2-Azacycl[3.2.2]azine. Polyhalogenation and Nucleophilic Displacement Reactions

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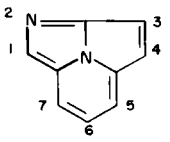
1,4-Dibromo-2-azacycl[3.2.2]azine (**2**) when treated with methanolic sodium methoxide affords the 1-methoxy-4-bromo derivative (**3**).

Perchloro-2-azacycl[3.2.2]azine (**7**) was prepared and treated with methanolic sodium methoxide to yield the 5-methoxy (**8**) and 5,7-dimethoxy (**9**) derivatives as major products, depending upon reaction conditions. Catalytic removal of the chlorine substituents of compounds **8** and **9** afforded the 5-methoxy (**10**) and 5,7-dimethoxy (**11**) derivatives. Treatment of compound **2** with butyllithium affords the 1-butyl derivative (**5**) of 2-azacycl[3.2.2]azine, while treatment with zinc in acetic acid yields 4-bromo-2-azacycl[3.2.2]azine (**6**). 4-Formyl-2-azacycl[3.2.2]-azine (**12**) when treated with phosphorus pentachloride affords the 1,3-dichloro-4-formyl derivative **13**. Possible rationals for the nucleophilic displacement are given.

In recent publications (1,2) we have described the synthesis and electrophilic substitution patterns of 2-azacycl-[3.2.2]azine (**1**). The relative ease of electrophilic brominations of this ring system at the different susceptible sites if 1 > 4 > 3. The earlier work (2) also establishes



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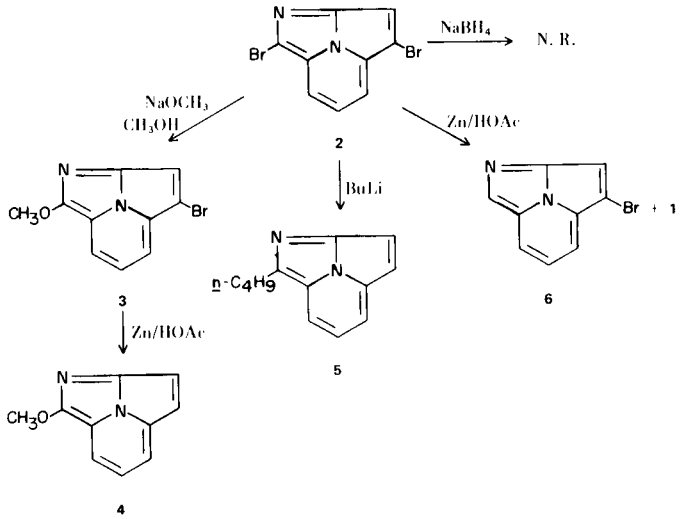
that butyllithium does not abstract a proton from any of the carbon atoms to generate, potentially, a reactive anion intermediate.

We now wish to describe some nucleophilic displacement reactions on some halogenated derivatives of 2-azacycl[3.2.2]azine (**1**).

Reactions of 1,4-Dibromo-2-azacycl[3.2.2]azine (**2**).

Treatment of 1,4-dibromo-2-azacycl[3.2.2]azine (**2**) with sodium methoxide affords a monomethoxy-monobromo derivative (**3**). (see Table I and Scheme I). In order to facilitate the structure identification, this compound was treated with zinc in acetic acid to remove the remaining bromine. The resulting compound (**4**) is a monomethoxy-2-azacycl[3.2.2]azine. The ^{1}H nmr spectrum of this material shows the presence of an AB as well as ABX pattern (see Table I). Consequently, it is the 1-methoxy derivative **4** and the monobromo-monomethoxy derivative

