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.

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## 14-Hydroxycodeinone. An Improved Synthesis

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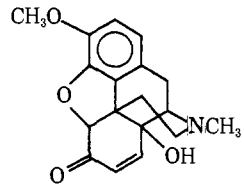
14-Hydroxycodeinone (1), an important synthetic intermediate for the preparation of several narcotic antagonists, is normally prepared by oxidation of thebaine with either hydrogen peroxide or potassium dichromate in acetic acid.[1] However, use of either of these oxidative procedures furnishes 1 in 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°.

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

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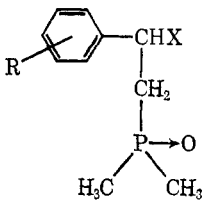
The literature of recent years contains many examples of 2-arylalkanoic acids which for the most part display potent antiinflammatory activity. Essentially all of these compounds can be thought of as arylacetic acids, with or without additional substitution in the $\alpha$ position. In general, substitution of these arylacetic acids in the $\alpha$ 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 $\pi$-value[6] range of 0.77–1.92, while $\sigma$[6] was allowed to vary from −0.32 to 0.23 in

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

**Table I.** 2-Aryl-3-dimethylphosphinylpropionitriles, -propionates, and -propionic Acids



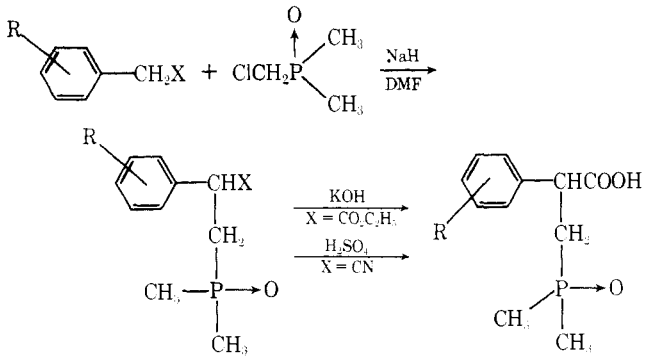
| No. | R | X | Mp, °C | % yield | Procedure[a] | Crystn solvent | Empirical formula | Analyses[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | 4-Cl | CN | 86–88 | 47 | A | *b* | $C_{11}H_{13}ClNOP$ | C,[d] H, Cl, N |
| 2[e] | 3,4-  | $CO_2C_2H_5$ | 109–110 | 27 | A | *b*; $Et_2O$ | $C_{17}H_{21}O_3P$ | C,[f] H |
| 3[g] | 4-*n*-$C_4H_9O$ | $CO_2C_2H_5$ | *h* | 22 | A | *b* | $C_{17}H_{27}O_4P$ | C,[i] H |
| 4 | 4-$C_6H_5$ | CN | 160–161 | 44 | A | $H_2O$ | $C_{17}H_{18}NOP$ | C,[j] H, N |
| 5 | 4-Cl | COOH | 182–183 | 47 | B | $H_2O$ | $C_{11}H_{14}ClO_3P$ | C, H |
| 6 | 3,4-  | COOH | 208–209 | 60 | C | $H_2O$ | $C_{15}H_{17}O_3P$ | C,[k] H |
| 7 | 4-*n*-$C_4H_9O$ | COOH | 133–134 | 14 | C | $H_2O$ | $C_{15}H_{23}O_4P$ | C, H |
| 8 | 4-$C_6H_5$ | COOH | 244–246 | 55 | B | $H_2O$ | $C_{17}H_{19}O_3P$ | C,[l] H |

[a] See Experimental Section. [b] Purified by column chromatography on E. Merck silica gel 7734 *via* gradient elution with methanolic chloroform. [c] Unless otherwise indicated, the analyses were within ±0.4% of the theoretical values. All analyses performed by Micro-Tech Labs., Skokie, Ill. [d] C: calcd, 54.66; found, 54.00. [e] Prepared starting with ethyl β-naphthoate derived from the esterification of commercial β-naphthoic acid: I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J. H. Fried, *J. Med. Chem.*, **13,** 203 (1970). [f] C: calcd, 67.11; found, 67.63. [g] Prepared starting with ethyl 4-*n*-butoxyphenylacetate: S. M. McElvain and T. P. Carney, *J. Amer. Chem. Soc.*, **68,** 2592 (1946); reference from footnote *e*. [h] Semisolid. [i] C: calcd, 62.58; found, 61.49. [j] C: calcd, 72.07; found, 71.54. [k] C: calcd, 65.22; found, 65.65. [l] C: calcd, 67.54; found, 66.92.

order to assess possible electronic effects on activity.

Synthesis of the desired compounds was achieved according to Scheme I. Thus, appropriately substituted

**Scheme I**




phenylacetonitriles or ethyl phenylacetates were alkylated (procedure A) with chloromethyldimethylphosphine oxide in DMF utilizing NaH as a base. The resulting 2-aryl-3-dimethylphosphinylpropionitriles (procedure B) or -propionates (procedure C) were hydrolyzed to the requisite acids.

Compounds 1–8 (Table I) were screened (200 mg/kg po) for antiinflammatory activity in the rat using the carrageenic paw edema assay.[7] Unfortunately, all compounds proved completely devoid of antiinflammatory activity, indicating that the bioisosteric relationship of methyl and dimethylphosphinylmethyl does not hold when applied to agents of this type.

## Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The structures of all compounds are supported by their ir (Perkin-Elmer 457) and nmr (Jeolco C60HR) spectra.

**Procedure A. 2-Aryl-3-dimethylphosphinylpropionitriles and -propionates.** To a suspension of NaH (20 mmol, 50% in mineral oil) in DMF (10 ml) at 10–20° was added dropwise over 10–15 min a solution of the appropriate phenylacetic ester or nitrile (20 mmol) in DMF (10 ml). After $H_2$ evolution had ceased, a solution of chloromethyldimethylphosphine oxide[8] (2.52 g, 20 mmol) in DMF (6 ml) was introduced and the mixture was heated (80–90° for nitriles; reflux for esters) for 3–4 hr. The mixture was poured into NaCl solution, extracted with $CHCl_3$, washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo* in yield the crude product which was purified as indicated in Table I.

**Procedure B.** Hydrolysis of the propionitriles was accomplished in 40% $H_2SO_4$ in a manner similar to published methods.[9]

**Procedure C.** Hydrolysis of the ethyl propionates was accomplished with two molar equivalents of KOH in ethanol–water (3:1, 20 ml/g of ester) at reflux. Concentration of the solvent *in vacuo* followed by acidification, filtration, and crystallization from water afforded the desired acids.

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