Methylation of 5-Phenyl-1,4-benzodiazepin-2-one Derivatives with *N,N*-Dimethylformamide-Dimethyl Acetal

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A novel method for *N*-methylation of the cyclic amide in the 1,4-benzodiazepine ring system is presented. Methods traditionally used involve treatment of the 1,4-benzodiazepinone anion with an alkyl halide. It has been demonstrated that these derivatives can be methylated on the amide nitrogen atom by use of dimethylformamide dimethyl acetal which acts as both reagent and solvent for the reaction.

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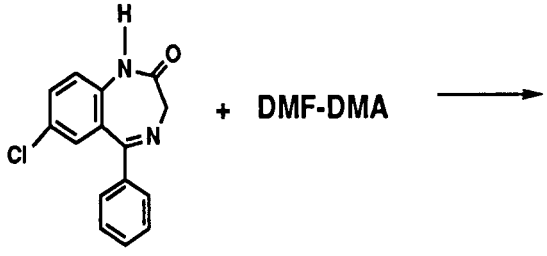
In work, related to the preparation of probe ligands at the benzodiazepine receptor, the dimethylaminomethylene derivative **2**, was required as a synthon. This product was obtained in high yield and in a high state of purity simply by heating a solution of substrate **1** in *N,N*-dimethylformamide diethyl acetal under the previously described conditions [1]. The reaction was followed by tlc evaluation.

It was somewhat surprising to find that if diethyl acetal was substituted for dimethyl acetal, two products were formed, the relative yields depending on the reaction condition used. The two products were separated by fractional crystallization and were determined by all of the usual criteria to be compound **2** and the 1-methyl-5-phenyl-1,4-benzodiazepin-2-one, **3**.



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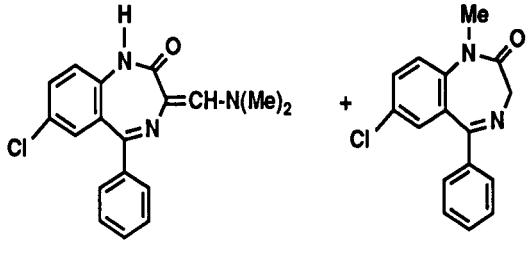


2 **3**

An examination of the literature disclosed that *N,N*-dimethylformamide dialkyl acetals have proven to be useful as both alkylating and formylating agents for a variety of heterocyclic substrates [2-4].

This method has proved to be useful for selective alkylation at a heteroatom usually resulting in the isolation of pure products in high yields. Alkylation at carbon was not observed in any of the compounds studied.

