Mannich Reactions of Heterocycles with Dimethyl(methylene) Ammonium Chloride: A High Yield, One-step Conversion of Estazolam to Adinazolam

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The readily prepared ammonium salt, $(CH_3)_2N^+=CH_2Cl^-$, **4**, functionalized heterocycles differently, but in a predictable fashion, under neutral, basic or acidic conditions. Triazolo- and imidazobenzophenones **1b′** and **5**, which primarily underwent intramolecular isomerization to indolols **2a′** and **6a** rather than intermolecular electrophilic substitution under conditions of the normal aqueous Mannich reaction, were converted with **4** to the desired benzophenone derivatives, **1c′** and **7**, respectively, in moderate yields. The 1-unsubstituted triazolo- or imidazobenzodiazepines, **10a** (estazolam) and **10b**, were transformed to the corresponding 1-(dimethylamino)methyl derivatives, **11a** (adinazolam) and **11b**, in good to moderate yields (61% and 32%, respectively.) Under acidic reaction conditions, 1-methyl triazolobenzodiazepine, **10d** (alprazolam), afforded **12e**, the product of attack at C-4 of the triazolo[4,3-*a*][1,4]benzodiazepine ring system. Under strongly basic conditions in which the anion of **10d** was generated prior to reaction with **4**, both **12e** and its isomer, **15**, were formed. These results complement the report that **4** may be used to functionalize the 1-methyl position of triazolobenzodiazepines, and further demonstrate the versatility of reagent **4** in heterocyclic synthesis.

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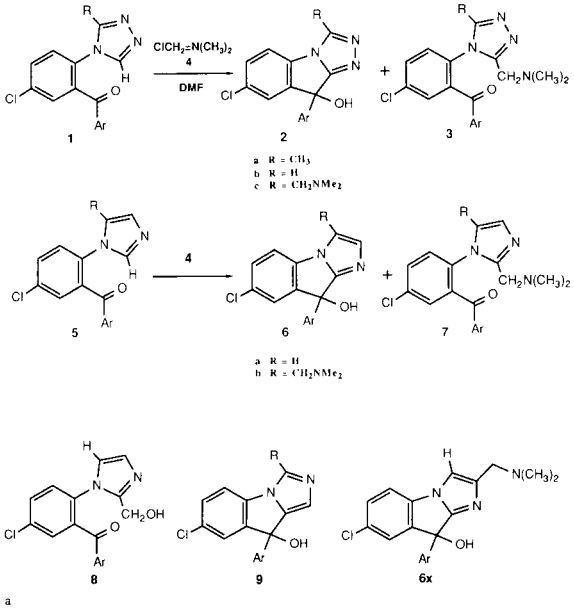
Introduction.

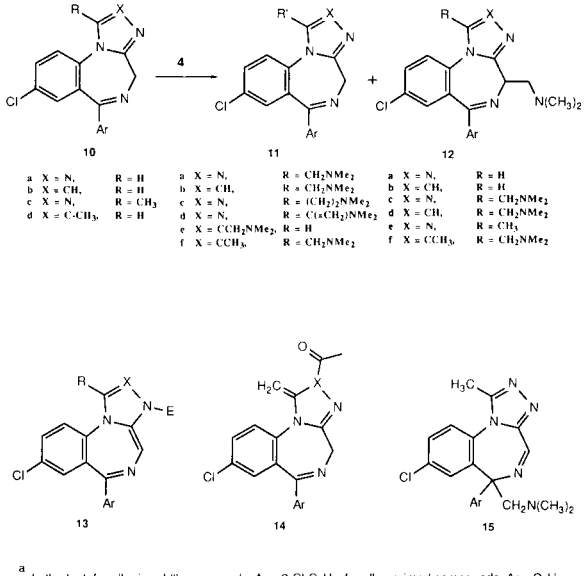
During the course of our work on the synthesis of benzophenone pro-drug forms of alprazolam and triazolam, we reported [1a] that 3-methyltriazolobenzophenone **1a′** underwent the normal Mannich reaction in aqueous medium to afford the expected 5-substituted product, **2a′**, in good yield, along with a small amount of the triazoloindolol product, **3a′** [1b] (see Scheme I). We later found that, under identical conditions, the 3,5-unsubstituted triazolobenzophenone, **1b′**, formed the unsubstituted indolol, **2b′**, in 63% yield directly from the reaction mixture; the Mannich substituted indolol adduct, **2c′**, also was isolated in

SCHEME I[a]



[a] In the text, for all primed (′) compounds, Ar = 2-Cl-C_6H_4; for all unprimed compounds, Ar = C_6H_5

SCHEME II[a]



[a] In the text, for all primed (′) compounds, Ar = 2-Cl-C_6H_4; for all unprimed compounds, Ar = C_6H_5

Table I

Physical Properties of the Benzophenone and Indolol Products

No.	Type [a]	Procedure [b]	% Yield	mp °C	UV nm λ max (ε)	1H NMR (deuteriochloroform) δ (ppm)	MS m/e	Analysis [c]
2b'	I	A	63	238-240 [d]	213 (42200)	9.2 [e] (1H, s), 8.3 (1H, d of	317, 282	C, H, N, Cl
		B	– –		255 (9800)	m, J ~ 9 Hz), 7.8 (1H, d, J = 9 Hz)		
2c'	I	A	2	229-231 [f]	214 (41950)	8.3 [g] (1H, d of m, J = 9	375, 331	C, H, N, Cl
		B	6		254 (9900)	Hz), 7.7 (1H, d, J = 9 Hz) 3.8 (4H, s), 2.3 (6H, s)	314	
3c'	II	A	– –	145-147 [h]	212 (35300)	7.2-7.8 (7H, m), 3.4 (4H, s),	432, 388	C, H, N, Cl
		B	45		244 (10650)	2.1 (12H, s)	353	
6a	I	A	42	189-191 [i]	206 (37000)	7.8 (1H, d, J ~ 1 Hz), 7.1	282, 265	C, H, N, Cl
		B	– –			(1H, d, J ~ 1 Hz), 3.6 (1H, br s, exch)	253	
6b	I	A	– –	233-236 [f]	206 (37200)	7.8 (1H, m), 6.9 (1H, s)	339, 296	C, H, N, Cl
		B	6			3.5 (2H, s), 2.2 (6H, s)	295	
7a	II	A	– –	[k]	– –	6.9 (1H, d, J ~ 1 Hz),	– –	– –
		B	35			6.8 (1H, d, J ~ 1 Hz), 3.3 (2H, s), 2.0 (6H, s)		
6a'	I	A	90	254-256 [f]	209 (35550)	8.2 [d] (1H, d of m, J = 8	316, 299	C, H, N, Cl
		B	– –			Hz), 7.6 (1H, d, J = 8 Hz), 3.4 (1H, s)	287	
6b'		A	– –	227-230 [f]	211 (42600)	8.0 [m] (1H, m), 6.8 (1H, s),	373, 329	C, H, N, Cl
		B	10			3.5 (2H, s), 2.2 (6H, s)		
7a'	II	A	– –	111-113 [h]	212 (36700)	6.8 (1H, d, J ~ 1 Hz), 6.7	373, 330	C, H, N, Cl
		B	12			(1H, d, J ~ 1 Hz), 3.2 (2H, s), 2.1 (6H, s)	267	

[a] Type I products are indolols; type II products are benzophenones. [b] Benzophenone **1b'** was used as starting material for **2b'**, **2c'** and **3c'** in both procedures A and B. Benzophenones **5a** and **5a'** were used as starting materials to prepare products **6a**, **6b**, **7a**, and **6a'**, **6b'**, **7a'**, respectively. Procedure A constitutes the standard conditions of the aqueous Mannich reaction. Procedure B utilized salt **4** in DMF, as described in the Experimental. [c] Satisfactory analyses were obtained on the elements indicated. [d] Crystallized from 2-propanol. [e] The ^{1}H nmr spectrum was run in DMSO-d_6. [f] Crystallized from methanol/ethyl acetate mixture. [g] The ^{1}H nmr spectrum was run in DMSO-d_6-deuteriochloroform mixtures. [h] Crystallized from ethyl acetate/hexane mixtures. [i] Crystallized from ethyl acetate. [j] The ^{1}H nmr spectrum was run in DMF-d_7. [k] The product was isolated as an oil and characterized on the basis of its ^{1}H nmr spectrum. [l] See R. Hodges and M. R. Grimmett, *Aust. J. Chem.*, **21**, 1085 (1968). [m] The singlet at δ 8.0 in deuteriochloroform becomes a d of m at 8.22 in DMSO-d_6-deuteriochloroform.

Table II

The Reaction of 8-Chloro-6-Phenyl-4*H*-Imidazo[1,2-*a*][1,4]benzodiazepine, **10b**, with **4** (see Scheme II)

Entry No.	Reaction Conditions [**10b**]/[**4**] = ⅔ Solvent	Temperature °	Time (hours)	Recovered 10b	Products: % crystallized 11b	12b	12d
1	DME	100	36	30.8 [a]	[b]	34.2	[b]
2	DMF	100	3	3.0	20.0	7.1	9.8
		25	20				
3 [d]	DMF	55-59	72	15.4	32.0	5.0	8.6
4	DMF/HCl(g)	100	4	[b]	[b]	46.0	[b]
5	DMF/[e]	100	4	74.5	[b]	11.4	[b]
		25	20				

[a] 58% crude starting material was isolated. [b] Not detected by tlc [c]. [c] The analysis was performed on silica gel G plates eluting with 10% methanol/chloroform mixtures. [d] The ratio of **10b**/**4** was ½. [e] One equivalent of "proton sponge" was present.

2.3% crystallized yield following column chromatography of the reaction mother liquors. None of the desired Mannich substituted benzophenone product, **3c'**, was detected (see Table I).

We now report that **3c'** is formed in good yield by heating **1b'** with 2.4 equivalents of dimethyl(methylene)ammonium chloride [$(CH_3)_2N^+=CH_2X^-$, where X = Cl], **4** [2,3,4,5], in dimethylformamide (DMF). We demonstrate that this readily available reagent [2] can be used to prepare Mannich derivatives of heterocyclic benzodiazepines in moderate to high yields from 1-unsubstituted triazolo- (**10a**) or imidazo- (**10b**) benzodiazepines [6] (see Scheme II and Table II). Specifically, the anti-depressant, adinazolam (**11a**) can be prepared in over 60% crystalline yield, without chromatography, from estazolam (**10a**) [7]. We also show that the course of the Mannich reaction of **4** with heterocycles varies dramatically with the reaction conditions and the nature of the substrate.

Reactions of **4** with Unsubstituted Triazolo- and Imidazobenzophenones.

The results are summarized in Table I. Heating **1b'** to 80° in DMF for twenty minutes with 2.4 equivalents of **4** afforded **3c'** in 40% yield following chromatographic separation of indolol, **2c'**, isolated in 6% yield. The monosubstituted triazolo benzophenone, **3b'**, was not detected, although it must have been formed during the early stages of the reaction.

