Facile Method for the Preparation of Some Novel Bicyclic Lactones

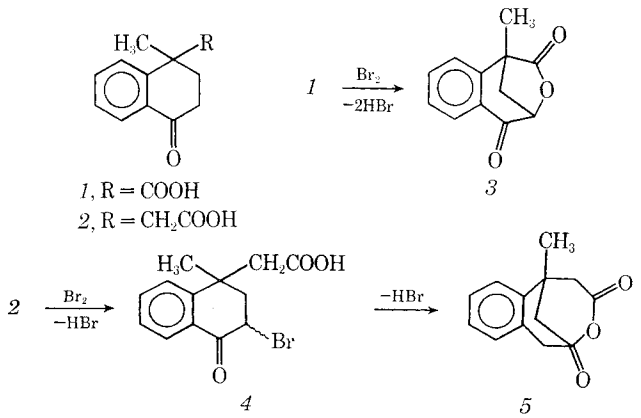
WENDEL L. NELSON and KENNETH F. NELSON

Abstract □ The preparation of 1-methyl-2,3-benzo-6-oxabicyclo[3.2.1]octane-4,7-dione and 1-methyl-2,3-benzo-6-oxabicyclo[3.3.1]nonane-4,7-dione is reported by facile intramolecular cyclization of the corresponding bromotetralone. 4-Methyl-4-carboxyl-1-tetralone is cyclized under the conditions of bromination. 4-Methyl-1-tetralone-4-acetic acid is cyclized only on continued heating of the α-bromoketone in acetic acid.

Keyphrases □ Lactones, bicyclic—synthesis □ IR spectrophotometry—structure □ UV spectrophotometry—structure □ NMR spectroscopy—structure

Various types of pharmacological activity have been reported for compounds containing the lactone functionality, including useful cardiotonic activity, anthelmintic activity, and suspected hallucinogenic activity (1, 2). However, interest in carcinogenic lactones and demonstrated antitumor activity among others has stimulated more recent research (3–5). Limited success has been made in attempts to correlate biological activity and chemical structure and reactivity (6, 7).

As a part of another study, substituted tetralone-acids *1* and *2* were available. The authors therefore sought to determine if, by proper derivatization of the carbon α to the carbonyl, these acids could be cyclized intramolecularly to the corresponding α-ketolactones which represent potential antitumor agents. The corresponding lactones, 1-methyl-2,3-benzo-6-oxabicyclo[3.2]octane-4,7-dione (*3*) and 1-methyl-2,3-benzo-6-oxabicyclo[3.3.1]nonane-4,7-dione (*5*) were readily obtained; the former from the attempted α-bromination process, the latter on further treatment of α-bromoketone (*4*) in acetic acid.



Scheme I

4-Methyl-4-carboxyl-1-tetralone (*1*) (see Scheme I) was prepared by slight modification of Green's procedure (8) for preparation of the corresponding amide. Methyl α-phenylpropionate was substituted for phenylacetonitrile in a Michael condensation using methyl acrylate as the acceptor. Saponification followed by cyclization with liquid hydrogen fluoride afforded *1*.

Attempted bromination utilizing pyridinium hydrobromide perbromide (9) afforded only lactone *3*, in good yield. None of the intermediate α-haloketone was isolated, indicating the internal lactonization process occurred readily under the reaction conditions used.

Acid *2*, the homolog of *1*, was prepared by the method of Herz (10). Bromination under identical conditions afforded the intermediate α-bromoketone (*4*). We were unable to determine the stereochemistry of this intermediate; however, intramolecular cyclization occurred readily on heating in glacial acetic acid, in the presence of sodium acetate.

Both lactones, *3* and *5*, were characterized based on spectral information and elemental analysis. Lactone *3* showed a 5.57-μ carbonyl stretching band indicative of a strained five-membered lactone, whereas *5* showed a carbonyl band at 5.73 μ. Both showed typical 1-tetralone UV spectra.

The NMR spectrum of *3* (Fig. 1) showed a quartet at 4.93 δ for the proton at C-5 with apparent coupling constants of 4 and 2 c.p.s. (11, 12). Two overlapping doublets for protons $H_{8\text{-syn}}$ and $H_{8\text{-anti}}$ were observed in a 1:1:2 triplet at approximately 2.75 δ also with apparent coupling constants of 2 and 4 c.p.s. It is not unexpected that these protons have different chemical shifts, considering the magnetic environment of each. All coupling constants are apparent in this ABX system because only the inner components of the expected quartets for $H_{8\text{-syn}}$ and $H_{8\text{-anti}}$ were observed. Neither calculation of the true coupling constants, nor the true chemical shifts of the protons at C-8, can be determined

