Diverse Reactivity of *N*-Aryl-α-ureidoacetals on Catalysis by Molecular Sieves or Acids

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The acid-catalyzed cyclocondensation of an *N'*-aryl-α-ureidoacetal (**1**), having a tetrasubstituted urea function, yields a 1,3-benzodiazepin-2-one (**2**), a quinazolinone (**3**), an oxazolidinone (**7**), or an arylaminoalcohol (**6**) depending upon conditions employed. Treatment of **1** with molecular sieves yields the *cis* and *trans* ureidoenolethers **4***a* and **4***b*. The *N'*-aryl-α-ureidoacetal **8** on treatment with molecular sieves undergoes intra- and inter-molecular condensations yielding the imidazolinones **9**, **10**, and **11**. The thioureidoacetal **12** on treatment with molecular sieves yielded the thiazolines **13** and **14**.

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La cyclocondensation acidocatalysé d'un *N'*-aryl-α-uréidoacétal (**1**), possédant une fonction urée tétrasubstituée, conduit, suivant les conditions expérimentales utilisées à une benzodiazépin-1,3-one-2 (**2**), à une quinazolinone (**3**), à une oxazolidinone (**7**) et à un aryl-aminoalcool (**6**). Le traitement de **1** avec des tamis moléculaires fournit les uréidoénoléthers *cis* et *trans* **4***a* et **4***b*. Le *N'*-aryl-α-uréidoacétal **8**, par traitement avec des tamis moléculaires, subit des décondensations intra- et inter-moléculaires conduisant aux imidazolinones **9**, **10** et **11**. Le thiouréidoacétal **12**, par traitement avec des tamis moléculaires, conduit aux thiazolines **13** et **14**.

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The 1,4-benzodiazepines constitute a class of compounds which has received a great deal of attention in recent years because of the widespread use of some examples as therapeutic agents. The 1,3-benzodiazepines have received much less attention and very few examples of this type are reported. We have employed *N*-aryl-α-ureidoacetals in the synthesis of the 1,3-benzodiazepin-2-one system by a cyclization reaction in which the acetal carbon alkylates the aromatic ring at the ortho position in a reaction similar to a Pomeranz–Fritz reaction (1). The formation of cyclic ureas by cycloalkylations at the urea nitrogen has recently been reviewed (2). We have found that *N*-aryl-α-ureidoacetals undergo a variety of interesting conversions which we wish to report here.

The α-ureidoacetal **1**, obtained by the reaction of 2,2-dimethoxyethyl methyl amine with *N*-methyl-*N*-phenyl carbamoyl chloride, was subjected to acid catalysis under different conditions in attempts to form a 1,3-benzodiazepine ring system. It was found that the 1,3-benzodiazepin-2-one, **2**, could be obtained from **1**, but a variety of other products could also be obtained depending upon the conditions employed in the reaction (See Scheme 1).

On treatment of **1** with relatively strong hydrochloric acid (varying in concentration from 2 to 12 *N*) at room temperature for about 12 h a good yield of **2** was obtained. The progress of the reaction could be easily monitored by carrying out the reaction in an n.m.r. tube using D_2O–DCl as solvent. The acetal **1** quickly hydrolyzes to the hemiacetal, which hydrolyzes more slowly to the hydrated aldehyde which is eventually converted to **2**.

At reflux temperature in 6 *N* HCl the major product from the reaction of **1** is the quinazolinone **3**. In order for **3** to be formed, the carbon α to the acetal group must alkylate the aromatic ring. The cyclization step must occur by means of some intermediate in which this α carbon is converted to a more electrophilic state. A possible mechanism utilizing the vinyl chloride as an intermediate is illustrated in Scheme 2.

