of H_2O containing 1 drop of 37% HCl. After addition of 0.5 ml of $CHCl_3$, the pH of the aqueous phase was adjusted to 9.0 (Hydrion paper) with concentrated NH_4OH while stirring. The crystalline material which soon separated was filtered, washed with cold H_2O and $CHCl_3$, and then dried to give 86 mg (total yield 2.76 g, 91%) of **2**·H_2O, mp 251–253 °C dec. Additional **2**·H_2O could be obtained by further extraction of the aqueous phase and (presumably) by chromatography of the foam (317 mg) which resulted from evaporation of the $CHCl_3$ phase from the original filtrate. This foam was shown by TLC ($CHCl_3$–MeOH, 85:15) to contain **1**, **2**, and three unidentified by-products.

References and Notes

(1) Proceedings, AMA Symposium on Supplies of Opium for Medical Use, March 3–4, 1975.

(2) United Nations Secretariat, Division of Narcotic Drugs, Scientific Research on *Papaver bracteatum*, No. 1, Report of the Working Group on *Papaver bracteatum*, Geneva, Dec 12–14, 1972, Document No. ST/SOA/SER.J/1.

(3) J. W. Fairbairn, *Planta Med.*, **29**, 26 (1976).

(4) H. Rapoport, C. H. Lovell, and B. M. Tolbert, *J. Am. Chem. Soc.*, **73**, 5900 (1951).

(5) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956).

(6) K. Goto and I. Yamamato, *Proc. Jpn. Acad.*, **30**, 769 (1954) [*Chem. Abstr.*, **50**, 1052*h* (1956)].

(7) M. Takeda and K. Kugita, Japanese Patent 29153 [*Chem. Abstr.*, **75**, 141030v (1971)]. The entry "O-demethylation" indexed in *Chem. Abstr., 8th Collect. Index*, under 7,8-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (B/C *cis*-codeine, natural codeine) actually refers to B/C *trans*-codeine and not to natural codeine.

(8) H. Inoue, M. Takeda, and H. Kugita, *Chem. Pharm. Bull.*, 18, 1569 (1970) [*Chem. Abstr.*, **73**, 99071r (1970)].

(9) Using the procedure described here, the total isolated yields of **2**·H_2O for three identical runs were 90–91%.

(10) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

(11) Significantly longer reaction times than reported here gave increased amounts of two by-products and lower yields of **2**·H_2O. Less satisfactory results were obtained with other solvents or with boron trichloride.

(12) Reagent grade $CHCl_3$ (J. T. Baker) containing 0.75% EtOH was used throughout in this work.

An Improved Method for O-Demethylation of Codeine

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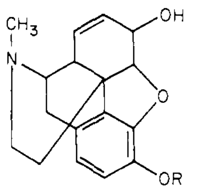
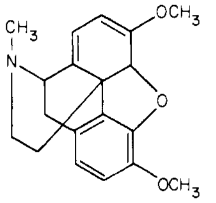
The O-demethylation of codeine was effected by sodium propylmercaptide in dimethylformamide at 125 °C to afford morphine in 80% yield. Similar treatment of thebaine was unrewarding.

Exposure of codeine or morphine to strong acid or alkaline conditions, respectively, at higher temperatures is known to promote substantial decomposition of these alkaloids. Thus, conventional procedures for ether cleavage have been unsuccessful when applied to the conversion of codeine to morphine. Rapoport et al.[1] reported the production of morphine in 22% yield when codeine was treated with pyridine hydrochloride for a brief period at 220 °C. Gates and Tschudi,[2] in their total synthesis of morphine, repeated this method and achieved a 34% yield of morphine by a slight modification of the work-up phase. The use of diphenyl phosphide ion was reported[3] in a patent claim to effect the demethylation of a compound related to codeine.



codeine, R = CH_3
morphine, R = H



thebaine

We report an improved and convenient procedure for O-demethylation of codeine that takes place under comparatively mild conditions and would appear to be applicable to most alkaloidal aromatic ethers. The method is based on the studies of Feutrill and Mirrington[4] who found that treatment of aromatic methyl ethers with sodium alkylmercaptides in dimethylformamide at elevated temperatures resulted in cleavage to phenolic products.

Treatment of codeine with an excess of sodium propylmercaptide in dimethylformamide solution at 125 °C for 45 min afforded morphine in 80% yield. Temperature and reaction time could be varied with similar results. Scrupulous exclusion of oxygen during the reaction coupled with the use of sodium bisulfite in aqueous solutions during work-up tended to decrease coloration in the product. When the O-demethylation reaction was applied to thebaine, however, none of the expected oripavine product was recovered. Thin-layer chromatography showed the disappearance of thebaine after 3 h at 110 °C, but an NMR spectrum of the product still showed strong signals for the 3- and 6-methoxy groups. Apparently, an alternate reaction course is available in the thebaine case, competitive with demethylation.

Morphine. A solution of 3.00 g (10 mmol) of codeine in 60 ml of dry dimethylformamide was degassed under nitrogen by repeatedly stirring under vacuum, followed by inletting nitrogen. Following the addition of 3.00 g (26.7 mmol) of potassium *tert*-butoxide, the degassing process was repeated and 3.0 ml (32.7 mmol) of *n*-propanethiol was injected by syringe. The mixture was stirred at 125 °C under nitrogen for 45 min (similar results at 110 °C for 3 h), cooled, and quenched with 3.0 ml of acetic acid. The solvent was removed under high vacuum and the residue dissolved in 30 ml of 1 N hydrochloric acid. The acid solution was washed with several portions of ether, treated with 5 ml of 20% sodium bisulfite, and alkalized to pH 9 with ammonium hydroxide. The precipitated solid was collected, washed with water, and dried in vacuo (100 °C) to leave 2.30 g (80%) of morphine as tan crystals. The material was pure by NMR and chromatographic comparison with authentic morphine. An acid solution of the product was treated with Norite ($NaHSO_3$ present) and reprecipitated to yield 1.58 g (55%) of off-white solid, mp 249–250 °C (authentic morphine, mp 246–248 °C).

