The Thiomethylation of Substituted Glutarimides

David E. Seitz and Fang-Ling Needham*

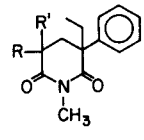
Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

Received September 24, 1980

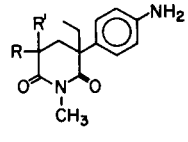
Conditions for the mono- and di(thiomethylation) of *N*-methyl-3-ethyl-3-phenylpiperidine-2,6-dione and the monothiomethylation of *N*-methyl-3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione, potential inhibitors of estrogen synthetase, are described and contrasted with a closely related lactam, *N*-methylpiperidone. The influence of solvent, base and electrophile on product distribution is explored.

J. Heterocyclic Chem., **18**, 687 (1981).

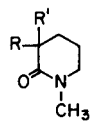
As part of a project to synthesize and evaluate potential inhibitors of estrogen synthetase, we required C-5 thiomethylated derivatives of the substituted glutarimides **1** (1) and **2** (2). Although sulfur is readily incorporated into a variety of organic molecules *via* direct sulfenylation at a position alpha to an activating group such as carbonyl (3), there are few examples of the application of this technique to imides (4). Herein the results of our studies on the influence of solvent composition, base and electrophile on the thiomethylation of **1** are reported and contrasted with the closely related lactam, *N*-methylpiperidone (**3**) reported earlier by Gassman (5).



1: R = R' = H
4: R = H, R' = SCH_3
5: R = R' = SCH_3



2: R = R' = H
6: R = H, R' = SCH_3
7: R = R' = SCH_3



3: R = R' = H
8: R = H, R' = SCH_3
9: R = R' = SCH_3

The products of the reaction of **1** with various ratios of lithium diisopropylamide (LDA), electrophile [dimethyl disulfide (**10**) or methyl benzenethiosulfonate (**11**) (6)] and hexamethylphosphoramide (HMPA) are tabulated in the Table. The results with excess LDA and **10** parallel those of Gassman; in tetrahydrofuran only monothiomethylation is observed. The addition of HMPA fails to promote di(thiomethylation), although an increase of **4** relative to **1** is attended by its use. In the absence of excess LDA and **10**, however, added HMPA seems to have no effect on the product distribution. With the more reactive sulfenylating agent **11**, mixtures of the mono- and di(thiomethylated) derivatives **4** and **5** are formed in tetrahydrofuran. Addition of HMPA to the reaction mixture suppresses the formation of **5** and, analogous to the results obtained with **10**, maximizes the yield of **4**. The optimum conditions for the monothiomethylation of **1** appear to be a 1:2:2:2 ratio of **1**:LDA:electrophile:HMPA.

The isolation of **5** utilizing **11** in tetrahydrofuran suggested that **5** might be formed reversibly when **10** is employed as sulfenylating agent. Exposure of **5** to two equivalents of lithium thiomethoxide in tetrahydrofuran afforded **4** in 96% yield while similar reaction of a tetrahydrofuran solution of **5** with two equivalents each of lithium thiomethoxide and HMPA gave **4** in 54% yield. The isolation of **1** remains problematical as this requires a proton source to protonate the putative anion of **4**. The possibility of trace amounts of adventitious moisture, especially in the hygroscopic solvent HMPA, cannot be discounted.

From these results, it appears a fundamental difference in reactivity exists between imide **1** and lactam **3**. Gassman attributed the lack of di(thiomethylated) products in the reaction of amides and lactams with LDA and **10** to the stability of the enolate anion of the monothiomethylated derivative, *e.g.*, **8**, in tetrahydrofuran. Confirmatory evidence for this suggestion was derived from two observations: a) no di(thiomethylation) was noted on use of the reactive sulfenylating agent methyl toluenethiosulfonate; and b) only a minor amount (20%) of desulfenylation occurred on treatment of **9** with lithium thiomethoxide in tetrahydrofuran during the normal reaction time. To confirm that differences in the experimental procedures were not responsible for the disparate reactivities of imide **1** and lactam **3**, the desulfenylation of **5** with lithium thiomethoxide in tetrahydrofuran and the thiomethylation of **1** with **11** in tetrahydrofuran were repeated utilizing the precise reaction conditions employed by Gassman. No changes in yield or product distribution were noted in either reaction.

A detailed study of the thiomethylation of **2** was precluded because of the insolubility of the anion of **2** in tetrahydrofuran. The desired monosulfenylated derivative **6** could be secured in 54% yield on reaction of **2** with two equivalents each of LDA and HMPA and one equivalent of **11**. No other discernible product was isolated, a result, presumably, of competing side reactions due to the negatively charged aniline nitrogen. Analogous to **1**, no evidence of di(thiomethylated) derivative **7** was evident on treatment of **6** with LDA, HMPA and **11**.

