Its melting point was unchanged after subjecting it to a nine-tube countercurrent distribution using *p*H 3.5 phosphate buffer–isopropyl ether as the distribution phases.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.81; H, 6.07.

Comparison of Natural and Synthetic Product.—The synthetic product was identical to a sample of natural β-(4-hydroxy-2-methylphenoxy)-lactic acid. A mixed melting point with the natural product, m.p. 168–169°[11] gave no depression. Both compounds exhibited an ultraviolet absorption maximum at 290 mμ and a minimum at 251 mμ and both gave a similar intensity of red color when their solutions were treated with Ehrlich reagent as described by Riley. When subjected to paper chromatography no difference could be detected between the natural product and the two synthetic isomers. In this study butanol saturated with 1.5 *M* ammonium hydroxide was used as the solvent. The location of the spots on the chromatogram was determined by spraying with brom thymol blue solution, and also by using a modification of Ehrlich reagent. The paper was sprayed with a freshly prepared mixture of one part of 0.5% $NaNO_2$ and 25 parts of solution containing 5 g. of sulfanilic acid and 50 ml. of hydrochloric acid per liter. Exposure of the sprayed paper to ammonia vapors located the positions of the compounds as well-defined intense red spots.

2-Benzyloxy-5-hydroxytoluene.—To confirm the location of the tetrahydropyranyl group in I (and the position of the hydroxyl group in IV) compound I was converted to the known toluhydroquinone monobenzyl ether (V). 1.04 g. (0.005 mole) of the monopyranylated ether was treated in the usual manner with one equivalent of benzyl chloride in an aqueous solution of one equivalent of sodium hydroxide. Hydrolysis of the intermediate mixed diether and subsequent workup of the hydrolysis mixture yielded a small quantity of white crystals which on recrystallization from ligroin melted at 69.5–70.5°. Baker and Brown[8] report a melting point of 69–70° for this compound.

(11) Riley (ref. 5, p. 5713) reports m.p. 165–166°.

WALLACE LABORATORIES
DIVISION OF CARTER PRODUCTS, INC.
NEW BRUNSWICK, N. J.

The Action of Peracids on the Desoxycodeines[1]

BY HENRY RAPOPORT AND ETHAN C. GALLOWAY

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The fact that a number of various desoxycodeines are now easily available led us to examine their reaction with peracids with the objective of preparing the corresponding epoxides. These in turn might be convertible to codeine isomers with an oxygen function at some position other than 6.

For the three possible sites of oxidation, *viz.*, the tertiary amine, the alicyclic double bond, and the aromatic ring,[2] the expectation was that the rates of oxidation would be appreciably different and would decrease in the above order.[3] Initial experiments with perbenzoic acid and Δ^7-desoxycodeine in chloroform at 0° did show an almost instantaneous consumption of one mole of peracid. That this was due to amine oxide formation was established by hydrogenation of the product to dihydrodesoxycodeine. However, after this very rapid one-mole uptake (less than 15 minutes) consumption of perbenzoic acid continued at a markedly decreased rate and did not reach two moles until after about forty hours.

(1) Supported by a grant from the National Institutes of Health, Bethesda, Md.

(2) (a) H. Fernholz, *Ber.*, **84**, 110 (1951); (b) S. L. Friess, A. H. Soloway, B. K. Morse and W. C. Ingersoll, THIS JOURNAL, **74**, 1305 (1952).

(3) D. Swern, *Chem. Revs.*, **45**, 1 (1949).

To gain insight as to whether the alicyclic double bond or the aromatic nucleus (or both) was being attacked, the rates of peracid consumption by Δ^7-desoxycodeine and dihydrodesoxycodeine were compared and found to be identical. From this it may be concluded that the aromatic nucleus was being oxidized at least as rapidly as the alicyclic double bond, if the latter were being attacked at all.[4] Δ^6-Desoxycodeine, Δ^8-desoxycodeine and 6-methyl-Δ^6-desoxycodeine were also subjected to perbenzoic acid under the same conditions to ascertain whether the position or degree of substitution of the alicyclic double bond might substantially affect its rate of oxidation. Oxidations were also conducted in benzene at 8 and 23°. In every case, irrespective of compound or conditions, the rate of perbenzoic acid consumption was identical with that found for dihydrodesoxycodeine.

In a number of examples, a deactivation of the aromatic nucleus to peracid oxidation has been effected by substitution of bromine into the ring.[5] This possibility was explored through the preparation of 1-bromodihydrodesoxycodeine, but again its rate of oxidation was identical with that of the unbrominated compound.