An analogous compound, the enol ether **4**, the preparation of which is described later, also undergoes a reaction requiring the intermediacy of an electrophilic α carbon atom. Compound **4** is hydrolyzed at room temperature in 2 *N* HCl to yield *N,N'*-dimethyl-*N*-phenylurea **5**. The double bond of the enol ether is activated to protonation at either carbon but it appears that the nitrogen in this case is better able to stabilize the positive charge so that protonation on the

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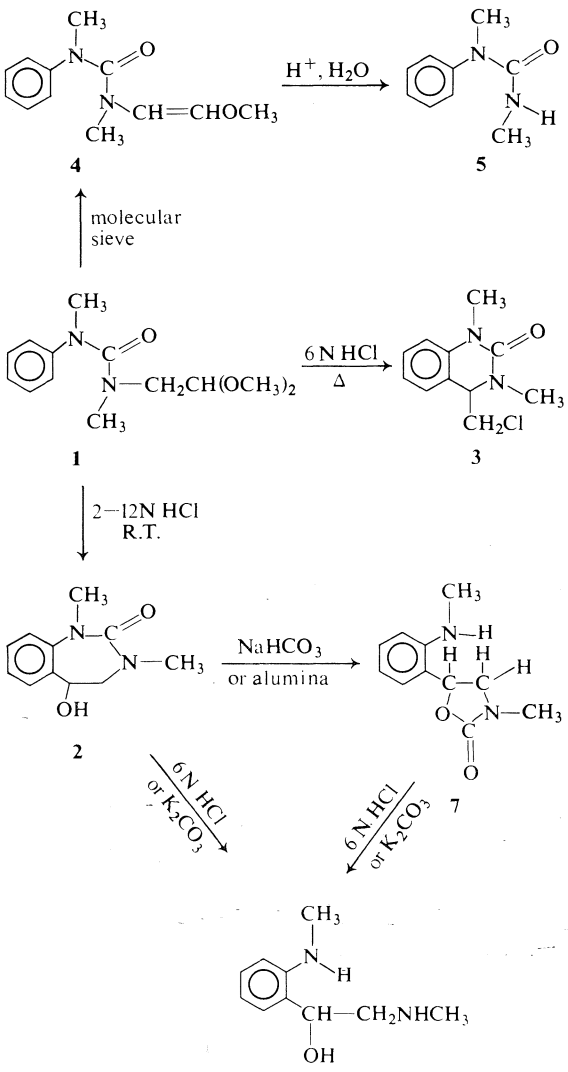


SCHEME 1

oxygen-bearing carbon is preferred. The carbonium ion in this instance, instead of alkylating the aromatic ring, is attacked by water leading to the urea **5**.

The 1,3-benzodiazepinone **2**, which could be formed by treatment of **1** with 6 *N* HCl at room temperature, was found to undergo further reaction on heating at reflux with the same acid. The product was *o*-methylamino-α-methylaminomethyl benzyl alcohol (**6**) formed by hydrolysis of the urea functionality. Hydrolysis of **2** with refluxing aqueous potassium carbonate also yielded **6**. However, under milder basic conditions such as refluxing aqueous sodium bicarbonate, **2** was converted to the oxazolidinone **7**, which could be hydrolyzed in stronger base or in acid to **6**. A good yield of **7** could also be obtained by heating **2** in the presence of alumina in refluxing toluene.

When an *N*-aryl-α-ureidoacetal having a proton on the aryl nitrogen is employed the possibility exists for alkylation to occur at the nitrogen instead of the aromatic ring. In the case of the reaction of **8** with acid, alkylation occurs on the nitrogen yielding 1-phenyl-4-imidazolin-2-one, **9**. The reaction occurs extremely rapidly, being complete in 2 *N* HCl at room temperature within the time required to dissolve the starting material and record the n.m.r. spectrum. This reaction is analogous to that reported for α-ureidoacetaldehyde diethyl acetal (3).