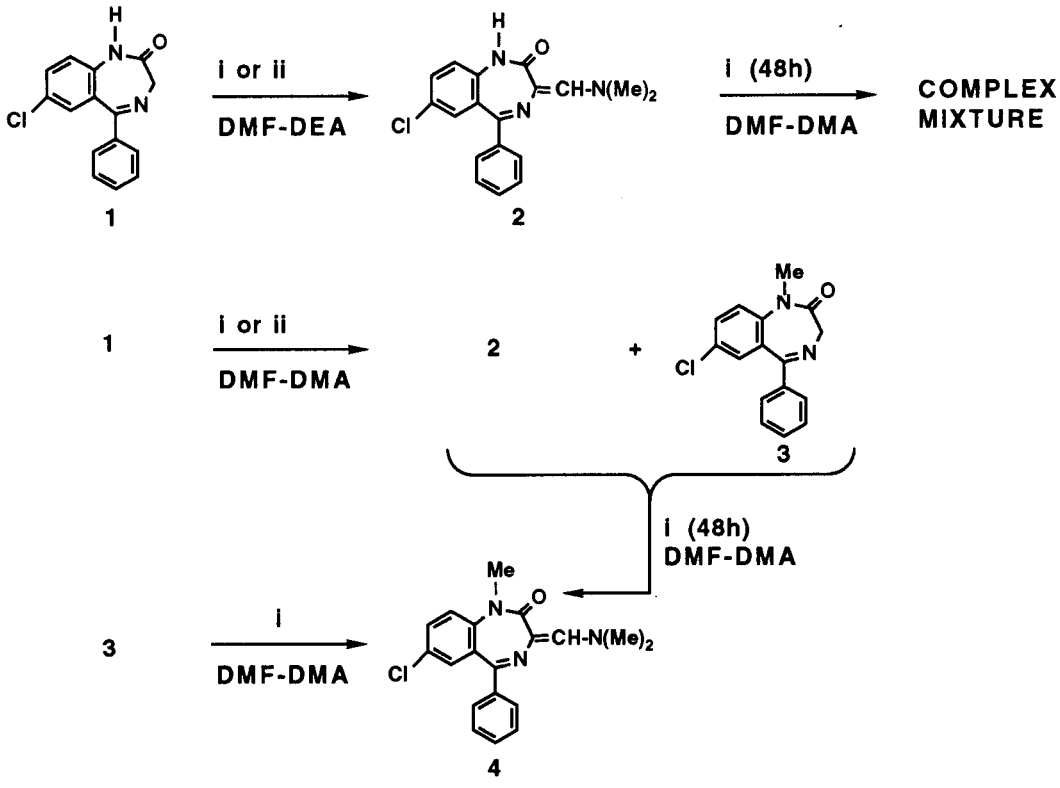
The preparation of **3** from **1**, using *N,N*-dimethylformamide dimethyl acetal, represents a novel method of *N*-methylation of the cyclic amide in the benzodiazepine ring system. The traditional method [5] of alkylation of benzodiazepine amides has involved initial treatment with an anhydrous base to give the anion of the secondary amide which was alkylated with an alkyl halide (or alkyl sulfate) in a variety of inert solvents. In parallel to the purine chemistry literature, it has now been shown that benzodiazepin-2-one derivatives can be methylated on the amide nitrogen atom simply by using *N,N*-dimethylformamide dimethyl acetal as both solvent and alkylating agent. This procedure does not involve base treatment and may be advantageous in certain cases (it has been previously shown that treatment of the product **3** with excess base may cause ring contraction and rearrangement of the seven membered ring [6]).

The reaction of *N,N*-dimethylformamide dialkyl acetals with benzodiazepines is known to give enamines at the 3-position [1]. Peiper, who used *N,N*-dimethylformamide diethyl acetal with a variety of benzodiazepine substrates (including compound **1**) reports only the isolation of the formylation product, namely the 3-dimethylamino methylene derivative.

This procedure required a continual distillation of the ethanol formed during the reaction. It appears that the dimethyl acetal was never used in this work. It has been found, in the work reported here, that reflux conditions afforded a viable alternative to distillation, the only difference noted being the rather slow rate of formation of the product(s).

Use of the dimethyl acetal under reflux or distillation conditions afforded the two products, compounds **2** and **3** (Scheme 1). Upon prolonged heating (reflux 48 hours), the formation of the 1,3-disubstituted product **4** was observed. Compound **4** could be obtained as the major product by

Scheme 1



refluxing **3** in dimethylformamide dimethyl acetal for 24 hours. Reacting **2** under the same conditions, yielded a complex mixture of products, including only a trace amount of **4** (determined by thin layer chromatography).

Based on the results shown in Scheme 1, it appears, that the formation of **4**, occurs mainly through the formylation of the *N*-alkylated product **3** rather than by alkylation of the formylated product **2**. Thus, continuous heating of the mixture of **2** and **3** in the formamide acetal solution, readily formylates **3** at the 3-position to form **4** while only a small amount of **2** will alkylate to form the same product.

The initial products, **2** and **3**, arising from the dimethyl acetal reaction were separated by fractional crystallization from methylene chloride and ether. The alkylated product **3** was isolated in about 38% yield and the formylated product **2** in about 35% yield. The yield of product **2**, using *N*,*N*-dimethylformamide diethyl acetal was 75% (stripping solvent and recrystallization of the residue from methylene chloride).

The disubstituted product, compound **4** was crystallized from ether in about 25% yield (based upon **1**).

