8.99, 12.02, 12.78, 13.27 μ; uv λ_{max}^{MeOH} 265 nm (ϵ 23,000), 314 (5070).

Anal. Calcd for $C_7H_7N_3O$: C, 56.36; H, 4.74; N, 28.17. Found: C, 56.20; H, 4.31; N, 28.04.

Solution of **10** in methanol–hydrogen chloride–ether gave **9**.

2-Amino-1-(2-carboxyethyl)pyrimidinium Betaine (11a).—To a solution of 0.75 g (0.0054 mol) of potassium carbonate in 25 ml of water was added 1.0 g (0.005 mol) of **9**. The nearly neutral solution was evaporated to dryness and the residue extracted with hot chloroform. The chloroform extracts were evaporated at reduced pressure. Recrystallization of the residue (ethanol–ether) gave 0.3 g of a light yellow solid, mp 171–172.5°.

2*H*-Pyrimido[1,2-*a*]pyrimidin-2-one Hydrobromide (15).—A mixture of 5 ml of dimethylformamide and 1.0 g (0.0032 mol) of **13** was slowly heated in an oil bath whereupon solution occurred. Near 80° a solid began to separate and heating was continued at 100–110° for *ca.* 45 min. The cooled mixture was filtered and the residue washed with dimethylformamide followed by chloroform. Recrystallization (TFA–methanol) gave 0.53 g (72.6%) of **15**: mp (darkening) 280°, bubbling 310° dec; $\nu_{C=O}$ 5.75 μ; uv λ_{max}^{MeOH} 240 nm (ϵ 9464), 320 (5986); λ_{max} (0.001 *N* NaOH) 247 (14,280), 275 (14,570), 313 (46,280); nmr (TFA) 6.85 (d, 1 H, 3 proton), 8.10–7.84 (m, 1 H, 7 proton), 8.40 (d, 1 H, 4 proton), 9.76–9.40 (m, 2 H, 6,8 protons).

Anal. Calcd for $C_7H_6BrN_3O$: C, 36.86; H, 2.66; Br, 35.04; N, 18.43. Found: C, 36.87; H, 3.09; Br, 35.03; N, 18.43.

If the resulting solid formed at 80° was filtered off and washed with chloroform, tlc analysis showed the presence of only a small amount of **15**, the major component being the intermediate **14**.

Registry No.—**4**, 27179-31-3; **5**, 27179-32-4; **7**, 27179-33-5; **8**, 27179-34-6; **9**, 27248-73-3; **10**, 27179-35-7; **11**, 27179-36-8; **12**, 27179-37-9; **13**, 27179-38-0; **15**, 27179-39-1.

Cyclic Lactams. II.[1] 1,7-Dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione and 3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione from 4-Methyl-1-tetralone-4-acetic Acid

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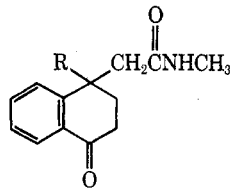
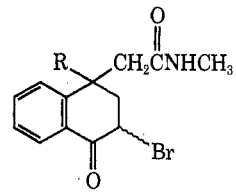
In a model study related to preparation of some benzomorphan analgesics,[3] we attempted to prepare the basic nucleus of this system from 4-methyl-1-tetralone-4-acetic acid. Various routes to this hexahydro-2,6-methano-3-benzazocine nucleus have been explored in considerable detail.[4–7] Walker and Alkalay[7] reported a successful ring closure to this skeleton from the *N*-methylamide of 4-phenyl-1-tetralone-4-acetic acid (**2**) by intramolecular displacement of the halide of the intermediate α-bromo ketone **4**. Because of the problems encountered in separation of the diastereomeric α-bromo ketones, and only partially successful cyclization using methanol–sodium methoxide, we sought to investigate the possibility of a solvolytic displacement process which would lead to benzazocine **5**. The isolation of the azabicyclo[4.3.0]nonane derivative from this process is reported.



