New Synthesis of 8-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4H-s-triazolo[4,3-a][1,4]-benzodiazepine, Which Has Antidepressant Properties

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An efficient, regiospecific synthesis of 8-chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine by an acetyl chloride catalyzed addition of dimethyl(methylene)ammonium chloride to 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine is described. A limited investigation of the scope of this reaction is also presented.

The 1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepines (viz. alprazolam, 1) have been found to have interesting anxiolytic activity in both experimental animals[1] and man.[2] Members of the 1-(aminoalkyl)-6-aryl-4H-s-triazolo[4,3-a][1,4]benzodiazepine series, on the other hand, are active in pharmacological tests designed to detect both antidepressant and antianxiety activity.[3] Since the antidepressant properties of this series appeared to be maximized in the analogues with a two-carbon side chain (viz. 2, Table I)[4] it became of interest to devise an efficient synthesis for these compounds.

Conceptually 2 could be obtained by adding a (dimethylamino)methylene moiety to the C-1 methyl substituent of 1. This type of transformation has historically been accomplished by the Mannich reaction, which has been effectively employed for this purpose with several heterocyclic systems.[5,6] Under the usual reaction conditions, however, this method has apparently not been reported for the triazoles; for this system nuclear rather than methyl substitution appears to be the preferred reaction.[7] Application of the Mannich reaction to 1 would be met with the added difficulty of obtaining a selective reaction at the C-1 methyl in the presence of the reactive C-4 methylene.[8] We were encouraged, however, by our discovery that 1 could be selectively hydroxymethylated at C-1 with paraformaldehyde in hot xylene.[9] Based on mechanistic considerations for this reaction it appeared that dimethyl(methylene)ammonium chloride[10] might react with 1 in a manner similar to that proposed for formaldehyde to give a reactive intermediate that could guide the Mannich reaction in the desired direction.[11] In support of this idea Böhme and Haake[12] have recently reported that dimethyl(methylene)ammonium chloride reacts with pyridine to form a quaternary ammonium salt that is stable at low temperatures. A similar reaction with 1 at N-2 would lead to the reactive intermediate in question.

When 1 was subjected to a reaction with dimethyl(methylene)ammonium chloride in DMF (expt 1, Table II) we found that the reaction proceeded at reasonable rates only at elevated temperatures (65–89 °C). Although 2 was the major product of this reaction it was obtained in poor yield (23%) and was mixed with two other Mannich products (16 and 17) as well as unreacted starting material. In an attempt to improve the yield of 2 various reaction conditions and catalysts were tried. It was found, for example, that triethylamine increased the yield of the C-4 substituted derivative (16) relative to 2 (expt 2 and 3). Small amounts of acetyl chloride, on the other hand, caused the reaction to proceed rapidly at 0 °C and to give compound 2 in 80% yield (expt 4). This reaction was conveniently carried out by adding acetyl chloride dropwise to an ice cold solution of 1 and *N,N,N',N'*-tetramethyldiaminomethane in DMF. Excess acetyl chloride over that required to convert the diamine to the reagent, dimethyl(methylene)ammonium chloride, served as the catalyst. Although this reaction was easily controlled at 0 °C to give exclusively 2, it proceeded further at ambient temperature in the presence of excess reagent to give a mixture of the diaddition products 17 and 18 (expt 5). Tetrahydrofuran and methylene chloride as well as DMF were effective solvents for this reaction (expt 6 and 7). Benzoyl chloride, trifluoroacetic anhydride, and ethyl chloroformate were effective catalysts (expt 8, 10, and 11); acetic anhydride was less effective (expt 9) and benzenesulfonyl chloride was ineffective (expt 12). In this regard it is interesting that with benzoyl chloride the reaction was much slower than with acetyl chloride, requiring about 22 h at 23 °C to go to completion. With trifluoroacetic anhydride the reaction was very rapid at 0 °C; in addition the reagent in this case was soluble in the reaction medium. This finding suggests that for other systems it should be possible to vary the catalyst, depending on the reactivity required. It should also be noted that with ethyl chloroformate a mixture of 2 and the 1,1-disubstituted derivative (17) was obtained (expt 8). When excess reagent was used with ethyl chloroformate as catalyst, 17 was the major product (compare expt 13 with 5).