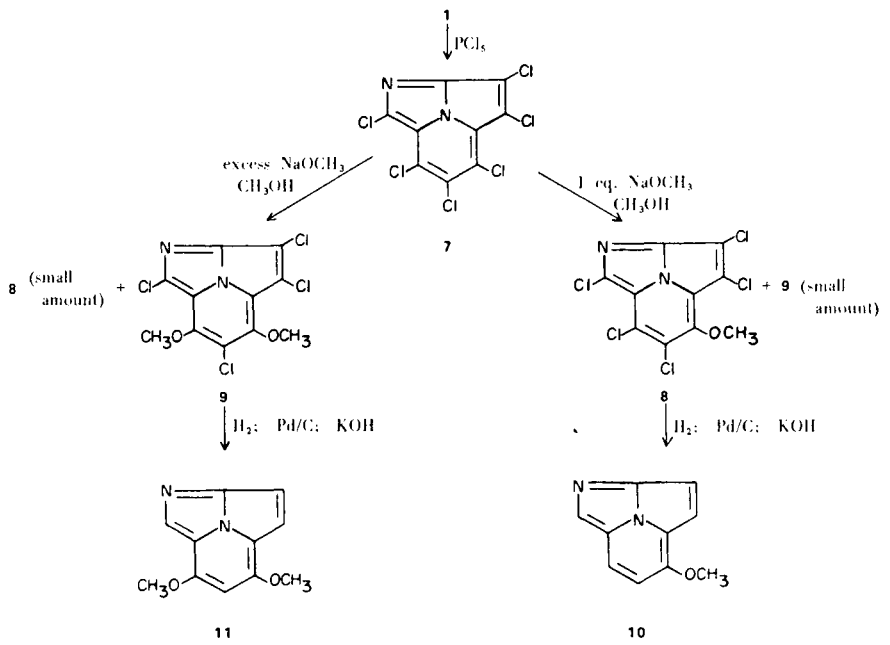
Scheme I



has structure **3** (Scheme I).

When the dibromo compound **2** is reacted with butyllithium, a monobutyl derivative, no longer containing bromine, is obtained. The ^{1}H nmr spectrum of this compound shows the presence of an AB as well as an ABX system. Thus, we are dealing with 1-*n*-butyl-2-azacycl-[3.2.2]azine (**5**). This compound is identical with the *n*-butyl derivative obtained from the reaction of 2-azacycl-[3.2.2]azine (**1**) with butyllithium (2). While attempted reduction of the 1,4-dibromo compound **2** with sodium

Scheme II



borohydride, even under severe conditions (see Experimental) did not cause removal of the bromine substituents, reduction with zinc in acetic acid afforded a monobromo derivative (**6**) as well as 2-azacycl[3.2.2]azine (**1**). The structure of the monobromo derivative was established as the 4-bromo compound (**6**) by an examination of its ^{1}H nmr as well as mass spectra.

Polychloro-2-azacycl[3.2.2]azines.

Our interest in the chemistry of perhalogenated polyazaindenes (3) prompted us to perchlorinate 2-azacycl-[3.2.2]azine (**1**). When the resulting perchloro-2-azacycl-[3.2.2]azine (**7**) was treated with one equivalent of sodium methoxide, a monomethoxypentachloro compound (**8**) along with a small amount of a dimethoxytetrachloro derivative (**9**) were obtained. The latter compound (**9**) becomes the major reaction product when an excess of sodium methoxide is used in this nucleophilic displacement reaction.

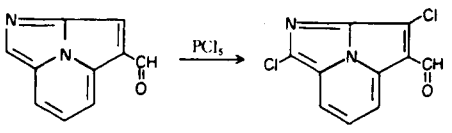
In order to establish the structures of these compounds, the chlorine substituents were catalytically removed to yield a monomethoxy (**10**) and a dimethoxy (**11**) 2-azacycl[3.2.2]azine, respectively.

The structure of the monomethoxy compound **10** was established by the observation that H-4 is more deshielded in this compound by 0.18 ppm, and H-6 more shielded by 0.30 ppm in comparison to the parent compound. While the deshielding effect on H-4 is, in all probability due to the anisotropic effect of the methoxyl oxygen, the shielding effect upon H-6 is due to the electronic effects of the methoxyl group (this effect is, 0.42 ppm in anisole as compared to benzene). This analysis establishes the structure of this compound, as the 5-methoxy derivative (**10**), and the methoxypentachloro derivative as having structure **8**.