1, R = CH_3
2, R = Ph



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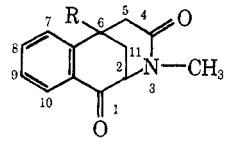
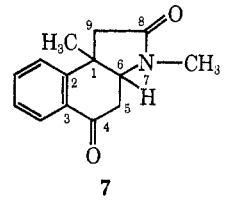
4, R = Ph

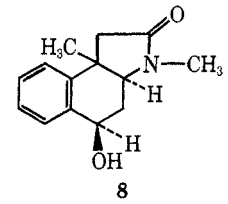


5, R = CH_3
6, R = Ph

The necessary 4-methyl-1-tetralone-4-acetic acid was available from the Friedel–Crafts alkylation of γ-methyl-γ-(carbethoxymethyl)butyrolactone and subsequent cyclization.[8] The amide formation process was very inefficient when the mixed anhydride formed from ethyl choroformate was treated with anhydrous methylamine. However, formation of the *N*-hydroxysuccinimide ester using dicyclohexylcarbodiimide followed by treatment with aqueous methylamine resulted in the desired amide in excellent yield. Bromination was performed in acetic acid–chloroform, or in benzene–tetrahydrofuran, with the latter method being preferable. The intermediate mixture of α-bromo ketones (**3**) was refluxed in dimethylformamide to attempt intramolecular displacement. Only a single ketone amide was isolated which was identified as 1,7-dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione (**7**), based on nmr evidence, reduction, and subsequent preparation of **5** by a related method.



7



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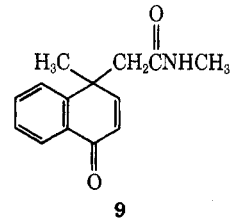

9

The nmr spectrum of the isolated product showed, in addition to the expected tetralone aromatic protons, singlets for methyl groups and methylene protons adjacent to the carboxamide function, a triplet, and a doublet at δ 3.83 and 2.90 (J = 4 Hz), integrating for one and two protons, respectively. The position of the

(1) Previous paper: W. L. Nelson, D. D. Miller, and R. S. Wilson, *J. Heterocycl. Chem.*, **6**, 131 (1969).

(2) Taken in part from the Ph.D. thesis of K. F. Nelson, submitted to the Graduate School, University of Washington, July 1970.

(3) K. F. Nelson, Ph.D. Thesis, University of Washington, 1970.

(4) E. L. May and L. J. Sargent in "Analgetics," Medicinal Chemistry Monographs, Vol. 5, G. deStevens, Ed., Academic Press, New York, N. Y., 1965, pp 123–177.

(5) N. B. Eddy and E. L. May in "Synthetic Analgesics," International Series of Monographs in Organic Chemistry, Vol. 8, D. H. R. Barton and W. von Doering, Ed., Pergamon Press, London, 1966, pp 115–137.

(6) G. deStevens, *Pure Appl. Chem.*, **19**, 89 (1969).

(7) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966), and references therein.

(8) W. Herz and A. Caple, *J. Amer. Chem. Soc.*, **84**, 3517 (1962).

doublet suggested structure **7** where the C-5 protons would be expected downfield with respect to the C-11 methylene protons in alternate structure **5**. The single coupling constant of 4 Hz may result from a combination of averaging of chemical shifts of the C-5 protons and the fact that the coupling constant may be large with respect to the difference in chemical shifts of these protons.

Deuterium exchange simplified the spectrum and provided data consistent only with **7**. The C-5 and C-9 protons are exchanged reducing the signal of H-6 to a singlet. Structure **5** is inconsistent with exchange of the methylene protons which would be exchangeable in **7**. Further evidence for **7** was obtained from the borohydride reduction product **8**, which showed quartets for H-4 and H-6 at δ 4.62 and 3.50, respectively, J = 4 and 10 Hz. The observation of one large coupling constant (J_{45} and J_{65}) is consistent with axial and pseudoaxial disposition of H-6 and H-4, compatible with either a cis- or trans-1,6 ring junction in **7**.