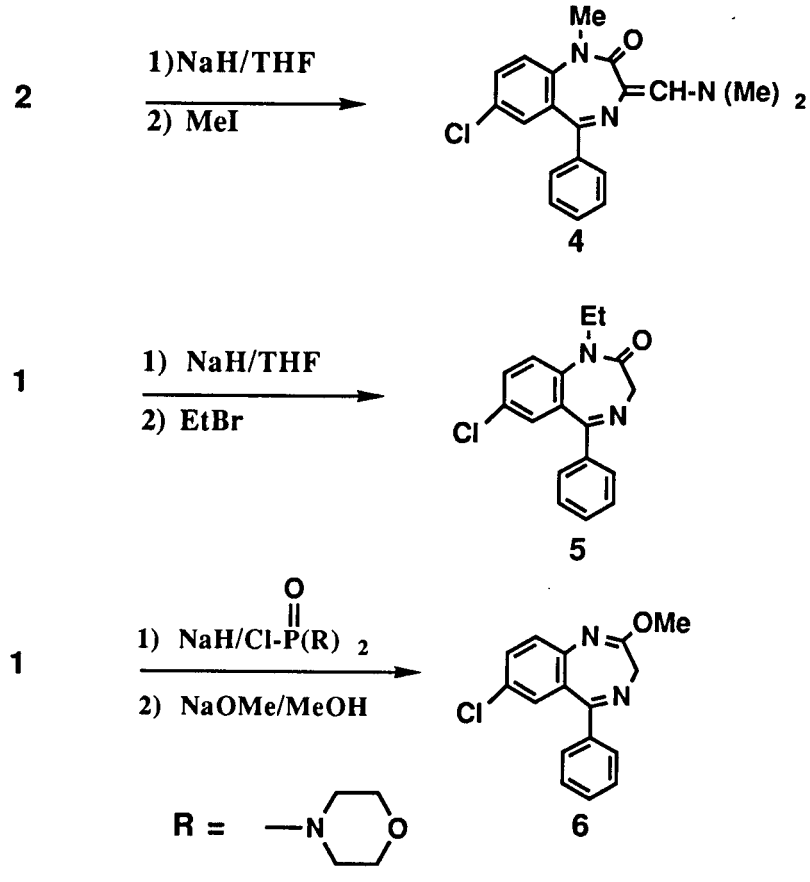
A study of the effects of time and temperature on the alkylation reaction was carried out in order to monitor the formation of the *N*-alkylated product **3**. The reaction was monitored by thin layer chromatography (tlc) and a 1 ml aliquot was taken out of the reaction mixture every 5 minutes recording the time and temperature. The study revealed that *N*-alkylation could be detected approximately 10 minutes after the reaction began and at a solution temperature of 75°. Heating was continued for an additional 30 minutes to a temperature of 110° (solvent boiling point). By this time methanol had distilled over (distillation conditions) and both products, **2** and **3** were obtained. Distillation was stopped after a reaction time of 45 minutes.

To further examine the reaction of *N*,*N*-dimethylformamide dimethyl acetal with compound **1**, several other compounds were synthesized as tlc standards in order to monitor their possible formation and involvement in the reaction, (Scheme 2).

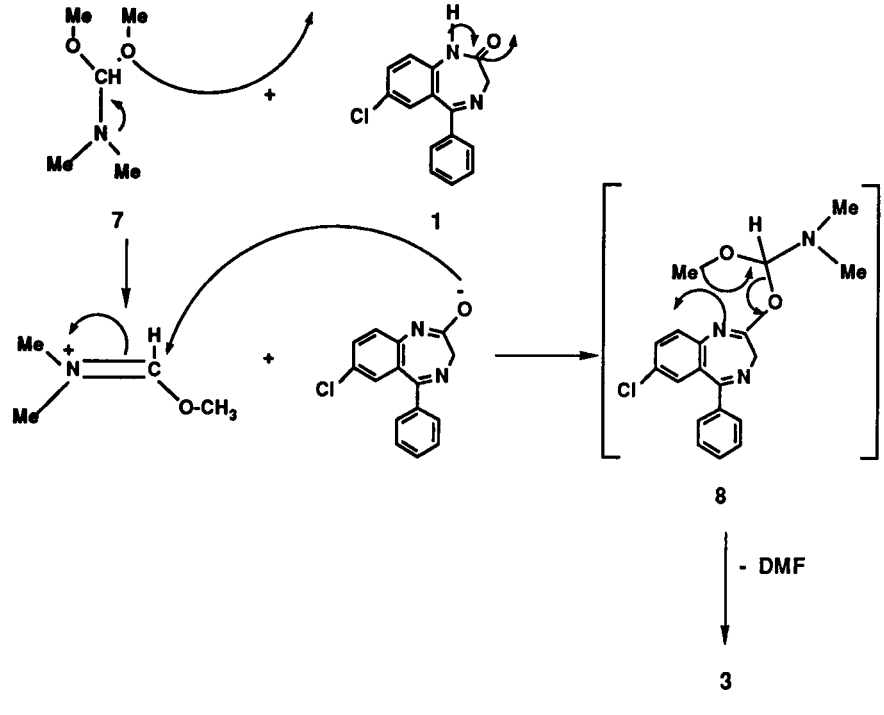
The 1,3-disubstituted compound **4** was synthesized by direct alkylation of compound **2** with methyl iodide (Scheme 2) and used as an authentic standard to monitor reaction mixtures described in Scheme 1.