0022-152X/81/040687-03$02.25

TABLE (*a*)

SULFENYLATION OF N-METHYLGLUTETHIMIDE (1)

Electrophile	Ratio of *1*:LDA:Electrophile:HMPA	Yield *1* (%)(*c*)	Yield *4* (%)(*c*)	Yield *5* (%)(*c*)
CH_3SSCH_3 (*10*)	1:2:2:2	35	65	—
10	1:1:1:1	52	44	—
10	1:2:2:0	57	42	—
10	1:1:1:0	58	38	—
10 (*b*)	1:2:2:2	21	69	—
CH_3SSO_2Ph (*11*)	1:2:2:0	—	47 (*d*)	47 (*d*)
11	1:2:2:2	18	73	—
11	1:1:1:0	—	50 (*d*)	20 (*d*)

(a) reactions were run for 3 hours at -78° and 16 hours at ambient temperature. (b) inverse addition. (c) unless otherwise specified, all yields refer to isolated products. (d) the ratio of 4 to 5 was determined by NMR.

With the appropriate base, solvent and electrophile combination, the mono- or di(thiomethylated) derivatives of **1** and the monothiomethylated derivative of **2** are readily available for biological evaluation. Investigation of the effect of structure on imide enolate anion reactivity and other aspects of the sulfenylation of imides is currently under investigation.

EXPERIMENTAL

Infrared spectra were obtained on solutions in chloroform on a Perkin-Elmer 567 spectrophotometer. Proton magnetic resonance spectra were recorded at 90 MHz in deuteriochloroform on a Brucker WH-90 spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS). Mass spectral analyses were determined on a Nuclide 12-90-G magnetic sector spectrometer. Thin-layer chromatography was performed on Merck 60 F-254 (0.25 mm) plates which were visualized with molybdophosphoric acid in ethanol. Merck 230-400 mesh silica gel 60 was employed for column chromatography. Reactions were run under nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Diisopropylamine was distilled from calcium hydride.

General Procedure for Thiomethylation.

To a 25 ml. septum-capped side arm round bottom flask equipped with a magnetic stirring bar was added a solution of tetrahydrofuran and diisopropylamine. The reaction mixture was cooled to -78° and *n*-butyllithium was added *via* syringe. After 45 minutes, a tetrahydrofuran solution of **1** or **4** was introduced dropwise *via* syringe and the reaction mixture was stirred at -78° for three hours and at ambient temperature for sixteen hours. Water was added and the mixture was extracted with four 20 ml. portions of ethyl acetate. The combined organic extracts were washed with 5% hydrochloric acid and saturated sodium chloride. The organic solution was dried (sodium sulfate), filtered, and concentrated *in vacuo* to give an oil. The reaction product was purified by column chromatography (70:1 absorbent ratio) with a mixture of hexane and acetone (19:1) as eluant.

Thiomethylation of *N*-Methyl-3-ethyl-3-phenylpiperidine-2,6-dione (**1**) with Dimethyl Disulfide (**10**). Synthesis of *N*-Methyl-3-ethyl-5-methylthio-3-phenylpiperidine-2,6-dione (**4**).

1:2:2:2 Ratio of **1**:LDA:**10**:HMPA.

The general thiomethylation procedure described above was employed. To a solution of 2 ml. of tetrahydrofuran and 0.58 ml. (4.1 mmoles) of diisopropylamine was added 1.72 ml. (4.10 mmoles) of *n*-butyllithium dropwise at -78°. The reaction mixture was stirred for 45 minutes whereupon a solution of 462 mg. (2.00 mmoles) of **1** in 0.5 ml. of tetrahydrofuran was added in one portion. After stirring at -78° for 1 hour, 0.70 ml. (4.0 mmoles) of hexamethylphosphoramide and 0.36 ml. (4.0 mmoles) of dimethyl disulfide (**10**) were added. The reaction mixture was stirred at -78° for 3 hours and at ambient temperature for 16 hours. Chromatography of the crude reaction product afforded 358 mg. (65%) of the oily monosulfenylated derivative **4** and 166 mg. (35%) of the starting material **1**; ir (chloroform): 3020, 2970, 2920, 1716, 1677, 1671, 1590, 1574, 1492 cm^{-1}; nmr (deuteriochloroform): δ 7.35-7.10 (m, 5H), 3.30 (dd, J = 12, 4 Hz, 1H), 3.27 (s, 3H), 2.69-1.90 (m, 4H), 2.27 (s, 3H), 0.85 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found: C, 64.77; H, 7.05; N, 4.88.

N-Methyl-3-ethyl-5,5-di(methylthio)-3-phenylpiperidine-2,6-dione (**5**).

