above-described solution of the silyl ester of I in toluene was added dropwise by syringe. Stirring was continued for 2 hr at −25°, and then a solution of 100 mg (0.99 mmol) of triethylamine in 0.2 ml of pentane was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 2 ml of ice-cold 1% aqueous hydrochloric acid and twice with 3 ml of cold water. Removal of dried (magnesium sulfate) solvents under vacuum produced 59 mg (92%) of the silyl ester of II as a colorless oil (homogeneous by tlc; $R_f$ 0.40, silica gel–methylene chloride): ir max (neat) 2970 (m), 1745 (s), 1710 (s), and 1150 cm$^{-1}$ (br s).

To a solution of 246 mg (3.00 mmol) of sodium acetate in 3 ml of acetone and 1 ml of water was added 180 mg (3.00 mmol) of acetic acid to give a standard solution of pH 4.5. To a solution of 59 mg of above-described silyl ester of II in 1 ml of acetone and 0.3 ml of water was added at 0° 0.4 ml of sodium acetate–acetic acid standard solution, and the mixture was stirred for 45 min. After warming to 25°, stirring was continued for 30 min, at which time tlc analysis indicated the absence of silyl ester. The solution was poured into 2 ml of ice–water and extracted with three 5-ml portions of ether. Removal of dried (magnesium sulfate) solvents under reduced pressure produced 48 mg (91% yield based on I) of the 11,15-bistetrahydropyranyl ether of prostaglandin $E_2$, chromatographically identical with authentic material. The infrared and nmr spectra were also identical with those of an authentic sample which had been prepared previously in this laboratory.[3,4]

**Oxidation of III to IV.**—To a solution of 21.3 mg (0.30 mmol) of chlorine in 1.5 ml of carbon tetrachloride was added at −10° a solution of 37.2 mg (0.30 mmol) of thioanisole in 0.5 ml of methylene chloride under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to −25°, and a solution of 56 mg (0.16 mmol) of the lactone alcohol III in 1 ml of methylene chloride was added dropwise. Stirring was continued for 90 min at −25°, and then a solution of 60.6 mg (0.60 mmol) of triethylamine in 0.5 ml of methylene chloride was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 1 ml of ice-cold 1% aqueous hydrochloric acid. Removal of dried (magnesium sulfate) solvents produced a white solid which was washed twice with 3 ml of cold pentane to give 52 mg (93%) of IV as colorless crystals ($R_f$ 0.25, silica gel–chloroform): nmr ($CDCl_3$) $\delta$ 2.0–3.6 (m, 6 H), 5.20 (br t, $J$ = 5 cps, 1 H), 5.6–5.8 (m, 1 H), 7.3–8.4 (m, 9 H, aromatic protons), 9.89 (s, 1 H, aldehyde); ir ($CHCl_3$) 2950 (m), 2850 (m), 1775 (s), 1725 (s), 1720 (s), 1610 (m), 1270 (s), 1100 (br), 910 cm$^{-1}$ (s). The chromatographic and spectral data agreed with those obtained for IV which had been prepared by Collins oxidation. The product IV could be used for the synthesis of prostaglandins as previously described[3,4] without further purification.

**Registry No.**—I, 37786-09-7; II, 38123-52-3; III, 32233-39-9; IV, 32233-41-3.

**Acknowledgment.**—We are indebted to the National Institutes of Health and the U. S. Agency for International Development for financial assistance.

## The Synthesis of 9-Ketotridecanolide and Related 13- and 16-Membered Ketolactones[1]

IRVING J. BOROWITZ,* VICTOR BANDURCO, MICHAEL HEYMAN, ROBIN D. G. RIGBY, AND SHOU-NAN UENG

*Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York 10033*

*Received October 4, 1972*

We have shown that keto lactones, including 7-ketoundecanolide, the parent system present in methymycin, can be synthesized by the oxidation of bicyclic enol ethers derived from the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones.[2-4] Previously, six- to eight-membered ring ketones have been utilized. We now demonstrate the further utility of this method in the synthesis of 8-ketododecanolide (**1**), 9-ketotridecanolide (**2**), and 12-ketopentadecanolide (**3**) from cyclooctanone, cyclononanone, and cyclododecanone, respectively, in overall yields of 46, 35, and 19%.

