Synthesis of the Triazolo[5,1-*a*][2,4]benzodiazepine Ring System

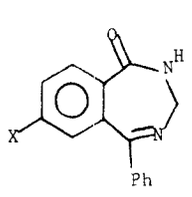
Peter C. Wade,* Thomas P. Kissick, B. Richard Vogt, and Barbara Toeplitz

The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540

Received May 26, 1978

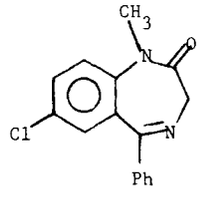
3-(4-Chlorophenyl)-5-methyl-1*H*-1,2,4-triazole was converted to its dilithio derivative and condensed with benzonitrile to yield the triazoloisoindole (**13b**), which on treatment with hexamethylenetetraamine and acid afforded 9-chloro-2-methyl-7-phenyl-5*H*-[1,2,4]triazolo[5,1-*a*][2,4]benzodiazepine (**5**). The structure of **5** was established by ^{13}C NMR and single-crystal X-ray analysis.

Recently,[1] Golik described the synthesis of a 2,4-benzodiazepine **1b** isomeric with the demethyl analogue of the therapeutically important 1,4-benzodiazepine diazepam (**2**). Subsequently,[2] he reported an unsuccessful attempt to convert **1a** to a fused [4,3-*a*]triazolo derivative **3a** analogous to the recently introduced hypnotic antianxiety drug alprazolam (**4**). We now report the synthesis of **5**, the [5,1-*a*] isomer of **3b**, in good yield by an unusual route.

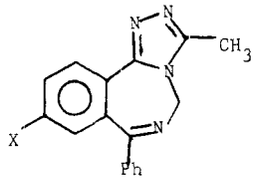


1a, X=H

1b, X=Cl

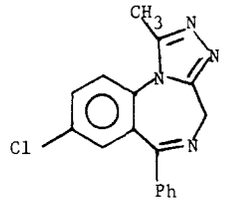


2

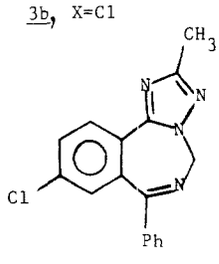


3a, X=H

3b, X=Cl



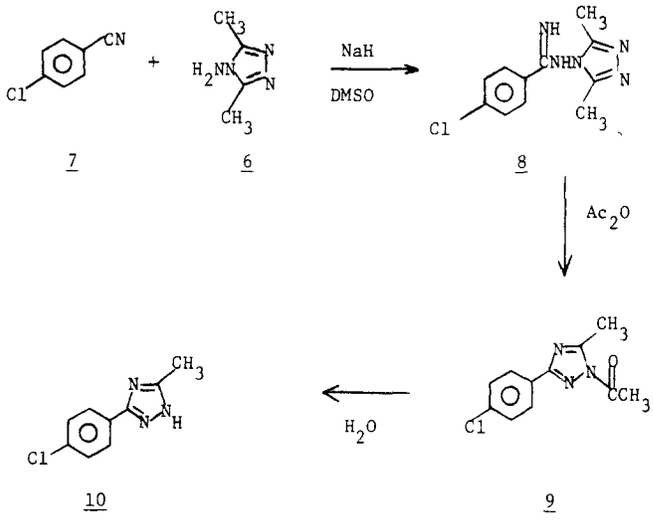
4



5

Golik's approach[2] involved the formation of the 2,4-benzodiazepine nuclei **1a** and **1b**, followed by attempted annelation of the triazole via the well-known thiolactam procedure. Experimental difficulties were encountered in constructing the seven-membered ring[1b] when the chlorine atom was present (**1b**) and with contraction of the seven-membered ring during the attempted annelation step.[2]

The method reported here involves the reverse approach, formation of the seven-membered ring on a preformed phenyltriazole nucleus. Very recently, Fryer and Earley[3] reported the synthesis of an imidazolo analogue by a related synthetic scheme. Condensation[4] of the anion of 4-amino-3,5-dimethyltriazole (**6**; generated with sodium hydride in Me_2SO) with 4-chlorobenzonitrile (**7**) gave the amidrazone **8**. Reaction of **8** with refluxing acetic anhydride[5] produced the acetylated triazole **9** in good yield. Hydrolysis under neutral conditions quantitatively converted **9** into 3-(4-chlorophenyl)-5-methyl-1*H*-1,2,4-triazole (**10**). This method proved



