of 80% formic acid was stirred and heated to 50° for 24 hr. Another 5 ml of 30% H_2O_2 was added and the heating and stirring were continued until an aliquot of the solution failed to give a positive Schiff test (another 24 hr). The volatile components were removed under reduced pressure and the residue was treated with 3.5 g (150 mmol) of LiOH in 35 ml of water. The resulting solution was heated in an autoclave at 120° for 12 hr. A white precipitate was isolated by filtration and washed with several portions of ethanol and then anhydrous ether. The resulting white powder was dried *in vacuo* to give 2.3 g (56%) of pure **4b**. The observed spectral and physical properties were in agreement with those previously reported for this compound.[3]

Acknowledgment. This work was supported by grants from the National Science Foundation (GB-33718) and the City University of New York Research Foundation.

References

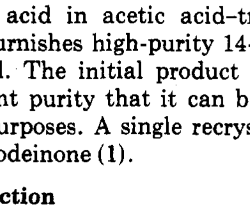
(1) J. Kabak, L. DeFilippe, R. Engel, and B. Tropp, *J. Med. Chem.*, **15**, 1074 (1972).
(2) S. L. Goldstein, D. Braksmayer, B. Tropp, and R. Engel, *J. Med. Chem.*, **17**, 363 (1974).
(3) F. R. Pfeiffer, J. D. Mier, and J. A. Weisbach, *J. Med. Chem.*, **17**, 122 (1974).
(4) A. Garen and C. Levinthal, *Biochim. Biophys. Acta*, **38**, 470 (1960).
(5) S. Hyashi, J. P. Koch, and E. C. C. Lin, *J. Biol. Chem.*, **239**, 3098 (1960).
(6) R. I. Hoaglin, D. G. Kubler, and A. E. Montagna, *J. Amer. Chem. Soc.*, **80**, 5460 (1958).

14-Hydroxycodeinone. An Improved Synthesis

Frank M. Hauser,* Tek-Kuei Chen, and Frank I. Carroll

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709.
Received April 29, 1974

14-Hydroxycodeinone (1), an important synthetic intermediate for the preparation of several narcotic antagonists, is normally prepared by oxidation of thebaine with either hydrogen peroxide or potassium dichromate in acetic acid.[1] However, use of either of these oxidative procedures furnishes 1 in low to moderate yield and then only as a dark resinous material which must be further purified by repetitive recrystallization.



1

We have devised an alternate oxidation procedure, *m*-chloroperbenzoic acid in acetic acid–trifluoroacetic acid mixture, which furnishes high-purity 14-hydroxycodeinone in excellent yield. The initial product is nearly colorless and is of sufficient purity that it can be used directly for most synthetic purposes. A single recrystallization affords pure 14-hydroxycodeinone (1).

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Nmr spectra were determined on a Varian HA-100 spectrophotometer ($CDCl_3$, TMS). Infrared spectra were taken on a Perkin-Elmer 267 spectrophotometer ($CHCl_3$).

14-Hydroxycodeinone (1). To a stirred solution of thebaine (30.1 g) in AcOH (120 ml) was added CF_3CO_2H (15 g) followed by *m*-chloroperbenzoic acid (12.5 g) added over 12 min. The reaction flask was placed in a preheated (95°) stirring wax bath for 15 min and then removed, and while stirring, additional *m*-chloroperbenzoic acid (10.3 g) was added over 18 min. The reaction was again placed in the heating bath for 20 min. After removing the flask from the wax bath, it was stirred an additional 10 min, cooled in an ice bath, and then poured into ice water (900 ml). After stirring for 30 min, the solid was removed by filtration. To the stirred, clear filtrate was added ice (500 g) and enough NH_4OH to make the solution basic. After 1 hr, the solution was filtered and the collected solid was washed with H_2O, 95% EtOH, and Et_2O. After drying, the nearly colorless product weighed 24.3 g (80%) and had mp 265–267° (lit. mp 275°). Recrystallization from EtOH containing a small amount of $CHCl_3$ gave 22.4 g (74%) with mp 274°.

Acknowledgment. This work was supported under Contract No. HSM-42-73-228 (ND) with the National Institute on Drug Abuse (formerly National Institute of Mental Health), Division of Biomedical Research, Biomedical Research Branch.

References

(1) M. Freund and E. Speyer, *J. Prakt. Chem.*, **94** (2), 135 (1916).

2-Aryl-3-dimethylphosphinylpropionic Acids as Potential Nonsteroidal Antiinflammatory Agents

V. Brian Anderson, Richard C. Allen,*

Chemical Research Department

Jeffrey C. Wilker, and William J. Novick, Jr.

Department of Pharmacology, Hoechst-Roussel Pharmaceuticals Inc., Somerville, New Jersey 08876.
Received April 8, 1974

The literature of recent years contains many examples of 2-arylalkanoic acids which for the most part display potent antiinflammatory activity. Essentially all of these compounds can be thought of as arylacetic acids, with or without additional substitution in the α position. In general, substitution of these arylacetic acids in the α position by a small group (CH_3, C_2H_5, OH) leads to retention and, in many cases, enhancement of activity. The dimethylphosphinylmethyl (DPM) moiety has recently been shown[1] to be bioisosteric with methyl in the benzodiazepines, imparting, in addition, interesting changes in the activity profile. The decision was made to test the generality of this bioisosteric relationship by preparing several 2-aryl-3-dimethylphosphinylpropionic acids. It was anticipated that antiinflammatory activity would be enhanced or at least maintained in comparison to 2-arylpropionic acids, with perhaps useful changes in the physical (water solubility, biological distribution, etc.) properties and/or spectrum of activity. A similar approach involving phosphorus analogs of the analgetic methadone has recently been reported.[2]

Our initial synthetic goals, compounds 5–8 (Table I), were selected for two reasons. It was anticipated that the utility of the DPM moiety as a bioisosteric replacement for methyl could best be tested with compounds closely analogous to known potent antiinflammatory agents.† Furthermore, since it was expected that the DPM moiety would increase the water solubility of the target compounds with reference to methyl-substituted analogs, lipophilic phenyl substituents were deemed most desirable to maintain good partitioning ability. The phenyl substituents were thus selected[5] to give a π-value[6] range of 0.77–1.92, while σ[6] was allowed to vary from −0.32 to 0.23 in

†6 is related to naproxen;[3] 8 is similar to namoxyrate.[4]