The C-alkylations of carbethoxycyclooctanone (**4**) and cyclononanone (**5**) *via* their sodium enolates with 1-bromo-4-acetaoxybutane (**6**) proceed as previously described for smaller ring ketones[2] to lead to 2-(4′-hydroxybutyl)cyclooctanone (**7**) and the corresponding cyclononanone **8**. Hemiketal formation and dehydration of **7** proceeds readily upon acid catalysis or slow distillation *in vacuo*. The corresponding closure of **8** is more difficult and is best performed by distillation from potassium pyrosulfate.[3]

The oxidation of the resultant bicyclic enol ethers **9** and **10** with excess *m*-chloroperbenzoic acid (MCPBA)[2-4] must be done for a short time period in order to keep Baeyer–Villiger oxidation of the product ketolactone to dilactones as a minor side reaction. The utilization of other oxidation procedures (which avoid dilactone formation but are not as good in yield) such as reaction with *tert*-butylhydroperoxide and molybdenum hexacarbonyl[4b] or lead tetraacetate oxidation of the corresponding glycol[5] was only briefly investigated for these cases.

It is noteworthy that **2** represents the parent system of the erythromycin macrolides.[6]

Finally, **3** is readily synthesized from 2-(3′-hydroxypropyl)cyclododecanone (**12**), which is formed from the pyrrolidine enamine of cyclododecanone (**11**) upon reaction with ethyl acrylate, followed by lithium aluminum hydride reduction.[3,7]

### Experimental Section[8]

**8-Ketododecanolide** (**1**).—Treatment of the sodium enolate of 2-carbethoxycyclooctanone[9] (from **4** and sodium hydride in toluene at reflux for 30 min) with 1-bromo-4-acetoxybutane (**6**, 1.1 equiv) for 2 days at reflux gave crude 2-carbethoxy-2-(4′-acetoxybutyl)cyclooctanone, which was hydrolyzed with potassium hydroxide in aqueous ethanol at reflux for 48 hr to give 2-(4′-hydroxybutyl)cyclooctanone (**7**, 62% yield): bp 127–129°

(1) This investigation was supported by Public Health Service Research Grant AI 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part 8 of the series, Medium Ring Compounds.

(2) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *J. Org. Chem.*, **37**, 581 (1972).

(3) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *ibid.*, **33**, 2013 (1968).

(4) (a) I. J. Borowitz and R. Rapp, *ibid.*, **34**, 1370 (1969); (b) I. J. Borowitz and R. Rapp, *Chem. Commun.*, 1202 (1969).

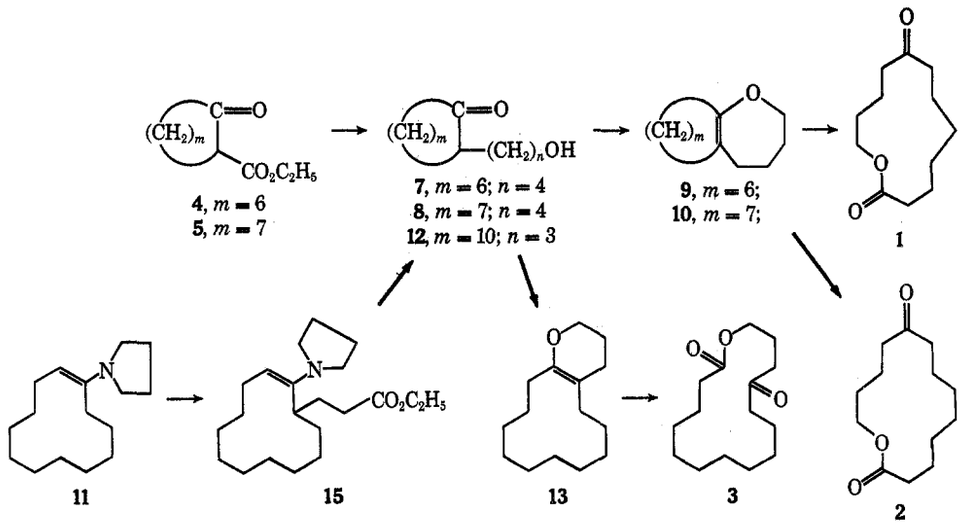
(5) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

(6) M. Berry, *Quart. Rev. Chem. Soc.*, **17**, 343 (1963).

