Kropf, and Stansfield in partial fulfillment of the requirements for the Ph.D degree.
(4) A. L. Bednowitz, W. C. Hamilton, R. G. Brown, L. G. Donaruma, P. L. Southwick, R. A. Kropf, and R. E. Stansfield, *J. Am. Chem. Soc.*, **90**, 291 (1968).
(5) A. L. Bednowitz, R. G. Brown, L. G. Donaruma, W. C. Hamilton, R. A. Kropf, P. L. Southwick, and R. E. Stansfield, *J. Org. Chem.*, **39**, 3537 (1974).
(6) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists", Academic Press, New York, N.Y., 1967, pp 166, 184.
(7) K. Brand and H. W. Stephan, *Chem. Ber.*, **72**, 2168 (1939).
(8) E. McNelis, *J. Org. Chem.*, **30**, 4326 (1965).
(9) (a) ^{1}H NMR: first number is chemical shift; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, the numbers in parentheses are relative intensities. (b) Isotopic analysis: P = parent peak, (P + 1) = parent peak + 1, (P + 2) = parent peak + 2; numbers are relative intensities.

Reduction of 6-Ketones of the Morphine Series with Formamidinesulfinic Acid. Stereoselectivity Opposite to That of Hydride Reductions

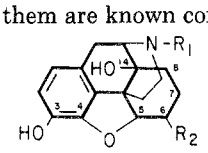
Nithiananda Chatterjie, Jason G. Umans, and Charles E. Inturrisi*

Department of Pharmacology, Cornell University Medical College, New York, New York 10021

Received April 23, 1976

We have previously reported that formamidinesulfinic acid in aqueous alkaline solution reduces N-substituted noroxymorphone derivatives such as naltrexone (**1**) and naloxone (**3**) to the corresponding 6β-hydroxy epimers (**2** and **4**), with no detectable amount of the corresponding 6α epimers.[1] The stereochemistry of these products was the opposite of that obtained in the corresponding hydride reductions.[2]

It was then necessary to examine whether this reagent also reduces other ketones of the morphine series, especially those lacking the hydroxyl at C-14 present in **1** and **3**, and whether such reduction generally yields compounds with the 6β-hydroxy configuration. We therefore reduced a selected number of such ketones with formamidinesulfinic acid, in order to answer these questions and also to obtain reference samples of possible metabolites. Some of these 6β-hydroxy compounds had not been accessible before by a stereoselective reduction procedure; several of them are known compounds obtained



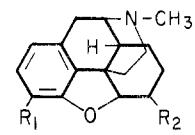
Compound	R_1	R_2
1	CH_2-cyclopropyl	=O
2	CH_2-cyclopropyl	β-OH[a]
3	CH_2-CH=CH_2	=O
4	CH_2-CH=CH_2	β-OH
5	CH_2-cyclobutyl	=O
6	CH_2-cyclobutyl	β-OH
7	CH_3	=O
8	CH_3	β-OH

[a] β-OH refers to the beta configuration

Table I. Partial Characterization of Reduction Products

Registry no.	Compd reduced	Reduction product	Yield, %	Mass spectrum, *m/e* (M)	Ref
16676-33-8	**5**	**6**	72	357	4
76-41-5	**7**	**8**	60	303	5
466-99-9	**9**	**10**	40	287	17
125-29-1	**11**	**12**	63	301	17, 18, 19

previously by more involved reaction sequences. We now report that 17-cyclobutylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (**5**), 17-methyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one (**7**), 17-methyl-4,5α-epoxy-3-hydroxymorphinan-6-one (**9**), and 17-methyl-4,5α-epoxy-3-methoxymorphinan-6-one (**11**) were reduced to their respective 6β-hydroxy derivatives in the yields shown in Table I. The reduction products were free of 6α-hydroxy epimers; they were isolated in pure form, and characterized by mass spectral and ^{1}H NMR data.[1,3]



Compound	R_1	R_2
9	OH	=O
10	OH	β-OH[a]
11	OCH_3	=O
12	OCH_3	β-OH

[a] β-OH refers to the beta configuration

Compound **6** had not been reported previously.[4] The pharmacology of **8** has been described earlier by Seki et al., who obtained this compound by a separation of 6-hydroxy epimers resulting from a Meerwein–Ponndorf–Verley reduction of 14-hydroxydihydrocodeinone (the 3-methyl ether of **7**), and further demethylation.[5] Weiss and Daum have reported a sodium borohydride reduction of **7**, to yield only the 6α epimer of **8**; however, these authors have indicated that no systematic search was made for the possible presence of 6β epimer, some of which might have been formed by the borohydride reduction.[6] A catalytic reduction of the 3-methyl ether of **7** has been shown to yield both 6-hydroxy epimers, with the 6β epimer as the minor product.[7]

