by Drs. Isbell, Fraser, Martin, and Jasinski at the Addiction Research Center, Lexington Ky. Clinical efficacy studies were by Dr. William Forrest, V.A. Hospital in Palo Alto and Drs. Louis Lasagna and Thomas DeKornfeld at Johns Hopkins. I must record also the stimulation and splendid collaboration I received from Glenn Ullyot and Maxwell Gordon, then at the Smith Kline & French Laboratories, and of the strong support and freedom tendered me by Bernhard Witkop, Chief of the Laboratory of Chemistry, NIH, since 1958. Receptor studies were expertly done by Candace Pert and Solomon Snyder at Johns Hopkins University and by Werner Klee and Richard Streaty of the National Institute of Mental Health. And last, but far from least, Alfred Burger, since I first met him in 1935, has constantly given me opportunities, sound advice, much encouragement, and redoubtable friendship.