The general thiomethylation procedure described above was employed. To a solution of 2 ml. of tetrahydrofuran and 0.14 ml. (1.0 mmole) of diisopropylamine was added 0.67 ml. (1.0 mmole) of *n*-butyllithium dropwise at -78°. The reaction mixture was stirred for 45 minutes whereupon a solution of 277 mg. (1.00 mmole) of the monothiomethylated derivative **4** in 0.5 ml. of tetrahydrofuran was added in one portion. After stirring at -78° for 1 hour, a solution of 207 mg. (1.10 mmoles) of methyl benzenethiosulfonate (**11**) in 0.5 ml. of tetrahydrofuran was added. The reaction mixture was stirred at -78° for 3 hours and at ambient temperature for 16 hours. Chromatography of the crude reaction product afforded 320 mg. (99%) of the oily bisulfenylated derivative **5**; ir (chloroform: 3012, 2972, 2920, 1712, 1670, 1596, 1576, 1496 cm^{-1}; nmr (deuteriochloroform): δ 7.21 (s, 5H), 3.27 (s, 3H), 2.72 (s, 2H), 2.10 (s, 3H), 1.93 (s, 3H), 2.10-1.93 (m, 2H), 0.85 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.65; H, 6.74; N, 4.26.

Desulfenylation of *N*-methyl-3-ethyl-5,5-di(methylthio)-3-phenylpiperidine-2,6-dione (**5**) in tetrahydrofuran.

To a solution of 1.5 ml. of tetrahydrofuran and 0.071 ml. (0.500 mmole) of diisopropylamine was added 0.21 ml. (0.50 mmole) of *n*-butyllithium dropwise at -78°. The reaction mixture was stirred at -78° for 45 minutes whereupon 0.028 ml. (0.500 mmole) of methanethiol was added in one portion *via* syringe. The reaction mixture was stirred at -78° for 1.5

hours. A solution of 80 mg. (0.25 mmole) of the bisulfenylated derivative **5** in 0.75 ml. of tetrahydrofuran was added. The reaction mixture was stirred at -78° for 3 hours and at ambient temperature for 16 hours. Chromatography of the crude reaction product afforded 70 mg. (96%) of oily monosulfenylated derivative **4**.

N-Methyl-3-(4-aminophenyl)-3-ethyl-5-methylthiopiperidine-2,6-dione (**6**).

The general sulfenylation procedure described above was modified. To a 100 ml. septum-capped side arm round bottom flask was added 6.56 ml. (10.5 mmoles) of *n*-butyllithium. The hexane was removed in a stream of dry nitrogen and 25 ml. of tetrahydrofuran was added. The reaction mixture was cooled to -78° and 1.47 ml. (10.5 mmoles) of diisopropylamine was added. After 45 minutes, 1.83 ml. (10.5 mmoles) of hexamethylphosphoramide and a solution of 1.23 g. (5.00 mmoles) of imide **2** in 25 ml. of tetrahydrofuran at -78° was added *via* cannula. After stirring at -78° for one hour, a solution of 940 mg. (5.00 mmoles) of methyl benzenethiosulfonate (**11**) in 2 ml. of tetrahydrofuran was added. The reaction mixture was stirred at -78° for 3 hours and at ambient temperature for 16 hours. Chromatography of the crude reaction product with a mixture of hexane and acetone (85:15) as eluant afforded 785 mg. (54%) of **6** as a white solid. Recrystallization from 95% ethanol gave the analytical sample which exhibited m.p. 145-146°: ir (chloroform): 3010 (broad), 1720, 1670, 1520, 1420, 1280, 1220 cm^{-1}; nmr (deuteriochloroform): δ 6.91 (d, J = 8 Hz, 2H), 6.69 (d, J = 8 Hz, 2H), 3.65 (broad s, 2H), 3.40 (dd, J = 12, 4 Hz, 1H), 3.22 (s, 3H), 2.69-1.90 (m, 4H), 2.28 (s, 3H), 0.85 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{15}H_{20}N_2O_2S$: C, 61.61; H, 6.89. Found: C, 61.47; H, 6.94.

Acknowledgement.

Support of this research by the American Cancer Society (Grant No. PDT-147) is gratefully acknowledged. We thank Dr. Hilton A. Salhanick of the Harvard School of Public Health and Dr. John L. Neumeyer of Northeastern University for helpful discussions.

REFERENCES AND NOTES

(1) E. Tagmann, E. Sury and K. Hoffmann, *Helv. Chim. Acta.*, **35**, 1541 (1952).

(2) R. Paul, R. P. Williams and E. Cohen, *J. Med. Chem.*, **17**, 539 (1974).

(3) For a review, see: B. M. Trost, *Chem. Rev.*, **78**, *363 (1978).*

(4) D. E. Seitz, F. E. Granchelli and J. L. Neumeyer, Synth. Commun., **7**, 367 (1977).

(5) P. G. Gassman and R. J. Balchunis, *J. Org. Chem.*, **42**, 3236 (1977).

(6) B. G. Boldyrev, E. N. Obukhova and O. E. Rochnyak, *J. Appl. Chem. USSR*, **45**, 906 (1972).