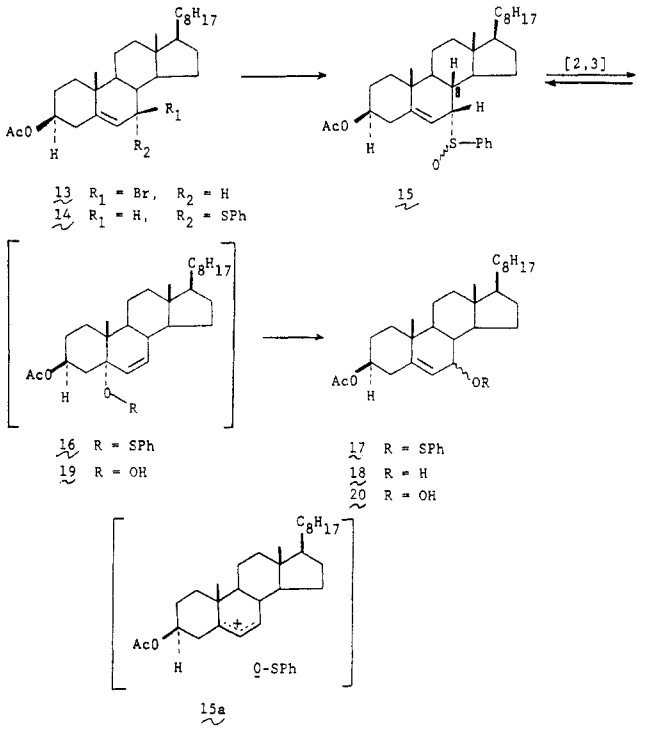
Scheme III



smoothly at 100 °C in toluene (vs. only 70 °C for the conversion of **10, 11 → 12**), presumably proceeds via the ion pair **15a**. This transient intermediate may result from dissociation of either the 7α-sulfoxide **15** or the Δ⁶-5α-phenylsulfenate ester **16**, expected to be in thermal equilibrium with **15**, interconverting by a facile [2,3] sigmatropic rearrangement. Eventual collapse of the ion pair **15a** could then generate the Δ⁵-7α,β-sulfenates **17**, yielding the observed alcohols **18** upon hydrolytic workup.[17] This pathway is precedented in the singlet-oxygen reaction[18] of cholesterol which yields the isolable Δ⁶-5α-hydroperoxide **19**, an unstable species which slowly rearranges on standing to the epimeric mixture of 7α,β-hydroperoxides **20**.

In practice, the overall conversion of cholesterol esters to their 7-dehydrocholesterol derivatives proceeds smoothly without the need to purify any of the intermediates. The desired 7-dehydrocholesterol ester (originating ultimately from the predominant 7α-bromide of type 8) is separated from the minor byproduct alcohols, e.g., **18** (derived from the 7β-bromide species **13**), by a simple filtration over silica. The overall yields are on average over 50%. This methodology is quite general and has been applied to a variety of cholesterol derivatives relevant to the synthesis of the human metabolites of vitamin $D_3$. We therefore believe that this process for the synthesis of 7-dehydrocholesterols offers a viable alternative to the existing technology for the preparation of these extremely important substances.

## Experimental Section

Melting points were determined on a Rinco Model M-50 melting-point apparatus and are uncorrected. IR spectra were obtained by using a Beckmanan IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were determined with Varian T-60 and HA-100 spectrometers, using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV, using a direct insertion probe. Thin-layer chromatography was carried out by using Merck F-254 silica gel plates. The general overall procedure will be exemplified by the synthesis of 7-dehydrocholesterol acetate (**12**) from cholesterol acetate (**7**).