Under similar conditions, the imidazobenzophenone, **5a**, afforded the monoadduct, **7a**, isolated as an oil in 35% yield; neither the benzophenone bis-adduct, **7b**, nor the isomeric monoadduct, **5b**, were detected [8a,b]. The substituted indolol, **6b**, identical to the product obtained from the reaction of unsubstituted indolol, **6a**, with salt **4**, was isolated as a by-product in 6% yield. The isomeric indolols, **9a,b**, were considered less likely structures because of the generally greater reactivity of the 2-position of the imidazole ring to electrophilic substitution reactions; we have observed this selectivity in the reaction of **5** with formaldehyde to afford **8**. The structure of **6a** was verified by an X-ray analysis of its (dimethylamino)ethyl ether derivative, **6c**, crystallized as a difumarate salt. (Crystal data and details of the X-ray study are provided in the Experimental. Fractional coordinates for this structure are listed in Table III; structure conformation and numbering are shown in Figure 1. The two molecules of fumaric acid have been deleted for clarity.) The Mannich reaction of **5a**, under aqueous conditions, afforded only the unsubstituted indolol, **6a**, isolated directly from the reaction mixture in over 90% yield.

The reaction of dichloro imidazobenzophenone, **5a'**, with salt **4** afforded benzophenone **7a'** and indolol **6b'** in only 12% and 10% crystallized yields (unoptimized), respectively. Compound **7a'** had spectral properties identical with those of an authentic sample prepared from imidazobenzodiazepine **10b'**, thereby ruling out alternative structure **5b'** [1a,9]. However, the major component of this

Table III

Fractional Coordinates (x10⁴) for the (Dimethylamino)ethyl Ether Derivative of **6a**, **6c** [a]. Estimated Standard Deviations are in Parentheses.

	x	y	z
CL	1192(1)	5681(1)	1917(1)
C(1)	4290(4)	2728(4)	−1704(2)
C(2)	4914(4)	1782(4)	−1784(3)
N(3)	4931(3)	1409(3)	−977(2)
C(4)	4324(3)	2147(3)	−445(2)
C(5)	3966(3)	2373(3)	525(2)
C(5A)	3258(3)	3438(3)	567(2)
C(6)	2646(3)	4032(3)	1255(2)
C(7)	2020(3)	4924(3)	1073(3)
C(8)	2019(4)	5228(4)	268(3)
C(9)	2640(4)	4617(4)	−434(3)
C(9A)	3236(3)	3725(3)	−262(2)
N(10)	3912(3)	2961(3)	−846(2)
C(11)	2900(3)	992(3)	540(2)
C(12)	1928(4)	−130(4)	−338(2)
C(13)	933(4)	−1350(4)	−317(3)
C(14)	896(4)	−1451(4)	556(3)
C(15)	1860(4)	−349(4)	1429(3)
C(16)	2841(4)	893(4)	1411(3)
O(17)	5272(2)	3126(2)	1369(1)
C(18)	6247(3)	2409(3)	1321(2)
C(19)	7509(3)	3308(4)	2262(3)
N(20)	7101(3)	3353(3)	3174(2)
C(21)	8399(4)	4361(4)	4060(3)
C(22)	6483(4)	1908(4)	3194(3)
C(1')	5509(3)	5648(3)	3723(2)
C(2')	4510(3)	6386(3)	3931(2)
C(3')	4799(3)	7695(3)	4025(2)
C(4')	3725(4)	8337(4)	4110(2)
O(1')	6710(2)	6256(2)	3605(2)
O(2')	5057(2)	4377(2)	3657(2)
O(3')	2624(2)	7673(2)	4400(2)
O(4')	3806(2)	9338(2)	3892(2)
C(1'')	1516(4)	2366(4)	3608(3)
C(2'')	448(3)	1065(4)	3655(3)
C(3'')	816(3)	113(4)	3837(2)
C(4'')	−239(3)	−1198(4)	3857(3)
O(1'')	2885(2)	2533(2)	3869(2)
O(2'')	1121(3)	3152(3)	3351(2)
O(3'')	−1574(2)	−1286(2)	3766(2)
O(4'')	130(2)	−2104(3)	3975(2)

[a] Atoms labelled with primes and double-primes belong to the two fumaric acid molecules in the asymmetric unit.

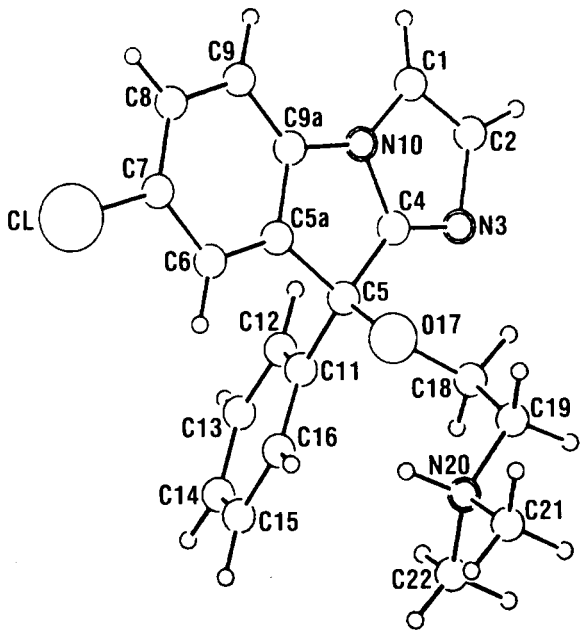


Figure 1. Conformation and numbering for the (dimethylamino)ethyl ether derivative of **6a**, **6c**. For clarity, the two fumaric acid molecules have been omitted.

reaction was a partially characterized solid, of low R_f value on silica gel tlc, and analyzing for an isomer of the expected products. The same product was obtained by treating unsubstituted indolol **6a'** with **4**, and is tentatively identified as **6x'**, the positional isomer of **6b'** (see the Experimental).

Reactions of **4** with Unsubstituted Triazolo- and Imidazobenzodiazepines - Conversion of Estazolam to Adinazolam.

The reaction of triazolobenzodiazepine **10a** (*i.e.* estazolam) with **4** in DMF for 1 hour at 75° afforded the desired 1-(dimethylamino)methyl adduct **11a** (*i.e.*, adinazolam) in 69-74% yield, following chromatographic separation from small amounts of 4-substituted products, **12a** and **12c** (Scheme II) [6].

This reaction was investigated in some detail when the clinical development of adinazolam became critically dependent upon the availability of large supplies of bulk drug. Constraints of time and availability of scale-up equipment required that undistilled reagents be used, even though this entailed the use of an excess, typically 1.3-1.5 equivalents, of salt **4** relative to starting material. In order to minimize the formation of side-products, the effect of lowering the reaction temperature was studied. At room temperature, most of the starting material was consumed within the first 15-24 hours; but some always remained even after 3-5 days. Moreover, the lower reaction temperature did not completely prevent the formation of the 4-(dimethylamino) products **12a** and **12c**. Since adinazolam was generated as its hydrochloride salt under the usual reaction conditions, we suspected that the acid formed catalyzed the tautomerization of starting material and product to afford the reactive enamine, **13** (where E = H or CH_2NMe_2), which would lead to the formation of by-products **12a** and **12c**. That such a mechanism was likely was demonstrated by treating **10a** with **4** under strongly acidic conditions, to afford primarily **12a** (48%). An exactly analogous reaction occurred with triazolam (**10c'**) under acidic reaction conditions to afford **12e'** in high yield (*vida infra*). These results suggested that the presence of an added base might slow the rate of formation of **13** and its by-products, thereby permitting the use of higher reaction temperatures. In the presence of solid potassium carbonate, the reaction was completed at 60° in 3 hours without increasing by-product formation [10]. The costly, time-consuming column chromatography was avoided by a selective methylene chloride extraction of the less basic product, **11a**, from a *p*H 3.5-4.0 buffered aqueous solution of the crude reaction mixture. Following back-wash of the organic extract with aqueous 10% sodium hydroxide solution to convert any hydrolyzed product back to the benzodiazepine ring system, and to remove any residual acid, adinazolam, **11a**, was isolated and crystallized in 61% yield (see the Experimental). Modifying this procedure to run at 40-50° for 6-18 hours permitted the conversion of 20 kg of estazolam to adinazolam in 82% yield [7].

Heating the imidazo[1,2-*a*][1,4]benzodiazepine, **10b** [11], with 2.0 equivalents of **4** in 1,2-dimethoxyethane (DME), afforded the 4-substituted addition product, **12b** in 34% crystallized yield (unoptimized); 31% starting material was recovered and no **11b** was detected. Changing the solvent to DMF reduced the yield of **12b** to 5-7%, and afforded the 1-substituted product, **11b**, in 32% crystallized yield. Between 9-10% of the 1,4-bis-adduct, **12d**, also was obtained. When the reaction mixture in DMF was saturated with dry, gaseous, hydrochloric acid prior to heating, only **12b** was formed, in 46% yield. Efforts to increase the yield of **11b** by trapping the hydrochloric acid generated *in situ* with 1,8-bis(dimethylamino)naphthalene ("proton sponge") or calcium hydride failed completely; the only product was **12b** obtained in poor yield (Table II). We did not determine the effect of potassium carbonate on this reaction (*vide supra*). When starting material, **10b**, was subjected to standard aqueous Mannich reaction conditions [1a,5,12] (*i.e.*, aqueous glyme solution of dimethylamine hydrochloride and formalin), only recovered starting material was obtained. When DMF was substituted for glyme, the major product of the reaction (41% crude, 25% recrystallized) was the 4-substituted benzodiazepine, **12b**; 24% starting material was also recovered. The structure of **11b** was established by the presence in its ^1H nmr spec-

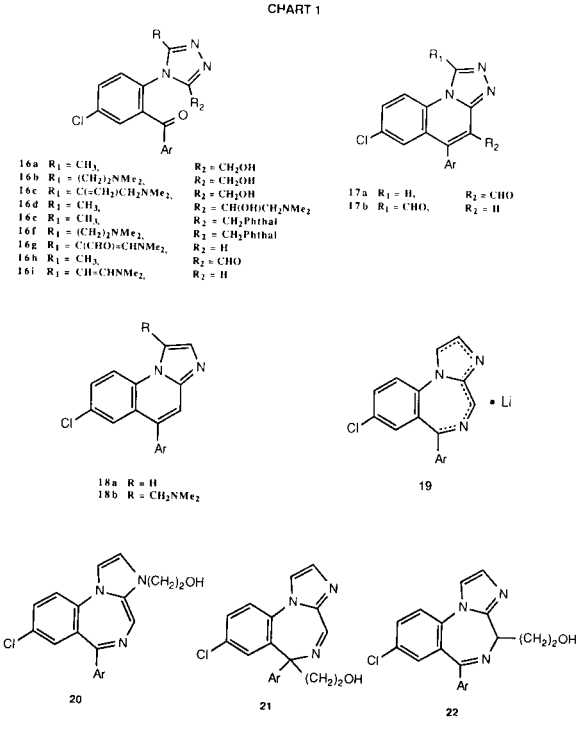
trum of a 4-methylene AB doublet of doublets (δ 5.40, J = 13 Hz, 3.90, J = 13 Hz) identical to the nmr pattern of an authentic sample [13] and characteristic of all 1-substituted imidazo- and triazolobenzodiazepines [14]. This coupling pattern was absent in the ^{1}H nmr of the starting material. Regardless of the reaction conditions used, no evidence was ever found for the formation of **11e**, the product of electrophilic substitution at the 2-position of the imidazobenzodiazepine [8].