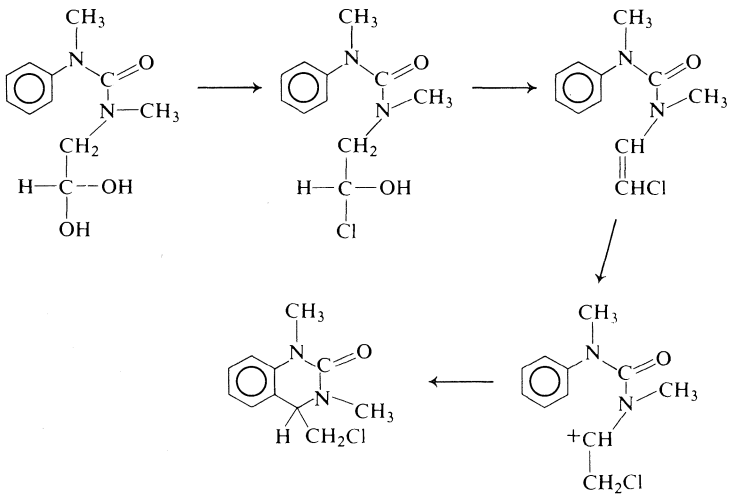
Since it appeared that the alkylation in this case occurred rapidly and exclusively at the nitrogen under acid catalysis an attempt was made to catalyse an aryl alkylation by molecular sieves. Treatment of **8** with molecular sieve 5A in refluxing toluene also gave the *N*-alkylation product **9** as one product. Two other products **10** and **11**, obviously formed from intermolecular reactions, were isolated (Scheme 3).

When the dimethyl analog, **1**, was treated with molecular sieve 5A in the same manner the major products were the *cis* and *trans* enol ethers **4***a* and **4***b*, formed in a ratio of *cis*: *trans* of 3:2. Minor products were *N'*-phenyl-*N*-methylurea and *N*,*N'*-dimethyl-*N'*-phenyl-α-ureidoacetaldehyde, apparently formed by a hydrolysis reaction with residual water in the molecular sieves.

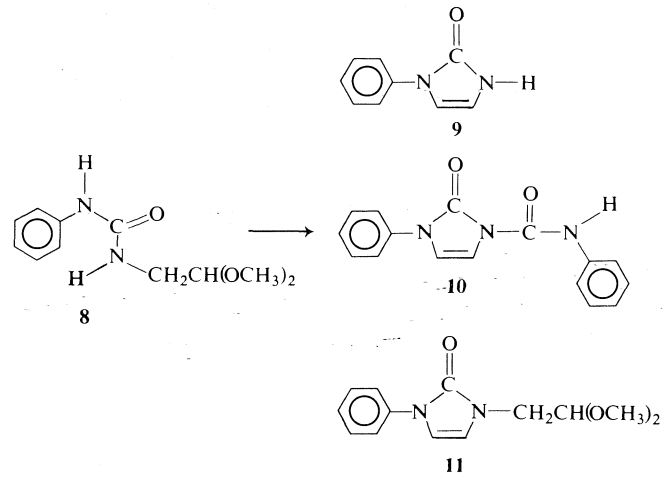
The thioanalogue of **8**, *N'*-phenyl-*N*-(2,2-dimethoxyethyl)thiourea (**12**) gave no aromatic substitution products on treatment with acid. The reaction of **12** with 2 *N* HCl at room temperature yielded the thiazoline **13** as the sole product. This reaction proceeded extremely rapidly as detected by recording the n.m.r. spectrum of **12** dissolved in 2 *N* DCl–D_2O. The formation of thiazolines from *N*-alkyl-α-ureidoacetals on treatment with acid has been reported (4). The reaction of the thioureiodacetal **12** with molecular sieve 5A in refluxing toluene yielded the same thiazoline (**13**) as obtained in the acid catalyzed reaction, as well as a second product the thiourea derivative **14** (Scheme 4).