Compound **6** (Scheme 2) was synthesized as a probe to exclude one possible mechanism of the *N*-alkylation reaction. The OMe compound has been shown to undergo a Chapman rearrangement to yield **3**, the N-Me isomer [7]. However, no evidence for the formation of the OMe enolate could be detected by a tlc examination of any of the reaction mixtures.

Scheme 2



Scheme 3



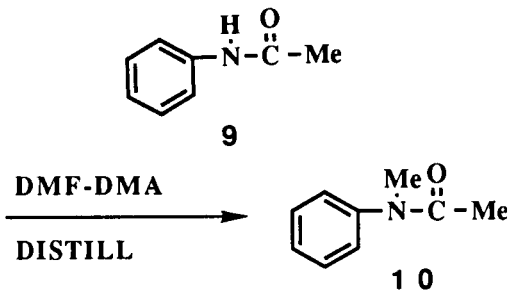
Further, a solution of **6** in *N,N*-dimethylformamide dimethyl acetal heated under reflux gave none of the rearranged *N*-methyl derivative. In the case of *N,N*-dimethylformamide diethyl acetal, the N-Et analog, compound **5**, was synthesized to monitor possible *N*-ethylation of compound **1** (Scheme 2).

Under the conditions used, this novel method of alkylation of benzodiazepin-2-ones could not be extended to the N-Et alkylated product. Use of the corresponding diethyl acetal, under either distillation or reflux conditions, no detectable trace of compound **5** was ever observed. The diethyl acetal, being a larger group, is moderately less reactive than the dimethyl acetal, which may be the main reason for the inability of the one to alkylate over the other. Since *N,N*-dimethylformamide diethyl acetal did not alkylate compound **1** to form the N-Me analog **3**, the mechanism for methylation must proceed through cleavage of an *O*-methyl bond rather than an *N*-methyl bond of *N,N*-dimethylformamide dimethyl acetal **7**.

It seems reasonable to propose that the mechanism of methylation with *N,N*-dimethylformamide dimethyl acetal may occur through a charged intermediate as shown in Scheme 3. The mechanism would involve shifting of the lone pair of electrons on the nitrogen atom of **7** to form the quaternary nitrogen with concomitant loss of methoxide. The ion can deprotonate the secondary amide nitrogen of the benzodiazepin-2-one **1**, forming the enolate anion on oxygen which can then attack the charged dimethylformamide species to give intermediate **8**. Rearrangement of the six-membered enolate would then lead directly to the *N*-methylated product **3**, plus *N,N*-dimethylformamide.

This mechanism is in contrast to that of formylation at the activated methylene group. In this instance, condensation formally requires the elimination of two moles of methanol and not formamide.

This method of alkylation has been extended to the simplest of secondary aromatic amides, acetanilide **9**. Alkylation by either of the two methods used earlier (Schemes 1 and 2), results in the formation of the same N-Me product **10**. The yields of *N*-methylacetanilide were low (20%) but were not optimized. A sample of **10** was prepared for comparative purposes.



EXPERIMENTAL

General.