The reaction of 2-methylimidazo[1,2-*a*][1,4]benzodiazepine, **10d'**, with **4** in DMF at 100° gave products **11f'** and **12f'**, but in only 10% and 11% crystallized yield. A third product of uncertain structure was also isolated and partly characterized (see the Experimental). The reaction conditions were not optimized for this transformation, the temperature probably being too high. However, the presence of a group larger than hydrogen at the 2-position clearly reduced the selectivity for 1-substitution *vs* 4-substitution.

Reactions of **4** and Vilsmeier Reagent with Methyl-Substituted Triazolobenzophenones and Triazolobenzodiazepines.

Our preliminary experiments indicated that reagent **4** could be used to functionalize 1-methyl-3-heteromethyl triazolobenzophenones, **16a,b**, (see Chart I) to afford (dimethylamino)ethyl products **16b,f**, but in low yields (10 and 25%, respectively) and contaminated with more polar by-products. We initially thought that one equivalent of **4** would serve as a Lewis acid which would complex one of the nitrogen atoms of the triazole ring and generate a tautomeric structure involving the methyl group. Such a tautomer would then react with a second equivalent of **4** to give the product of methyl substitution. That a Lewis acid might catalyze a substitution reaction on a triazole methyl group was suggested by the results of the reaction of triazole **1a** with the Vilsmeier reagent (DMF/phosphorus pentachloride). X-ray analysis confirmed that the major product (14%) of this reaction at room temperature was **16g**. Table IV lists fractional coordinates for **16g** and Figure 2 shows conformation and numbering (also see Chart I and the Experimental). None of the expected aldehyde product, **16h**, resulting from addition of the reagent [$(CH_3)_2N^+=CHClCl^-$] to the triazole ring nucleus was detected. The only other product found was characterized as the highly insoluble triazoloquinoline, **17a** or **17b**; **17a**, resulting from intramolecular condensation of enamine, **16i**, onto the benzophenone carbonyl group, was preferred on mechanistic grounds. Our disappointingly low yields suggested that neither **4** nor the Vilsmeier reagent were satisfactory catalysts under our reaction conditions. However, that an appropriate Lewis acid could promote functionalization at the methyl group of a methyl triazole was elegantly demonstrated by Hester, who reported [15a] that the yields and selectivity for the formation of **16f** were dramatically improved (to 65%) when the reaction of **16e** with **4** was carried out using a 10% excess of acetyl chloride to generate the Mannich salt. Utilizing similar reaction conditions, he showed that alprazolam, **10c**, was selectively converted to the 1-(dimethylamino)ethyl derivative, **11c**, in over 85% yield [15b,c]. By contrast, when alprazolam was first treated with *n*-BuLi in dry THF at low temperatures a dark green solution formed, characteristic of the highly delocalized benzodiazepine anion. Adding this anion to a suspension of salt **4** in dry THF afforded a small amount of the previously unknown 6-substituted derivative, **15**, (8% yield) along with a 22% crystalline yield of 4-substituted product, **12e** [16]. The structure of **15** was based on its ^{1}H nmr spectrum (δ 8.85, s, 1H, N=CH), uv (no intense absorption between 200-215 nm) and mass spectral data [M^+ at m/z 365, with a strong fragment ion at m/z 307 (M^+ - $CH_2N(CH_3)_2$)]. Finally, heating a solution of triazolam, **10c'**, dissolved in a 5/2 mixture of DME/DMF saturated with dry hydrochloric acid afforded **12e'** in 52% crystalline yield as the only observed product.

CHART 1



Discussion.

Our results demonstrate that the Mannich salt **4** prepared by Böhme and his colleagues [2] is an excellent and versatile reagent for (dimethylamino)methyl nuclear substitution of moderately reactive triazoles and imidazoles, particularly in cases of competing intramolecular side-reactions (*i.e.*, indolol formation from **1b'** or **5a**). The optimal conditions for carrying out these hetero-nuclear addition reactions require the use of DMF as solvent and

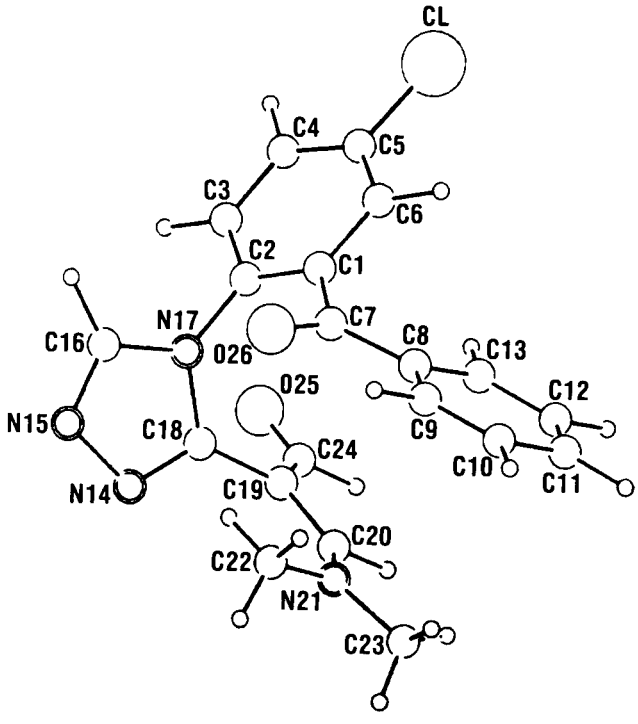


Figure 2. Conformation and numbering for **16g**.

Table IV

Fractional Coordinates (x10⁴) for **16g**.
Estimated Standard Deviations are in Parentheses

	x	y	z
CL	6646(2)	1903(1)	6568(1)
C(1)	2827(5)	946(2)	3683(3)
C(2)	1944(5)	518(2)	4107(3)
C(3)	2571(5)	489(2)	5282(3)
C(4)	4039(6)	907(2)	6040(3)
C(5)	4857(5)	1351(2)	5619(3)
C(6)	4287(5)	1373(2)	4451(3)
C(7)	2417(5)	886(2)	2442(3)
C(8)	2049(5)	1477(2)	1715(3)
C(9)	2043(6)	1397(2)	671(3)
C(10)	1605(6)	1922(2)	−64(3)
C(11)	1169(7)	2525(2)	213(4)
C(12)	1176(6)	2610(2)	1247(4)
C(13)	1610(6)	2079(2)	1988(3)
N(14)	−2492(4)	−278(1)	1934(2)
N(15)	−1254(5)	−814(1)	2498(3)
C(16)	422(6)	−572(2)	3323(3)
N(17)	369(4)	92(1)	3333(2)
C(18)	−1508(5)	255(2)	2437(3)
C(19)	−2229(5)	927(2)	2204(3)
C(20)	−2987(5)	1266(2)	1171(3)
N(21)	−3140(5)	1140(1)	156(3)
C(22)	−2524(6)	531(2)	−146(3)
C(23)	−4054(6)	1622(2)	−778(3)
C(24)	−2399(6)	1257(2)	3094(3)
O(25)	−1938(4)	1048(1)	4061(2)
O(26)	2437(4)	343(1)	2087(2)

the absence of acid. Acid inactivates the heterocyclic ring to nuclear substitution and catalyzes competing reactions *via* otherwise unstable tautomeric derivatives of the starting materials. Higher yields of nuclear (dimethylamino)-methylation products from triazole rings *vs* imidazole rings were usually obtained. However, imidazoquinoline, **18a**, afforded the expected addition product, **18b**, in 69% crystallized yield, indicating that, when the 2-position is blocked and other side reactions are not possible, substitution at the 5-position of the imidazole is a very efficient process.

However, when functionalization of the alkyl group on the heterocycle is required, it may be achieved by adding either a proton or Lewis acid to the reaction mixture. In the case of 1-methyltriazolo[4,3-*a*][1,4]benzodiazepines, the presence of proton acid generates the enamine structure **13** (X = N), leading to substitution at the 4-position of the ring system in good yield. In contrast, acylium ion generates the alternative enamine, **14** (X = N), leading to functionalization of the 1-position of this ring system [15]. Since the N-2 position of the triazolobenzodiazepine ring system is reported to be more nucleophilic and basic than N-3 [17], an explanation for the preferences of **13** and **14** under the different reaction conditions is not obvious, but may reflect the relative thermodynamic stabilities of the specific enamines. For example, the acyl enamine related to **13** (*i.e.*, E = CH_3CO) would be more hindered than acyl enamine **14** [18]. The protonated enamine, **13** (E = H),

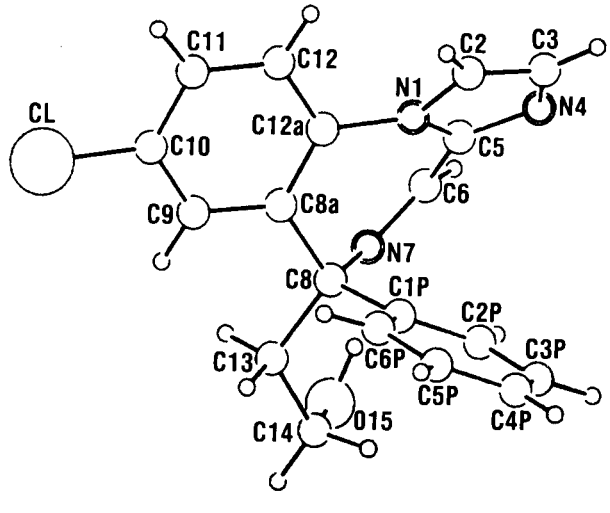


Figure 3. Conformation and numbering for **21**.