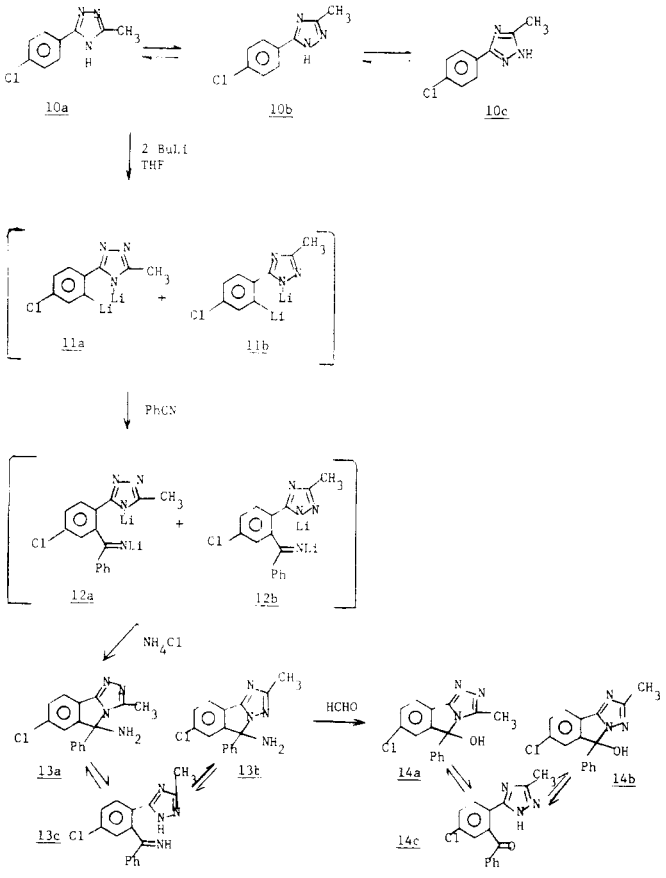
7 **6** **8** **9** **10**

superior in both yield and ease of handling to the other more direct triazole syntheses which were investigated, such as condensing *p*-chlorobenzoic hydrazide with acetamide[6] or reacting acetohydrazide with ethyl *p*-chlorobenzimidate.[7] The assignment of the position of the proton in **10** and hence the acetyl group in **9** is based on the findings of Kubota and Uda[8] that the predominant tautomer at equilibrium was that with protonation (and hence greatest electron density) at the 1- or 2-nitrogen adjacent to the most electron-donating substituent. The assignment of the position of the acetyl group in **9** was subsequently confirmed by shift reagent studies and an X-ray analysis of a derivative.[9]

Reaction of secondary benzamides with 2 mol of butyllithium has been shown to give a dianion capable of condensing with benzonitrile to yield ring–chain tautomeric isoindoles.[10] Thus, analogous treatment of the phenyltriazole **10** with 2 equiv of butyllithium gave the dilithio derivative **11** which was condensed with benzonitrile to give the presumed mixture of dilithio compounds **12a** and **12b**. The presence of a mixture of tautomers in **10**, **11**, or **12** was not established but was assumed from Breuer's findings.[11] The isomers that would correspond to "**11c**" and "**12c**" are not shown since they could not lead to a tricyclic product.

Decomposing **12** with ammonium chloride gave a single compound **13** as the only product isolated. The absence of a strong absorption at ca. 1640 cm^{-1} in the IR indicated the absence of significant amounts of **13c** in the solid state. Although the structure has not been rigorously established, the work of Breuer[11] and the results discussed below suggest that the [5,1-*a*]triazole (**13b**) rather than the [4,3-*a*]triazole (**13a**) moiety is the thermodynamically more stable isomer. In the NMR ($CDCl_3$), the wide line widths of the methyl group and C-6 proton suggested a slow equilibrium between the ring-