All starting materials, except where noted, were purchased from the Aldrich, Fisher or Janssen Companies and were used as purchased. Most solvents were used as purchased from Fisher. Anhydrous tetrahydrofuran where required, was either purchased in sure seal cap bottles (Aldrich) or was distilled with lithium metal. Standard workup of most reactions, except where noted, was carried out by washing the organic phase with an equal volume of water followed by washings with an equal volume of saturated sodium chloride solution (x3). The organic phase was then dried (magnesium or sodium sulfate), filtered (gravity) and then the filtrates were concentrated, under reduced pressure (water aspirator) on a rotary evaporator. Analytical samples were prepared by recrystallization to a constant melting point (±2°) in the solvents indicated. The crystals were filtered and dried in a vacuum oven overnight. Reported yields were not optimized, although for repetitive experiments, the procedure reported was for the experiment giving the best yield.

Melting points were determined in a capillary tube with a "Mel-Temp" apparatus and are not corrected. The ^{1}H nmr spectra were determined using a Bruker Model 200 spectrometer, an IBM Model WP-200sy spectrometer, or with a Bruker Model AM 400 spectrometer. Spectra were recorded in deuteriochloroform or in perdeuteriodimethyl sulfoxide and chemical shifts are expressed in parts per million (ppm) on the δ scale relative to TMS as the internal standard. Infrared spectra were determined using a Nicolet Model 2DX Fourier transform infrared spectrophotometer. Mass spectra were recorded on a Hewlett Packard HP5890 gas chromatography-Finnigan Mat Incos 50 mass spectrometer (70 eV).

3-(Dimethylaminomethylene)-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2**) (Method A, B) and 7-Chloro-5-phenyl-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one (**3**) (Method A).

Method A.

A mixture of 3 g (11 mmoles) of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **1** [8] in 25 ml of dimethylformamide dimethylacetal was slowly distilled at 130° for 30 minutes and then cooled to room temperature. Upon standing compound **2** crystallized as an orange solid. Filtration and washing the crystals with a little cold diethyl ether gave 1.4 g (39%), mp 236-239° (lit mp 237-240°) [1]; ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.1-7.6 (8 H, m), 6.8 (2 H, d), 3.3 (6 H, s); ir (potassium bromide): 3574, 3052, 1667, 1604, 1541, 1427 cm^{-1}; ms: (+) (M^+, 325), (M H^+, 326).

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95; N, 12.90. Found: C, 66.68; H, 4.86; N, 12.61.

Upon standing the mother liquors deposited **3** as off white needles, 1.2 g (38%), mp 124-127° (lit mp 125-126°) [5]; ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.1-7.7 (8 H, m), 4.8 (1 H, dd, J = 10.5 Hz), 3.8 (1 H, dd, J = 10.5 Hz), 3.3 (3 H, s); ir (potassium bromide): 3037, 2984, 1678, 1444; ms: (+) (M^+ Na^+, 307), M H^+, 285), (M^+, 284).

Anal. Calcd. for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60; N, 9.80. Found: C, 67.55; H, 4.59; N, 9.89.

Method B.

A mixture of 15 g of **1** [8] (56 mmoles) in 50 ml of dimethylformamide diethyl acetal was distilled for 1 hour at 110°. The reac-

tion was concentrated and the product was crystallized from methylene chloride to yield 14 g (78%) of **2** as an orange solid; mp 233-236° (lit mp 237-240°) [1].

1-Methyl-3-(dimethylaminomethylene)-5-phenyl-7-chloro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**4**).

Method A.

A mixture of 0.5 g (1.8 mmoles) of **3**, and 25 ml of dimethylformamide dimethyl acetal was refluxed for 30 hours. The solution was concentrated and the product crystallized from ether as orange prisms (0.3 g, 50%), mp 197-200°. A mixture mp with product obtained in Method B, showed no depression, mp 198-202°.

Method B.

A solution of 0.25 g (0.8 mmoles) of compound **2** in 50 ml dimethylformamide maintained at 0° and under an atmosphere of nitrogen was treated with 0.025 g (1.1 mmoles) of an 80% dispersion of sodium hydride in mineral oil. The reaction mixture was stirred for 30 minutes and then a solution of methyl iodide (0.13 g, 0.96 mmoles) in 10 ml dimethylformamide was added dropwise at room temperature. The reaction mixture was stirred for 2 hours and was then concentrated. Methylene chloride (25 ml) was added to the residue and the organic phase was washed, dried, filtered and concentrated. The product was recrystallized from ether/hexane to give 0.15 g (55%) of **4** as orange prisms, mp 199-203° (lit mp 204-205°) [1]; ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.7-7.0 (8 H, m), 6.9 (1 H, s), 3.2 (9 H, s).