**7-Dehydrocholesterol Acetate (12).** A mixture of 50 g (0.117 mol) of cholesterol acetate (**7**), 23.82 g (0.082 mol) of dibromantin, and 53.04 g (0.631 mol) of sodium bicarbonate in 2 L of hexane was heated under reflux (argon) for 0.5 h. The reaction was cooled and filtered to remove 5,5-dimethylhydantoin (and inorganic salts), and the filtrate was evaporated to dryness. The residue was taken up in 400 mL of toluene and treated with 20.32 g (0.233 mol) of anhydrous lithium bromide in 270 mL of acetone. The mixture was stirred at 0 °C for 2 h, removed from the ice bath, and treated with 22.1 mL (0.157 mol) of triethylamine and 16.0 mL (0.157 mol) of benzenethiol. After being stirred for 1.25 h at 25 °C, the reaction was diluted with 1 L of ethyl acetate, washed with 500 mL of 1 N HCl, and two 500-mL portions of water. The organic phase was dried over sodium sulfate and evaporated.[19] The residue was dissolved in 770 mL of ethyl acetate, cooled to 0 °C, and treated with 26.05 g (0.128 mol) of *m*-chloroperbenzoic acid (85%) for 2 h. The mixture was washed with 10% $NaHCO_3$ and water. The organic phase was dried over sodium sulfate and evaporated.[20] The residue was dissolved in 1 L of toluene, treated with 36 mL (0.256 mol) of triethylamine, heated at 70 °C for 28 h, cooled, and washed twice with water. The organic phase was dried over sodium sulfate and evaporated. The residue was filtered through 1.5 kg of silica, eluting with methylene chloride. fractions containing the product were combined and evaporated to yield 33.97 g (68%) of 7-dehydrocholesterol acetate (**12**). The product was recrystallized from methylene chloride/methanol to afford 26.56 g (53%) of pure **12**: white needles; mp 129–130 °C (lit.[21] mp 129–130 °C); IR (KBr) 2950, 1735 (OAc), 1260 $cm^{-1}$; NMR ($CDCl_3$) δ 5.56, 5.48 [br q, 2 H, C(6)-H, C(8)-H], 4.7 (br m, 1 H, CHOAc), 2.03 (s, 3 H, Ac); mass spectrum *m/e* 426 ($M^+$),366 ($M^+$ – HOAc), 351, 281, 253; UV max (hexane) 271 nm (ε 11 620), 281 (12 320), 294 (7050). Anal. Calcd for $C_{29}H_{46}O_2$ (mol wt 426.694): C, 81.63; H, 10.87. Found: C, 81.58; H, 10.78.

**Acknowledgment.** We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of spectral and analytical data.

**Registry No.** 7, 604-35-3; 12, 1059-86-5.

(17) Esters of sulfenic acids (RSOH) are known to be very readily hydrolyzed. See: Kharasch, N.; Potempa, S. J.; Wehrmeister, H. L.; *Chem. Rev.* **1946**, *39*, 323–26.

(18) Schenck, G. O.; Neumueller, O. A.; Eisfeld, W. *Justus Liebigs Ann. Chem.* **1958**, *618*, 202–210.

(19) The pure 7β-phenyl sulfide **9** may be obtained at this point as a white solid, mp 99–100 °C (2-propanol), by chromatography over silica, eluting with methylene chloride/hexane, 1:1.

(20) The sulfoxides **10** and **11** may be isolated at this point by chromatography over silica, eluting with methylene chloride/ethyl acetate, 9:1. The (*R*)-sulfoxide **11** was obtained as white needles, mp 128–130 °C ($CH_3OH$); the (*S*)-sulfoxide **10** was an amorphous white solid.

(21) Schaltegger, H. *Helv. Chim. Acta* **1950**, *33*, 2101–2110.