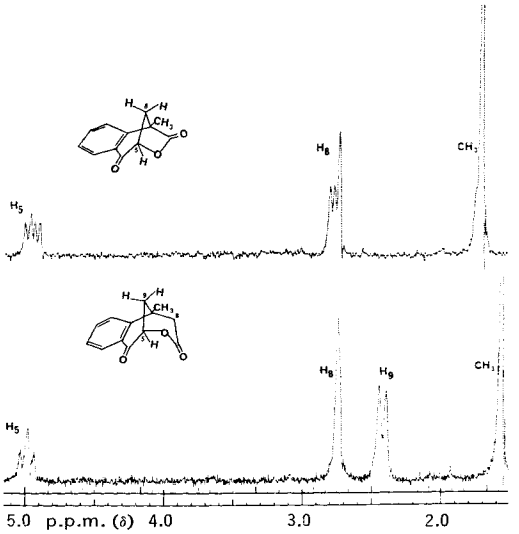


Figure 1—*NMR spectra of the aliphatic protons of 1-methyl-2,3-benzo-6-oxabicyclo[3.2.1]octane-4,7-dione* (**3**) *and 1-methyl-2,3-benzo-6-oxabicyclo[3.3.1]nonane-4,7-dione* (**5**).

[1] Syn and anti refer to the position of these protons with respect to the benzene ring.

because the outer components were not observed. The small difference in their chemical shifts with respect to $J_{gem.}$ probably accounts for this situation. Inspection of Dreiding models indicates the di-hedral angles between H_5 and $H_{8\text{-anti}}$ and H_5 and $H_{8\text{-syn}}$ are 45 and 75°, respectively. This is consistent with the larger coupling constant, 4 c.p.s., being $J_{8\text{-anti},5}$, and $J_{8\text{-syn},5}$ = 2 c.p.s. based on a modified Karplus equation (13).

The NMR spectrum of *5* indicated approximately equal *J*-values for the couplings H_5 and $H_{9\text{-anti}}$ and H_5 and $H_{9\text{-syn}}$, and approximately identical chemical shifts for the C-9 protons. The signal for H_5 was a symmetrical triplet, J = 3 c.p.s., and the signal for C-9 protons doublet J = 3 c.p.s.

The difference in ease of formation of lactones *3* and *5* is explicable on the basis of formation of a five-membered lactone *versus* a six-membered one. For example, sulfuric acid-catalyzed lactonization of cyclohexene-4-carboxylic acid affords only the five-membered lactone, and none of the six-membered one (14). In a similar fashion, sulfuric acid cyclization of 4-pentenoic acid produces γ-valerolactone, and no α-lactone (15).

This lactonization process represents a facile replacement of the active α-halogen by a poor nucleophile, the carboxyl group, which seems to occur quite readily when proper orientation of the two groups is possible. A possible mechanism, consistent with the reaction conditions, would be the solvolytic loss of the halogen, followed by carboxyl group attack. Other mechanisms are also possible.

Compounds *3* and *5* have been submitted to Cancer Chemotherapy National Service Center for screening.

EXPERIMENTAL[2]

1-Methyl-2,3-benzo-6-oxabicyclo[3.2.1]octane-4,7-dione (3)—To a stirred solution of 4.0 g. (18.5 mmoles) of *1* in 150 ml. of a mixture of equal volumes of chloroform and glacial acetic acid was added 6.14 g. (18.5 mmoles) of pyridinium hydrobromide perbromide (9) in several portions over a period of 20 min. The mixture was warmed on a steam bath for 20 min., then poured into a mixture of 75 ml. of hexane and 500 ml. of water containing 0.5% sodium sulfite. The layers were separated and the aqueous layer washed with an additional two portions of hexane. The organic layers were combined, washed with water and saturated brine solution and dried over anhydrous magnesium sulfate. Evaporation afforded a solid, 3.0 g. (75% of theory), m.p. 145–146° when crystallized from ether; IR (potassium bromide), 3.40, 5.57 (lactone carbonyl), 5.90 (aryl ketone carbonyl), 6.28, 6.90, 7.50, 7.80, 7.95, 8.32, 9.30, 9.55, 9.90, 10.30, 10.50, 12.15, 13.15, 13.75 μ; UV $\lambda_{max.}^{EtOH}$ 259 (log ε = 3.92), 292.5 (log ε = 3.28); NMR (deuterochloroform), δ 1.78 (singlet, C—CH_3), 2.75 and 2.77 (overlapping doublets, —CH_2— with $J_{apparent}$ = 4 and 2 c.p.s., respectively), 4.93 (quartet, H—C—O, apparent $J_{5,8\text{-ant}}$: = 4 c.p.s. and $J_{5,8\text{-syn}}$ = 2 c.p.s.), 7.50 (multiplet, 3 aromatic protons), 8.08 (distorted doublet with major coupling of 8 c.p.s., 1 aromatic proton).

Anal.—Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.19; H, 5.16.