Method C.

A mixture of 0.5 g (1.5 mmoles) of **2**, and 25 ml of dimethylformamide dimethylacetal was refluxed for 36 hours. The reaction was concentrated and the presence of **4** was identified from a complex mixture of products by comparative thin layer chromatogram with product from Method B (R_f = 0.34, ethyl acetate as eluant on silica gel 60 F_{254} plates).

Method D.

A mixture of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **1** [8] (1 g, 3.7 mmoles) and 25 ml of dimethylformamide dimethyl acetal was refluxed for 48 hours. The reaction was concentrated and **4** was crystallized from ether as orange prisms (0.25 g, 25%). The product was identified by thin layer chromatogram (R_f = 0.34, ethyl acetate as eluant using silica gel 60 F_{254} plates) with product from Method B, mp and mixture mp with **4** obtained from A, mp 198-202°.

7-Chloro-5-phenyl-1,3-dihydro-1-ethyl-2*H*-1,4-benzodiazepin-2-one (**5**).

This compound has been prepared previously by reduction of the corresponding 4-oxide [9].

Sodium hydride (80% dispersion in mineral oil, 0.33 g, 14 mmoles) was added portionwise at 0° and under an atmosphere of nitrogen to a solution of **1** [8] (2.7 g, 10 mmoles) in 50 ml of dimethylformamide. The reaction stirred for 15 minutes when a solution of ethyl bromide (1.3 g, 12 mmoles) in 10 ml of dimethylformamide was added dropwise at 0°. The mixture was stirred at ambient temperature for 48 hours when 10 ml of methanol was added. The reaction was concentrated on a rotary evaporator. Methylene chloride (20 ml) was added to the residue and the solution was washed, dried, filtered and concentrated. The product was crystallized from ether to give 1.77 g (60%) of **5** as an off white powder, mp 125-127° (lit mp 127-128°); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.65-7.25 (8 H, m), 4.8 (1 H, dd, J = 10.5 Hz), 4.3 (2 H, q, J = 7.1 Hz), 3.7 (1 H, dd, J = 10.5 Hz), 1.1 (3 H, t, J = 7.1 Hz); ms: m/z (relative intensity) 297 (M^+, 95), 270 (100), 241 (25), 205 (12), 193 (7), 177 (14), 165 (30), 151 (17), 138 (13), 102 (12), 91 (43), 77 (25), 65 (12), 51 (15), 39 (9).

7-Chloro-2-methoxy-5-phenyl-3*H*-1,4-benzodiazepine (**6**) was made according to literature procedures [10] in 47% yield, mp 89-92° (lit mp 94-97°); ^{1}H nmr (200 MHz, deuteriochloroform): δ 7.7-7.1 (8 H, m), 4.1 (1 H, s), 3.9 (3 H, s), 3.7 (1 H, s).

N-Methylacetanilide (**10**).

Method A.

A mixture of acetanilide **9**, (1 g, 7.4 mmoles) with dimethylformamide dimethyl acetal (10 ml) was distilled for 1 hour at 110°. The residue was concentrated and the product was crystallized from ether (0.21 g, 20%), mp 95-98° (lit mp 100°) [11].

Method B.

Sodium hydride (0.23 g, 10.7 mmoles, 80% dispersion in mineral oil) was added to a solution of **9** (1 g, 7.8 mmoles) in 25 ml of dimethylformamide. The reaction was stirred at 0° under nitrogen. A solution of methyl iodide (1.3 g, 9.36 mmoles) in 10 ml of dimethylformamide was added dropwise and the reaction was allowed to stir for 1 hour. The mixture was concentrated, and methylene chloride (20 ml) was added to the residue. The solution was washed, dried, filtered, and concentrated. Ether (5 ml) was added to the residue to yield **10** (0.17 g, 15%) mp 98-100°. A mixture melting point with a sample prepared as in Method A above, showed no depression.

Acknowledgement.

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* To whom correspondance should be addressed.

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