(7) (a) G. Stork and S. Etheredge, unpublished; (b) S. Etheredge, Ph.D. Thesis, Columbia University, 1965; *Diss. Abstr.*, **26**, 4232 (1966).

(8) Infrared spectra were recorded on Perkin-Elmer 257 and Beckman IR-8 spectrophotometers. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on Mel-Temp and Thomas-Hoover apparatus and are corrected while boiling points are uncorrected. Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical College, N. Y., and Columbia University. Solvents were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under prepurified nitrogen. All vpc columns employed Chromosorb W and were 5 or 10 ft × 0.25 in.

(9) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Syn.*, **47**, 20 (1967).




(0.55 mm); nmr ($CCl_4$) $\tau$ 8.55 (m, 16), 7.70 (m, 3, $\alpha$-H), 6.54 (t, 2, $CH_2O$), 6.02 (s, 1, OH).

*Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.40; H, 10.92.

Slow distillation of crude **7** *in vacuo* gave 2-oxabicyclo[5.6.0]-tridec-1(7)-ene (**9**, 58% from **4**): bp 70–75° (0.15 mm); ir (film) 1660 $cm^{-1}$ (C=CO–), no OH; nmr ($CCl_4$) $\tau$ 6.1 (t, 2, $CH_2O$), 7.88 (m, 6, allylic H), and 8.2–8.5 (m, 12).

Addition of **9** to 85% pure MCPBA (2.2 equiv) in $CH_2Cl_2$ for 5 min, followed by reaction for 10 min at 25° and work-up,[3,5] gave crude **1** (80%, 95% purity by vpc at 210° on 10% SE-30). Repeated molecular distillation at 90° (0.1 mm) gave **1** as an oil: single peak by vpc as above; nmr ($CDCl_3$) $\tau$ 6.0 (t, 2, $CH_2O$), 7.7 (m, 6, $\alpha$-CH), 8.4–8.6 (m, 12).

*Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.66; H, 9.56.

Oxidation of **9** (1.0 g, 0.0056 mol) in benzene (50 ml) containing $Mo(CO)_6$ (0.003 g) with 60% *tert*-butyl hydroperoxide (1.9 g, 0.012 mol)[4b] at reflux for 48 hr gave a mixture (by vpc) which was chromatographed on silica to give **1** (90% purity, 50% yield).

**9-Ketotridecanolide (2).**—Pyrrolidinocycloheptene (**14**) was consistently formed in *ca.* 68% yield from cycloheptanone and pyrrolidine by the use of benzene *and hexane* (4:1) as the azeotropic solvent. Other procedures gave generally lower yields, as previously noted.[3] Cyclononanone (from **14** in 37% overall yield[10]) was converted to carbethoxycyclononanone (**5**, 82% mixture of keto and enol forms): bp 85–100° (0.1 mm); nmr ($CCl_4$) $\tau$ −2.7 (3, 0.3 H, enolic OH), 5.8 (2 q, 2, $OCH_2CH_3$), 6.5 (t, 0.7, $C_2H$), 7.4–8.8 (m, 17). Alkylation of the sodium enolate of **5** with **6** (procedure as for **4**) gave 2-(4′-hydroxybutyl)-cyclononanone (**8**, 74% from **5**): bp 125° (0.02 mm); ir (film) 3400, 1695 $cm^{-1}$; nmr ($CCl_4$) $\tau$ 6.3–6.8 (m, 3, $CH_2OH$), 7.8–9.1 (m, 21); mass spectrum (80 eV) *m/e* 212 ($M^{\cdot+}$), 194 (M − $H_2O$), 165, 140, 112, 98, 84, 67, and 55.

*Anal.* Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.58; H, 11.48.

A mixture of **8** (1.3 g, 0.006 mol) and potassium pyrosulfate (0.13 g, 0.0005 mol) was slowly distilled (5 hr) through a short coiled column at bath temperature 110° (0.01 mm) to give 2-oxabicyclo[5.7.0]tetradec-1(7)-ene (**10**, 0.6 g, 0.003 mol, 50%), which was trapped at −70°: ir (film) 1660 $cm^{-1}$, no OH; nmr ($CCl_4$) $\tau$ 6.1 (t, 2, $OCH_2$), 7.85 (m, 6, allylic H), 8.53 (m, 14). A repetittion on a larger scale gave 77% of **10**. Conversion of **10** to a dimer (*m/e* 388) of unknown structure occurred if it was kept at room temperature for more than several hours.