Table V

Fractional Coordinates (x10⁴) for **21**.
Estimated Standard Deviations are in Parentheses

	x	y	z
CL	−6296(1)	−1184(1)	1372(1)
N(1)	1630(2)	1402(1)	3801(1)
C(2)	2735(3)	607(2)	3866(2)
C(3)	4393(3)	1559(2)	4597(2)
N(4)	4392(2)	2922(2)	5029(1)
C(5)	2711(2)	2802(2)	4522(2)
C(6)	2088(3)	4008(2)	4683(2)
N(7)	903(2)	4265(1)	3902(1)
C(8)	37(2)	3315(2)	2633(2)
C(8A)	−1106(2)	1720(2)	2690(2)
C(9)	−2989(3)	1069(2)	2142(2)
C(10)	−3970(2)	−387(2)	2138(2)
C(11)	−3152(3)	−1247(2)	2693(2)
C(12)	−1306(3)	−628(2)	3252(2)
C(12A)	−287(2)	834(2)	3242(2)
C(13)	−1146(3)	4068(2)	1957(2)
C(14)	−153(3)	5709(2)	2003(2)
O(15)	265(3)	6648(2)	3168(2)
C(1P)	1436(2)	3272(2)	1931(1)
C(2P)	3186(2)	4363(2)	2269(2)
C(3P)	4355(2)	4325(2)	1567(2)
C(4P)	3805(3)	3211(2)	530(2)
C(5P)	2077(3)	2134(2)	186(2)
C(6P)	894(3)	2162(2)	875(2)

Table VI

Analytical Data

No.	Formula	MW	C	H	N	Cl	C	H	N	Cl
1b'	$C_{15}H_9Cl_2N_3O$	318.16	56.62	2.85	13.21	22.29	56.81	3.01	13.25	22.14
2b'	$C_{15}H_9Cl_2N_3O$	318.16	56.62	2.85	13.21	22.29	56.81	3.01	13.25	22.14
2c'	$C_{18}H_{16}Cl_2N_4O$	375.26	57.61	4.30	14.93	18.89	57.71	4.25	14.78	18.77
3c'	$C_{21}H_{23}Cl_2N_5O$	432.35	58.34	5.36	16.20	16.40	58.40	5.30	16.06	16.50
5a	$C_{16}H_{11}ClN_2O$	282.73	67.97	3.92	9.91	12.54	67.54	3.96	10.22	12.57
6a	$C_{16}H_{11}ClN_2O$	282.73	67.97	3.92	9.91	12.54	67.96	4.09	9.54	12.46
6b	$C_{19}H_{18}ClN_3O$	339.83	67.15	5.34	12.37	10.43	66.80	5.36	12.12	10.32
6c	$C_{20}H_{20}ClN_3O{\cdot}2C_4H_4O_4$	585.98	57.38	4.81	7.17	6.05	57.73	4.83	7.11	6.04
5a'	$C_{16}H_{10}Cl_2N_2O$	317.17	60.59	3.18	8.83	22.36	60.92	3.38	8.97	22.26
6a'	$C_{16}H_{10}Cl_2N_2O$	317.17	60.59	3.18	8.83	22.36	60.92	3.38	8.97	22.26
6b'	$C_{19}H_{17}Cl_2N_3O$	374.26	60.97	4.58	11.23	18.94	60.79	4.67	11.18	18.94
6x'	$C_{19}H_{17}Cl_2N_3O$	374.26	60.97	4.58	11.23	18.94	60.61	4.54	10.91	18.70
11b	$C_{20}H_{19}ClN_4$	350.85	68.46	5.46	15.97	10.10	68.50	5.50	15.92	10.37
12a	$C_{19}H_{18}ClN_5{\cdot}½H_2O$	360.84	63.24	5.31	19.41	9.82	62.98	5.11	19.30	9.98
12c	$C_{22}H_{25}N_6Cl$	408.93	64.61	6.16	20.56	8.67	64.61	6.22	20.42	8.59
12b	$C_{20}H_{19}ClN_4$	350.85	68.46	5.46	15.97	10.10	68.50	5.50	15.92	10.37
12d	$C_{23}H_{26}ClN_5$	407.95	67.71	6.42	17.17	8.69	67.84	6.43	17.17	8.69
11f'	$C_{21}H_{20}Cl_2N_4$	399.32	63.16	5.06	14.03	17.76	63.47	5.09	14.19	17.69
12f'	$C_{24}H_{27}Cl_2N_5{\cdot}HBr{\cdot}H_2O$	555.35	51.90	5.45	12.61	12.77	51.95	5.07	12.61	12.87 [a]
12x'	$C_{25}H_{27}Cl_2N_5{\cdot}2HBr$	630.25	47.64	4.64	11.11		47.34	4.50	11.03	
12e	$C_{20}H_{20}ClN_5$	365.87	65.65	5.51	19.15	9.69	65.42	5.62	18.67	9.80
15	$C_{20}H_{20}ClN_5$	365.87	65.65	5.51	19.15	9.69	65.52	5.45	19.07	10.00
12e'	$C_{20}H_{19}Cl_2N_5$	400.31	60.00	4.78	17.50	17.71	59.95	4.97	17.47	17.82
16b	$C_{20}H_{21}ClN_4O_2$	384.86	62.41	5.50	14.56	9.21	62.61	5.44	14.50	9.18
16g	$C_{20}H_{17}ClN_4O_2$	380.83	63.07	4.50	14.72	9.31	63.17	4.76	14.65	9.36
17a	$C_{17}H_{10}ClN_3O$	307.73	66.35	3.28	13.66	11.52	66.16	3.21	14.07	11.79
18b	$C_{20}H_{18}ClN_3$	335.82	71.52	5.40	12.52	10.56	71.41	5.30	12.35	10.55
20	$C_{19}H_{16}ClN_3O$	337.80	67.55	4.77	12.44	10.49	67.59	4.84	12.55	10.57
21	$C_{19}H_{16}ClN_3O$	337.80	67.55	4.77	12.44	10.49	67.52	4.97	12.30	10.41
22	$C_{19}H_{16}ClN_3O$	337.80	67.55	4.77	12.44	10.49	67.33	4.81	12.55	10.45

however, is more highly conjugated than would be the protonated analog of **14**. For the case of non-fused methyl triazoles, acetyl chloride very effectively promotes substitution at the methyl group by the reagent, **4** [15a,b].

The use of a strong base to generate the highly delocalized anion derivatives of either triazolo- or imidazobenzodiazepines leads to products very likely reflective of the relative electronic charge density at particular atoms of the anion. This is supported by the formation of the 6-substituted isomer, **15**, in addition to the 4-substituted product, **12e**, from the reaction of the alprazolam anion with **4**. However, the overall mass balance is low . In a separate experiment, we found that the imidazobenzodiazepine anion, **19**, formed *three* products when the electrophile was ethylene oxide: **20** (21%), **21** (3.6%) and **22** (3.4 %). The crystal and molecular structure of **21** was determined by X-ray. (Crystal data and details of the study are in the Experimental.) Table V lists fractional coordinates for **21**, and Figure 3 shows conformation and numbering. Again, the mass balance (of recrystallized products) was low, but the major product of this reaction, **20**, resulted from attack at the nitrogen at the 3-position. The analogous product from a reaction with the Mannich salt would not be stable to the aqueous work-up conditions, suggesting a possible explanation for the poor mass balance in the reaction of the anion of alprazolam with **4**.

In conclusion, we have demonstrated that the salt, **4**, is a versatile reagent which can be used under a variety of reaction conditions to functionalize heterocylic rings in a number of predictable ways. We anticipate additional reports of the utility of **4** and its analogs [2,3] in the synthesis of heterocyclic compounds.

EXPERIMENTAL

Methods and Reagents.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared (ir) spectra were determined in Nujol on a Perkin-Elmer Model 421 recording spectrophotometer. Ultraviolet (uv) spectra were determined in 95% ethanol on a Cary Model 14 spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Varian Model A-60D spectrometer; chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (TMS, δ 0.0) as an internal standard. Mass spectra were obtained with a Varian MAT CH7 or LKB. Unless otherwise stated, analytical thin-layer chromatography (tlc) was conducted by eluting the products with 10% methanol-90% chloroform mixtures on 2.5 x 10 cm precoated silica gel GF plates, layer thickness 0.25 mm, manufactured by Analtech. Columns for chromatography utilized E. Merck (Darmstadt) Silica Gel 60, 70-230 mesh ASTM. Chloroform, suitable for chromatography and preserved with 1% (v/v) ethanol, was purchased from Burdick and Jackson, Inc. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and dimethylformamide (DMF) were used as received ("distilled in glass") from Burdick and Jackson, Inc. Bis-(dimethylamino)methane (*N,N,N'N'*- tetramethyldiaminomethane-99%) was purchased from Aldrich Chemical Co. and used as received.

In those cases where reaction intermediates or products were isolated "by chloroform extraction", the procedure followed was to dilute the reaction mixture with chloroform, add it to an excess of a 10% aqueous sodium hydroxide solution and extract the organic products into chloroform. After the combined chloroform extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, the solution was filtered and concentrated under reduced pressure using a rotary evaporator. When reference is made to isolating or separating products by means of silica gel chromatography by eluting with methanol/chloroform mixtures, the procedure followed was to load the products onto a gravity column containing 100 g of silica gel 60/g of crude product and elute with several liters of methanol/chloroform (3/97) mixtures.

Imidazo[1,2-*a*][1,4]benzodiazepines, **10b** and **10d'** [11,13], triazolo-[4,3-*a*][1,4]benzodiazepines, **10a**, **10c** and **10c'** [17], and triazolobenzophenone, **1b'**, [6b,17], were prepared according to the literature procedures. The imidazobenzophenones, **5a** and **5a'**, were prepared by the following procedure. 4-Chloro-2-benzylaniline [1a] (50.6 g, 0.233 mole) was heated with 82.85 g (0.510 mole) of triethylorthoformate to distill 75 ml of ethanol and other low boiling materials. The resulting formimino ether was cooled to room temperature dissolved in 500 ml of reagent grade methanol, treated with 83.5 g (0.795 mole) of aminoacetaldehyde, dimethyl acetal (Aldrich) and refluxed for 3 hours. After removing the alcohols *in vacuo*, the resulting formamidine, dissolved in 1 l of distilled DME, was treated with 34.9 g (60.4 g, 0.318 mole) of titanium tetrachloride (Fisher). The reaction mixture was stirred at ambient temperature for 10 minutes, refluxed 4 hours, then cooled overnight. Following the usual chloroform extraction from aqueous sodium hydroxide, the product was dried over magnesium sulfate, concentrated *in vacuo*, chromatographed over 2.5 kg of silica gel by eluting with ethyl acetate and

crystallized from ether-hexane. The product, 1-(4-chloro-α-phenyl-*o*-tolyl)imidazole, was isolated in 48% yield (29.8 g), mp 69-70.5°; ir (nujol): 1630, 1580, 1490 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 262 nm (ϵ 699); ^{1}H nmr (deuteriochloroform): δ 6.88-7.57 (11H, m, aromatic and N-CH=CHN), 3.85 (2H, s, benzylic); ms: molecular ion peak at m/z 268 with fragment ions at m/z 241 (M^+ - HCN).

Anal. Calcd. for $C_{16}H_{13}ClN_2$ (MW 268.75): C, 71.51; H, 4.87; N, 10.43; Cl, 13.19. Found: C, 71.81; H, 4.82; N, 10.42; Cl, 13.31.

In the same way, 1-[4-chloro-α-(2-chlorophenyl)-*o*-tolyl]imidazole was prepared in 26% crystalline yield, mp 63.5-64.6° (crystallized from ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2$ (MW 303.19): C, 63.38; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 63.15; H, 3.94; N, 9.19; Cl, 23.18.

In a 500 ml round bottomed flask, 27.0 g (0.10 mole) of 1-(4-chloro-α-phenyl-*o*-tolyl)imidazole dissolved in 100 ml of acetic acid was treated with 100 ml of Jones' reagent and refluxed 4 hours on a steam bath. The mixture was cooled and, following the usual chloroform extraction and Darco treatment, the imidazobenzophenone, **5a**, was crystallized as prisms from ethyl acetate in 54% yield, mp 106-108°; ir (nujol): 1660 cm^{-1} (C=O); uv (95% ethanol): λ max 210 nm (ϵ 28,000); ^{1}H nmr (deuteriochloroform): δ 7.11-7.75 (9H, m, aromatic and N-CH=N), 6.91 (2H, br s, N-CH=CH-N); ms: molecular ion peak at m/z 282 with a fragment ion at m/z 255 (M^+ - HCN).