In the present study the reduction products **8** and **10** could not be precipitated from an aqueous alkaline reaction mixture as in the isolation of the products **2**, **4**, and **6**; hence these compounds were extracted from the aqueous reaction mixture, after adjusting to pH 9–10, with a mixture of chloroform–ethanol (2:1). The phenolic compounds dissolve in aqueous NaOH solution and are thus amenable to reduction with formamidinesulfinic acid in aqueous alkaline solution.[1] This method presents a marked advantage over the Meerwein–Ponndorf–Verley reduction, which requires appreciable solubility of the substrates in common organic solvents.[8] Dihydrocodeinone (**11**) was reduced by formamidinesulfinic acid in aqueous ethanol, because of its limited solubility in water.

Since the phenolic hydroxyl groups of morphine compounds are generally convertible to their methyl ethers (codeine compounds), this procedure of obtaining 6β-hydroxy derivatives[1] should prove useful for the syntheses of various compounds of the isocodeine series, either by reduction of morphine derivatives and subsequent conversion to codeine derivatives, or by direct reduction of 6-keto derivatives of the codeine series. Thus, the present procedure obviates the necessity of an epimerization[10] step, and of the separation of products resulting from the hydrolysis of α-chlorocodide[11,12] or bromocodide,[12-14] which are alternate routes to obtaining isocodeine derivatives.[15]

These preliminary observations reveal that formamidinesulfinic acid reduces the 6-keto group of morphine derivatives stereoselectively to the 6β-hydroxy epimers, and that this reduction does not require the presence of the 14-hydroxy group. We also find, contrary to a recent report, that this reagent reduces carbonyl groups (at least in the morphine series) in the absence of alkoxide ions.[16] These considerations warrant further investigations to determine the scope and limitations of this potentially useful reagent.

Experimental Section

Melting points of compounds were determined on a Thomas-Hoover apparatus and are uncorrected. General experimental details were as reported earlier.[1] Experimental procedures which are similar to those mentioned earlier are not given.

17-Methyl-4,5α-epoxy-6β-hydroxy-3-methoxymorphinan (12). To a solution of **11** (75 mg, 0.25 mmol) in 20 ml of EtOH was added 10 ml of aqueous NaOH (150 mg) containing formamidinesulfinic acid (95 mg, 0.88 mmol). The resulting mixture was stirred for 1 h at 80 °C under a current of nitrogen. This reaction mixture was then stripped of EtOH and extracted with $CHCl_3$. Upon evaporation a residue of **12** was obtained in a yield of 63%. The ^1H NMR spectrum of **12** ($CDCl_3$) was superimposable with a published reference spectrum.[9]

Acknowledgment. We wish to thank Dr. Ulrich Weiss for his help and encouragement during several phases of this work. Our thanks are due to Mr. S. Theodore Bella of the Rockefeller University, New York, N.Y., for performing elemental analyses, and Mr. Charles H. Strom for proton nuclear magnetic resonance spectra. Drs. F. H. Field and D. V. Bowen of the Rockefeller University Mass Spectrometric Resource provided mass spectrometric analysis. This research was supported in part by Grant DA-00297 and SAODAP Grant DA-00458 and NIH, Division of Research Resources Grant RR-00862. Dr. Inturrisi is an Andrew W. Mellon Teacher Scientist, 1975–1976.

Registry No.—**6** HCl, 60018-68-0; **12**, 795-38-0.