As a final alternative, oxidation with monoperphthalic acid was examined, since the aromatic ring is relatively unreactive toward this oxidant.[2a] Dihydrodesoxycodeine, Δ^6-, Δ^7-, Δ^8- and 6-methyl-Δ^6-desoxycodeine were subjected to the action of monoperphthalic acid in acetone at 0°. In every case, there was a one-mole consumption of peracid requiring about thirty minutes, and beyond that no further oxidation occurred. Although the alicyclic double bond again was inert, the clean-cut one-mole consumption and no further oxidation at any other site in the molecule indicated that this might be a useful method for preparing amine oxides.

When the oxidations with monoperphthalic acid were conducted with the objective of preparing amine oxides, a good yield of the desired product was obtained with facility in each instance, as shown in Table I. Considering the vigor of the alkaline hydrogen peroxide usually used for this purpose,[6] and the selectivity of monoperphthalic acid in acetone at 0°, the latter reagent appears to be advantageous for amine oxide formation.

Experimental

Δ^6-Desoxycodeine was prepared by dehydrochlorination of dihydrochlorocodide using a 20-hour reflux period in a solution of sodium cyclohexylate in cyclohexanol instead of sodium methylate in methanol at 140°.[7]

Δ^7- and Δ^8-desoxycodeine were prepared by lithium aluminum hydride reduction of *p*-toluenesulfonylcodeine and *p*-toluenesulfonylneopine, respectively.[8] Hydrogenation of Δ^7-desoxycodeine gave **dihydrodesoxycodeine.**[8]

(4) This oxidation of the aromatic ring most probably occurs at C_3–C_4, since this is the position most susceptible to ozonolysis [E. Speyer and A. Popp, *Ber.*, **59**, 390 (1926); E. Speyer, *ibid.*, **62**, 209 (1929); H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950)] even when an alicyclic double bond is present [E. Speyer and L. F. Roell, *Ber.*, **63**, 539 (1930)].

(5) J. Böeseken and C. F. Metz, *Rec. trav. chim.*, **54**, 345 (1935); W. F. Short and H. Wang, *J. Chem. Soc.*, 2979 (1951).

(6) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, England, 1954.

(7) L. F. Small and F. L. Cohen, THIS JOURNAL, **53**, 2214 (1931).

(8) H. Rapoport and R. M. Bonner, *ibid.*, **73**, 2872 (1951).

TABLE I

AMINE OXIDES OF SOME DESOXYCODEINES

Compound	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Δ^6-Desoxycodeine-N-oxide	80	94–98	$C_{18}H_{21}O_3N \cdot {}^1/_3H_2O$[a]	70.8	70.9	7.2	7.0
Picrate		212–217	$C_{24}H_{24}O_{10}N_4$	54.6	54.3	4.6	4.8
Δ^7-Desoxycodeine-N-oxide	84	173–176	$C_{18}H_{21}O_3N$	72.2	71.9	7.1	6.9
Δ^8-Desoxycodeine-N-oxide	77	160–164	$C_{18}H_{21}O_3N \cdot {}^1/_3H_2O$[a]	70.8	71.1	7.2	7.2
Picrate		188–192	$C_{24}H_{24}O_{10}N_4$	54.6	54.8	4.6	4.9
6-Methyl-Δ^6-desoxycodeine-N-oxide	91	183–187 192–196[b]	$C_{19}H_{23}O_3N$	72.8	72.5	7.4	7.3
Dihydrodesoxycodeine-N-oxide	64	95–98	$C_{18}H_{23}O_3N$	71.7	71.3	7.7	7.4
Picrate		118–121	$C_{24}H_{26}O_{10}N_4$	54.3	54.5	4.9	4.8

[a] Extremely hygroscopic; drying at elevated temperatures caused partial decomposition. [b] Dimorphic forms.

6-Methyl-Δ^6-desoxycodeine was formed by the action of thionyl chloride on 6-methyldihydrocodeine.[9]

1-Bromodihydrodesoxycodeine.—A solution of 800 mg. (5 mmoles) of bromine in 10 ml. of glacial acetic acid was added over a ten-minute period to a cold solution of 715 mg. (2.5 mmoles) of dihydrodesoxycodeine in 20 ml. of 3 *N* acetic acid. The aqueous solution was made distinctly alkaline with concd. sodium hydroxide and was extracted with three 25-ml. portions of chloroform. Drying with sodium sulfate and evaporation of the chloroform left 810 mg. (89% yield) of solid residue which was crystallized from methanol, m.p. 159–161°.