Anal. Calcd. for $C_{16}H_{11}ClN_2O$ (MW 282.73): C, 67.97; H, 3.92; N, 9.91; Cl, 12.54. Found: C, 67.54; H, 3.96; N, 10.22; Cl, 12.57.

In the same way, **5a'** was prepared and crystallized from ethyl acetate, mp 146-148°.

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O$ (MW 317.17): C, 60.59; H, 3.18; N, 8.83; Cl, 22.36. Found: C, 60.92; H, 3.38; N, 8.97; Cl, 22.26.

Mannich Reactions of **1b'**, **5a** and **5a'**.

Procedure A.

The following conditions correspond to Procedure A in Table I and are illustrative of the general conditions referred to in the text as " the aqueous Mannich reaction". Triazolobenzophenone **1b'** [6b,17] (3.18 g, 10.0 mmoles) in 20 ml of DME was heated to 100° for 2 hours with 6.0 ml of 37% aqueous formalin (~2.2 g, 74 mmoles) and 5.40 ml of 25% aqueous dimethylamine (1.35 g, 30 mmoles) in 15 ml of 2*N* hydrochloric acid. After cooling the reaction mixture to room temperature, the

resulting solid A was filtered to afford 2.0 g (63%) of **2b'** as a powder, mp 237-238.5°. The analytical sample crystallized from 2-propanol had mp 238-240° (see Table I for physical and spectral properties). The mother liquor from A, following chloroform extraction and silica gel chromatography, afforded an oil which crystallized from methanol-ethyl acetate mixtures to yield 85 mg of indolol **2c'**, mp 229-231° (*vida infra*, and see Table I).

Procedure B.

The following procedure corresponds to Procedure B in Table I and is illustrative of reactions of heterocyclic benzophenones with salt **4**. Triazolobenzophenone **1b'** (3.18 g, 10.0 mmoles) dissolved in 15 ml of DMF was added to 24 mmoles of salt **4** generated in 10 ml of DMF at 0° (see the procedures for **11a**). The mixture was heated in an oil bath at 80° for ⅓ hour. Following the usual chloroform extraction and silica gel chromatography, there was obtained 265 mg (6.1%) of **2c'** crystallized from methanol/ethyl acetate mixtures, mp 225-226°; ir (nujol) 3060 (OH), 2780 (*N*-alkyl), 1615, 1580, 1565, 1545, 1520 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 214 nm (ε 41,950), 254 nm (ε 9,900); ^1H nmr (deuteriochloroform/DMSO-d_6): δ 8.2-8.3 (1H, m of d, J = 4.0 Hz, aromatic C_8H), 7.0-7.8 (7H, m and s, aromatic CH and OH), 3.8 (2H, s, N-CH_2), 2.3 (6H, s, CH_3NCH_3); ms: no parent ion at m/z 374, however, there were peaks at 375, 373 and fragment ions at m/z 331 (333, 335) and 314 (316, 318).

Anal. Calcd. for $C_{16}H_{16}Cl_2N_4O$ (MW 375.25): C, 57.61; H, 4.30; N, 14.93; Cl, 18.89. Found: C, 57.71; H, 4.25; N, 14.78; Cl, 18.77.

There was also obtained 1.94 g (45%) of **3c'** crystallized as prisms from ethyl acetate-hexane, mp 145-147.5°; ir (nujol): 2760 (*N*-alkyl), 1690 (C=O), 1595, 1565, 1530, 1490 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 212 nm (ε 35,300), 244 nm (ε 10,650); ^1H nmr (deuteriochloroform): δ 7.30-7.75 (7H, m, aromatic CH), 3.40 (4H, s, two CH_2N), 2.03 (12H, s, two CH_3NCH_3); ms: weak molecular ion peak at m/z 432 with fragment ions at m/z 388 (390, 392, M^+ - CH_3NCH_3), 353 (355, M^+ - CH_3NCH_3 - Cl), 345 (347, 349, M^+ - two $CH_2=NCH_3$ - H), 317 (319, 321, M^+ - two $CH_2N(CH_3)_2$ + H).

Anal. Calcd. for $C_{21}H_{23}Cl_2N_5O$ (MW 432.34): C, 58.34; H, 5.36; N, 16.20; Cl, 1640. Found: C, 58.40; H, 5.30; N, 16.06; Cl, 16.50 (see Table I).

By similar procedures, imidazobenzophenones **5a** and **5a'** afforded **6b** and **7a** and **6b'** and **7a'**, respectively, as reported in Table I. Under the conditions of Procedure B, imidazoindolol, **6a**, was heated with **4** for 10 minutes to afford, following the usual chloroform extraction and silica gel chromatographic procedures, **6b** in 17% crystallized yield (mp 233-236° dec), identical to the product obtained in 6% yield from benzophenone **5a**. A more polar reaction product seen in the crude reaction mixture was not further characterized. Imidazoindolol, **6a'**, (4.2 g, 13 mmoles) was added to 15 mmoles of salt **4** prepared in 10 ml of DMF in the usual way. The resulting suspension was stirred at room temperature for 1 hour, then heated in oil bath at 65° for 2.5 hours, treated with an additional 15 mmoles of **4**, and heated at 65° for another 2 hours. Following the usual work-up and chromatographic separation on 300 g of silica gel (using 3% methanol/97% chloroform eluent), 2.0 g of starting material was collected, followed by 200 mg of **6b'**, mp 227-230°; ir (nujol): 3060 (OH), 2760 (*N*-alkyl), 1615, 1590, 1560, 1515, 1485 cm^{-1} (C=C/C=N); uv (95% ethanol) λ max 211 nm (ε 42,600), 269 nm (ε 6,500); ^1H nmr (deuteriochloroform): δ 7.86-8.19 (1H, br m, one aromatic CH), 6.84-7.62 (8H, m, aromatic and imidazole CH and exchangeable OH), 3.52 (2H, s, N-CH_2), 2.24 (6H, s, CH_3NCH_3); ms: molecular ion peak at m/z 373 (375, 377) with a strong fragment ion at m/z 329 (331, 333, M^+ - CH_3NCH_3).

Anal. Calcd. for $C_{19}H_{17}Cl_2N_3O$ (MW 374.26): C, 60.97; H, 4.58; N, 11.23; Cl, 18.94. Found: C, 60.79; H, 4.67; N, 11.18; Cl, 19.01.

Further elution of the column with absolute methanol afforded 800 mg of crude solid, **6x'**, mp 236-238°. The analytical sample crystallized from methanol/chloroform mixtures had mp 238-240°; ir (nujol): 2720, 2600 (*N*-alkyl), 2520, 2400, 1620, 1570, 1510, 1490 cm^{-1} (C=N/C=C); uv (95% ethanol): λ max 209 nm (ε 37,400), 274 nm (ε 6,950), 278 nm (ε 7,050): ^1H nmr (DMSO-d_6): δ 8.16-8.21 (1H, m, one aromatic CH), 7.62 (1H, s, imidazole CH ?), 7.14-7.60 (6H, m, aromatic CH and exchangeable OH at 7.14), 6.95 (1H, m, aromatic C_5H), 3.28 (2H, s, CH_2N), 2.07 (6H, s, CH_3NCH_3); ms: weak molecular ion peak at m/z 373 (375, 377) with strong fragment ions at m/z 330 (332, 334, M^+ - $CH_2=NCH_3$) and 313 (315, 317, M^+ - $CH_2=NCH_3$ - OH).

Anal. Calcd. for $C_{19}H_{17}Cl_2N_3O$ (MW 374.26): C, 60.97; H, 4.58; N, 11.23; Cl, 18.94. Found: C, 60.61; H, 4.54; N, 10.91; Cl, 18.70. The structure of this product is uncertain.

7-Chloro-9-[2-(dimethylamino)ethoxyl]-9-phenyl-9*H*-imidazo[1,2-*a*]indole, **6c**.

A suspension of 1.72 g (6.00 mmoles) of **6a** and 0.5 g of sodium hydride (as a 57% dispersion in oil) in 20 ml of dimethyl formamide was heated to 95° in an oil bath for 30 minutes at which time 2.6 g (24.0 mmoles) of dimethylamino ethyl chloride in 2.6 g of benzene was added in one portion. After heating for 2 hours, an additional 1.3 g (12.0 mmoles) of chloroamine was added. After a total heating period of 5 hours the reaction mixture was cooled to room temperature, quenched on ice, made basic with a 10% aqueous sodium hydroxide solution, and extracted with chloroform.

Removal of the solvent *in vacuo* from the dried (magnesium sulfate) chloroform extracts afforded 1.9 g of an orange oil which was crystallized from ethanol as 2.2 g of a fumarate salt, mp 153-158° dec. An analytical sample had mp 158-161°; ir (nujol): 2950, 2600, 2440, (NH), 1720, 1695, 1675 (C=O/C=N) 1645, 1615, 1560, 1520, 1495 cm^{-1} (C=N/C=C); uv (95% ethanol): λ max 206 nm (ε 65,500), 269 nm (ε 7,550), 278 nm (ε 6,680); ^1H nmr (DMSO-d_6): δ 7.91 (1H, multiplet, aromatic CH), 7.08-7.72 (9H, multiplet, aromatic and imidazol CH), 6.61 (4H, singlet, CH=CH), 3.30-3.72 (2H, broad multiplet, OCH_2), 2.88-3.30 (2H, broad multiplet, CH_2N), 2.62 (6H, singlet overlapping DMSO proton impurity, $N(CH_3)_2$); ms: very weak molecular ion peak at 353 (355) (free base, $C_{20}H_{20}ClN_3O$, mw 353), with fragmenet ions at m/e 283 (285), 266 (268), 116, 98, 99, 88.

Anal. Calcd. for $C_{20}H_{20}ClN_3O \cdot 2C_4H_4O_4$, mw 585.98: C, 57.38; H, 4.81; N, 7.17; Cl, 6.05. Found: C, 57.73; H, 4.83; N, 7.11; Cl, 6.04.

The structure of **6c** was confirmed by X-ray analysis (see Figure 1 and Table III).

5-Chloro-2-(2-hydroxymethylimidazol-1-yl)benzophenone, **8**.

Imidazobenzophenone **5a** (2.82 g, 10.0 mmoles) was treated with 700 ml of a 37% aqueous formalin solution and heated in a bomb to 125° for 30 hours. Following the usual chloroform extraction procedure, the crude products were chromatographed over 250 g of silica gel by eluting with 3% methanol/chloroform mixtures. Following a 250 ml forerun, 10 ml fractions were collected. Mixtures of starting material and indolol **6a** were collected in fractions 32-40. The desired product, **8**, was collected in fractions 41-80 and crystallized from ethyl acetate mixtures as 420 mg of prisms, 185-187°; ir (nujol): 3150 (OH), 1670 (C=O), 1595, 1585, 1490 cm^{-1} (C=C/C=N); (95% ethanol): λ max 251 nm (ε 14,300); ^1H nmr (DMSO-d_6): 7.18-7.98 (8H, m, aromatic CH), 7.04 (1H, d, J = 1 Hz, imidazole C_5H), 6.71 (1H, d, J = 1 Hz, imidazole C_4H); ms: molecular ion peak at m/z 312 (314) with fragment ions at m/z 283 (285, M^+ - CH_2O + H), 265 (267), 105 and 77.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$ (MW 312.74): C, 65.28; H, 4.19; N, 8.96; Cl, 11.34. Found: C, 65.57; H, 4.20; N, 8.63; Cl, 11.38.