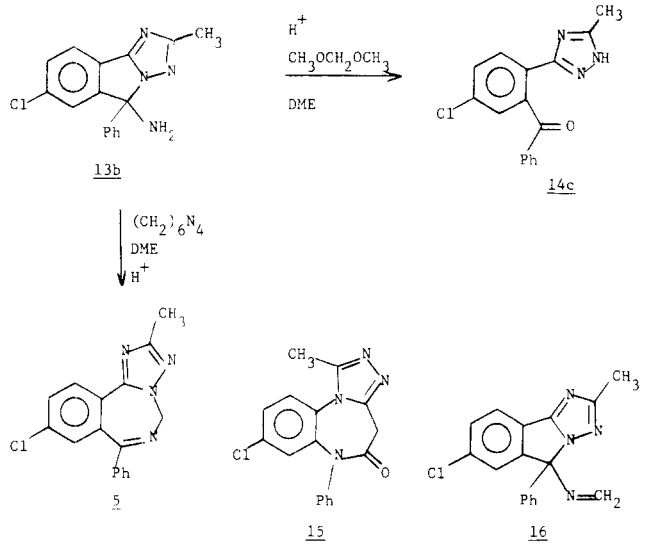
0022-3263/79/1944-0084$01.00/0



opened and ring-closed forms. While in the more polar Me_2SO-d_6, the sharpness of the methyl group and the analogous aromatic proton as well as two separate N–H resonances indicated that **13c** predominates at equilibrium.

While it was somewhat surprising that the chlorine atom in **10** was not affected by the presence of the strong base, butyllithium, a recent report by Gschwend et al. described analogous findings in the synthesis of aryl ketones.[12]

The addition of a CH_2 group to the isoindole **13b** under conditions favoring ring expansion would be expected to yield the triazolobenzodiazepine **3b** or **5**. The Mannich reaction is known to produce N–CH_2–N structures under neutral[13,14] conditions, but ring expansion of **13b** to **3b** or **5** would not be expected to occur using formaldehyde under such circumstances. Since the 2,4-benzodiazepine ring system has been synthesized via a related ring expansion under acid catalysis,[1] **13b** was reacted with formaldehyde under acid conditions.



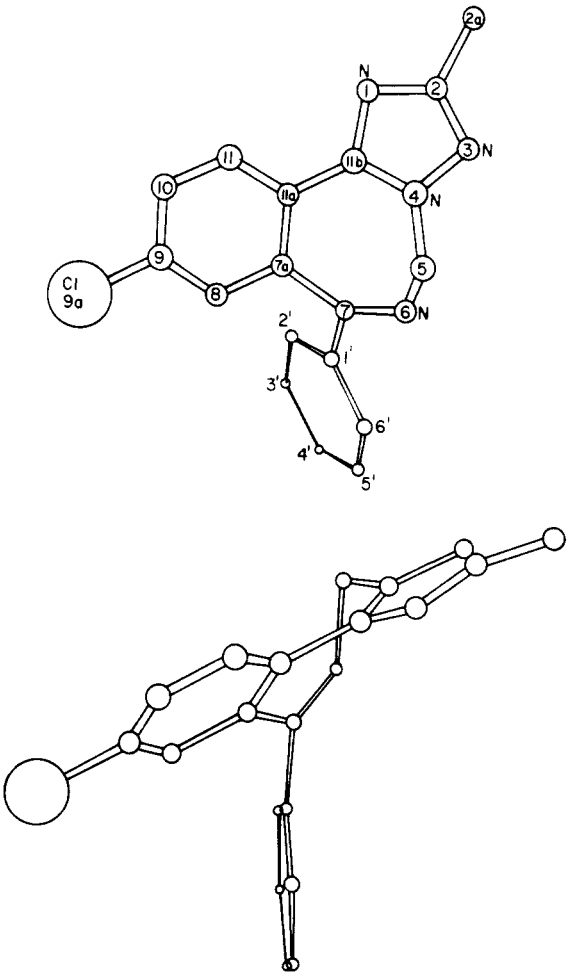


Figure 1. Two computer drawn views of **5**.

The only product formed in this case was the ketone **14c** obtained by hydrolysis of the starting material. From previous studies,[1] one would expect **14c** to exist predominantly as one of the tricyclic ring–chain tautomers **14a** or **14b**. However, the presence of a strong sharp absorption at 1664 cm^{-1} in the IR ($CHCl_3$) and of a sharp singlet for the methyl group in the NMR suggests that the equilibrium lies heavily in favor of the open ketonic structure **14c**. Substitution of the acetal dimethoxymethane (methylal) for formaldehyde gave the same results. In contrast, use of hexamethylenetetraamine[15] as a formaldehyde equivalent devoid of labile oxygen atoms produced a new compound A with little or no evidence of hydrolysis to **14c**. A possessed the correct molecular formula (microanalysis and mass spectrum) for **3b** or **5**, but had a much higher R_f on silica gel TLC than authentic samples of the closely related **4**[16] or **15**[17] and showed the unexpected loss of 28 mass units in the mass spectrum. These data, as well as the new two-proton resonance in the NMR at δ 5.60, could be accounted for by the azomethine structure **16**, as well as by **5**.