Addition of crude **10** (0.55 g, 0.0028 mol) to 85% pure MCPBA (1.5 g, 0.0074 mol, 2.6 equiv) in $CH_2Cl_2$ (7 ml) as described for **9** (see above) gave an oily mixture (0.6 g) from which was crystallized 0.085 g of a solid: mp 84–85°; vpc (20% SE-30 at 275°), 85% dilactones (*m/e* 242) and 15% 9-ketotridecanolide (**2**, *m/e* 226). Molecular distillation of the mother liquor gave **2** (0.42 g, *ca.* 60%) containing 10% of dilactones (by vpc). An aliquot was separated by preparative vpc (20% SE-30 at 245°) to give pure **2**: mp 28°; high-resolution mass spectrum[11] (70 eV) *m/e* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1543; *m/e* (rel intensity) 226 (3), 111 (20), 101 (36), 98 (100), 84 (13), 83 (30), 69 (15), 55 (70); ir (Nujol mull) 1740, 1710 $cm^{-1}$; nmr ($CCl_4$) $\tau$ 5.95 (t, 2, $OCH_2$), 7.5–7.9 (m, 6, $CH_2C{=}O$), 8.1–8.9 (m, 14).

The semicarbazone had mp 172–172.5°. *Anal.* Calcd for $C_{14}H_{25}N_3O_3$: C, 59.34; H, 8.89; N, 14.83. Found: C, 59.54; H, 9.30; N, 15.08.

A larger scale oxidation of **10** utilizing 2.0 equiv of MCPBA gave 15% of dilactones and 69% of **2**.[12]

**12-Ketopentadecanolide (3).**—Pyrrolidinocyclododecene (**11**)[13] was treated with ethyl acrylate (1.3 equiv) in benzene to give the pyrrolidine enamine of 2-(2′-carbethoxyethyl)cyclododecanone (**15**, 72%, procedure previously described):[3,7] bp 165–175° (0.2 mm); ir (neat) 1727, 1640, 1610 $cm^{-1}$; nmr ($CCl_4$) $\tau$ 5.94 (t, 2, $CO_2CH_2CH_3$), 6.53 (m, 1, vinyl H),[14] 7.04 (t, 4, $NCH_2$), 8.0–8.87 (m, 30).

The enamine ester **15** gave the 2,4-dinitrophenylhydrazone of 2-(2′-carbethoxyethyl)cyclododecanone: mp 102–104° [diethyl ether–petroleum ether (bp 30–60°)]; ir ($CHCl_3$) 3330, 1730, 1615, 1600, 1520, 1350 $cm^{-1}$ ($NO_2$). *Anal.* Calcd for $C_{23}H_{34}N_4O_6$: C, 59.70; H, 7.41; N, 12.11. Found: C, 59.48; H, 7.46; N, 12.13.

Reduction of **15** with lithium aluminum hydride[3,7] gave 2-(3′-hydroxypropyl)cyclododecanone (**12**, 84%): bp 150–170° (0.17 mm); ir (neat) 3360, 1700 $cm^{-1}$; nmr ($CCl_4$) $\tau$ 6.52 (t, 2, $CH_2O$), 6.72 (s, OH), 7.53–8.7 (m, 25), Slow distillation of **12** from *p*-toluenesulfonic acid *in vacuo* gave 2-oxabicyclo[4.10.0]hex-1(6)-ene (**13**, 85%): bp 102–105° (0.33 mm); vpc (5% SE-30), one peak at 160–173°; ir (neat) 1670 $cm^{-1}$; nmr ($CCl_4$) $\tau$ 6.18 (t, 2, $OCH_2$), 7.87–8.64 (m, 24); mass spectrum (7 eV) *m/e* (rel intensity) 222 ($M^{\cdot+}$, 10), 123 (33), 111 (29), 110 (17), 98 (56), 67 (40), 55 (65).