1-[(dimethylamino)methyl]-6-phenyl-8-chloro-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine, **11a** (Adinazolam).

A solution of 1.53 g (15.0 mmoles) of bis-(dimethylamino)methane dissolved in 4.0 ml of DMF was cooled to 0° in an ice bath and treated with 1.178 g (15.0 mmoles) of acetyl chloride dissolved in 2.0 ml of DMF. The resulting mixture of salt, **4**, was treated with 2.488 g (18.0 mmoles) of granular potassium carbonate, stirred for 5 minutes, and treated with 2.947 g (10.0 mmoles) of estazolam, **10a**, dissolved in 15.0 ml of DMF. The mixture was heated to 60° for 3 hours and quenched in water buffered to *p*H 4. Sixty ml of 2% aqueous hydrochloric acid was added to adjust the *p*H to 3.5, at which point the aqueous layer was extracted with 5 x 200 ml of methylene chloride. The organic layer was washed with a

10% aqueous sodium hydroxide solution, dried over anhydrous sodium sulfate, and filtered and concentrated *in vacuo* to 2.75 g of oil. The oil was crystallized from ethyl acetate to afford 1.303 g (37% yield) of adinazolam, **11a**, mp 167.5-169°. (An authentic sample had mp 169-170° [6b]). The aqueous layer was re-extracted with methylene chloride (4 x 200 ml) to afford an additional 0.444 g of crude **11a** which, when combined with the mother liquors from the first crop afforded 0.470 g (13% of prisms, mp 167-169°. Repeating this process a third time afforded a final fraction of 0.390 g (11%), mp 166-167.5°. The total yield of **11a** was 62%. When a similar experiment was carried out on a 10 mmole scale using benzoyl chloride to generate the Mannich salt, **4**, followed by column chromatography over silica gel (using 2% methanol/98% methylene chloride mixtures as eluent) to separate the products, **11a** was isolated in 74% crystalline yield. The polar 1,4-bis-dimethylamino adduct, **12c**, was collected and crystallized from ethyl acetate as prisms, mp 190-192°; ir (nujol): 2925, 1606, 1595, 1566 and 1519 cm^{-1}; uv (95% ethanol): λ max 222 nm (ε 39,250), 245 nm (sh, ε 16,500), 265 nm (sh, ε 7,550); ^1H nmr (deuteriochloroform): δ 8.33 (1H, d, J = 8.75 Hz, $C_{10}H$), 7.75 (1H, d of d, J_1 = 8.75 Hz, J_2 = 2.5 Hz, C_9H), 7.25-7.75 (6H, m, other aromatic CH), 4.23 (1H, d of d, $J_{AB} \sim J_{AB'}$ = 6.3 Hz, 4-methine CH), 3.65 (4H, m, two CH_2N), 2.50 (6H, s, one CH_3NCH_3), 2.36 (6H, s, one CH_3NCH_3); ms: molecular ion peak at m/z 408 (410) with weak fragment ions at 365 (367), 350 (352), 320 (322), 307 (309), 218 (220), and a strong ion at 58.

Anal. Calcd. for $C_{22}H_{25}ClN_6$ (MW 408.93): C, 64.61; H, 6.16; N, 20.56; Cl, 8.67. Found: C, 64.61; H, 6.22; N, 20.42; Cl, 8.59.

4-[(dimethylamino)methyl]-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine, **12a**.

The Mannich salt, **4**, generated in the usual fashion in a total of 15 ml of DMF, was treated with a warm solution of 10.0 mmoles of **10a** in 10 ml of DMF. The mixture was stirred 5 minutes at ice bath temperature, then treated with gaseous hydrochloric acid, passed over the surface of the reaction mixture. The acid was added for a total of 5 minutes, at which time the flask was placed in an oil bath at 100° and heated for 2.5 hours. The resulting solution was stirred at ambient temperature for 3 days, and filterd to afford a gummy solid, which was immediately recrystallized from methanol/ethyl acetate mixtures to give 2.02 g (48%) of a powder, mp, dec >190°. Two recrystallizations afforded 0.729 g of **12a** as prisms, mp, dec 210-220°.

Anal. Calcd. for $C_{19}H_{18}ClN_5 \cdot HCl \cdot CH_3OH$ (MW 420.33): C, 57.15; H, 5.51; N, 16.67; Cl, 16.87. Found: C, 56.81; H, 5.53; N, 16.41; Cl, 16.73.

The mother liquors were converted to the free base which crystallized from ethyl acetate/hexane mixtures to afford 0.362 g of prisms, mp, dec >180°. The analytical sample (0.203 g) had mp 188-189°; ir (nujol): 2933, 2854 (*N*-alkyl), 1606, 1518, 1466-1454 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 222 nm (ε 40,150), 245 nm (sh, ε 16,550), 265 nm (sh, ε 7,150); ^1H nmr (deuteriochloroform): δ 8.55 (1H, s, triazole CH), 7.26-7.63 (8H, m, aromatic CH), 4.27, (1H, m, 4-methine CH), 3.78 (1H, d of d, J_{AB} = 13.1 Hz, J_{AX} = 5.5 Hz), 3.45 (1H, d of d, J_{AB} = 13.1 Hz, J_{BX} = 7.0 Hz), 2.46 (6H, s, NMe_2), 1.63 (2H, s, H_2O); ms: molecular ion at m/z 351 (353) with fragment ions at m/z 307 (309), 293 (295), 204 (206), 77 and a large ion at m/z 58.

Anal. Calcd. for $C_{19}H_{18}ClN_5 \cdot \frac{1}{2} H_2O$ (MW 360.84): C, 63.24; H, 5.31; N, 19.41; Cl, 9.82. Found: C, 62.98; H, 5.11; N, 19.30; Cl, 9.98.

1-[(Dimethyamino)methyl]-8-chloro-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]-benzodiazepine. Reactions of **10b** with **4** (Table II).

The following procedure corresponds to the conditions of entry c in Table II and is meant to be illustrative of the general method. When required, gaseous hydrochloric acid was bubbled through the reaction mixture prior to heating. Salt **4**, prepared at 0° to 5° by slowly adding 2.82 ml (3.14 g, 40.0 mmoles) of acetyl chloride to 4.08 g (40.0 mmoles) of bis-(dimethylamino)methane in 20 ml of DMF, was treated with 5.86 g (20.0 mmoles) of imidazobenzodiazepine **10b** dissolved in 30 ml of DMF. The mixture was heated in an oil bath between 55-59° for 72 hours, cooled, and the products isolated following the usual chloroform extraction. The crude product mixture was chromatographed over silica gel by eluting with methanol/chloroform mixtures to afford 15% of starting material, R_f 0.51, mp 145-147° (ethyl acetate/hexane) (lit [11a] mp 138°); 32% of the 1-(dimethylamino)methyl adduct, **11b**, R_f 0.34, mp 183-185° (ethyl acetate/hexane) identical to an authentic sample [9,13]; 5% of **12b**, R_f 0.21, mp 174-177° (ethyl acetate/hexane): ir (nujol): 2760 cm^{-1} (*N*-alkyl); uv (95% ethanol): λ max 223 nm (ε 37,700); ^1H nmr (deuteriochloroform) δ 7.23-7.24 (9H, m, aromatic and imidazole C_1H), 7.15 (1H, d, J ~ 1.5 Hz, imidazol C_2H [11a]), 4.17 (1H, d of d, J_{AX} = 5 Hz, J_{BX} = 7 Hz, 4-methine CH), 3.30-3.90 (m, 2H, CH_AH_BN), 2.45 (s, 6H, CH_3NCH_3); ms: molecular ion peak at m/z 350 with fragment ions at m/z 307 ($M^+ - CH_3\text{-}N{=}CH_2$), 305, and 58 [$\text{-}CH_2\text{-}N(CH_3)_2$].

Anal. Calcd. for $C_{20}H_{19}ClN_4$ (MW 350.85): C, 68.46; H, 5.46; N, 15.97; Cl, 10.10. Found: C, 68.45; H, 5.67; N, 15.94; Cl, 10.12.

There was also obtained 8.6 % of bis-adduct, **12d**, R_f 0.11, mp 204-208° dec (from methanol/ethyl acetate); ir (nujol): 2780, 2760 cm^{-1} (*N*-alkyl); uv (95% ethanol): λ max 222 nm (ε 37,450); ^1H nmr (deuteriochloroform): δ 8.31 (1H, d, J = 9 Hz, aromatic $C_{10}H$), 7.28-7.72 (7H, m, aromatic CH), 6.99 (1H, s, imidazole C_2H), 4.13 (1H, d of d, J_{AX} = 7 Hz, 4 methine CH), 3.20-3.8 (4H, m, CH_2 singlet over CH_AH_BN), 2.44 (6H, s, CH_3NCH_3); 2.22 (6H, s, CH_3NCH_3); ms: molecular ion peak at m/z 407 with fragment ions at m/z 364 ($M^+ - CH_2{=}N\text{-}CH_3$), 347 ($M^+ - CH_2\text{-}N(CH_3)_2$) and 305 ($M^+ \text{-}CH_2N(CH_3)_2 - CH_3NCH_3$).

Anal. Calcd. for $C_{23}H_{26}ClN_5$ (MW 407.95): C, 67.71; H, 6.42; N, 17.17; Cl, 8.69. Found: C, 67.84; H, 6.43; N, 17.17; Cl, 8.69.

1-[(dimethylamino)methyl]-2-methyl-8-chloro-6-(*o*-chlorophenyl)-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine, **11f'**.

Following the general conditions of the method described above, **10d'** [9,11a,13] (20.0 mmoles) was heated with 40.0 mmoles of **4** in 50 ml of DMF for 2 hours at 100°. Following chloroform extraction and silica gel chromatography, the products were crystallized to afford the follwing: 10% of **11f'** partially purified as a hydrobromide salt, then crystallized as the free base, R_f 0.66, mp 191-194° (from methanol/ethyl acetate); ir (nujol): 2770 cm^{-1} (*N*-alkyl); ^1H nmr (deuteriochloroform): δ 8.55 (1H, d, J = 9 Hz, aromatic $C_{10}H$), 7.25-7.70 (5H, m, aromatic), 7.11 (1H, d, J = 2.5 Hz, aromatic C_7H), 5.29 (1H, d, J = 12.5 Hz, equatorial 4-methine CH), 4.05 (1H, d, J = 12.5 Hz, axial 4-methine CH), 3.23 (s, 2H, CH_2N), 2.27 (9H, two s, C-CH_3 and CH_3NCH_3); ms: molecular ion peak at m/z 398 with an intense fragment ion at m/z 354 ($M^+ - CH_3NCH_3$).

Anal. Calcd. for $C_{21}H_{20}Cl_2N_4$ (MW 399.32): C, 63.16; H, 5.05; N, 14.03; Cl, 17.76. Found: C, 63.47; H, 5.09; N, 14.19; Cl, 17.69.