# Diastereoisomers of 3-Methylpyroglutamic Acid and β-Methylglutamic Acid

Anthony B. Mauger

*Research Foundation of the Washington Hospital Center, Washington, D.C. 20010*

*Received October 7, 1980*

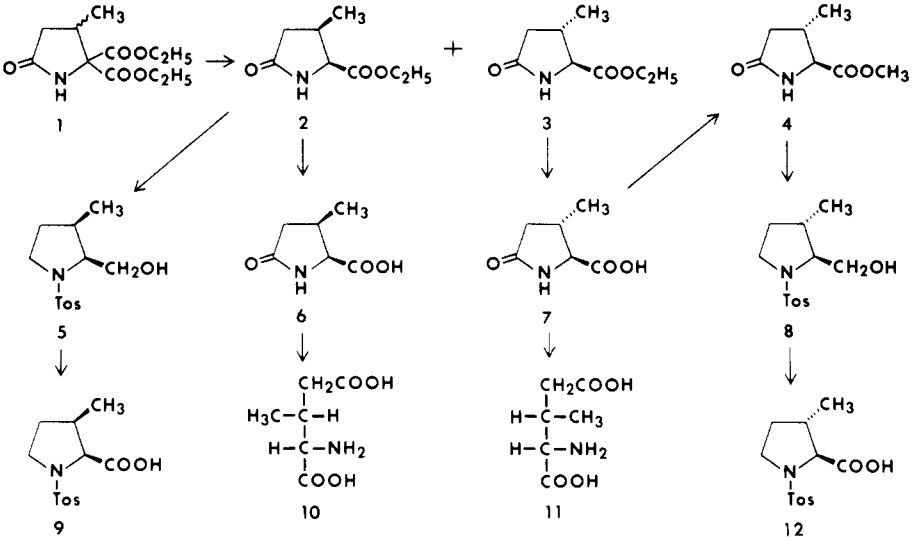
Compared with numerous publications concerning α- and γ-methylglutamic acids, reference to β-methylglutamic acid in the literature is relatively scant. Although several syntheses have been reported [1-6], none describes the sep-

(1) J. Smrt and F. Šorm, *Collect. Czech. Chem. Commun.*, **18**, 131 (1953).

(2) A. Meister, L. Levintow, R. E. Greenfield, and P. A. Abendschein, *J. Biol. Chem.*, **215**, 441 (1955).

**Scheme I. Synthesis of the Diastereoisomers of 3-Methylpyroglutamic Acid and β-Methylglutamic Acid and Correlation with Those of 3-Methylproline[a]**



[a] All compounds are racemic but for clarity are represented here as L enantiomers.

**Table I. Proton NMR Data for *cis*- and *trans*-3-Methylpyroglutamic Acids and Their Esters[a]**

| | chemical shifts, δ | | | | | coupling constants, Hz | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| compd | 2 | 3 | 4α | 4β | Me | $J_{2,3}$ | $J_{3,4\alpha}$ | $J_{3,4\beta}$ | $J_{4\alpha,4\beta}$ | $J_{3,Me}$ |
| **6** | 4.42 | 2.91 | 2.60 | 2.10 | 1.05 | 8.1 | 8.5 | 7.1 | 17.1 | 7.2 |
| **7** | 4.02 | ~2.65 | 2.12 | ~2.65 | 1.28 | 5.0 | *b* | *b* | *b* | 6.7 |
| **2** | 4.25 | 2.83 | 2.48 | 2.10 | 1.06 | 7.9 | 8.4 | 7.3 | 16.6 | 7.0 |
| **3** | 3.82 | ~2.57 | 2.07 | ~2.57 | 1.30 | 5.0 | *b* | *b* | *b* | 6.7 |
| **4** | 3.84 | ~2.58 | 2.02 | ~2.58 | 1.29 | 5.1 | *b* | *b* | *b* | 6.7 |

[a] Solvents for the acids and esters were $D_2O$ (internal DSS) and $CDCl_3$ (internal $Me_4Si$), respectively. Protons 4α and 4β are trans and cis to carboxyl, respectively. [b] Coupling constants not determined due to overlap of 3-H with 4β-H.

aration and characterization of the individual diastereoisomers. Mention has been made of the four enantiomers,[7] but subsequent publication of the details has not appeared. Failure to separate the diastereoisomers by paper chromatography in several solvent systems has been reported;[5] however, they can be distinguished by paper electrophoresis.[8] When the complete isomeric mixture was incubated with glutamine synthetase and hydroxylamine, only the *threo*-D isomer was converted to the hydroxamate.[8] The stereochemistry of this isomer was assigned after its chemical conversion, in several steps, to allo-D-isoleucine. A synthesis of 3-methylpyroglutamic acid (no diastereoisomeric separation) has been described[9] and also one of its ethyl ester;[10] however, the melting point given for the latter compound is higher by 58 °C than that reported here for the one crystalline diastereoisomer.