Structure **16** was eliminated and the presence of a seven-membered ring in A was indicated by the lack of vinyl C–H stretching in the IR and by the presence of two saturated carbons at δ 13.66 (CH_3) and 61.69 (CH_2) in the ^{13}C NMR spectrum.

Finally, single-crystal X-ray analysis of A (Figure 1) confirmed not only the presence of the seven-membered ring, but also that the annelated triazole possessed the [5,1-*a*] (**5**) rather than the isomeric [4,3-*a*] (**3b**) structure. No evidence of **3b** was found in the reaction mixture, suggesting that the ring ex-

Table I. Relative R_f's of Various Triazolobenzodiazepines

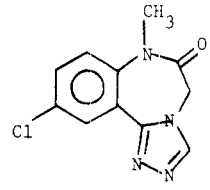
compd	registry no.	R_f[a]
5	66492-65-7	0.40 (0.78)
4	28981-97-7	0.03 (0.11)
15	54748-06-0	0.03 (0.09)
17[18]		0.07 (0.21)
18[11]		0.42 (0.62)

[a] Silica gel plates (EM Laboratories catalog no. 5760) were developed with 3:2 chloroform–ethyl acetate; detected by short wave UV light. Values in parentheses were obtained on Eastman Chromagram silica gel (catalog no. 13181) under the same conditions.

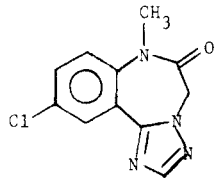
pansion reaction does not involve a freely rotating triazole group or that any equilibrium heavily favors **5**.

Since the structure of **5** was unequivocally established, the loss of 28 atomic mass units in the mass spectrum therefore must be due to an electron impact induced rearrangement of **5** to **16** and subsequent loss of the N=CH_2 moiety.

The unusually high R_f of **5** relative to **4** and **15** prompted further studies with additional model compounds on the hypothesis that any difference in R_f of various isomers might be explained largely or entirely by which triazole nitrogen was incorporated in the seven-membered ring rather than the structure of the diazepine ring itself as originally anticipated. That this is the case can be seen from the data in Table I. Both compounds (**5** and **18**) wherein the triazole moiety is fused [5,1] are less polar and hence have higher R_f's. The three compounds (**4**, **15**, and **17**) possessing the fused [4,3] moiety



17



18

are more polar and have lower R_f's. The observed increased polarity can be attributed to the increased availability of the electron pair on the 1-nitrogen relative to the 4-nitrogen of the 1,2,4-triazole portion of these molecules. This property is consistent with the preference for protonation and alkylation at the triazole 1 position observed both here and elsewhere.[8,11] Thus, TLC analysis can at least in certain cases serve as a useful method for distinguishing between two isomeric fused 1,2,4-triazoles where spectral techniques may be inconclusive.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Routine ^1H nuclear magnetic reasonance (NMR) spectra were obtained on a Varian T-60, Varian XL-100-15, or Perkin-Elmer R12B spectrometer, and chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (Me_4Si) as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 621 as KBr pellets or on a Perkin-Elmer 137 spectrophotometer as mineral oil mulls. Ultraviolet spectra were obtained on a Cary 15 spectrophotometer in methanol. All characterized compounds were dried at 1 torr in a vacuum oven at a temperature between 25 and 90 °C unless otherwise indicated. Temperatures are in degrees centigrade.

^{13}C NMR were recorded on a Varian XL-100-15 NMR spectrometer equipped with Fourier accessories obtained from Nicolet Technology Corp. The spectrometer was operated at 25.16 MHz and was internally locked to the ^2H frequency of the solvent. Chemical shifts are reported in δ (parts per million) relative to Me_4Si and calculated from $\Delta CDCl_3$ = 76.9 ppm.

Low-resolution mass spectra were obtained on an Associated Electrical Industries Model MS-902 double-focusing mass spectrometer. The source, maintained at 170 °C, had an electron energy of 70 eV. Samples were introduced via the direct insertion probe. All spectra were recorded on frequency modulated analog magnetic tapes, which were subsequently processed on a PDP-11 computer using Squibb programs.