Experimental

Nuclear magnetic resonance spectra were recorded on a Varian T60 spectrometer using tetramethylsilane as in-



SCHEME 2



SCHEME 3

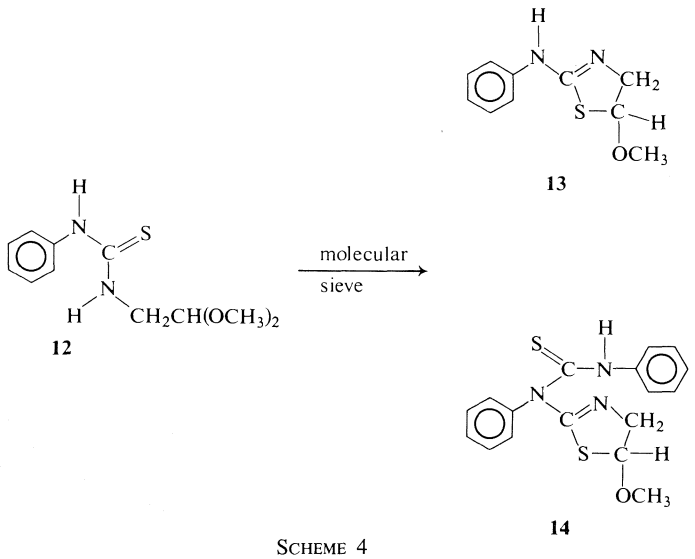
ternal standard. Chemical shifts are reported as δ values and absolute values of couplings in Hz with the following abbreviations: s = singlet, d = doublet, t = triplet, b = broad. Infrared spectra were recorded on a Perkin-Elmer 237 B spectrometer. Silica gel (Fisher A-288) was used for chromatography. Mass spectra were determined on a DuPont 21-104 mass spectrometer at 30 eV. Melting points are uncorrected.

*N,N′-Dimethyl-N-phenyl-N′-(2,2-dimethoxyethyl)urea (**1**)*

N-Methyl-*N*-phenylcarbamoyl chloride (5) (16 g, 0.1 mol) in benzene (100 ml) was stirred vigorously for 18 h with 2,2-dimethoxyethyl methylamine (12 g, 0.1 mol) in aqueous sodium carbonate (10%, 600 ml). The benzene layer was then separated, dried (Na_2SO_4), and the solvent removed *in vacuo*; yield 23 g, 92%; b.p. 130–135°/0.4 mm Hg; n.m.r. ($CDCl_3$) δ 2.56 (s, NCH_3), 3.17 (s, NCH_3), 3.35 (d, J = 6 Hz, CH_2), 3.35 (s, OCH_3), 4.42 (t, J = 6 Hz, CH), 6.9–7.4 (b, aromatic H's); i.r. 1660 cm^{-1}.

*1,3-Dimethyl-5-hydroxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one (**2**)*

N,N′-Dimethyl-*N′*-phenyl-*N*-(2,2-dimethoxyethyl)urea (**1**) (6.3 g, 0.025 mol) was added to 2 *N* aqueous hydrochloric acid (200 ml) and stirred at room temperature for 18 h. The solution was then made basic with 2 *N* sodium hydroxide solution and extracted once with ether (30 ml) which removes a small quantity of *N*-methylaniline. The aqueous layer is then extracted several times with benzene. The combined benzene layers are dried (Na_2SO_4) and the solvent removed to yield **2** as a colorless oil; yield 4.5 g, 90%; b.p. 160–162°/0.7 mm Hg; n.m.r. (C_6D_6) δ 2.13 (s, NCH_3), 2.98 (s, NCH_3), 2.62 (B), 2.78, (A), 5.10 (X of ABX, J_{AB} = 16 Hz, J_{AX} = 10 Hz, J_{BX} = 5 Hz), 6.30–7.00 (m, aromatic H's); i.r. 3600, 1700 cm^{-1}; mass



12 13 14

SCHEME 4

spectrum 206(29), 163(8), 162(9), 148(11), 134(14), 132(23), 106(23), 44(100).