In the present investigation the racemic diastereoisomers of 3-methylpyroglutamic acid and β-methylglutamic acid were prepared and their stereochemistry rigorously assigned. It was assumed that diastereoisomeric separation would be easier with the cyclic (3-methylpyroglutamic acid or derivative) compounds than with their acyclic counterparts. The known, crystalline pyrrolidone **1**, which is available in one step from Michael condensation of diethyl acetamidomalonate with ethyl crotonate,[9] was the starting point of the present synthesis (Scheme I). Partial saponification of **1**, followed by decarboxylation, afforded a mixture of cis and trans isomers (**2** and **3**) of ethyl 3-methylpyroglutamate in good yield. The diastereoisomers were readily distinguishable by gas chromatography. Attempted chromatographic separation on an open silica gel column gave only a partial separation. It was more convenient, especially on a large scale, to isolate the cis isomer (**2**) by low-temperature crystallization from ether. The isomeric mixture (72% trans) obtained from the filtrate was saponified to the acid which, after several recrystallizations from water, afforded the pure trans isomer (**7**). The corresponding cis isomer (**6**) was obtained by saponification of **2**. In addition, the crystalline methyl ester (**4**) was produced by reaction of **7** with diazomethane.

Proton NMR parameters for the diastereoisomeric 3-methylpyroglutamic acids and their esters are shown in Table I. Comparisons with the proton NMR data for *cis*- and *trans*-3-methylprolines and their derivatives[10] reveal striking parallels upon which the stereochemical assignments of **6** and **7** are partly based. Thus, in both series, the α-protons are at higher field in the trans compounds than in the cis (due to the shielding effect of the 3-methyl group). In addition, the 3-methyl protons are at lower field in the cis isomers than in the trans (due to deshielding by the carboxyl group). Similar effects have been observed in other proline analogues, for example the diastereoisomers of 3-hydroxy-5-methylproline.[11] Coupling constant data support these assignments. Thus, in the 3-methylpyroglutamic series the $J_{2,3}$ values are larger for the cis

(3) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 6072 (1955).
(4) T. Haga and M. Sato, *Nippon Kagaku Zasshi*, **83**, 609 (1962).
(5) Y. C. Kim and G. H. Cocolas, *J. Med. Chem.*, **8**, 509 (1965).
(6) H. Gershon, R. Parmegiani, V. R. Giannasio, and I. S. Krull, *J. Pharm. Sci.*, **64**, 1855 (1975).
(7) T. Harada, M. Imaida, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **44**, 1419 (1971).
(8) H. M. Kagan and A. Meister, *Biochemistry*, **5**, 725 (1966).
(9) G. H. Cocolas and W. H. Hartung, *J. Am. Chem. Soc.* **79**, 5203 (1957).
(10) A. B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 2019 (1966).
(11) A. B. Mauger, O. A. Stuart, E. Katz, and K. T. Mason, *J. Org. Chem.*, **42**, 1000 (1977).

isomers (~8 Hz) than for the trans (~5 Hz). This parallels the case of the diastereoisomeric *N*-acetyl-3-methylproline esters[10] ($J_{2,3}$ = 7.9 and 5.1 Hz, respectively).

The stereochemical assignments were confirmed by chemical conversion of the *cis*- and *trans*-3-methylpyroglutamic esters **2** and **4** to the corresponding diastereoisomers of *N*-(*p*-toluenesulfonyl)-3-methylproline (**9** and **12**, Scheme I). Reduction of **2** and **4** with lithium aluminum hydride and tosylation in situ afforded the corresponding *N*-(*p*-toluenesulfonyl)-3-methylprolinols **5** and **8**. Chromic acid oxidation of these alcohols gave **9** and **12** respectively, identical with the authentic diastereoisomers prepared from *cis*- and *trans*-3-methylprolines. Gas chromatographic distinction between **9** and **12** and comparisons with the authentic compounds were also made after their conversion to the methyl esters with diazomethane. Since the diastereoisomers of 3-methylproline have been correlated by chemical conversions with those of isoleucine,[10,12,13], the above manipulations effect correlation of the latter with those of 3-methylpyroglutamic acid.