There was also obtained 11% of **12f'**, R_f 0.30, mp (HBr salt) dec 191-193° (from methanol/ethyl acetate); ir (nujol): 2760, 2700, 2620 cm^{-1} (HN^+-alkyl); ^1H nmr of free base (deuteriochloroform): δ 8.53 (1H, d, J = 9 Hz, aromatic $C_{10}H$), 7.20-7.78 (5H, m, aromatic), 7.13 (1H, d, J = 5 Hz, one aromatic CH), 4.18 (1H, m, 4-methine CH), 3.55 (2H, m, CH_AH_BN), 3.22 (2H, br s, CH_2N), 2.40 (6H, s, CH_3NCH_3), 2.25 (9H, two s, C-CH_3 and CH_3NCH_3); ms: molecular ion peak at m/z 455 with fragment ions at m/z 397 ($M^+ - CH_2N(CH_3)_2$), and 354 ($M^+ - CH_2N(CH_3)_2 - CH_2{=}N\text{-}CH_3$).

Anal. Calcd. for $C_{24}H_{27}Cl_2N_5 \cdot HBr \cdot H_2O$ (MW 555.35): C, 51.90; H, 5.45; N, 12.61; Cl, 12.77; Br, 14.39. Found: C, 51.95; H, 5.07; N, 12.61; Cl, 12.87; Br, 14.50.

There was also obtained about 3% of an unknown compound, **12x'**, R_f 0.12, mp (of the di HBr salt) dec 223-226° (from methanol/ethyl acetate); ir (nujol): 2670, 2510 and 2470 cm^{-1} (NH-alkyl); ^1H nmr (for free base) (deuteriochloroform): δ 8.43 (1H, d, J = 9 Hz, aromatic $C_{10}H$), 7.26-7.82 (5-6H, m, aromatic CH), 7.04 (1H, d, J = 2.5 Hz, one aromatic CH), 5.81 (1H, t, J = 7 Hz, =CH), 3.24-3.54 (4H, d + s, CH_2N, CH_2N), 2.30 and 2.27 (15H, two s, C-CH_3 and two CH_3NCH_3); ms: molecular ion peak at m/z 467 with fragment ions at m/z 424 ($M^+ - CH_2{=}NCH_3$) and 380 ($M^+ \text{-}CH_2{=}N\text{-}CH_3 - CH_3N\text{-}CH_3$).

Anal. Calcd. for $C_{25}H_{27}Cl_2N_5 \cdot 2HBr$ (MW 630.25): C, 47.64; H, 4.64; N, 11.11. Found: C, 47.34; H, 4.50; N, 11.03.

Reaction of Triazolobenzophenone, **1a**, with the DMF/Phosphorus Pentachloride.

Solid phosphorus pentachloride (6.0 g, 28.8 mmoles) was added to a

solution of **1a** (5.94 g, 20.0 mmoles) dissolved in 60 ml of DMF at 0° and the mixture stirred for 6 hours at which time tlc of an aliquot worked up from aqueous sodium hydroxide solution indicated the disappearance of starting material (R_f 0.49), and the presence of two products, **17a** (R_f 0.55), and **16g** (R_f 0.35). The reaction mixture was stirred at ambient temperature for 4 days, quenched in cold 10% aqueous sodium hydroxide solution and the products extracted with chloroform, and concentrated *in vacuo* to a dark oil. On standing overnight, the oil deposited yellow plates, (400 mg, 6.5%), mp, dec 310-320°. Recrystallization from dimethyl sulfoxide/chloroform mixtures afforded 160 mg of **17a** as yellow plates, mp, dec 297-310°: ir (nujol): 3060 (=CH), 2750 (CHO), 1690 (C=O), 1600, 1590, 1540, 1509, 1495 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 225 nm (ε 36,850), 241 nm (ε 35,900), 256 nm (sh, ε 14,900), 291 nm (ε 7675), 301 nm (ε 7900), 315 nm (ε 6275), 329 nm (ε 5575); due to insolubility, a satisfactory nmr spectrum was not obtained; ms: molecular ion peak at m/z 307 (309), with a strong fragment ion at m/z 278 (280, M^+ - CHO).

Anal. Calcd. for $C_{17}H_{10}ClN_3O$ (MW 307.73): C, 66.35; H, 3.28; N, 13.66; Cl, 11.52. Found: C, 66.16; H, 3.21; N, 14.07; Cl, 11.79.

The mother liquors from the filtration were chromatographed over 300 g of silica gel G by eluting with 4/96 methanol/chloroform mixtures. Compound **16g** was collected and crystallized from methanol/ethyl acetate mixtures to afford 1.08 g (14%) of prisms, mp 136-138°; ir (nujol): 3160 (=CH), 2700 (*N*-alkyl and/or CHO), 1665 (C=O), 1610, 1525, 1495 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 260 nm (ε 22,750), 282 nm (ε 22,500); ^1H nmr (deuteriochloroform): δ 8.69 (1H, s, CH=O), 8.36 (1H, s, N=CH), 7.3-7.85 (8H, m, aromatic CH), 6.53 (1H, br s, C=CHN), 2.65, 2.60 (6H, two s, two $(CH_3)_2N$ isomers); ms: molecular ion at m/z 380 (382), with fragment ions at m/z 362 (M^+ - H_2O), 352 (354, M^+ - CO), 351 (353, M^+ - CHO), 310 (312, M^+ - CH_3NCH_3 - CN), 275 (277, M^+ - C_6H_5CO), 228 (230, M^+ - C_6H_5 - H_2O - CHO).

Anal. Calcd. for $C_{20}H_{17}ClN_4O_2$ (MW 380.83): C, 63.07; H, 4.50; N, 14.72; Cl, 9.31. Found: C, 63.17; H, 4.76; N, 14.65; Cl, 9.36.

The structure of **16g** was confirmed by X-ray analysis [19] (see Figure 2 and Table IV).

1-Methyl-4-[(dimethylamino)methyl]-8-chloro-6-(*o*-chlorophenyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, **12e'**.

Solid triazolam, **10c'**, (6.86 g, 20.0 mmoles) was added to 30.0 mmoles of salt **4** suspended in 50 ml of freshly distilled glyme. Gaseous hydrochloric acid was bubbled through the reaction mixture for 10 minutes. Despite a noticeable exothermic reaction, the solids did not dissolve and only starting material was observed on tlc analysis of a reaction aliquot. Addition of 20 ml of DMF caused the solids to dissolve, at which point the reaction mixture was stirred and heated on a steam bath for 2.5 hours. Following the usual chloroform extraction and silica gel chromatography, 4.18 g (52%) of **12e'** was crystallized from ethyl acetate/hexane mixtures, mp 165-169°. Recrystallization from methanol/ethyl acetate mixtures afforded 3.5 g of analytically pure product, mp 172.5-175°; ir (nujol): 2760 cm^{-1} (*N*-alkyl); uv (95% ethanol): λ max 220.5 nm (ε 41,000); ^1H nmr (deuteriochloroform): δ 7.14-7.78 (7H, m, aromatic CH), 4.27 (1H, m, 4-methine CH), 3.23-3.92 (2H, m, CH_AH_BN), 2.59 (3H, s, C-CH_3), 2.42 (6H, s, CH_3NCH_3); ms: molecular ion peak at m/z 399 with fragment ions at m/z 355 (M^+ - CH_3NCH_3) and 353.

Anal. Calcd. for $C_{20}H_{19}Cl_2N_5$ (MW 400.31): C, 60.00; H, 4.78; N, 17.50; Cl, 17.71. Found: C, 59.95; H, 4.97, N, 17.47; Cl, 17.82.

1-Methyl-4-[(dimethylamino)methyl]-6-phenyl-8-chloro-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine, **12e**.

Alprazolam, **10c** (3.09 g, 10.0 mmoles) suspended in 50 ml of distilled THF was treated with 6.3 ml of 1.6 *M* *n*-butyllithium (10.1 mmoles) at 5-10°. After stirring for 1 hour, the solution of the dark green anion was transferred, *via* cannula and under nitrogen pressure, to a flask containing a suspension of 20.0 mmoles of salt **4**, prepared by adding acetyl chloride to bis-(dimethylamino)methane in ether, and washing with ether and then THF to remove dimethylacetamide and unreacted acetyl chloride. Following the 10 minutes addition period, the reaction mixture was stirred for 1 hour at which time it was subjected to chloroform extraction and silica gel chromatography to afford 300 mg (8.2%) of adduct **15**, R_f 0.53, crystallized as flowers from ethyl acetate/hexane mixtures, mp 148-150°; ir (nujol): 2770 (*N*-alkyl), 1635 cm^{-1} (C=C); uv (95% ethanol): no λ max between 215-280 nm; ^1H nmr (deuteriochloroform): δ 8.85 (1H, s, N=C_4H), 8.05 (1H, d, J = 2.5 Hz, aromatic C_7H), 7.52 (1H, d of d, J_{AX} = 8.2 Hz, J_{AY} = 2.5 Hz, aromatic C_9H), 7.19 (1H, d, J = 8.2 Hz, aromatic C_{10}H), 6.68-7.19 (5H, m, aromatic CH), 2.38 (2H, s, CH_2N), 2.31 (3H, s, CH_3), 2.15 (6H, s, CH_3NCH_3); ms: weak molecular ion peak at m/z 365 with a strong fragment ion at m/z 307 (M^+ - $CH_2N(CH_3)_2$).

Anal. Calcd. for $C_{20}H_{20}ClN_5$ (MW 365.87): C, 65.65; H, 5.51; N, 19.15; Cl, 9.69. Found: C, 65.52; H, 5.45; N, 19.07; Cl, 10.00.

There was also obtained 22% of **12e**, R_f 0.19, crystallized as flowers from ethyl acetate, mp 187-188°; ir (nujol): 2770 cm^{-1} (*N*-alkyl); uv (95% ethanol): λ max 222 nm (ε 43,500); ^1H nmr (deuteriochloroform): δ 7.30-7.83 (8H, m, aromatic), 4.20 (1H, d of d, J_{AX} = 5 Hz, J_{BX} = 7 Hz, 4-methine CH), 3.72 (1H, d of d, J_{AX} = 5 Hz, J_{AB} = 13 Hz, CH_AN), 3.48 (1H, d of d, J_{BX} = 7 Hz, J_{AB} = 13 Hz, CH_BN), 2.60 (3H, s, CH_3), 2.44 (6H, s, CH_3NCH_3); ms: molecular ion peak at m/z 365 with fragment ions at m/z 321 (M^+ - CH_3NCH_3) and 320 (M^+ - CH_3NHCH_3).

Anal. Calcd. for $C_{20}H_{20}ClN_5$ (MW 365.87): C, 65.65; H, 5.51; N, 19.15; Cl, 9.69. Found: C, 65.42; H, 5.62; N, 18.67; Cl, 9.80.

2-[3-(hydroxymethyl)-5-(2-dimethylamino)ethyl]-4*H*-1,2,4-triazol-4-yl-5-chloro-benzophenone, **16b**.