These interesting results with 1 prompted us to study the behavior of other 1-substituted benzodiazepines under similar reaction conditions. Thus 8-chloro-1-ethyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (13) reacted with dimethyl(methylene)ammonium chloride and triethylamine at ambient temperature to give only the C-4 substituted product (15) in 54% yield. With acetyl chloride catalysis, although 15 was still the major product, some of the 1-substituted analogue (14) was also obtained (expt 24). Similarly, with the 1-methoxymethyl analogue (8) the 4-substituted derivative 10 was produced in 19% yield in a slow reaction with triethylamine and dimethyl(methylene)ammonium chloride. Acetyl chloride catalysis gave a more rapid reaction, and the 1-substituted derivative 9 was formed in addition to 10. With the 1-isopropyl derivative 11 only the 4-substituted compound 12 was

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(7) See, for example: M. Gall, U. S. Patent 3 914 245 (1975).
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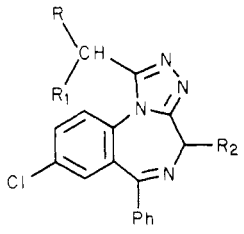
Table I. Structures and Physical Data for the 4*H*-*s*-Triazolo[4,3-*a*][1,4]benzodiazepines[e]



no.	R	R_1	R_2	mp, °C	recrystn solvent	ref[c]	formula
1	H	H	H			1	
2	$CH_2N(CH_3)_2$	H	H	195.5-197.5 dec	*i*-C_3H_7OH-H_2O	3	$C_{27}H_{28}ClN_5O_3S$[b]
3	$N(CH_3)_2$	H	H	171-172.5	EtOAc-Sk B	3	$C_{19}H_{18}ClN_5$
4	$N(CH_3)_2$	H	$CH_2N(CH_3)_2$	194.5-196	EtOAc		$C_{22}H_{25}ClN_6$
5	Ph	H	H			1	
6	Ph	$CH_2N(CH_3)_2$	H	169.5-171.5	EtOAc-Sk B		$C_{26}H_{24}ClN_5$
7	Ph	H	$CH_2N(CH_3)_2$	190.5-191.5	EtOAc-Sk B		$C_{26}H_{24}ClN_5$
8	OCH_3	H	H	193-194	MeOH		$C_{18}H_{15}ClN_4O$
9	OCH_3	$CH_2N(CH_3)_2$	H	239.5-240.5 dec	EtOH-EtOAc		$C_{21}H_{23}Cl_2N_5O$[a]
10	OCH_3	H	$CH_2N(CH_3)_2$	169-170.5	EtOAc-Sk B		$C_{21}H_{22}ClN_5O$
11	CH_3	CH_3	H	202	EtOAc		$C_{19}H_{17}ClN_4$
12	CH_3	CH_3	$CH_2N(CH_3)_2$	213-213.5	EtOH-EtOAc		$C_{29}H_{32}ClN_5O_3S$[b,d]
13	CH_3	H	H			1	
14	CH_3	$CH_2N(CH_3)_2$	H	187.5-188.5	MeOH-EtOAc		$C_{21}H_{22}ClN_5$
15	CH_3	H	$CH_2N(CH_3)_2$	209-210	EtOH-EtOAc		$C_{29}H_{30}ClN_5O_3S$[b]
16	H	H	$CH_2N(CH_3)_2$	187-188	EtOAc	20	
17	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	H	155-156.5	EtOAc-Sk B		$C_{23}H_{27}ClN_6$
18	$CH_2N(CH_3)_2$	H	$CH_2N(CH_3)_2$	197-199 dec	MeOH-EtOAc		$C_{23}H_{28}Cl_2N_6$[a]