Following the separation and stereochemical assignment of *cis*- and *trans*-3-methyl-DL-pyroglutamic acids, *threo*- and *erythro*-β-methyl-DL-glutamic acids (**10** and **11**) were obtained by their acid hydrolysis. *N*-(*p*-Toluenesulfonyl) derivatives (**13** and **14**) of the latter compounds were also prepared. The melting points of **10** and **11** were 185–186 and 172.5–173.5 °C, respectively. In syntheses of the isomeric mixture,[1-6] melting points in the region 162–170.5 °C have been reported, which in some instances probably reflect concentration of the less soluble erythro isomer during recrystallization. In contrast to their cyclic counterparts (**6** and **7**), the proton NMR spectra of **10** and **11** were almost identical. Likewise, gas chromatographic separations (in this case with the *N*-trifluoroacetyl dimethyl esters) were more difficult. Accordingly, a superior derivatization procedure for GC was devised involving thermal conversion to the corresponding 3-methylpyroglutamic acids without epimerization (see experimental section), followed by methyl esterification with diazomethane. On the amino acid analyzer, the threo isomer emerged before the erythro.

## Experimental Section

$^1$H NMR spectra were obtained on a Varian HR-220 in the CW mode, with 0.2 M solutions at 18 °C.

For gas chromatography (GC) a Shimadzu Model 4BM, equipped with flame-ionization detectors, was employed with argon (60 mL/min) as carrier gas. Glass columns (2.5 m × 3 mm) contained 3% Poly-A 103 (column A), OV-225 (column B), or OV-17 (column C) on Gas Chrom Q (100–120 mesh).

**Diastereoisomeric analysis of β-methylglutamic acid** was effected in three ways. (a) On the amino acid analyzer (Beckman Model 121 MB), retention times were 144 and 153 min for the threo and erythro isomers (**10** and **11**), respectively (and 155 min, for glutamic acid). (b) GC of the *N*-trifluoroacetyl dimethyl esters on column A at 140 °C gave retention times of 31.0 and 33.2 min, (partial peak overlap) for the erythro and threo isomers, respectively. (c) Thermal conversion to 3-methylpyroglutamic acid (without detectable epimerization) was performed in a vacuum tube at 18 °C (0.1 torr) and the resulting sublimate esterified with diazomethane. The resulting diastereoisomeric methyl esters were distinguished by GC on column B at 180 °C, the cis (from threo) and trans (from erythro) isomers having retention times of 6.0 and 7.0 min, respectively (baseline separation).

**Cis and Trans Isomers of Ethyl 3-Methylpyroglutamate (2 and 3).** 5,5-Bis(ethoxycarbonyl)-4-methylpyrrolidone (**1**; 36.45 g, 0.150 mol) in ethanol (500 mL) was mixed with 1 N sodium hydroxide (150 mL). After 16 h at 24 °C, 1 N hydrochloric acid (150 mL) was added and the solution evaporated. The residue was treated with warm ethanol (175 mL) and filtered to remove sodium chloride. After evaporation, the residual half-ester was heated at 150 °C for 0.5 h, cooled, dissolved in ether (100 mL), filtered and evaporated. The residual oil was distilled at 116–119 °C (0.25 torr) to afford a mixture of **2** and **3** as a colorless oil which gave two peaks (retention times, 2.1 and 2.5 min) on GC (column C at 200 °C), yield 23.20 g (79%). An aliquot (277 mg) was chromatographed on a column (31 × 1.8 cm) of silica gel (grade 62, 60–200 mesh) with chloroform/ethyl acetate (2:1). Fractions were analyzed by GC, indicating only partial separation. Early fractions afforded **3** (72 mg), with the shorter GC retention time, and late fractions gave **2** (42 mg); both were purified by short-path distillation at 130 °C (0.25 torr). Only the latter crystallized. For NMR spectra see Table I. The remainder of the isomeric mixture (22.92 g) was dissolved in ether (140 mL) and kept at −15 °C for 18 h, after which prisms (7.3 g) were filtered off and washed with cold ether. This product was identified as **2** by GC, and the filtrate, evaporation of which gave an oil (16.06 g), was 72% **3** and 28% **2**. Recrystallization of **2** from ether at −15 °C gave needles, mp 77.5–78 °C.

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found for **2**: C, 56.31; H, 7.61; N, 8.24. Found for **3**: C, 56.38; H, 7.38; N, 8.01.