An ^{1}H nmr spectral analysis of the dimethoxy compound (**11**) revelas that H-3 is more shielded by 0.31 ppm in comparison to the parent compound. This shielding effect is similar to that caused by a methoxy group on the *para* proton of anisole (0.37 ppm as compared to benzene). H-6 in compound **11** is more shielded by 0.43 ppm in comparison to the 5-methoxy derivative **10**, and by 0.73 ppm when compared to the chemical shift of H-6 in the parent compound (**1**). The chemical shift of H-4 in the dimethoxy compound is not changed when compared to the 5-methoxy compound (**10**) (amazingly, the singlet ascribed to H-1 is not significantly effected by the introduction of the second methoxyl group).

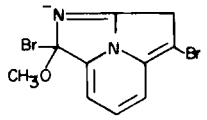
Based upon these analyses we can suggest that the dimethoxy compound is 5,7-dimethoxy-2-azacycl[3.2.2]-azine (**11**).

Interestingly, when 2-azacycl[3.2.2]azine 4-carboxaldehyde (**12**), a readily available derivative of this ring system (1), was treated with phosphorus pentachloride under mild conditions, a dichloro-carboxaldehyde derivative (**13**) was obtained as the major product. Its structure was readily established as **13** by an examination of its ^{1}H nmr spectrum (see Table I).



Discussion of Results.

The Wheland-type intermediates in the nucleophilic displacement of the 1- and 4-bromo substituents in this ring system have structures **14** and **15**, respectively.



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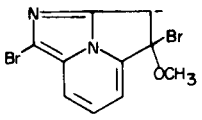

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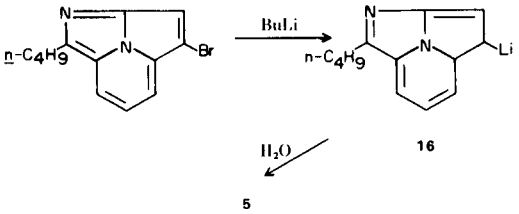
Clearly, intermediate **14** is expected to have considerably greater stability than **15**. Thus, the selective displacement of the bromine at C-1, to form compound **3**, as well as the displacement of the same bromine by a butyl group are to be expected. The observation that butyl lithium, in addition to causing a nucleophilic displacement of the bromine at C-1, also affects removal of the bromine at C-4 and displacement by a proton is rather unexpected.

We might suggest that this occurs *via* the following methathetical reaction:



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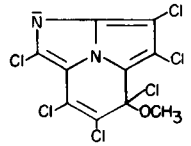
However, when the reaction mixture was quenched with deuterium oxide, none of the 4-deuterated derivative of compound **5** was obtained. It is possible that the lithium intermediate **16** may abstract a proton from the β-carbon atom of the butyl bromide formed in the reaction mixture.

The formation of the 4-bromo compound **6** is expected based upon similar considerations applied to H^- attack as proposed for the nucleophilic displacements discussed.

The stability of the dibromo compound **2** towards sodium borohydride is noteworthy and difficult to explain.

The great nucleophilic reactivity differences between a bromine at C-1 (long reflux times are needed to replace it by a methoxyl group; see Experimental) and chlorine substituents at C-5 and C-7 (room temperature displacement by a methoxyl group is extremely facile; see Experimental) are amazing. The experimental results clearly show the relative ease towards nucleophilic displacements at various sites in this ring system to be C-5 > C-7 > C-1. A consideration of the three applicable Wheland-intermediates (**17**, **18** and **19**), is unfortunately of no help in explaining these reactivity differences. It is clear, however, that intermediate **19**, containing an aromatic 10-π system



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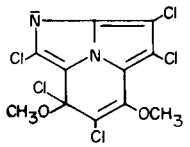

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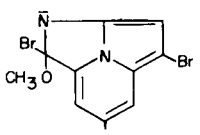

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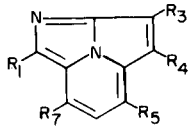
Table I