The formation of **7** is best rationalized in terms of an intermediate α,β-unsaturated ketone, **9**, resulting from elimination of hydrogen bromide, followed by intramolecular conjugate addition of the amide nitrogen. These results are probably a consequence of the poor nucleophilic character of the amide nitrogen under reaction conditions where elimination could readily occur.[9]

When the mixture of α-bromo ketones (**3**) was subjected to reaction conditions favoring formation of a better nucleophile, the anion of the amide nitrogen (sodium methoxide–methanol), benzazocine **5** was isolated, a result of the direct displacement of the halogen rather than elimination, followed by conjugate addition.

The nmr spectrum of **5** showed the C-11 protons at δ 2.33 (multiplet, W_h = 6 Hz), and H-2 at δ 3.97 (distorted quartet, J = 4 and 3 Hz), consistent with the expected methylene and methine resonances, respectively. Deuterium exchange removed only the C-5 signal leaving the other resonances intact as expected.

Experimental Section[13]

4-Methyl-1-tetralone-4-*N*-methylacetamide (1). A. Mixed Anhydride Method.—To a cooled solution (0°) of 2.18 g (10 mmol) of 4-methyl-1-tetralone-4-acetic acid[8] dissolved in 150 ml of chloroform was added a solution of 1.60 g (14.8 mmol) of ethyl chloroformate in 25 ml of chloroform. This mixture was heated slowly to 40° and maintained at this temperature for 2 hr. After cooling at 0°, 620 mg (20 mmol) of anhydrous methylamine was bubbled into the solution. The amount was determined by weight difference. The solution was stirred for 2 hr while being allowed to warm to room temperature and then heated at 40° for an additional 2 hr. The white, granular precipitate that formed was removed by filtration. This solid was washed several times with chloroform and the chloroform extracts were combined and dried ($MgSO_4$). The chloroform was removed leaving 5.0 g of a brown oil. Thin layer chromatography on silica gel G (Brinkman) with a chloroform–methanol mixture (5:1) showed two major peaks with R_f 0.6 and 0.5. Careful column chromatography on a 150-g silica gel (Brinkman) column separated the two components.

The second component was the amide isolated as a colorless solid, 462 mg (20% of theory): mp 103–104° (acetone–ether); λ_{max}^{KBr} 3.08, 3.42, 3.50, 6.05 (C=O) (very broad), 6.34, 6.50, 6.95, 7.13, 7.80, 9.60, 13.15; $\delta_{TMS}^{CDCl_3}$ 1.55 (s, CCH_3), 2.20 (m, 4 methylene protons at C-2 and C-3), 2.58 (s, $CH_2C(=O)N$), 2.70 (d, NCH_3, with J = 5 Hz), 7.22 (q, broad, NH, coupling constant undiscernible), 7.50 (m, 3 aromatic protons), 8.00 (d, distorted, 1 aromatic proton with J = 7 Hz).

B. *N*-Hydroxysuccinimide Method.—A suspension of 1.00 g (4.6 mmol) of the tetralone acid and 946 mg (4.6 mmol) of dicyclohexylcarbodiimide in 20 ml of dioxane was cooled to 15°. To this cooled solution was added 527 mg (4.6 mmol) of *N*-hydroxysuccinimide, prepared by the method of Anderson.[14] This mixture was stirred overnight at room temperature. Dicyclohexylurea was removed by suction filtration and the dioxane evaporated affording the *N*-hydroxysuccinimide ester as a colorless oil: λ_{max}^{film} 3.38, 3.50, 5.45, 5.55, 5.73, 5.90, 6.18, 6.50, 6.65, 6.80, 7.25, 7.70, 7.90, 8.20, 8.50, 8.87, 9.25, 9.70, 11.10, 11.30, 12.20, 12.75, 15.20, and 15.65.