[a] HCl salt. [b] *p*-Toluenesulfonic acid salt. [c] Literature reference. [d] Hydrate, analytical data recalculated for 1.81% H_2O. [e] See paragraph on supplementary data at end of paper.

produced with either the triethylamine or the acetyl chloride conditions; acetyl chloride catalysis, however, appeared to give a faster reaction and higher yield of product (compare expt 15 with 14). The 1-(dimethylamino)methyl analogue (**3**) of **1** reacted very slowly with dimethyl(methylene)ammonium chloride and gave only the product (**4**) of C-4 addition under both the acetyl chloride and the triethylamine conditions. Perhaps the most interesting example of this reaction was obtained with 1-benzyl-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**5**). In this case the reaction with dimethyl(methylene)ammonium chloride and triethylamine was slow and gave only the 4-substituted product (**7**). With acetyl chloride, on the other hand, the reaction was complete within 2 h at 0 °C and gave exclusively the 1-substituted product (**6**) in 77% yield (expt 19).

From a mechanistic standpoint we believe that any influence that triethylamine might have on the reaction of the 4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with dimethyl(methylene)ammonium chloride is due to a base-catalyzed facilitation of proton removal at the site of reaction. This conclusion is supported by the fact that the C-4 substituted products that would result from removal of the more acidic methylene protons[8] predominate in this reaction. An interpretation of the acyl-catalyzed reaction is illustrated in Scheme I for the conversion of **1** to **2**.

We propose that the acylating agent reacts with **1** to give an acyltriazolium derivative (A). Analogous acylpyridinium salts have been observed[13] and are generally believed to be intermediates in pyridine-catalyzed acylation reactions. Elimination of HX from A would give B, which we believe to be the reactive intermediate. Precedent for the reaction of B with dimethyl(methylene)ammonium chloride is supplied by the analogous reaction of dicyano[1,2,2,7,7,12,12-heptamethylcorrin]cobalt(III) with dimethyl(methylene)ammonium iodide.[14] The result of this reaction with B would be the acyltriazolium ion (C), which via nucleophilic attack by X^- could lose the acyl group to give the product (**2**). Since the acetylpyridinium ion has been shown to be relatively transient[6] we would expect this (C → **2**) to be the preferred reaction for C (R = CH_3); however, (ethoxycarbonyl)pyridinium ions apparently have a greater stability than the corresponding acetyl derivatives.[15-17] If this were also true for C (R = OEt) then this intermediate would be more available for additional chemistry than C (R = CH_3). Since C is analogous to A, elimination of HX from C would give a reactive intermediate which could condense with a second molecule of the dimethyl(methylene)ammonium salt to give the disubstituted derivative (**17**). The preponderance of **17** in the ethyl chloroformate catalyzed reaction (expt 13) supports this idea. Compound **2**, once formed in the reaction mixture, would be susceptible to an additional reaction with the acylating agent and condensation with the dimethyl(methylene)ammonium salt. Acylation of compound **1** is apparently directed to N-2 by the greater nucleophilicity of this nitrogen (vide supra). Although the N-2 nucleophilicity of **2** might not be appreciably influenced by the additional C-1 substituent, the steric effects of the 2-(dimethylamino)ethyl group at N-2 would be considerable.[18] Since steric effects have been found to exert a strong influence on the catalytic efficiency of 2-methylpyridine,[19] the steric effects exerted by the C-1 side chain of **2** might be expected to inhibit acylation of N-2 and, therefore, to promote acylation of the less crowded N-3 with the concomitant activation of C-4 for the condensation reaction.