***trans*-3-Methylpyroglutamic Acid (7).** The foregoing mixture of **2** and **3** (28 and 72%, respectively, 16.06 g, 93.8 mmol) in ethanol (150 mL) was mixed with 5 N sodium hydroxide (50 mL). After 4 h at 24 °C, 5 N hydrochloric acid (50 mL) was added and the solution evaporated. After three recrystallizations from water, **7** was obtained as needles: mp 160–161.5 °C; yield 5.68 g (59%); NMR, see Table I.

Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.50; H, 6.45; N, 9.74.

***cis*-3-Methylpyroglutamic Acid (6).** A solution of **2** (12.17 g, 71.1 mmol) in ethanol (50 mL) was mixed with 5 N sodium hydroxide (30 mL). After 4 h at 24 °C, 5 N hydrochloric acid (30 mL) was added and the solution evaporated. Recrystallization of the residue from water afforded **6** as large prisms: mp 153–155 °C; yield 6.17 g (61%); NMR, see Table I.

Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.38; H, 6.41; N, 9.80.

***threo*-β-Methylglutamic Acid (10).** A solution of **6** (1.00 g, 6.99 mmol) in 2.5 N hydrochloric acid (20 mL) was heated under reflux for 2.5 h and then evaporated in vacuo. The residue was dissolved in hot water (4 mL) and ethanol (40 mL) was added, followed by pyridine (4 mL). After 16 h at 5 °C the crystals were filtered off and dried in vacuo at 78 °C. Recrystallization from aqueous ethanol afforded **10** as needles: mp 185–186 °C dec; yield 0.72 g (64%); NMR ($D_2O$, internal DSS) δ 1.05 (d, $J$ = 6.9 Hz, β-$CH_3$, 3), 3.82 (d, $J$ = 3.9 Hz, α-H, 1).

Anal. Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.52; H, 6.96; N, 8.75.

***erythro*-β-Methylglutamic acid (11)** was prepared from **7** (1.00 g) by the same procedure as the above (**6** → **10**) and recrystallized from water as needles: mp 172.5–173.5 °C dec; yield 0.69 g (61%); NMR ($D_2O$, internal DSS) δ 1.05 (d, $J$ = 6.9 Hz, β-$CH_3$, 3), 3.83 (d, $J$ = 4.0 Hz, α-H, 1).

Anal. Calcd for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.53; H, 6.60; N, 8.32.

***N*-(*p*-Toluenesulfonyl)-*threo*-β-methylglutamic Acid (13).** A mixture of **10** (100 mg, 0.621 mmol), water (1 mL), tetrahydrofuran (0.5 mL), and triethylamine (0.5 mL) was stirred during addition of *p*-toluenesulfonyl chloride (181 mg, 0.949 mmol) over 10 min. After 1 h, water (15 mL) was added and the solution was washed with ether, acidified with hydrochloric acid, and extracted with ethyl acetate. The extracts were washed with water and evaporated. The residue was dried in vacuo and recrystallized from ethyl acetate/petroleum ether as needles: mp 184–185 °C; yield 148 mg (76%).

Anal. Calcd for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.44; N, 4.44; S, 10.17. Found: C, 49.12; H, 5.57; N, 4.42; S, 10.23.

***N*-(*p*-Toluenesulfonyl)-*erythro*-β-methylglutamic acid (14)** was prepared from **11** (100 mg) by the same procedure as the above (**10** → **13**) and crystallized from ethyl acetate/petroleum

(12) A. B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, 87, 4975 (1965).

(13) J. Kollonitsch, A. N. Scott, and G. A. Doldouras, *J. Am. Chem. Soc.*, 88, 3624 (1966).

ether as prisms: mp 170–171.5 °C; yield 156 mg (80%).

Anal. Calcd for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.44; N, 4.44; S, 10.17. Found: C, 49.79; H, 5.59; N, 4.18; S, 10.10.

**Methyl *trans*-3-Methylpyroglutamate (4).** A suspension of **7** (1.00 g, 6.99 mmol) in methanol (10 mL) was treated with an excess of ethereal diazomethane. After evaporation the residual solid was recrystallized from ethyl acetate/petroleum ether as plates: mp 70–71 °C; yield 1.05 g (95%); NMR, see Table I.