4-Chloromethyl-1,3-dimethyl-3,4-dihydro-2(1H)-quinazolinone (3)

N,N'-Dimethyl-*N'*-phenyl-*N*-(2,2-dimethoxyethyl)urea (**1**) (5 g, 0.02 mol) was added to refluxing 6 *N* hydrochloric acid (50 ml) and the solution heated under reflux for 10 min. The solution was then poured into ice cold 2 *N* sodium hydroxide solution (200 ml). The aqueous solution was extracted with ether and after removal of the ether the residue was chromatographed on a silica gel column using chloroform as eluant. The first fraction yielded 4-chloromethyl-1,3-dimethyl-3,4-dihydro-2(1*H*)-quinazolinone (**3**) (yield 2.7 g, 60%) and the second fraction yielded the 1,3-benzodiazepinone (**2**) (yield 0.4 g, 20%). Compound **3** was recrystallized from petroleum ether – benzene (30–60°); m.p. 73°; n.m.r. ($CDCl_3$) 3.13 (s, NCH_3); 3.25 (s, NCH_3), 3.58 (d, J = 5.5 Hz, CH_2), 4.43 (t, J = 5.5 Hz, CH), 6.7–7.4 (m, 4 aromatic H's) mass spectrum 226(1.4), 224(4.1), 175(100), 131(3.2); i.r. 1650 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}N_2OCl$: C, 58.80; H, 5.83; N, 12.47; Cl, 15.78. Found: C, 58.95; H, 6.07; N, 12.48; Cl, 15.66.

N-N'-Dimethyl-N'-phenyl-N-(2-methoxyvinyl)urea (4)

N,N'-Dimethyl-*N'*-phenyl-*N*-(2,2-dimethoxyethyl)urea (**1**) (5 g, 0.02 mol) was heated under reflux in toluene (100 ml) with molecular sieve 5A (100 g) for 18 h. The solution was filtered and the molecular sieves washed with fresh toluene. The toluene was then removed *in vacuo* and the residue chromatographed on silica being eluted with chloroform. The first fraction contained a mixture of the *cis* and *trans* isomers of (**4**) (2.4 g, 55%), the second fraction contained α-(*N,N'*-dimethyl-*N'*-phenylureido) acetaldehyde (0.2 g, 5%), and the third fraction contained *N,N'*-dimethyl-*N*-phenylurea (0.3 g, 9%). The *cis* and *trans* isomers of **4** which were obtained in a ratio of about *cis*: *trans* 3:2, were separated by chromatography of the mixture on silica using benzene as eluant.

Compound **4***a* (*cis*): n.m.r. ($CDCl_3$) 3.00 (s, NCH_3) 3.25 (s, NCH_3), 3.44 (s, OCH_3), 5.03 (A), 5.07, (B, of AB, J_{AB} = 5 Hz, 2 olefinic H's) 6.8–7.4 (m, 5 aromatic H's); i.r. 1630 cm^{-1}; mass spectrum 220(55), 134(100), 106(40).

Compound **4**b (*trans*): n.m.r. ($CDCl_3$) 2.80 (s, NCH_3), 3.20 (s, NCH_3), 3.26 (s, OCH_3), 6.07 (A), 6.13 (B, of AB, J_{AB} = 12 Hz, 2 olefinic H's); i.r. 1630 cm^{-1}; mass spectrum 220(17), 134(100), 106(64).

o-Methylamino-α-methylaminomethylbenzyl Alcohol 6

1,3-Dimethyl-5-hydroxy-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepine (**2**) (1 g, 0.005 mol) or 3-methyl-5-(o-methylaminophenyl)-2-oxazolidinone (**7**) (1 g, 0.005 mol) was heated under reflux for 18 h with an aqueous 10% K_2CO_3 solution (10 ml) or 2 *N* HCl (10 ml). The solution was cooled and extracted with benzene (after basification in the HCl case). After evaporation of the benzene, the residue was crystallized from petroleum ether (30–60°); yield 0.75 g, 85%; m.p. 86 °C; n.m.r. ($CDCl_3$) δ 2.37 (s, NCH_3), 2.79 (s, NCH_3), 2.82 (B), 3.05 (A), 4.72 (X of ABX, J_{AB} = 12.5 Hz, J_{AX} = 9.5 Hz, J_{BX} = 4 Hz), 6.50–7.34, (m, aromatic H's); mass spectrum 180(100), 162(18), 137(64), 122(20), 118(55), 136(32).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.55. Found: C, 66.76; H, 9.15; N, 15.36.