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R01-Da-01023-01, National Institute on Drug Abuse.

References and Notes

(1) H. Rapoport, C. H. Lovell, and B. M. Tolbert, *J. Am. Chem. Soc.*, **73**, 5900 (1951).

(2) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956).

(3) M. Takeda and H. Kugita, Japanese Patent 71 29 153 (1971). Demethylation is reported for the C-14 trans epimer of codeine. We are currently exploring the use of lithium diphenyl phosphide for demethylation of codeine and thebaine.

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(2-Carboxy-1,4-dihydro-4-oxoquinolyl)oxamic Acids and (2-Carboxy-1,4-dihydro-4-oxobenzo[*h*]quinolyl)oxamic Acids as Antiallergy Agents

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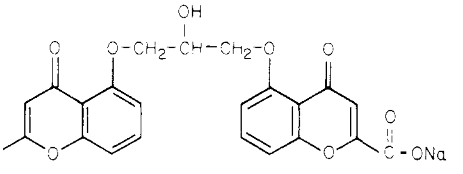
A group of (2-carboxy-1,4-dihydro-4-oxoquinolyl)oxamic acids (5) containing the oxamic acid group in the 5, 6, or 7 positions were synthesized and investigated for antiasthma activity as indicated by the passive cutaneous anaphylaxis (PCA) reaction in rats. Also synthesized and investigated were two (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]quinolyl)oxamic acids (**9** and **10**). Several of the compounds synthesized (viz. **5e**, **5f**, and **10**) showed activity in the PCA test approximately 25 times that shown by disodium cromoglycate (1), as measured by the ID$_{50}$ doses.

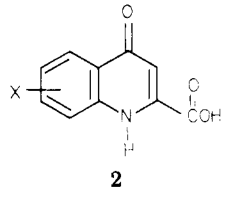
Disodium cromoglycate (1) is an antiasthma agent that



1

is thought to act by inhibition of the liberation of the mediators of allergic reactions initiated by antigen–antibody interactions.[1] This activity has been measured conveniently in rats by means of the passive cutaneous anaphylaxis (PCA) reaction.[2]

Previously we[3] have reported on 2-carboxy-1,4-dihydro-4-oxoquinolines (2) which, like disodium cromoglycate, show antiallergy activity, as measured by the rat



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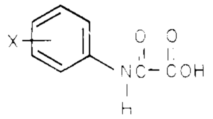
PCA test. In previous publications, various investigators[4–6] have reported on the activity of oxanilic acids (3) and of dioxanilic acids (4).



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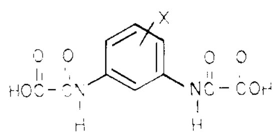

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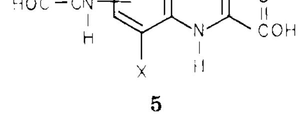
It appeared of interest, therefore, to investigate the effect of the introduction of the oxamic acid moiety, present in 3 and 4, into the quinoline structure 2 to prepare compounds of the type 5.



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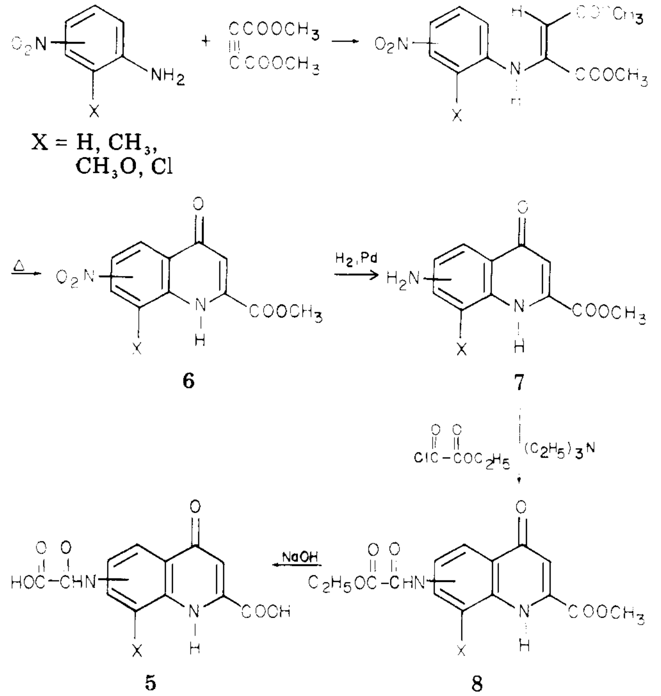
Scheme I



Chemistry. The compounds were synthesized according to Scheme I. Most of the nitro-substituted quinolones (6) and amino-substituted quinolones (7) were reported previously.[3] Treatment of the aminoquinolones (7) with ethyloxalyl chloride in the presence of triethylamine gave the ethyl oxanilates (8) in good yields. Hydrolysis of the ester with sodium hydroxide solution followed by acidification gave the desired (2-carboxy-1,4-dihydro-4-oxoquinolyl)oxamic acids (5) (see Table I).

In an analogous way (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-6-yl)oxamic acid (**9**) and (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-7-yl)oxamic acid (**10**) were prepared from the corresponding suitably substituted aminonitronaphthalenes (Scheme II). All of the steps in the reaction sequence proceeded readily and in good yield.

In the two synthetic schemes mentioned above, the compounds synthesized are written in the 4-oxo form. It is understood, however, that the compounds may exist