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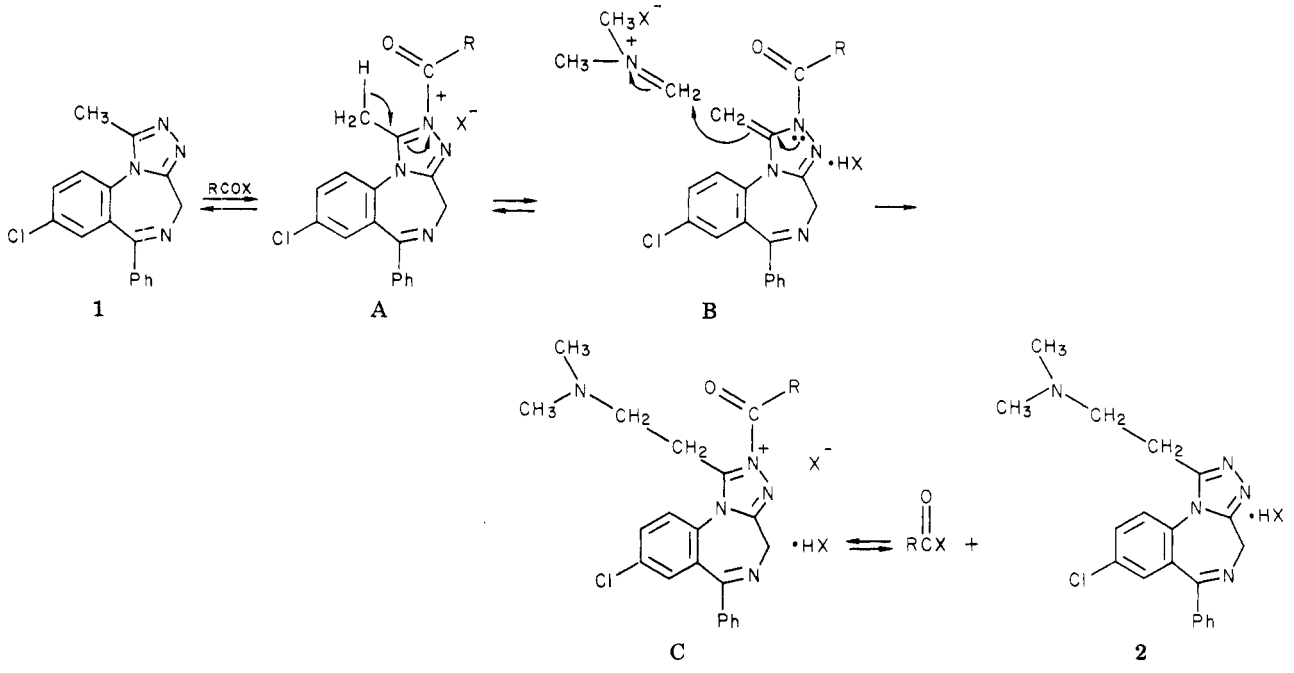
Table II. Experimental Conditions for the Reaction of the 4H-s-Triazolo[4,3-a][1,4]benzodiazepines with Dimethyl(methylene)ammonium Salts