4-Chloro-*N*-(3,5-dimethyl-4*H*-1,2,4-triazol-4-yl)benzenecarboximidamide[4] (8). Sodium hydride (15.32 g, 364 mmol, 57% oil dispersion) was washed with ether (5×) in a sintered glass funnel to remove the oil. The free sodium hydride was washed with a little Me_2SO into a stirred suspension of 50.0 g (363 mmol) of 4-chlorobenzonitrile (Aldrich) and 40.7 g (363 mmol) of 4-amino-3,5-dimethyltriazole[19] in 200 mL of Me_2SO (distilled from CaH_2 under vacuum). After the addition, the mixture was stirred in an ice bath for 1 h and for 3 h at room temperature. The reaction mixture was poured into 2 L of ice water and stirred for 15 min until the floculant precipitate coagulated into a filterable state. The product was then filtered out, washed with water, and dried at 50 °C under vacuum overnight to yield 94.2 g of crude **8**, mp 303–306 °C. This material was suitable for use in the subsequent reaction.

The crude triazole (6.0 g) was digested with isopropyl alcohol, filtered off, and dried to yield 4.1 g of pure **8**: mp 310–312 °C; IR (KBr) ν 3410 (NH), 3320 (NH), 1645 (C=NH), 1598 (C=N) cm^{-1}; NMR (Me_2SO-d_6) δ 2.15 (s, 6 H, CH_3), 7.40 (broad s, 2 H, NH), 7.58 (d, J = 8 Hz, 2 H, Ph 3- and 5-H), 7.95 (d, J = 8 Hz, 2 H, Ph 2- and 6-H).

Anal. Calcd for $C_{11}H_{12}N_5Cl$: C, 52.91; H, 4.85; N, 28.05; Cl, 14.20. Found: C, 53.12; H, 4.96; N, 28.33; Cl, 14.45.

1-Acetyl-3-(4-chlorophenyl)-5-methyl-1*H*-1,2,4-triazole (9). A mixture of 63.6 g (254 mmol) of **8** and 67 mL of acetic anhydride in a 300-mL round-bottom flask equipped with a distillation head was heated to 170 °C in an oil bath. A solution formed from which acetic acid distilled off in the first few minutes. The mixture was refluxed for 2.5 h, and the excess acetic anhydride was removed under vacuum. The residue was triturated with 120 mL of water and filtered. The filter cake was dissolved in 1 L of hot 95% EtOH and filtered while hot, and the product was precipitated from the hot filtrate by the addition of 3 L of cold water. The product was filtered off, washed with water, and dried at 80 °C under vacuum to yield 37.6 g (63%) of **9**: mp 132–133 °C; IR (KBr) ν 1748 (C=O), 1600 (amide C–N) cm^{-1}; NMR ($CDCl_3$) δ 2.74 (s, 3 H, CH_3), 2.78 (s, 3 H, CH_3), 7.42 (d, J = 8 Hz, Ph 3- and 5-H), 8.05 (d, J = 8 Hz, Ph 2- and 6-H); UV (MeOH) λ_{max} (ϵ) 251 nm (16 900).

Anal. Calcd for $C_{11}H_{10}ClN_3O$: C, 56.06; H, 4.28; N, 17.83; Cl, 15.05. Found: C, 56.34; H, 4.34; N, 17.86; Cl, 15.21.

3-(4-Chlorophenyl)-5-methyl-1*H*-1,2,4-triazole (10). A mixture of 27 g (114 mmol) of **9** and 800 mL of water was refluxed for 9 h and stirred overnight at room temperature. The product was collected by filtration, washed with water, and dried at 90 °C under vacuum overnight to yield 23.4 g (quantitative) of the triazole: mp 173–175 °C; IR (KBr) ν 3200–2500 cm^{-1} broad absorption (the bands at 1748 and 1600 cm^{-1} seen in **9** were absent); NMR ($CDCl_3$) δ 2.46 (s, 3 H, CH_3), 7.40 (d, J = 8 Hz, 2 H, Ph 3- and 5-H), 7.95 (d, J = 8 Hz, 2 H, Ph 2- and 6-H); UV (MeOH) λ_{max} (ϵ) 248 nm (18 000).