Triazolobenzophenone **16a** [1a] (3.28 g 10.0 mmoles) was heated with 30.0 mmoles of **4** in 45 ml of DMF at 75° for 21 hours. Following the usual extraction and chromatographic procedures, **16b** was obtained as an oil (R_f 0.28) which crystallized from ethyl acetate/hexane mixtures as 400 mg of powder, mp 128-139°. The analytical sample (300 mg) had mp 146-148.5°; ir (nujol): 3220 (OH), 2740 (*N*-alkyl) 1665 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.38-7.89 (8H, m, aromatic CH), 4.87 (1H, br s, OH), 4.43 (2H, d of d, CH_2O), 2.60 (4H, m, CH_2-CH_2N), 2.08 (6H, s, CH_3NCH_3); ms: molecular ion at m/z 384 with fragment ions at m/z 383 (M^+ - H), 369 (M^+ - CH_3), 340 (M^+ - CH_3NCH_3) and 310 (M^+ - CH_3NCH_3 -CH_2O).

Anal. Calcd. for $C_{20}H_{21}ClN_4O_2$ (MW 384.86): C, 62.41; H, 5.50; N, 14.56; Cl, 9.21. Found: C, 62.61; H, 5.44; N, 14.50; Cl, 9.18.

A slightly more polar material (R_f 0.25) was also obtained (500 mg) but not fully characterized. It may have corresponded to **16c**.

1-[(dimethylamino)methyl]-7-chloro-5-phenylimidazo[1,2-*a*]quinoline, **18b**.

Ten mmoles of **18a** was heated with 15 mmoles of **4** in 15 ml of DMF to 75° for 1 hour. Following the usual work-up, the product was crystallized from acetone to give 2.33 g (69%) of solid, mp 150-152.5°; ir (nujol): 3040 (=CH), 2800, 2780, 2760 (*N*-alkyl), 1625, 1555, 1545, 1510 cm^{-1} (C=N/C=C); uv (95% λ max 238 nm (ε 38,350), 261 nm (ε 15,950), 330 nm (ε 11,350); ^1H nmr (deuteriochloroform): δ 8.90 (1H, d, J = 9 Hz, aromatic C_5H), 7.41-7.81 (8H, m, 7 aromatic and imidazole C_2H), 3.85 (2H, s, CH_2N), 2.38 (6H, s, CH_3NCH_3); ms: molecular ion peak at m/z 335 (337), with a large fragment ion at m/z 291 (293).

Anal. Calcd. for $C_{20}H_{18}ClN_3$ (MW 335.82): C, 71.52; H, 5.40; 12.52; Cl, 10.56. Found: C, 71.41; H, 5.30; N, 12.35; Cl, 10.55.

The Reaction of Imidazobenzodiazepine Anion **19** with Ethylene Oxide.

Imidazobenzodiazepine **10b** (5.86 g, 20.0 mmoles) dissolved in 25 ml of freshly distilled DME cooled to −50° was added, under nitrogen, to a flame-dried reaction flask containing lithium di-isopropylamide (prepared from 24.0 mmoles of methyllithium and 30.0 mmoles of di-isopropylamine in 10 ml of distilled DME at −60°). The resulting dark green anion, **19**, was stirred for 1 hour at −40° and then treated with a large excess of ethylene oxide. The resulting black solution was stirred for 1 hour from −40 to −10°, at which time it was quenched in cold aqueous 10% sodium hydroxide solution and the products extracted with chloroform. The dried extract was concentrated *in vacuo*, and the resulting oil chromatographed over 700 g of silica gel G by eluting with

several liters of 3/97 methanol/chloroform mixtures to afford **20**, 1.40 g (21%), crystallized from ethyl acetate/hexane mixtures as prisms, mp 117-120°, R_f 0.67; ir (nujol): 3460 (OH), 3130, 3110 (=CH), 1630, 1595, 1580, 1490 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 234 nm (ε 21,000), 264 nm (sh, ε 7,500); ^1H nmr (deuteriochloroform): δ 7.21-7.84 (9H, m, aromatic and one imidazole CH), 6.81 (1H, br s, imidazole CH), 5.32 (1H, br s, C=CH), 3.76-4.32 (3H, m and exchangeable s, CH_2OH), 2.85-3.62 (2H, m, CH_2N); ms: weak molecular ion peak at m/z 337 with fragment ions at m/z 128 (130), and 109.

Anal. Calcd. for $C_{19}H_{16}ClN_3O$ (MW 337.80): C, 67.55; H, 4.77; N, 12.44; Cl, 10.49. Found: C, 67.59; H, 4.84; N, 12.55; Cl, 10.57.

There was also obtained **21**, 240 mg (3.6%), crystallized from ethyl acetate/hexane mixtures as prisms, mp 188-194°, R_f 0.50; ir (nujol): 3330 (OH), 3130, 3110 (=CH), 1640, 1595, 1495 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 237 nm (ε 16,400), 291 nm (ε 5,400), 320 nm (sl sh, ε 1,630); ^1H nmr (deuteriochloroform): δ 8.72 (1H, s, N=CH), 7.91 (1H, d, J ~ 2 Hz, =CH), 6.69-7.64 (9H, m, aromatic and imidazole CH), 3.65-4.22 (3H, m and exchangeable s, CH_2OH), 2.83-3.46 (1H, m, CH_A), 1.97-2.61 (1H, m, CH_B); ms: weak molecular ion peak at m/z 337 (339), with fragment ions at m/z 306 (308, $M^+ - CH_2OH$) and 293 (295, $M^+ - (CH_2)_2O$). The structure of **21** was confirmed by X-ray analysis (see Figure 3 and Table V).

Anal. Calcd. for $C_{19}H_{16}ClN_3O$ (MW 337.80): C, 67.55; H, 4.77; N, 12.44; Cl, 10.49. Found: C, 67.52; H, 4.97; N, 12.30; Cl, 10.41.

There was also obtained **22**, 230 mg (3.4%), crystallized from ethyl acetate/hexane mixtures, mp 173-175°, R_f 0.38; ir (nujol): 3380 (OH), 3130, 3110 (=CH), 1610, 1575, 1565, 1525, 1500 cm^{-1} (C=C/C=N); uv (95% ethanol): λ max 223 nm (ε 37,750), 251 nm (sh ε 15,800); ^1H nmr (deuteriochloroform): δ 7.22-7.68 (10H, m, aromatic and one imidazole CH), 7.12 (1H, d, J ~ 1.5 Hz, imidazole CH), 3.70-4.40 (4H, m and exchangeable s, 4-methine CH and CH_2OH), 2.51-3.00 (2H, m, aliphatic CH_2); ms: molecular ion peak at m/z 337 (339) with fragment ions at m/z 306 (308, $M^+ - CH_2OH$), 293 (295, $M^+ - (CH_2)_2O$), 279 (281) and 203 (205).

Anal. Calcd. for $C_{19}H_{16}ClN_3O$ (MW 337.80): C, 67.55; H, 4.77; N, 12.44; Cl, 10.49. Found: C, 67.33; H, 4.81; N, 12.55; Cl, 10.45.

Crystal Data for (Dimethylamino)ethyl Ether of **6a**, *i.e.* **6c**:

$C_{20}H_{20}ClN_3O \cdot 2(C_4H_4O_4)$; MW = 353.89·2 (116.08); triclinic, space group P1; cell parameters: a = 10.088(1), b = 10.860(1), c = 15.090(1)Å, α = 109.89(1), β = 98.59(1), γ = 109.52(1)°, V = 1399.2(2)Å^3; Z = 2; calculated density = 1.39 g cm^{-3}; absorption coefficient μ = 1.6 mm^{-1}.

Crystal Data for **16g**:

$C_{20}H_{17}ClN_4O_2$; MW = 380.83; monoclinic, space group $P2_1/c$; cell parameters: a = 7.735(1), b = 20.487(1), c = 13.294(1)Å, β = 119.99(1)°, V = 1824.4(2)Å^3, Z = 4; calculated density = 1.39 g cm^{-3}; absorption coefficient μ = 1.9 mm^{-1}.

Crystal Data for **21**:

$C_{19}H_{16}ClN_3O$; MW = 337.81; triclinic, space group P1; cell parameters: a = 8.179(1), b = 9.809(1), c = 11.398(1)Å, α = 97.04(1), β = 103.16(1), γ = 110.33(1)°, V = 814.3(2)Å^3, Z = 2; calculated density = 1.38 g cm^{-3}; absorption coefficient μ = 2.0 mm^{-1}.

X-ray Procedure.

For all three crystal structures, **6c**, **16g** and **21**; intensity data were collected at room temperature on a Nicolet P1 diffractometer with a graphite monochromator controlled by a Harris computer. CuKα radiation was used, (λ(CuKα = 1.5418Å), and the maximum 2θ was 145°. The number of unique reflections measured for **6c**, **16g** and **21**, respectively, were: 5579, 3628 and 3230 and the number of reflections having intensities >2σ were 3065, 2040 and 2564. θ/2θ step scans with scan widths >3.4° were used; scan rates were 2-6°/minute for *6c*, 1°/minute for **16g**, and 2°/minute for **21**. For all three data collections, 10 reflections were periodically monitored; for **16g** and **21**, these showed no trend towards deterioration; the data for **6c** was corrected using a time-dependent polynomial function with 6 terms. $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(dI)^2$, where d was calculated from the variations in intensities of the monitored reflections; d was 0.007 for **6c**, and 0.004 for both **16g** and **21**. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values (λ(CuKα_1 = 1.5402) for 20 high 2θ reflections (15 reflections for **16g**) [19]. An Lp correction appropriate for a monochromator with 50% perfect character was applied to the data; the data were also corrected for absorption [20]. The structures were solved by direct methods using DIREC [21]. Hydrogens for all three structures were found in difference maps; for **21**, the hydrogen coordinates were refined; for **6c** and **16g**, generated hydrogen coordinates were used, except for methyl and hydroxy hydrogens. Least squares refinement included: all coordinates and anisotropic thermal parameters for nonhydrogen atoms, and, for **21**, hydrogen atom coordinates. Hydrogens were assigned isotropic thermal parameters 0.5 unit higher than attached atoms. The function minimized in the refinement was $\Sigma w(F_o^2 - F_c^{2*})^2$, where weights w were $1/\sigma^2(F_o^2)$, and where F_c^* was the usual calculated structure factor except, for 21 only, F_c^* was as defined by Larson [22]. Atomic form factors were from International Tables for X-ray Crystallography [23] for **6c** and **21**; from Doyle & Turner [24] for **16g**; and, for hydrogen in all three structures, from Stewart, Davidson & Simpson [25]. In the final refinement cycles, all shifts were $<0.33\sigma$. The final agreement indices R were: for **6c**., R = 0.107 for all 5579 unique reflections, and 0.047 for the 2239 reflections with intensities $>3\sigma$; for **16g**, R = 0.105 for all 3628 reflections, and 0.052 for the 1603 reflections with intensities $>3\sigma$; for **21**, R = 0.053 for all 3230 unique reflections and 0.037 for the 2259 reflections with intensities $>3\sigma$. For **21**, the secondary extinction parameter, g was 10.1 x 10^{-6}. The CRYM system of computer programs was used for all calculations [21].

Supplementary Material.

Tables of hydrogen atom coordinates, bond distances and angles, torsion angles, hydrogen bonds, close intermolecular contacts and anisotrobic thermal parameters are available upon request from the authors.

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