Addition of **13** to MCPBA (2.6 equiv) in $CH_2Cl_2$ over 10 min followed by reaction at room temperature for 30 min and work-up[5] gave 12-ketopentadecanolide (41%): bp 127–132° (0.2 mm);

(10) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

(11) High-resolution mass spectra were done by Dr. R. Foltz, Battelle Memorial Institute, Columbus, Ohio, on an MS-9 mass spectrometer under NIH contracts 69-2226 and 71-2483.

(12) Reaction of **10** with MCPBA (3 equiv) in $CH_2Cl_2$ for 30 min gave a mixture of 76% of dilactones (*m/e* 242; vpc one peak with a shoulder; not further characterized) and 24% of **2** (by vpc relative areas).

(13) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(14) Enamine **15** apparently exists mainly as the less substituted isomer, as is the case for the pyrrolidine enamines of 2-alkylcyclohexanones.[15]

(15) (a) M. E. Kuehne, *J. Amer. Chem. Soc.*, **81**, 5400 (1959); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

ir (neat) 1715, 1735 $cm^{-1}$; nmr ($CDCl_3$) $\tau$ 5.94 (t, 2, $OCH_2$), 7.61 (m, 6, $CH_2C{=}O$), 8.0–8.65 (m, 18); mass spectrum (10 eV) *m/e* (rel intensity) 254 ($M\cdot^+$, 72), 236 (78), 226 (18), 222 (13), 208 (30), 156 (87), 153 (10), 139 (10), 112 (28), 111 (11), 98 (34), 97 (30), 86 (57), 85 (100).

The semicarbazone (79%) had mp 156.5–158°. *Anal.* Calcd for $C_{16}H_{29}N_3O_3$: C, 61.71; H, 9.39; N, 13.49. Found: C, 61.71; H, 9.43; N, 13.66.

**Registry No.**—**1,** 38223-26-6; **2,** 38223-27-7; **2** semicarbazone, 38223-28-8; **3,** 38223-29-9; **3** semicarbazone, 38223-30-2; **4,** 4017-56-5; **5,** 4017-57-6; **6,** 4753-59-7; **7,** 38223-49-3; **8,** 38223-50-6; **9,** 38223-51-7; **10,** 38223-52-8; **12,** 32539-82-5; **13,** 32539-83-6; **15,** 38223-55-1; 2-(2′-carbethoxyethyl)cyclododecanone dinitrophenylhydrazone, 38223-56-2; cyclonoanone, 3350-30-9; 1,6-dioxacyclopentadeca-1,15-dione, 38223-57-3; 1,7-dioxacyclopentadeca-2,8-dione, 38223-58-4.

**Acknowledgment.**—We are indebted to Dr. Gary Koppel for experimental assistance.

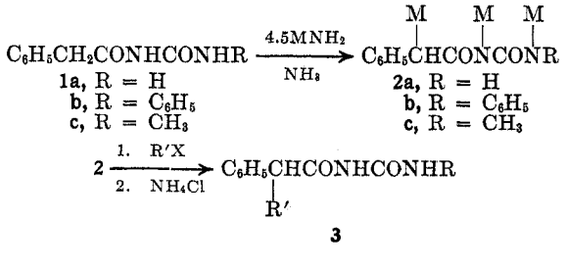
## Selective C-Alkylation of Phenylacetylureas through 1,3,5-Trialkali Salt Intermediates[1]

JACK D. TAYLOR,[2] GEORGE B. TRIMITSIS, TOMAS HUDLICKY,[3] AND JAMES F. WOLFE*

*Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061*

*Received August 22, 1972*

Recently,[4–6] we have found that 1,3,5 trianions derived from certain imides and β-keto imides can serve as useful synthetic intermediates by virtue of the high degree of regioselectivity accompanying their reactions with electrophilic reagents. During the course of these studies it occurred to us that arrangement of potential anion-stabilizing groups in phenylacetylurea (**1a**) might permit conversion of this compound into the 1,3,5-trialkali salt **2a**, which would represent the first example of a ureide trianion. It was anticipated that alkylation might then be directed selectively to the carbanion site of **2a** to afford *C*-alkyl derivatives **3**, a class of compounds which continue to attract considerable attention as anticonvulsant agents.[7] Moreover, such a direct new synthesis involving a single precursor, **2a**, could offer a more expedient method for certain structural variations than the multistep procedures[8] currently used for the preparation of compounds **3**.