3-Methyl-5-(o-methylaminophenyl)-2-oxazolidinone 7

1,3-Dimethyl-5-hydroxy-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one (**2**) (6 g, 0.03 mol) and alumina (Baker Analyzed, p*H* of 10% slurry 8.0, 20 g) in toluene (100 ml) was heated under reflux with stirring for 3 h. The alumina was removed by filtration and washed with an additional 100 ml of toluene. Evaporation of the toluene from the combined filtrates yielded a solid which was recrystallized from petroleum ether (60–80°): yield 5.5 g, 92%; m.p. 88–89°; i.r. 1750 cm^{-1}; n.m.r. (acetone-d_6) δ 282 (bs, NCH_3), 2.84 (s, NCH_3), 3.47 (B), 3.97 (A), 5.60 (X, of ABX, J_{AB} = 8.5 Hz, J_{AX} = 8.5 Hz, J_{BX} = 7.5 Hz), 4.68 (bs, NH), 6.55–7.40 (m, aromatic H's); mass spectrum 206(26), 162(7), 161(6), 132 (85), 131(53), 106(29), 91(23), 77(20), 44(100).

*N′-Phenyl-N-(2,2-dimethoxyethyl)urea (**8**)*

Phenyl isocyanate (17.9 g, 0.15 mol) was added over a period of 5 min to 2,2-dimethoxyethylamine (15.8 g, 0.15 mol) while cooling in an ice bath. The reaction mixture was allowed to remain at room temperature for 1 h during which time a crystalline mass formed. The solid was washed with petroleum ether (30–60°); yield 32 g, 95%; m.p. 86–87°; i.r. 1700, 1650 cm^{-1}; n.m.r. ($CDCl_3$) δ 3.32 (s, OCH_3's) ≃3.30 (CH_2), 4.35 (t, J = 5 Hz, CH), 6.09 (bt, J = 5.5 Hz, NH), 6.80–7.36 (aromatic H's), 7.95 (bs, NH); mass spectrum 224(3.6), 209(0.5), 193(2.5), 119(2.5), 93(17), 75(100).

*1-Phenyl-4-imidazolin-2-one (**9**)*

N′-Phenyl-*N*-(2,2-dimethoxyethyl)urea (5 g, 0.22 mol) was dissolved in 2 *N* hydrochloric acid (50 ml). After 10 min at room temperature the solution was made basic with 2 *N* sodium hydroxide and extracted with ether. Evaporation of the ether yielded a crystalline solid; yield 3.5 g, 99%; m.p. 123°; i.r. 1690 cm^{-1}; n.m.r. ($CDCl_3$) δ 6.32 (d, J = 3 Hz, H-4), 6.44 (d, J = 3 Hz, H-5), 10.9 (bs, NH), 7.00–7.64 (m, aromatic H's); mass spectrum 160(100), 139(42), 104(36), 77(44), 51(23).

*Molecular Sieve Treatment of N′-Phenyl-N-(2,2-dimethoxyethyl)urea (**8**)*

N′-Phenyl-*N*-(2,2-dimethoxyethyl)urea (1 g, 0.0044 mol) was heated under reflux in toluene (25 ml) in the presence of molecular sieves 5A (10 g) for 16 h. The molecular sieves were removed by filtration and washed with an additional portion (10 ml) of toluene. The combined filtrates were concentrated *in vacuo* yielding an oily residue. Addition of ether caused precipitation of a solid which was recrystallized from ether–hexane to yield 0.16 g, 23% of **9**.

The mother liquor from the recrystallization of **9** was concentrated *in vacuo* and the residue separated by chromatography on silica gel (solvent, hexane–ether 9:1).