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.31; H, 6.98; N, 8.76.

***N*-(*p*-Toluenesulfonyl)-*cis*-3-methylprolinol (5).** A solution of **2** (855 mg, 5.00 mmol) in dry tetrahydrofuran (10 mL) was gradually added to a stirred suspension of powdered lithium aluminum hydride (532 mg, 14 mmol) in dry tetrahydrofuran (15 mL) in a stream of nitrogen. After being heated under reflux for 18 h, the mixture was cooled and treated with acetone (5 mL) for 1 h. Water (20 mL) and sodium bicarbonate (1.0 g) were added, and the mixture was stirred during addition of *p*-toluenesulfonyl chloride (955 mg, 5.01 mmol) in acetone (15 mL). After 2 h, 1 N hydrochloric acid (75 mL) was added and the solution was extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate and sodium chloride and dried ($Na_2SO_4$). Evaporation gave a gum which was chromatographed on a column (17 × 2 cm) of silica gel with 2:1 chloroform/ethyl acetate. The residue from the appropriate fractions crystallized from ethyl acetate/petroleum ether as prisms: mp 74–75 °C; yield 848 mg (63%); NMR ($CDCl_3$, internal $Me_4Si$) $\delta$ 0.98 (d, $J$ = 6.3 Hz, 3-$CH_3$, 3), 2.44 (s, Ar$CH_3$, 3), 7.34 (d, Ar H, 2), 7.75 (d, Ar H, 2).

Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.96; H, 7.11; N, 5.20; S, 11.91. Found: C, 57.79; H, 7.33; N, 5.28; S, 12.18.

***N*-(*p*-Toluenesulfonyl)-*trans*-3-methylprolinol (8)** was prepared from **4** (785 mg, 5.00 mmol) by the same procedure as the above (**2** → **5**) and crystallized from ethyl acetate/petroleum ether at −15 °C as needles: mp 61–62 °C; yield 873 mg (65%); NMR ($CDCl_3$, internal $Me_4Si$) $\delta$ 0.67 (d, $J$ = 6.9 Hz, 3-$CH_3$, 3), 1.01 (dd, $J$ = 7.6 and 12.4 Hz, 4$\alpha$-H, 1), 1.86 (dd, $J$ = 6.2 and 12.4 Hz, 4$\beta$-H, 1), 2.05 (m, 3-H, 1), 2.45 (s, Ar$CH_3$, 3), 7.35 (d, Ar H, 2), 7.75 (d, Ar H, 2).

Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.96; H, 7.11; N, 5.20; S, 11.91. Found: C, 57.72; H, 7.13; N, 5.06; S, 11.52.

**Oxidation of 5 to *N*-(*p*-Toluenesulfonyl)-*cis*-3-methylproline (9).** A solution of **5** (641 mg, 2.38 mmol) in acetone (40 mL) was mixed with a solution of chromium trioxide (1.20 g, 12.0 mmol) in water (5 mL) containing sulfuric acid (1 mL). After 1.5 h, methanol (10 mL) was added, and after a further 15 min, the mixture was poured into aqueous sodium chloride (200 mL) and extracted with ethyl acetate. The extracts were washed with aqueous sodium chloride and dried ($Na_2SO_4$). A small aliquot was treated with ethereal diazomethane and analyzed by GC on column B at 230 °C. The product was 95% cis and 5% trans when compared with the authentic diastereoisomers of *p*-toluenesulfonyl-3-methylproline methyl ester (retention times 15.7 and 13.6 min, respectively). The bulk of the extract was evaporated and the residual solid recrystallized from ethyl acetate as needles, mp 181.5–183 °C, alone or mixed with an authentic sample (mp 181.5–183 °C) prepared from *cis*-3-methylproline,[10,14] yield 573 mg (84%).