Anal. Calcd for $C_9H_8ClN_3$: C, 55.82; H, 4.16; N, 21.70; Cl, 18.31. Found: C, 55.48; H, 4.12; N, 21.67; C, 18.25.

7-Chloro-2-methyl-5-phenyl-5*H*-[1,2,4]triazolo[5,1-*a*]isoindol-5-amine (13b). To a solution of 2.0 g (10.3 mmol) of **10** in 50 mL of THF (freshly distilled from $LiAlH_4$) mechanically stirred in a 250-mL round-bottom three-neck flask equipped with a septum and nitrogen inlet and cooled in an ice bath was added, by syringe, 13.6 mL (22.7 mmol) of *n*-butyllithium (1.67 M in hexane), and the mixture was stirred in the ice bath for 30 min. Then 2.12 g (20.6 mmol) of benzonitrile was added in a little THF. After stirring for 30 min in the ice bath and for 30 min at room temperature, the mixture was poured into a chilled, stirred mixture of 100 mL of 2.5 M NH_4Cl and 200 mL of $CHCl_3$. The layers were separated, and the aqueous layer was washed with $CHCl_3$. The combined $CHCl_3$ layers were washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from toluene to yield 1.5 g (50%) of **13b**: mp 173–175 °C; IR (KBr) ν 3300–2600 broad absorption, 1608 (C–NH_2) cm^{-1}, and no indication of C=NH absorption at 1640–1690 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 7.35 (m, 7 H, aromatic), 7.83 (m, 1 H, 6-H); NMR (Me_2SO-d_6) δ 2.20 (s, 3 H, CH_3), 7.36 (m, 7 H, aromatic), 8.00 (d, 1 H, 6-H); UV (MeOH) λ_{max} (ϵ) 244 nm (20 300).

Anal. Calcd for $C_{16}H_{13}ClN_4$: C, 64.78; H, 4.41; N, 18.88; Cl, 11.95. Found: C, 64.72; H, 4.51; N, 18.93; Cl, 12.18.

9-Chloro-2-methyl-7-phenyl-5*H*-[1,2,4]triazolo[5,1-*a*][2,4]-benzodiazepine (5). To a stirring solution of 3.1 g (10.4 mmol) of **13b** and 3.1 g (22 mmol) of hexamethylenetetraamine (Hexamine-Borden)

Table II. Interatomic Distances, Å (Error)

Cl9a–C9	1.746 (7)	C11a–C11b	1.436 (12)
C9–C10	1.406 (5)	C11b–N1	1.357 (11)
C10–C11	1.389 (5)	N1–C2	1.361 (11)
C11–C11a	1.381 (5)	C2–C2a	1.563 (10)
C11a–C7a	1.440 (5)	C2–N3	1.296 (15)
C7a–C8	1.393 (7)	N3–N4	1.367 (9)
C8–C9	1.356 (5)	C7–C1′	1.514 (4)
C7a–C7	1.509 (4)	C1′–C6′	1.405 (3)
C7–N6	1.250 (3)	C5′–C6′	1.387 (7)
N6–C5	1.494 (4)	C4′–C5′	1.392 (7)
C5–N4	1.498 (5)	C3′–C4′	1.391 (14)
N4–C11b	1.327 (8)	C2′–C3′	1.442 (11)
		C1′–C2′	1.394 (10)

Table III. Interatomic Angles[a]

angle	deg	angle	deg
9a 9 10	116.5 (3)	3 4 5	122.5 (5)
9a 9 8	119.5 (4)	5 4 11b	125.5 (3)
8 9 10	124.0 (3)	11a 11b 1	127.2 (8)
9 10 11	116.0 (4)	11a 11b 4	124.3 (7)
10 11 11a	122.6 (5)	1 11b 4	108.5 (6)
11 11a 7a	119.3 (3)	5 6 7	119.6 (2)
11 11a 11b	119.2 (5)	4 5 6	106.7 (3)
7a 11a 11b	121.5 (6)	6 7 7a	129.4 (2)
11a 7a 8	118.3 (5)	7a 7 1′	115.3 (2)
7 7a 11a	122.2 (3)	6 7 1′	115.3 (3)
7 7a 8	119.5 (3)	2′ 3′ 4′	119.8 (6)
7a 8 9	119.8 (4)	3′ 4′ 5′	119.5 (4)
2 3 4	101.0 (4)	5′ 6′ 1′	118.0 (2)
2a 2 3	122.8 (9)	7 1′ 2′	120.2 (7)
1 2 2a	120.2 (6)	2′ 1′ 6′	122.0 (4)
1 2 3	117.0 (7)	7 1′ 6′	117.7 (4)
2 1 11b	101.7 (7)	4′ 5′ 6′	122.3 (5)
3 4 11b	111.8 (7)	1′ 2′ 3′	118.2 (3)