Without further purification the *N*-hydroxysuccinimide ester was dissolved in 25 ml of 1,2-dimethoxyethane and with stirring 2 ml of aqueous 40% methylamine was added. Dimethoxyethane may be substituted for dioxane in the esterification procedure to reduce the procedure to a single manipulation. After 24 hr the solvents were evaporated; the resulting oil was partitioned between 50 ml of ether and 50 ml of water. The ether solution was then washed with 20 ml of saturated brine solution, dried ($MgSO_4$), and filtered, and the ether was evaporated yielding 857 mg of 1 (81% of theory), mp 103–104° (acetone–ether).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.57; H, 7.34; N, 6.40.

1,7-Dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione (7).—To a refluxing solution of 8.30 g (35.9 mmol) of tetraloneacetamide **1** in 75 ml of glacial acetic acid was added dropwise a solution of 5.73 g (36 mmol) of bromine in 10 ml of acetic acid. The solution was refluxed for 10 min, cooled, and then thoroughly partitioned between water and ethyl acetate. The ethyl acetate fractions were combined, washed with water, aqueous 10% sodium bicarbonate solution, water, and saturated brine solution, and dried ($MgSO_4$). The solvent was evaporated, leaving 2.04 g (18% of theory) of crude α-bromo ketone: λ_{max}^{neat} 3.00 (broad), 3.30, 3.42, 3.47, 5.88, 6.06, 6.25, 6.45, 6.85, 7.17, 7.50, 7.69, 8.03, 8.62, 9.09, 9.66, 10.00, and 13.00.

The crude bromo ketone was dissolved in 60 ml of dimethylformamide and refluxed overnight. The dimethylformamide was evaporated affording an oil which contained several components as determined by thin layer chromatography. Column chromatography on 120 g of silica gel using 7:3 chloroform–ethyl acetate as eluent gave a total of 880 mg of **7**, mp 156–157° (60% yield based on crude α-bromo ketone), which was eluted in the fifth and sixth 100-ml portion of solvent: λ_{max}^{KBr} 3.35, 3.38, 5.82, 6.11, 6.25, 6.37, 6.82, 7.00, 7.15, 7.53, 7.90, 8.00, 8.88, 9.23, 9.53, 10.00, 10.40, 10.90, 11.10, 11.90, 12.20, 12.65, 13.00, 14.30, 14.90, and 15.65; $\delta_{TMS}^{CDCl_3}$ 1.59 (s, CCH_3), 2.70 (s, $CH_2C(=O)N$), 2.80 (s, NCH_3), 2.97, (d, CH_2CH, J = 4 Hz), 3.87 (CH, J = 4 Hz), 7.50 (m, 3 aromatic protons), 7.87 (d, distorted, 1 aromatic proton, J = 7 Hz).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.10; H, 6.58; N, 6.12.

To 50 mg (0.218 mmol) of **7** dissolved in 3.0 ml of dioxane was added 2.0 ml of deuterium oxide and 100 mg of sodium methylate. This mixture was stirred at room temperature overnight, neutralized with aqueous 10% hydrochloric acid, and thoroughly extracted with ethyl acetate. The ethyl acetate extracts were combined and dried ($MgSO_3$) and the solvent was evaporated affording deuterated **7**: $\delta_{TMS}^{CDCl_3}$ 1.59 (s, CCH_3), 2.80 (s, NCH_3), 3.87 (s, CHN), 7.50 (m, 3 aromatic protons), and 7.87 (d, distorted, 1 aromatic proton, J = 7 Hz).

1,7-Dimethyl-8-hydroxy-2,3-benzo-7-azabicyclo[4.3.0]-nonane-

(9) The intramolecular conjugate addition of the amide function would be expected to occur from a developing axial position on intermediate **9**, probably affording the cis-1,6 product, similar to reported preponderant axial conjugate additions of cyanide anion,[10,11] and certain carbanions.[12] The alternate structure with a trans-1,6 ring juncture cannot be eliminated.