References and Notes

(1) N. Chatterjie, C. E. Inturrisi, H. B. Dayton, and H. Blumberg, *J. Med. Chem.*, **18**, 490 (1975).
(2) I. J. Pachter and Z. Matossian, U.S. Patent 3 393 197 (1968); *Chem. Abstr.*, **69**, 87282q (1968).
(3) N. Chatterjie, J. M. Fujimoto, C. E. Inturrisi, S. Roerig, R. I. H. Wang, D. V. Bowen, F. H. Field, and D. D. Clarke, *Drug Metab. Dispos.*, **2**, 401 (1968).
(4) Compound **6** as its hydrochloride, mp 200–205 °C, was slightly hygroscopic. Anal. ($C_{21}H_{27}NO_4$·HCl·1.25H_2O) C, H, N, Cl. TLC R_f 0.58 (silica gel, EtOAc/C_6H_{14}/EtOH/NH_4OH, 60:25:14:1). The 6β-OH configuration was confirmed by ^1H NMR ($CDCl_3$, Me_4Si) δ 4.50 (d, 1, J = 6 Hz, 5β H), 368–3.45 (m, 1, 6α H).
(5) I. Seki, H. Taragu, and S. Kobayashi, *Yakugaku Zasshi*, **84**, 280 (1964); we are indebted to Dr. Seki for a personal communication on the preparation of this compound. Our mp 248–250 °C and elemental analysis are in agreement with Dr. Seki's data (mp 248–252 °C).
(6) U. Weiss and S. J. Daum, *J. Med. Chem.*, **8**, 123 (1965).
(7) R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939).
(8) I. Seki, personal communication.
(9) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.*, **12**, 104 (1964).
(10) M. M. Baizer, A. Loter, K. S. Ellner, and D. R. Satriana, *J. Org. Chem.*, **16**, 543 (1951).
(11) L. Knorr and H. Hörlein, *Chem. Ber.*, **40**, 4883 (1907).
(12) F. H. Lees, *J. Chem. Soc.*, **91**, 1408 (1907).
(13) S. B. Schryver and F. H. Lees, *J. Chem. Soc.*, **79**, 563 (1901).
(14) F. H. Lees and F. Tutin, *Proc. Chem. Soc., London*, **22**, 253 (1906).
(15) For a discussion on the acetolysis of 14-hydroxycodeine 6-tosylate, see I. Seki, *Ann. Sankyo Res. Lab.*, **17**, 21 (1965).
(16) R. Caputo, L. Mangoni, P. Monaco, G. Palumbo, and L. Previtera, *Tetrahedron Lett.*, 1041 (1975).
(17) L. F. Small and B. F. Faris, *J. Am. Chem. Soc.*, **57**, 364 (1935).
(18) L. F. Small, B. F. Faris, and J. E. Mallonee, *J. Org. Chem.*, **5**, 286 (1940).
(19) M. M. Baizer, U.S. Patent 2 577 948 (1951); *Chem. Abstr.*, **46**, 6164c (1952).

A Synthesis of (*E*)-4,6-Dimethyl-4-octen-3-one (Manicone)[1]

P. J. Kocienski,* J. M. Ansell, and R. W. Ostrow

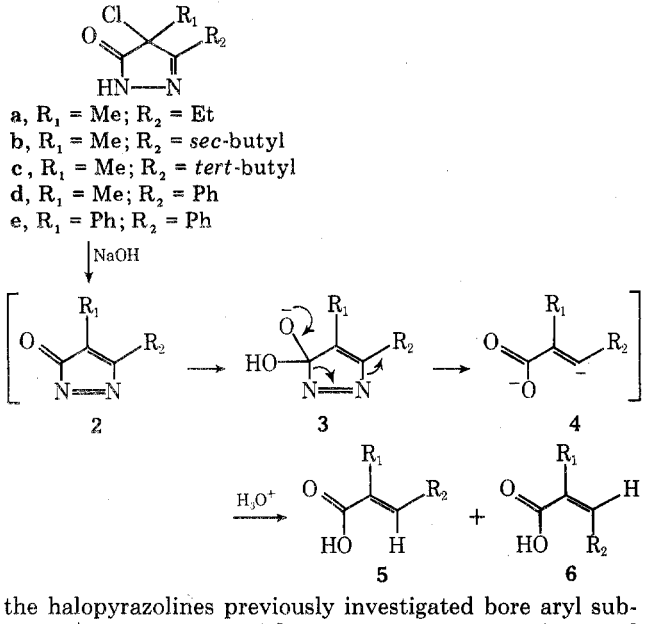
Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901

Received May 25, 1976

Manicone, the principal alarm pheromone of certain species of *Manica* ants, was isolated from the mandibular glands of *M. mutica* and *M. bradleyi* by Fales and co-workers and identified as (*E*)-4,6-dimethyl-4-octen-3-one (**9**).[2] The *E* stereochemistry was tentatively assigned on the basis of NMR data[2] and subsequently corroborated by a stereorational synthesis.[3] We would like to report herein a novel synthesis of manicone, the key feature of which entails the introduction of the α,β-unsaturated carbonyl moiety via the reaction of a 4-chloro-2-pyrazolin-5-one with aqueous NaOH first reported by Carpino in 1958.[4] Since the α,β-unsaturated carboxylic acids which result from this reaction can be readily converted by standard procedures to enones, the Carpino reaction was intended to serve as the fulcrum of our synthetic plan.

Carpino originally observed mixtures of both isomeric acids **5** and **6** in which the *Z* isomer **6** always predominated,[4] whereas for the manicone synthesis, the *E* isomer **5** was required. The decision to proceed in spite of these contradicting stereochemical results was based on a consideration of the proposed mechanism[4] (Scheme I). With one exception, all of

Scheme I



the halopyrazolines previously investigated bore aryl substituents at C-3 (R_2 = Ar);[5] consequently, an aryl-substituted vinyl carbanion **4** would be generated. The mixture of products observed could then be rationalized by the known relative configurational instability of aryl-substituted vinyl carbanions.[6] In the present case, however, a vinyl carbanion **4** would