^{1}H Nmr Spectra of Some 2-Azacycl[3.2.2]azine Derivatives



	Compound (a)	Chemical Shifts (τ)						Substituents		
		H_1	H_3	H_4	H_5	H_6	H_7			
1	$R_1 = R_3 = R_4 = R_5 = R_7 = H$	1.55	2.35	2.70	2.04	2.49	2.18			
2	$R_1 = R_4 = Br$, $R_3 = R_5 = R_7 = H$	—	2.31	—	1.89	2.23	1.97			
3	R_1 = OMe, $R_4 = Br$, $R_3 = R_5 = R_7 = H$	—	2.57	—	2.04	2.51	2.06	OMe	5.70	
4	R_1 = OMe, $R_3 = R_4 = R_5 = R_7 = H$	—	2.83	2.52	2.00	2.50	2.00	OMe	5.66	
5	$R_1 = n$-C_4H_9, $R_3 = R_4 = R_5 = R_7 = H$	—	2.33	2.65	1.88	2.32	2.00	Bu-	3.36,	2.2-0.8
6	$R_4 = Br$, $R_3 = R_1 = R_5 = R_7 = H$	1.48	2.26	—	1.92	2.26	1.98	—	—	
10	$R_1 = R_3 = R_4 = R_7 = H$, R_5 = OMe	1.62	2.52	2.52	—	2.79	2.07	OMe	5.74	
11	$R_1 = R_3 = R_4 = H$, $R_5 = R_7$ = OMe	1.59	2.66	2.51	—	3.22	—	2 (OMe)	5.74,	5.71
12	R_4 = CHO, $R_1 = R_3 = R_5 = R_7 = H$	1.28	1.86	—	1.45	2.02	1.74	-CHO	-0.32	
13	$R_1 = R_3$ = Cl, R_4 = CHO, $R_5 = R_7 = H$	—	—	—	1.45	2.00	1.79	-CHO	-0.36	

(a) J_{56} = 7.8-8.0; J_{67} = 7.0-7.5; J_{34} = 4.5-5.0.

would be more stable than intermediate **17** and **18**, if the latter were not polyhalogenated. The effect of this polyhalogenation upon the nucleophilic displacement reactivity in this and other related ring systems will be the content of future publications.

EXPERIMENTAL

General.

Melting points are uncorrected. ^{1}H nmr spectra were obtained in deuteriochloroform solution, unless stated otherwise, on a Varian Associates HA-100 with TMS as internal standard. Mass spectra were measured with a Hitachi Perkin-Elmer, RMU-6M instrument at 80 ev. Microanalyses were performed by Atlantic Microlab Inc., Altanta and by the Analytical Services Division, Chemistry Department, The University of Alabama.

1-Methoxy-4-bromo-2-azacycl[3.2.2]azine (**3**).

To a solution of **2** (70 mg., 0.350 mmole) in 10 ml. of methanol was added a methanolic solution of sodium methoxide prepared *in situ* by adding 12.5 mg. of sodium metal to 10 ml. of methanol. The mixture was refluxed for 45 hours and the resulting solution was evaporated to dryness. The remaining solid was dissolved in 5 ml. of water. The aqueous solution was extracted with chloroform (3 x 25 ml.) and the combined extracts were dried over anhydrous sodium carbonate. The solvent was evaporated under reduced pressure. The solid was purified by sublimation (70°/0.3 torr) to afford compound **3** as an orange solid (50 mg., 86%), m.p. 95-96°, ^{1}H nmr (see Table I); mass spectrum m/e 252 (M^++2), 250 (M^+), 235 (M^+-15), 207 (M^+-43), 128 (M^+-122).

Anal. Calcd. for $C_{10}H_7BrON_2$: C, 47.80; H, 2.79; N, 11.15; Br, 31.87. Found: C, 47.88; H, 2.75; N, 11.07; Br, 31.74.

1-Methoxy-2-azacycl[3.2.2]azine (**4**).

To **3** (160 mg., 0.64 mmole) dissolved in 20 ml. of glacial acetic acid was added zinc dust (300 mg.) during a 30 minute period. The mixture was stirred at room temperature for 24 hours and the solid was removed by filtration. The filtrate was made basic with solid potassium hydroxide, and the mixture was diluted with 20 ml. of water and extracted with chloroform (3 x 50 ml.). The combined chloroform extracts were dried over anhydrous sodium carbonate and the solvent was removed under vacuum. The liquid residue was chromatographed on neutral alumina (grade III) and eluted with *n*-hexane. Compound **4** was obtained as a fluorescing greenish liquid (70 mg., 64%); ^{1}H nmr spectrum (see Table I), mass spectrum m/e (M^+), 157 (M^+-15), 129 (M^+-43).