expt no.	starting material[a]	$CH_2(NMe_2)_2$, mmol	RCX[u]	catalyst (mmol)	procedure	solvent[w]	t, h	T, °C	product (%)
1	1	15	AcCl		A[b]	DMF[v]	29	50–89	1[c] (15), 16[d] (7.5) 17[d] (5.7), 2 (23.1)
2	1	22	AcCl	Et_3N (10)	B[e]	DMF	27	23	1[c] (13.7), 16[d] (20.9) 17[d] (5.7), 2 (11.4)
3	1	25	AcCl	Et_3N (10)	C[b]	DMF	4	23	1[c,f] (45), 16 (17.2) 2 (19.1)
4	1	12	AcCl	AcCl (1)[m]	D[b]	DMF[g]	1.9	0	2 (80[i])
5	1	27	AcCl	AcCl (2)	D	DMF[g]	1.8	0[h]	17 (27.4), 18 (25.9)
							25.5	23	2 (13.8)
6	1	12	AcCl	AcCl (1)	D	THF	3.2	0	2 (89.4[i])
7	1	12	AcCl	AcCl (1)	D	CH_2Cl_2	3.2	0	2 (85.9[i])
8	1	12	EtOCOCl	EtOCOCl (1.6)	D	CH_2Cl_2	5	0	1[c] (3.7[j]), 2 (53.8[i]) 17 (14.3[j])
9	1	12	AcCl	Ac_2O (2)[k]	C[l]	THF	27.2	23	2 (87.8[i])
10	1	12	$(CF_3CO)_2O$	$(CF_3CO)_2O$ (2)	D	THF	1.5	0	2 (68.9[i])
11	1	12	PhCOCl	PhCOCl (2)	D	THF	2	0	2 (85.6[i])
							21.5	23	
12	1	12	$PhSO_2Cl$	$PhSO_2Cl$ (2)[n]	D	THF	2	0	nr[o]
							26	23	
13	1	24	EtOCOCl	EtOCOCl (4)	D	CH_2Cl_2	21	0–12	17 (61.3), 2 (8.1) 18 (7.5)
14	11	22	AcCl	Et_3N (10)	B[b]	DMF	15	23	11[c] (30.1), 12 (50.3)
15	11	12	AcCl	AcCl (1)	D	DMF	1.25	0	12 (75.9)
							3.7	23	
16	8	22	AcCl	Et_3N (10)	B[r]	DMF	34	23	8[c] (60.7), 10 (19.4)
							7.5	50	
17	8	12	AcCl	AcCl (1)	D[q]	DMF	1.25	0	8[c] (14.7), 9 (22.2)
							5.7[p]	23	10 (30.7)
18	5	22	AcCl	Et_3N (10)	B[r]	DMF	19	23	5[c] (30), 7 (32.4)
							7	47–52	
19	5	12	AcCl	AcCl (1)	D[j]	DMF	2	0	6 (77.4)
20	3	22	AcCl	Et_3N (10)	B[r]	DMF	19	23	3[c] (52.5), 4 (28)
							5	48–53	
21	3	12	AcCl	AcCl (1)	D[r]	DMF	96	23	3[c] (56.8), 4 (23.2)
22	3[s]	24	AcCl	AcCl (3)	D[r,t]	DMF	51	23	3[c] (16.5), 4 (43.5)
23	13	22	AcCl	Et_3N (10)	B[j]	DMF	13	23	13[c] (33.3), 15 (53.5)
24	13	12	AcCl	AcCl (1)	D[j]	DMF	1.3	0	15 (30.7), 14 (13.5)
							3	23	

[a] 10 mmol of the appropriate starting material was used in each reaction. [b] See Experimental Section. [c] Recovered starting material. [d] Compounds 16 and 17 could not be separated by chromatography and were isolated by fractional crystallization. [e] Et_3N added to the reaction mixture just prior to 1. [f] Crude yield. [g] Burdick and Jackson DMF analyzed to contain 0.05 mg/mL of H_2O and stored under N_2 over Davison 4A molecular sieves. [h] By TLC on silica gel with MeOH 1 had been converted completely to 2 after 1.5 h. [i] Isolated without chromatography by crystallization from EtOH. [j] Isolated by silica gel chromatography with MeOH. [k] Additional Ac_2O (4 mmol) added after 20.2 h. [l] This reaction started slowly; by TLC there had been little or no reaction after 5 h. [m] In procedure D the acylating agent added in excess of the N,N,N′,N′-tetramethyldiaminomethane is assumed to be the catalyst. [n] Additional $PhSO_2Cl$ (5 mmol) added after 21 h. [o] No reaction by TLC. [p] Additional acetyl chloride (1.4 mmol) was added after 3 h. [q] Products isolated by chromatography on silica gel with mixtures of MeOH–$CHCl_3$ containing 2–5% MeOH. [r] Products isolated by chromatography on silica gel with MeOH–$CHCl_3$ containing 5–10% MeOH. [s] Methanesulfonate salt (ref 3). [t] Additional acetyl chloride (7 mmol) was added after 28 h. [u] Used in molar amounts equivalent to the $CH_2(NMe_2)_2$. [v] 45 mL. [w] 50 mL of solvent was employed in each reaction.