(10) W. Nagata and I. Kikkawa, *Chem. Pharm. Bull.*, **11**, 289 (1963).

(11) M. P. Mertes, A. A. Ramsey, P. E. Hanna, and D. D. Miller, *J. Med. Chem.*, **13**, 789 (1970).

(12) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).

(13) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR-5A and IR-20 spectrophotometers. Nmr spectra were determined with Varian A-60 and T-60 spectrometers using tetramethylsilane as internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Microanalyses were conducted by Drs. G. Weiler and F. B. Stauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(14) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **86**, 1839 (1964).

4-one (8).—To 100 mg (0.437 mmol) of **7** and in 10 ml of absolute methanol was added 17 mg (0.437 mmol) of sodium borohydride and 1.0 mg of sodium hydroxide and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between 50 ml of ethyl acetate and 100 ml of water. The water layer was extracted with additional ethyl acetate (three 25-ml portions). The combined ethyl acetate fractions were washed with water and saturated brine solution and dried ($MgSO_4$). Removal of the solvent afforded 45 mg (22.3% of theory) of a colorless oil: λ_{max}^{neat} 2.94, 3.38, 3.44, 6.05, 6.80, 7.00, 7.23, 7.70, 7.87, 8.05, 8.47, 9.10, 9.35, 9.50, 9.80, 10.02, 13.30, 14.10, 14.60, 15.30, and 15.80 μ; $\delta_{TMS}^{CDCl_3}$ 1.43 (s, CH_3), 2.43 (m, C-5 CH_2), 2.67 (s, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.50 (q, CHN, J = 4 and 10 Hz), 4.62 (q, CHO, J = 4 and 10 Hz), and 7.25 (m, 4 aromatic protons).

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione (5).—Bromination of ketone amide **1** was more efficiently performed using a mixture of benzene and tetrahydrofuran as cosolvents. To a solution of 1.55 g (5.0 mmol) of **1** in 100 ml of benzene and 25 ml of tetrahydrofuran was added over 30 min a solution of 850 mg (5.3 mmol) of bromine in 10 ml of tetrahydrofuran. After the addition was complete and the bromine color disappeared, the solution was diluted with ethyl acetate, washed with 5% aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$), and evaporated affording crude α-bromo ketone **3**, 1.05 g (67% of theory), identical spectrally with the product obtained from the acetic acid method.

To a solution of sodium methoxide in methanol prepared by adding 0.92 g (0.004 g-atom) of sodium to 25 ml of absolute methanol was added 0.825 g (2.3 mmol) of crude α-bromo ketone **3** in 10 ml of methanol. The mixture was refluxed for 2 hr during which time sodium bromide precipitated. The mixture was partitioned between water and ethyl acetate and extracted with several portions of ethyl acetate. The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), and evaporated affording a brown oil which was chromatographed on 40 g of silica gel eluted with chloroform. The benzazocinedione (**5**) was obtained in fractions 5–8 (100-ml fractions). A total of 350 mg (67% of theory), mp 163–164° (benzene–petroleum ether), was collected: λ_{max}^{KBr} 3.38, 3.42, 3.48, 5.92, 6.05, 6.25, 6.85, 7.18, 7.41, 7.56, 7.71, 7.83, 8.07, 8.59, 9.03, 9.48, 10.05, 10.30, 12.23, 12.78, 13.03, 13.74, and 14.08; $\delta_{TMS}^{CDCl_3}$ 1.52 (s, CCH_3), 2.39 (m, $W_h \simeq 6$ Hz, CH_2CH), 2.55 (s, broadened, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.97 (q, distorted, J = 4 and 3 Hz, CHN), 7.45 (m, 3 aromatic protons), 8.02 (d, distorted, 1 aromatic proton).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.61; H, 6.64; N, 6.38.

Deuterium exchange was performed in a manner similar to that described for exchange on **7**. Only the signal at δ 2.55 disappeared.