The first fraction yielded compound **10**, m.p. 123 °C; yield 0.22 g, 19%; n.m.r. δ 6.61 (d, J = 3 Hz, H-5), 7.20 (d, J = 3 Hz, H-4) 7.20–7.64 (m, aromatic H's); 10.9 (bs, NH); i.r., 1730, 1685 cm^{-1}; mass spectrum 279(12), 160(100), 131(24).

The second fraction yielded compound **11**; m.p. 75°; yield 0.26 g, 24%; n.m.r. δ 3.44 (s, OCH_3's) 3.84 (d, J = 5 Hz, CH_2) 4.54 (t, J = 5 Hz, CH), 6.41 (d, J = 3 Hz, H-4) 6.55 (d, J = 3 Hz, H-5) 7.05–7.70, m, aromatic H's; i.r. 1685 cm^{-1}; mass spectrum 248(30), 217(15), 160(20), 75(100).

When the above reaction was attempted using molecular sieve 4A, the starting material was recovered unreacted and when molecular sieve 10A was used no starting material or products could be recovered.

*N′-Phenyl-N-(2,2-dimethoxyethyl)thiourea (**12**)*

Phenylisothiocyanate (19.2 g, 0.14 mol) was added over a period of 5 min to 2,2-dimethoxyethylamine (15.8 g, 0.15 mol) while cooling in an ice bath. The reaction mixture was allowed to remain at room temperature for 1 h during which time a crystalline mass formed. The solid was washed with petroleum ether (30–60°); yield 34.8 g, 99%; m.p. 56°; n.m.r. ($CDCl_3$) δ 3.35 (s, OCH_3's) 3.75 (t, J = 5 Hz, CH_2), 4.50 (t, J = 5 Hz, CH), 6.45 (bt, J = 5 Hz, NH), 7.10–7.45 (m, aromatic H's) 8.80 (bs, N′H).

*2-Anilino-5-methoxy-2-thiazoline (**13**)*

N′-Phenyl-*N*-(2,2-dimethoxyethyl)thiourea (**12**) (3.8 g, 0.02 mol) was dissolved in 2 *N* hydrochloric acid (50 ml) (6). After 10 min at room temperature the solution was made basic with 2 *N* sodium hydroxide and extracted with ether (2 × 100 ml). Evaporation of the ether yielded a solid residue which was crystallized from ether–petroleum ether (30–60°); yield 3.0 g, 95% (m.p. 140°); i.r. 1650 cm^{-1}; n.m.r. (C_6D_6) δ 2.96 (s, OCH_3), 3.74 (A), 3.91 (B), 4.92 (X or ABX, J_{AB} = 13.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 1.5 Hz), 6.62 (bs, NH), 6.85–7.40 (m, aromatic H's).

*Molecular Sieve Treatment of N′-Phenyl-N-(2,2-dimethoxyethyl)thiourea (**12**)*

N′-Phenyl-*N*-(2,2-dimethoxyethyl)thiourea (**12**) (1 g, 0.0042 mol) was heated under reflux in toluene (25 ml) in the presence of molecular sieves 5A (10 g) for 16 h. The molecules sieves were removed by filtration and washed with toluene (10 ml). The toluene was removed from the combined filtrates by distillation under reduced pressure (0.5 torr). The solid which formed was washed with ether leaving a crystalline residue of **13**, 0.3 g, 36%. The ether washings were subjected to silica gel column chromatography (eluant, hexane–ether 9:1) yielding compound **14**; 0.26 g, 18%; m.p. 103°; i.r. 1620 cm^{-1}; n.m.r. ($CDCl_3$) δ 3.34 (s, OCH_3), 4.48 (dd, J = 5 Hz, J = 13 Hz, H-4), 5.07 (d, J = 5 Hz, H–5), 5.49 (d, J = 13 Hz, H–4), 6.85–7.64 (aromatic H's); mass spectrum 208(100), 207(83), 177(25), 150(10), 132(50), 104(44).

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