Scheme I



Thus the reaction of **2** with acetyl chloride and dimethyl(methylene)ammonium chloride might be expected to give a mixture of the C-1 and C-4 substituted products; this was found to be the case (expt 5). This explanation should also apply to the acetyl chloride catalyzed reaction of dimethyl(methylene)ammonium chloride with **11** and **13**, which gave mainly or exclusively the C-4 substituted products. It should be realized, however, that the steric influence of the C-1 substituent on the acylation of N-2 is just one of many factors that may influence the course of this reaction. Both steric and electronic effects, for example, undoubtedly influence the formation of intermediate B and/or the reactive intermediate required for the catalyzed addition to C-4. In this regard the influence of the phenyl substituent of **5** on the acetyl chloride catalyzed reaction is particularly interesting. Apparently in this case the phenyl ring is able to stabilize the reactive intermediate (viz. B), which thus promotes the reaction at C-1.

We are currently studying the scope and limitations of the acyl-catalyzed Mannich reaction using several amine reagents and different heterocyclic systems.

Experimental Section

Chemistry. Melting points, taken in a capillary tube, are corrected. The structures of all compounds were supported by IR, UV, and NMR spectra. IR spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. UV spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A-60A or XL100 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were obtained with a Varian MAT CH7 or LKB spectrometer. The silica gel used for chromatography was obtained from E. Merck AG, Darmstadt, Germany. Skellysolve B (Sk B) is a commercial hexane, bp 60–70 °C, made by Skelly Oil Co., Kansas City, Mo.

Uncatalyzed Reaction of Dimethyl(methylene)ammonium Chloride with 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (1). Procedure A. A stirred solution of *N,N,N',N'*-tetramethyldiaminomethane (1.53 g, 0.015 mol) in dry DMF (45 mL) was cooled in an ice bath, under N_2, and treated dropwise with acetyl chloride (1.06 mL, 0.015 mol). The resulting mixture which contained a suspended white solid was allowed to stand at ambient temperature for 45 min, treated with **1** (3.09 g, 0.01 mol), and warmed to 50 °C in an oil bath for 1.5 h; it was then warmed to 65–68 °C and kept for 16.5 h. The bath temperature was increased to 88 °C during 6 h and kept at 84–89 °C for an additional 4 h and 40 min. The cooled mixture was poured into ice water, neutralized with sodium bicarbonate, saturated with sodium chloride, and extracted several times with chloroform. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with MeOH. The unreacted starting material was eluted first from the column and crystallized from MeOH–EtOAc to give 0.468 g of **1**, mp 228.5–229 °C. A mixture of **16** and **17** was next eluted from the column. Fractional crystallization first from EtOAc–Skellysolve B and then EtOAc gave 0.130 g (mp 187.5–188 °C) and 0.146 g (mp 183.5–185.5 °C) of **16**. Crystallization of the mother liquor from Skellysolve B gave 0.24 g of crude **17**, mp 96–108 °C, which was recrystallized from EtOAc–Skellysolve B to give **17**, mp 155–156.5 °C. Further elution of the column gave **2** (free base), which was treated with 1 equiv of *p*-toluenesulfonic acid in EtOH. The resulting salt was recrystallized from EtOH to give 1.03 g, mp 197 °C dec, and 0.214 g, mp 198.5 °C dec, of **2**.