Anal. Calcd. for $C_{18}H_{22}NO_3Br$: C, 59.3; H, 6.1; Br, 21.9. Found: C, 59.3; H, 6.3; Br, 21.7.

Oxidations with Perbenzoic Acid.—Perbenzoic acid was prepared from benzoyl peroxide[10] and stored as a 0.5 *M* solution in chloroform at 5°. Prior to a rate of oxidation determination, a sufficient portion of this stock was diluted to 0.15 *M* and allowed to stand overnight at 0°, by which time its titer had become constant. In this solution was then dissolved a quantity of alkaloid equal to about 15 mole % of the peracid present, and the progress of the oxidation was followed by withdrawing aliquots and comparing their titer with those of a parallel solution to which no alkaloid had been added.

A perbenzoic acid solution in benzene was prepared in the same manner as above, using benzene as the initial extractant rather than chloroform. Oxidations in benzene were followed at 8 and 23°.

Oxidations with Monoperphthalic Acid. Amine Oxide Formation.—Ethereal monoperphthalic acid was prepared from phthalic anhydride and alkaline hydrogen peroxide,[11] and the ether was evaporated and replaced with purified acetone (distilled from potassium permanganate and then potassium carbonate). Such an acetone solution was completely stable at 0° for at least 24 hours and was used in the oxidation studies.

The general procedure for preparing the amine oxides consisted in treating the codeine derivative with approximately 300 mole % of monoperphthalic acid as a 0.1 *M* solution in acetone and allowing the solution to stand at 0° for 30 minutes. Excess saturated sodium bicarbonate solution was then added, the mixture was filtered, and the filtrate was evaporated to dryness. The residue was distributed between chloroform and water using three additional portions of chloroform. Drying and evaporating the chloroform left a residue which was either crystallized from benzene or chromatographed on alumina (Merck). In the latter case, benzene was used for development and 5% isopropyl alcohol in benzene for elution. Evaporation of the combined isopropyl alcohol-benzene fractions gave residues which were crystalline in some instances or were crystallized from benzene in others.

Amine oxide picrates were prepared in and were recrystallized from methanol.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

(9) L. Small and H. Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(10) G. Braun, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

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The Aminomethylation of Olefins. III. The Synthesis of 1-Methyl-4-phenyl-4-acetoxypiperidine

BY CLAUDE J. SCHMIDLE AND RICHARD C. MANSFIELD

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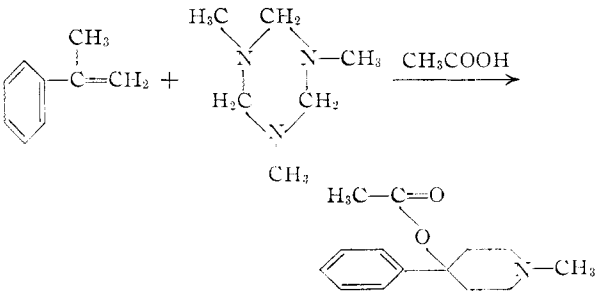
The analgesic activity of a series of 1-alkyl-4-aryl-4-acyloxypiperidines has been reported.[1] A previous communication[2] has described studies in our laboratories concerned with a new method of preparation of 1-alkyl-4-aryl-4-piperidinols. The synthesis of 1-methyl-4-phenyl-4-acetoxypiperidine has now been accomplished by a one-step process involving the reaction of α-methylstyrene, acetic acid and N,N′,N″-trimethyltrimethylenetriamine. The latter material can be easily prepared[3] from methylamine and formaldehyde.



The reaction proceeded without a catalyst but the addition of concentrated sulfuric acid or phosphoric acid gave improved yields. When 85% orthophosphoric acid was used it was necessary to eliminate water by introduction of a calculated amount of acetic anhydride to the reaction mixture prior to addition of the amine and olefin. Excess acetic acid acted as solvent in the reaction which was carried out using N,N′,N″-trimethyltrimethylenetriamine and α-methylstyrene on an equimolar basis.

TABLE I

PREPARATION OF 1-METHYL-4-PHENYL-4-ACETOXYPIPERIDINE

Mole catalyst per mole α-methylstyrene	Time, hr.	Temp., °C.	Yield, %
None	4	115	17.2
1.0 H_3PO_4	4	115	30.1
0.8 H_2SO_4	5	115	20.6

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