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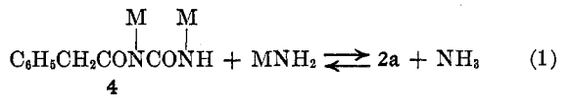
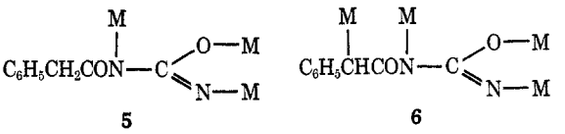
Treatment of **1a** with 2 mol equiv of potassium amide in liquid ammonia resulted in essentially complete consumption of the base as evidenced by the absence of stilbene formation upon addition of benzyl chloride.[9] Removal of the ammonia, followed by quenching with excess deuterium oxide, gave a good recovery of **1a** containing only N-bonded deuterium, indicating that 2 equiv of base produced the weakly nucleophilic dianion **4**, which failed to undergo appreciable alkylation at −33°.[10] Reaction of **1a** with 3 mol equiv of potassium amide in liquid ammonia followed by benzyl chloride afforded a mixture of *C*-benzyl derivative **3a**, unreacted **1a**, and stilbene. Since these results appeared to be consistent with an unfavorable equilibrium involving abstraction of a benzylic proton from dianion **4** to form trianion **2a** (eq 1), attempts were made to increase the




(1)

concentration of **2a** by replacing the ammonia with ether. This proved to be unsatisfactory because of extensive ammonolysis of the trianion during solvent exchange.[11] However, treatment of **1a** with 4.5 mol equiv of potassium amide in liquid ammonia, followed by a series of representative halides, afforded C-alkylation derivatives **3a–e** in good yields (Table I). Similarly, reaction of *N′*-phenyl- and *N′*-methylureides **1b** and **1c** with excess potassium amide in liquid ammonia followed by benzyl chloride afforded *C*-alkyl products **3f** and **3i** in good yields, while attempted benzylations in the presence of stoichiometric amounts of base gave mixtures consisting of **3f** and **3i**, unreacted starting materials, and stilbene.

It is conceivable that reaction of dianion **4** with a third equivalent of potassium amide could lead to a mixture of intermediates more complex than that illustrated in eq 1, possibly consisting of **2a** and the isomeric trianion **5**.[12] The excess amide necessary for

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(1) This investigation was supported by the National Institutes of Health, Grants GM-14340 and NS-10197.

(2) Abstracted from the Ph.D. dissertation of J. D. T., Virginia Polytechnic Institute and State University, July 1971.

(3) NSF undergraduate research participant, summer 1971.

(4) J. F. Wolfe, C. L. Mao, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, **31**, 3726 (1966).

(5) J. F. Wolfe and C. L. Mao, *ibid.*, **32**, 1977 (1967).

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(7) J. M. Delgado and E. I. Isaacson, "Medicinal Chemistry," 3rd ed, A. Burger, Ed., Interscience, New York, N. Y., 1970, Chapter 52; C. D. Lunsford, *Annu. Rep. Med. Chem.*, **4**, 30 (1969).

(8) For examples of traditional synthesis of compounds **3**, see (a) E. H. Volwiler and D. L. Tabern, *J. Amer. Chem. Soc.*, **58**, 1352 (1936); (b) M. A. Spielman, A. O. Geiszler, and W. J. Close, *ibid.*, **70**, 4189 (1948); (c) H. Takamatsu, S. Umemoto, S. Kanoh, and T. Isozaki, U. S. Patent 3,110,728 (1963); *Chem. Abstr.*, **60**, 2861*a* (1964); (d) H. Takamatsu, S. Umemoto, T. Tatsumi, and T. Isozaki, Japan, Patent 22,932 (1965); *Chem. Abstr.*, **64**, 3432*d* (1966).

(9) C. R. Hauser, W. R. Barsen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

(10) D. R. Bryant, S. D. Work, and C. R. Hauser, *J. Org. Chem.*, **29**, 235 (1964).

(11) W. S. Murphy and C. R. Hauser, *Chem. Ind. (London)*, 832 (1969).

(12) For examples of related trianions, see E. M. Kaiser, R. L. Vaux, and C. R. Hauser, *J. Org. Chem.*, **33**, 3640 (1967).