**Oxidation of 8 to *N*-(*p*-Toluenesulfonyl)-*trans*-3-methylproline (12).** A solution of **8** (369 mg, 1.37 mmol) in acetone (23 mL) was mixed with a solution of chromium trioxide (583 mg, 5.83 mmol) in water (2.5 mL) containing sulfuric acid (0.5 mL). After 1.5 h, the reaction was worked up as for **9** and similar GC analysis indicated that the crude product was 99% trans. After recrystallization from ethyl acetate/petroleum ether, **12** formed needles, mp 123–124 °C, alone or mixed with an authentic sample (mp 123–124 °C) prepared from *trans*-3-methylproline,[10,14] yield 361 mg (93%).

**Acknowledgment.** I thank Dr. E. Becker (National Institute of Arthritis, Metabolism and Digestive Diseases, NIH) for the use of an NMR spectrometer and Dr. D. F. Johnson (same Institute) for analytical services. This investigation was supported by U.S. Public Health Service Grant CA-11627 from the National Cancer Institute.

**Registry No.** **1**, 2446-12-0; **2**, 76318-70-2; **3**, 76318-71-3; **4**, 76251-46-2; **5**, 76251-47-3; **6**, 76318-72-4; **7**, 76318-73-5; **8**, 76251-48-4; **9**, 76318-74-6; **10**, 63088-04-0; **11**, 76318-75-7; **12**, 76318-76-8; **13**, 76251-49-5; **14**, 76251-50-8; methyl *cis*-3-methylpyroglutamate, 76251-51-9; methyl *N*-(trifluoroacetyl)-*erythro*-$\beta$-methylglutamate, 76251-52-0; methyl *N*-(trifluoroacetyl)-*threo*-$\beta$-methylglutamate, 76251-53-1; glutamic acid, 617-65-2.

(14) D. A. Cox, A. W. Johnson, and A. B. Mauger, *J. Chem. Soc.*, 5024 (1964).

# *Communications*

## Correlation between the Basicity of Carbanions and Their Ability to Transfer an Electron

*Summary:* In $Me_2SO$ solution electron transfer from 9-arylfluorenyl carbanions, 9-ArFl$^-$, to electron acceptors including $PhSO_2CH_2Br$, $PhSO_2CH_2I$, or $R_2C(NO_2)_2$ follows second-order kinetics and results in the formation of dimers, (9-ArFl–)$_2$, in high yields. Brønsted-type correlations of log $k_2$ vs. p$K_a$ (Table I) show that these electron-transfer processes have a much higher sensitivity to changes in 9-ArFl$^-$ ion basicity ($\beta_{Nu}$ > 1.0) than do $S_N2$ reactions of RX with these carbanions ($\beta_{Nu}$ = 0.3–0.5).

*Sir:* Carbanions and other nucleophiles are known to react in dipolar nonhydroxylic ("aprotic") solvents with electron acceptors, RX, of the type *p*-$NO_2C_6H_4CR_2X$ (X = Cl or $NO_2$) and $NO_2CR_2X$ (X = Cl or Br) by substitution reactions (eq 1) involving electron-transfer chain mechanisms.[1,2]

$$Nu^- + RX \rightarrow RNu + X^- \quad (1)$$

A number of other electron-transfer reactions are known in which the nucleophile is dimerized;[3,4] for example, a few 9-substituted fluorenyl anions, 9-G-Fl$^-$, have been shown to react with nitrobenzene to form (9-G-Fl–)$_2$ dimers.[3] We have observed similar dimerizations of 9-ArFl$^-$ anions in reactions with excess $PhSO_2CH_2Br$, $PhSO_2CH_2I$, $Me_2C(NO_2)_2$, and 1,1-dinitrocyclohexane ($c$-$C_6H_{10}(NO_2)_2$) as electron acceptors. The major products (>85% material

(1) Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1964**, *86*, 3904–3905; **1965**, *87*, 4520–4528. Kornblum, N.; Michel, R. E.; Kerber, R. C. *Ibid.* **1966**, *88*, 5660–5662.

(2) Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 5663–5665.

(3) Guthrie, R. D.; Wesley, D. P.; Pendygraft, G. W.; Young, A. T. *J. Am. Chem. Soc.* **1976**, *98*, 5870–5877.

(4) Russell, G. A.; Jawdosiuk, M.; Makosza, M. *J. Am. Chem. Soc.* **1979**, *101*, 2355–2362.

0022-3263/81/1946-1035$01.25/0 