4-Methyl-4-carboxymethyl-2-bromo-1-tetralone (4)—To a stirred solution of 1.0 g. (46 mmoles) of 4-methyl-1-tetralone-4-acetic acid in 50 ml. of a mixture of equal volumes of chloroform and glacial acetic acid was added 1.46 g. (46 mmoles) of pyridinium hydrobromide perbromide (9) in small portions over a few minutes This mixture was heated on a steam bath for 20 min., then poured into a mixture of 50 ml. of ethyl acetate and 150 ml. of water containing 0.5% sodium sulfite. The layers were separated and the aqueous layer extracted with an additional two portions of ethyl acetate. The organic layers were combined, washed with water and saturated brine solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 450 mg. (33%), m.p. 160–161° when recrystallized from hexane-ethyl acetate mixture; IR (potassium bromide), 2.85 (broad), 3.35, 5.83, 6.20, 6.70, 6.80, 7.05, 7.18, 7.65, 7.70, 8.01, 9.05, 9.45, 9.72, 10.35, 11.10, 12.15, 13.05, 13.45, 13.46, 14.15, 14.70 μ; NMR (DMSO-d_6), δ 1.55 (singlet C—CH_3), 2.62 and 2.95 (overlapping multiplets of —CH_2— groups), 5.69 (quartet H—C—Br, J = 13 and 5 c.p.s.), 7.63 (multiplet, 3 aromatic protons), 8.00 (distorted doublet with major coupling 7 c.p.s., 1 aromatic proton), 9.22 (broad singlet —COOH).

Anal.—Calcd. for $C_{13}H_{13}O_3Br$: C, 52.53; H, 4.41; Br, 26.89. Found: C, 52.23; H, 4.83, Br, 26.85.

1-Methyl-2,3-benzo-6-oxabicyclo[3.3.1]nonane-4,7-dione (5)—To 0.125 g. (4.2 mmoles) of 4-methyl-4-carboxymethyl-2-bromo-1-tetralone (4) in 20 ml. of glacial acetic acid was added 34.4 mg. (4.2 mmoles) of sodium acetate and the mixture heated on a steam bath for 30 min. This mixture was poured into 100 ml. of water and extracted with three 50-ml. portions of ethyl acetate. The organic portions were combined, washed with water and brine solution, and dried with anhydrous magnesium sulfate. Removal of ethyl acetate afforded a solid, 63 mg. (69.3% of theory); recrystallization from ethyl acetate-hexane gave m.p. 127–129°; IR (potassium bromide): 3.38, 5.73, 5.85, 6.23, 6.88, 7.10, 7.40, 7.55, 7.70, 8.12, 8.50, 8.70, 8.80, 8.95, 9.40, 10.05, 10.20, 13.10, 14.00 μ; $\lambda_{max.}^{EtOH}$ 252.5 mμ (log ε = 4.02), 290 mμ (log ε = 3.20); NMR (deuterochloroform), δ 1.57 (singlet, C—CH_3), 2.40 (doublet, C-9 protons, J = 3 c.p.s.), 2.74 (singlet, C-7 protons), 4.97 (triplet, H—C—O, J = 3 c.p.s.), 7.60 (multiplet, 3 aromatic protons), 8.15 (distorted doublet with major coupling of 7 c.p.s., 1 aromatic proton).

Anal.—Calcd. for $C_{13}H_{12}O_3$: C, 72.22; H, 5.59. Found: C, 72.32; H, 5.69.

REFERENCES

(1) L. J. Haynes, *Quart. Rev. (London)*, **2,** 46(1948).

(2) D. G. Wenzel and C. M. Smith, *J. Am. Pharm. Assoc., Sci. Ed.*, **47,** 792(1958).

(3) F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, **19,** 392 (1956), and earlier work.

(4) S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *Tetrahedron Letters*, **1968,** 149.

(5) S. M. Kupchan, J. C. Hemingway, J. M. Cassady, J. R. Knox, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **89,** 465 (1967).

(6) F. Dickens and J. Cooke, *Brit. J. Cancer*, **19,** 303(1965).

(7) J. B. Jones and J. M. Young, *J. Med. Chem.*, **11,** 1176(1968), and earlier work.

(8) D. E. Green, Ph.D. thesis, Washington State University, 1962.

(9) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **70,** 417 (1948).

(10) W. Herz and G. Caple, *ibid.*, **84,** 3514(1962).

(11) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39,** 216 (1961).

(12) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, San Francisco, Calif., 1964, Chap. 6 and references therein.

(13) M. Karplus, *J. Am. Chem. Soc.*, **85,** 2870(1963).

(14) D. S. Noyce, H. J. Weingarten, and L. J. Dolby, *J. Org. Chem.*, **26,** 2101(1961).

(15) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Rheinhold, New York, N. Y., 1954, p. 574.

ACKNOWLEDGMENTS AND ADDRESSES

Received December 9, 1968, from the *College of Pharmacy, University of Washington, Seattle, WA 98105*

Accepted for publication March 4, 1969.

This investigation was supported by grant GM-13,782 from the National Institutes of Health, U. S. Public Health Service, Bethesda, MD

[2] Melting points were determined on a calibrated Thomas-Hoover Unimelt and are corrected. IR spectra were recorded on Beckman IR-8A and IR-20 spectrophotometers. NMR spectra were determined with a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. UV data were determined on a Cary 14 spectrophotometer. Microanalysis was conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England, and by Midwest Microlab, Inc., Indianapolis, Ind.