1-Butyl-2-azacycl[3.2.2]azine (**5**).

To a stirred solution of **2** (100 mg., 0.33 mmole) in 25 ml. of dry THF was added 0.28 ml. of 2.4 *M* butyllithium (in hexane) under a nitrogen atmosphere and at room temperature. After 5 minutes, the reaction mixture was treated with water and the solution was extracted with chloroform (2 x 50 ml.). The combined chloroform extracts were dried over anhydrous sodium carbonate and the solvent was evaporated *in vacuo*. The resulting liquid was chromatographed on neutral alumina (grade III), using *n*-hexane as eluent, to give compound **5** (45 mg., 68%) as compared with an authentic sample.

When the reaction was quenched with deuterium oxide, no deuterium was incorporated at the bromine sites.

4-Bromo-2-azacycl[3.2.2]azine (**6**).

To a solution of **2** (250 mg., 0.83 mmole) in 40 ml. of glacial acetic acid was added, in portions, 360 mg. of zinc dust. The mixture was stirred for 24 hours. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and washed with 30 ml. of water. The chloroform layer was separated and dried over anhydrous sodium carbonate. Column chromatography on neutral alumina (grade III), using *n*-hexane as the eluent, gave several fractions. The second fraction afforded compound **6** (30 mg., 17%), m.p. 74-75°; ^{1}H nmr (see Table I); mass spectrum: m/e 222 (M^++2), 220 (M^+), 141 (M^+-79).

Anal. Calcd. for $C_9H_5BrN_2$: C, 48.87; H, 2.28; N, 12.67. Found: C, 48.63; H, 2.21; N, 12.66.

The first fraction gave 14 mg. (5.6%) of starting material.

The third fraction afforded compound **1** (80 mg., 68%) as compared with an authentic sample.

Perchloro-2-azacycl[3.2.2]azine (**7**).

A mixture of compound **1** (100 mg., 0.705 mmole) and phosphorus pentachloride (1.470 g., 7.05 mmoles) was heated in a sealed tube at 200° for 2 hours. To the cooled mixture was added 50 g. of ice and the solution was made basic with solid sodium carbonate. The mixture was extracted with chloroform (3 x 25 ml.) and the combined chloroform extracts were dried over anhydrous sodium carbonate. The solvent was removed under vacuum and the resulting solid was purified either by sublimation (140°, 0.3 mm) or by column chromatography, using *n*-hexane as eluent. Compound **7** was obtained as orange crystals (210 mg., 86%), m.p. 184-185°; ^{1}H nmr (see Table I); mass spectrum: m/e 356 (M^++10), 354 (M^++8), 352 (M^++6), 350 (M^++4), 348 (M^++2), 346 (M^+), 311 (M^+-35), 276 (M^+-2 x 35), 241 (M^+-3 x 35), 206 (M^+-4 x 35).

Anal. Calcd. for $C_9N_2Cl_6$: C, 30.98; N, 8.03; Cl, 60.90. Found: C, 30.97; N, 7.90; Cl, 61.00.

5-Methoxy-1,2,3,4,6,7-penyachloro-2-azacycl[3.2.2]azine (**8**).

To 10 ml. of absolute methanol was slowly added 10 mg. (0.43 mmole) of sodium. When the sodium had completely reacted, the solution was cooled to room temperature and compound **7** (130 mg., 0.37 mmole), dissolved in 30 ml. of methanol-chloroform was added to the reaction flask. The mixture was refluxed for 3 hours and the solvent was removed under reduced pressure. The remaining solid was chromatographed on neutral alumina (grade III), using *n*-hexane eluent. Two fractions were separated. The first fraction gave compound **8** (60 mg., 47%), m.p. 169-171°; ^{1}H nmr (deuteriochloroform): δ = 4.33 (s, 3H); mass spectrum: m/e 350 (M^++8), 348 (M^++6), 346 (M^++4), 344 (M^++2), 342 (M^+), 327 (M^+-15), 299 (M^+-43).