8-Chloro-4-[(dimethylamino)methyl]-1-isopropyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *p*-Toluenesulfonate Hydrate (12). Procedure B. A stirred solution of *N,N,N',N'*-tetramethyldiaminomethane (2.24 g, 0.022 mol) in dry DMF (50 mL) was cooled under N_2 in an ice bath and treated dropwise with acetyl chloride (1.55 mL, 0.022 mol). The resulting mixture was kept at ambient temperature for 1 h, treated with **11** (3.37 g, 0.01 mol), stirred for an additional 2 h at ambient temperature, cooled in an ice bath, and treated with triethylamine (1.39 mL, 0.01 mol). It was kept at ambient temperature for 15 h, mixed with cold, dilute $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with 6% MeOH–$CHCl_3$. The first material eluted from the column was crystallized from EtOAc to give 0.867 g (mp 160.5 °C, resolidified and mp 202–204 °C) and 0.147 g (mp 160.5–162.5 °C) of recovered **11**. The mixture melting point with an authentic sample of **11** was undepressed. The second compound eluted from the column was dissolved in EtOAc and acidified with 1 equiv of *p*-toluenesulfonic acid in EtOH. The salt was crystallized from EtOH–EtOAc to give 2.32 g (mp 220–221 °C), 0.194 g (mp 213.5–215.5 °C), 0.260 g (mp 215–217 °C), and 0.081 g (mp 211.5–212.5 °C) of **12**.

Reaction of 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (1) with Dimethyl(methylene)ammonium Chloride and Triethylamine. Procedure C. A stirred solution of *N,N,N',N'*-tetramethyldiaminomethane (2.56 g, 0.025 mol) in dry Et_2O (50 mL), under N_2, was

treated dropwise with acetyl chloride (1.78 mL, 0.025 mol). The precipitate was stirred for 30 min and the solvent was removed via a filter stick and washed several times with dry Et_2O. The residue was suspended in dry DMF (50 mL) and treated with **1** (3.09 g, 0.01 mol). This mixture was stirred at ambient temperature for 1 h and 50 min, cooled in an ice bath, and treated with triethylamine (1.39 mL, 0.01 mol). The mixture was kept at ambient temperature for 4 h, poured into cold, dilute $NaHCO_3$, and extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with MeOH. The first material eluted from the column corresponded to recovered **1** by TLC and amounted to 1.4 g (crude weight). The second material eluted from the column was recrystallized from EtOAc to give 0.438 g (mp 187–188 °C) and 0.191 g (mp 187–188 °C) of **16**. The third compound eluted from the column was treated with 1 equiv of *p*-toluenesulfonic acid and crystallized from EtOH–EtOAc to give 1.03 g of **2**, mp 196–197 °C.

Reaction of 8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (1) with Dimethyl(methylene)ammonium Chloride and Acetyl Chloride. Procedure D. A stirred solution of 1 (3.09 g, 0.01 mol) in dry DMF (50 mL) was cooled in an ice bath, under nitrogen, and treated successively with *N,N,N',N'*-tetramethyldiaminomethane (1.23 g, 0.012 mol) and then dropwise with acetyl chloride (0.923 mL, 0.013 mol). The cloudy mixture was kept in the ice bath for 1 h and 55 min and poured into a mixture of ice and saturated $NaHCO_3$. The solution was saturated with NaCl and extracted five times with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. A solution of the resulting oil in absolute ethanol was acidified to pH 3.5–4 with a solution of *p*-toluenesulfonic acid (1 equiv) in absolute ethanol. The salt was crystallized to give 3.69 g (mp 196–197 °C), 0.612 g (mp 197–198 °C), and 0.022 g (mp 198.5–199 °C) (79.9%) of **2**.

8-Chloro-1-isopropyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11). A stirred mixture of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[21] (7.13 g, 0.025 mol) in dry THF (60 mL) was cooled in an ice bath and treated during 4 min with a solution of isobutyryl chloride (2.65 g, 0.025 mol) in THF (12 mL). The resulting dark red solution was kept in the ice bath for 20 min and at ambient temperature for 2 h. It was then poured into a stirred mixture of crushed ice and saturated $NaHCO_3$. The solid was collected by filtration, washed with water, and dried in vacuo. A solution of the solid in AcOH (60 mL) was placed in an oil bath that had been preheated to 130 °C, refluxed for 30 min, cooled, and concentrated in vacuo. The residue was mixed with ice and dilute $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOAc to give 4.32 g (mp 202–202.5 °C) and 1.63 g (mp 200–202 °C) (70.7% yield) of **11**.