Registry No.—**1**, 27093-03-4; **1** *N*-hydroxysuccinimide ester, 27093-04-5; **3**, 27093-05-6; **5**, 27093-06-7; **7**, 27141-07-7; **8**, 27093-07-8; 4-methyl-1-tetralone-4-acetic acid, 27093-08-9.

Acknowledgment.—This investigation was supported by Grant GM-13,782 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and by the State of Washington Initiative 171 Funds for Research in Biology and Medicine.

Synthesis of 2-Acetyl-1,4,5,6-tetrahydropyridine, a Constituent of Bread Aroma

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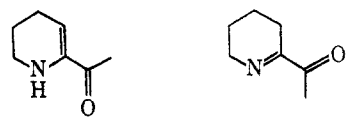
Received August 24, 1970

Of the aromas associated with man's food, that of baked bread is one of the most perishable. Efforts to stabilize the taste of fresh bread have met with little success mainly because the compounds responsible for this unique aroma remained unknown. Recent analysis of a methylene chloride extract of freshly baked bread led to the isolation of a compound with an overpowering odor of crackers.[1] This aroma principle was identical with a substance produced in low yield by heating proline with dihydroxyacetone[2] or glycerol,[1] and structural studies suggested the presence of 2-acetyl-1,4,5,6-tetrahydropyridine (**1**).[3] To confirm this and to further evaluate the organoleptic properties of this important compound, we have developed a rational synthesis.

Hydrogenation of 2-acetylpyridine (**3**) over a rhodium-on-alumina catalyst yielded 2-(1-hydroxyethyl)-piperidine (**4**) in 78% yield.[4] Oxidation of the alcohol **4**



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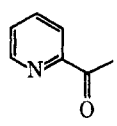

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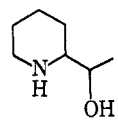

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with Celite suspended silver carbonate[5] in benzene solution did not give the anticipated saturated ketone but the desired enamino ketone **1** directly. This one-step procedure should be useful for the preparation of other α-amino-α,β-unsaturated ketones from 1,2-amino alcohols. The nuclear magnetic resonance spectrum of synthetic material was identical with that of the natural bread aroma constituent,[3] but a series of resonances previously[3] attributed to decomposition products are in fact caused by the imino tautomer **2** (see Experimental Section). Oxidation of the amino alcohol **4** for a short period of time gave a mixture of tautomers with ultraviolet absorption (pentane) at 312 nm (ϵ 2020) judged by nmr analysis to contain approximately two-thirds of the imine **2** and one-third of the enamine **1**. Further heating in benzene produced a new mixture with ϵ 3360 containing approximately two-thirds of the enamine **1** and one-third of the imine **2**. Consequently imine **2** is the initial product of oxidation while the enamine **1** represents the more stable tautomer. Infrared spectra confirmed the identities of synthetic and natural material and are in full accord with the presence of tautomers. Mixtures rich in imine form show intense absorption at 1695 cm^{-1}, while the enamine tautomer gives rise to bands at 1670 and 1650 cm^{-1}. Synthetic 2-acetyl-1,4,5,6-tetrahydropyridine (**1**) has the organoleptic properties characteristic of the bread constituent. In agreement with earlier findings the substance is exceptionally sensitive to air, but we have stored the corresponding

(1) I. R. Hunter, M. K. Walden, W. H. McFadden, and J. W. Pence, *Cereal Sci. Today*, **11**, 493 (1966).

(2) L. Wiseblatt and H. F. Zoumut, *Cereal Chem.*, **40**, 162 (1963).

(3) I. R. Hunter, M. K. Walden, J. R. Scherer, and R. E. Lundin, *ibid.*, **46**, 189 (1969). We are indebted to Dr. R. Teranishi for sending us a preprint of this paper.

(4) This reduction was mentioned in an article by M. Freifelder, *J. Org. Chem.*, **29**, 2895 (1964), but no details were given.

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