Anal. Calcd. for $C_{10}H_3Cl_5N_2O$: C, 34.85; H, 0.87; N, 8.13. Found: C, 34.70; H, 0.90; N, 8.23.

5,7-Dimethoxy-1,3,4,6-tetrachloro-2-azacycl[3.2.2]azine (**9**).

A procedure similar to that described for the preparation of compound **8** was employed, except that 27 mg. of sodium was used. Column chromatography gave compound **9** as a yellow solid (86 mg., 67%), m.p. 141-143°; ^{1}H nmr (deuteriochloroform): δ = 4.37 (s, 3H), δ = 4.31 (s, 3H); mass spectrum: m/e 346 (M^++8), 344 (M^+36), 342 (M^++4), 340 (M^++2), 388 (M^+), 323 (M^+-15), 295 (M^+-43), 280 (M^+-58).

Anal. Calcd. for $C_{11}H_6Cl_4N_2O_2$: C, 39.13; H, 1.76; N, 8.23; Cl, 41.70. Found: C, 38.91; H, 1.83; N, 8.20; Cl, 41.80.

Compound **8** was obtained in 12.5% yield.

5-Methoxy-2-azacycl[3.2.2]azine (**10**).

To a solution of compound **8** (175 mg., 0.51 mmole) in 100 ml. of methanol was added 430 mg. of potassium hydroxide and 130 mg. of palladium carbon. The mixture was hydrogenated in a Parr shaker (20 lb/in^2) for 1 hour. The suspended catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 25 ml. of water and the solution extracted with chloroform (2 x 100 ml.). Removal of the dried (anhydrous sodium carbonate) left a yellow residue which was purified by chromatography (neutral alumina, grade III), using chloroform-*n*-hexane (1:10) as eluent. Compound **10** was thus obtained as a pale green solid (40 mg., 46%), m.p. 74-76°; ^{1}H nmr (see Table I); mass spectrum: m/e 172 (M^+), 157 (M^+-15), 142 (M^+-30), 129 (M^+-43).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.76; H, 4.65; N, 16.28. Found: C, 69.95; H, 4.93; N, 15.53.

5,7-Dimethoxy-2-azacycl[3.2.2]azine (**11**).

A procedure similar to the above described was employed, except that the hydrogenation time was reduced to 5 minutes. Compound **11** was obtained as a pale yellow solid, after sublimation, in 38% yield, m.p. 81-83°; ^{1}H nmr (see Table I); mass spectrum: m/e 202 (M^+), 187 (M^+-15), 173 (M^+-29), 159 (M^+-43).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 65.35; H, 4.95; N, 13.86. Found: C, 65.30; H, 5.01; N, 13.75.

1,3-Dichloro-2-azacycl[3.2.2]azine-4-carboxaldehyde (**13**).

A mixture of compound **12** (140 mg., 0.32 mmole) and 2 g. of phosphorus pentachloride was heated in a sealed tube at 120° for 5 minutes. To the cooled tube was added water, 50 ml. of chloroform and solid sodium carbonate until basic. After shaking, the chloroform layer was separated. The aqueous solution was further extracted with an additional 50 ml. of chloroform. The combined chloroform extracts were dried over anhydrous sodium carbonate. The solvent was evaporated under vacuum and the solid chromatographed over alumina (grade III), using *n*-hexane as eluent. The crude product was recrystallized from methanol to give compound **13** as an orange solid (80 mg., 42%), m.p. 204-206°; ^{1}H nmr (see Table I); mass spectrum: 238 (M^+), 209 (M^+-29), 174 (M^+-64).

Anal. Calcd. for $C_{10}H_4Cl_2N_2O$: C, 50.24; H, 1.67; N, 11.72. Found: C, 49.48; H, 1.70; N, 11.11.

Attempted Reduction of Compound **2** with Sodium Borohydride.

When compound **2** (150 mg., 0.5 mmole) was treated with an excess of sodium borohydride (46.7 mg., 1.5 mmoles) in 30 ml. of methanol and the mixture was refluxed for 2 days, no reduced products were formed. The starting material **2** was completely recovered.

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