8-Chloro-1-(methoxymethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (8). Compound **8** was prepared from 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine[21] and methoxyacetyl chloride in a manner similar to that described for compound **11**. The yield was 66%.

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Registry No. **1**, 28981-97-7; **2**, 60218-33-9; **2** free base, 53257-71-9; **3**, 37115-32-5; **3** methanesulfonate salt, 57938-82-6; **4**, 71616-85-8; **5**, 28910-96-5; **6**, 71616-86-9; **7**, 71616-87-0; **8**, 37952-16-2; **9**, 71616-88-1; **10**, 71616-89-2; **11**, 28910-94-3; **13**, 28910-97-6; **14**, 66490-98-0; **15**, 66490-97-9; **16**, 71616-90-5; **17**, 71616-91-6; **18**, 71616-92-7; 8-chloro-4-[(dimethylamino)methyl]-1-isopropyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine *p*-toluenesulfonate, 71616-94-9; 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine, 18091-89-9; *N,N,N',N'*-tetramethyldiaminomethane, 51-80-9; isobutyryl chloride, 79-30-1; methoxyacetyl chloride, 38870-89-2.

Supplementary Material Available: Complete physical and analytical data for compounds in Table I (3 pages). Ordering information is given on any current masthead page.

(20) This compound was prepared in these laboratories by Dr. Martin Gall, unpublished results.

(21) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).

Sensitized Photooxygenations of Δ^2-Oxazolin-5-ones and Related Studies[1]

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Sensitized photooxygenations of a few Δ^2-oxazolin-5-ones such as 2,4-diphenyl-Δ^2-oxazolin-5-one (**3a**), 4-benzyl-2-phenyl-Δ^2-oxazolin-5-one (**3b**), and 4-benzylidene-2-phenyl-Δ^2-oxazolin-5-one (**17**) have been studied, using Rose Bengal as a sensitizer. The photooxygenation of **3a** in a mixture of benzene and methanol for 0.25 h gave a mixture of bi-4,4'-(2,4-diphenyl-Δ^2-oxazolin-5-one) (**9a**, 44%) and benzamide (28%), whereas the photooxygenation of **3a** in methanol for 0.5 h gave a mixture of dibenzamide (**8a**, 40%) and benzamide (49%). In contrast, the irradiation of **3a** in either benzene or cyclohexane gave only benzamide. Nickel peroxide oxidation of **3a** gave a 38% yield of the bioxazolinone **9a**. Direct irradiation of **9a** in either benzene or acetone gave benzamide, whereas the thermolysis of **9a** in refluxing *o*-dichlorobenzene gave a 3% yield of 2,3,5,6-tetraphenylpyrazine (**16**). Photooxygenation of **3b** gave a 42% yield of *N*-benzoylphenylacetamide (**8b**), whereas the direct irradiation of **3b** gave only benzamide. Nickel peroxide oxidation of **3b** gave bi-4,4'-(4-benzyl-2-phenyl-Δ^2-oxazolin-5-one) (**9b**, 40%). Direct irradiation of **9b** gave exclusively benzamide. The photooxygenation of **17** in methanol gave a mixture of the α-benzamidocinnamate **18** (53%) and benzamide (29%), whereas the direct irradiation of **17** gave a mixture of α-benzamidocinnamic acid (**20**) (31%) and benzamide (52%). Resonable mechanisms have been suggested for the formation of the different products in these reactions.

Although the chemistry of Δ^2-oxazolin-5-ones has been fairly well studied,[3] only very few reports concerning the photochemistry of these ring systems are available in the literature.[4-8] Recently, Johnson and Sousa,[8] for example,

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