[a] Values in parentheses denote error.

in 75 mL of DME was added 1.5 mL of 4 N HCl (dioxane). A precipitate formed immediately, and the two-phase mixture was refluxed. After 5 h, another 1.0 g of hexamethylenetetraamine was added and reflux was continued overnight. An additional 1.5 mL of the HCl solution was added after 12 h and again after an additional 24 h. After another 24 h, TLC (silica gel, 3:2 $CHCl_3$–EtOAc) showed the disappearance of starting material. The mixture was filtered, and the solvent was removed from the filtrate under vacuum. The residue was taken up in $CHCl_3$ and applied to a 5 × 10 cm silica gel column (Baker 60–200 mesh). The column was eluted with $CHCl_3$ until all of the high R_f material (followed by TLC) was recovered. The solvent was removed under vacuum, and the residue recrystallized from 20 mL of CH_3CN to yield 1.3 g of pure product (suitable for X-ray analysis). Concentration of the mother liquor gave an additional 0.2 g for a total yield of 1.5 g (46.6%): mp 150.5–152 °C; IR (KBr) no absorption between 2850 and 1610 cm^{-1}; ^1H NMR (100 Hz, $CDCl_3$) δ 2.44 (s, 3 H, CH_3), 5.60 (s, 2 H, CH_2), 7.40 (m, 6 H, Ph and 8-H), 7.64 (dd, J = 8.5, 2.5 Hz, 10-H), 8.06 (d, J = 8.5 Hz, 1 H, 11-H). ^{13}C NMR[20] ($CDCl_3$): δ 13.66 (q, CH_3), 61.69 (t, CH_2); CH (aromatics), δ129.74, 131.38, 131.48 (C-8, -10, -11), 128.01 (C-3′, -5′), 129.50 (C-2′, -6′), 129.74 (C-4′); C, δ 127.10 (t, J = 7.0 Hz), 134.65, 134.76, 139.26 (t, J = 7.0 Hz, C-1′), 151.90 (dd, J = 7.0, 3.0 Hz), 160.31 (q, J = 7.0 Hz, C-2), 172.48 (m, C-11b). UV (MeOH) λ_{max} (ϵ) 227 (34 100), 259 (17 400) nm; mass spectrum, *m/e* (% total ionization) 308 (4, M^+), 280 (9, base peak), 239 (3).

Anal. Calcd for $C_{17}H_{13}N_4Cl$: C, 66.15; H, 4.24; N, 18.15; Cl, 11.48. Found: C, 66.18; H, 4.28; N, 18.35; Cl, 11.55.

5-Chloro-2-(5-methyl-2*H*-1,2,4-triazol-3-yl)benzophenone (14c). A mixture of 250 mg of **13b**, 100 mg of dimethoxymethane (methylal), and a catalytic amount of *p*-toluenesulfonic acid in 5 mL of benzene was refluxed for 24 h. TLC (silica gel, 3:2 $CHCl_3$–EtOAc) showed the appearance of a new higher R_f spot as well as unreacted starting material. The mixture was evaporated to dryness and the residue chromatographed on a 20-g column of silica gel (Woelm, activity I) with 3:2 $CHCl_3$–EtOAc. The elution was followed by TLC, and the eluate containing the new spot was collected and evaporated to dryness to yield ca. 100 mg of slightly impure (by microanalysis) ketone: mp 144–148 °C; IR ($CHCl_3$) ν 3440 (NH), 1663 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3 H, CH_3), 7.1–7.8 (m, 7 H, aromatic), 8.05 (d, J = 8 Hz, 1 H, Ph 2-H).

Anal. Calcd for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.24; H, 4.01; N, 13.34.

Use of an equivalent amount of 37% aqueous formaldehyde in place of the methylal in the above reaction gave the same product mixture (by TLC), which was not worked up.

Crystallographic Analysis of 5. Crystals from acetonitrile were used in the analysis. Unit cell parameters and errors calculated diffractometrically from 15 well-centered reflections were the following: a = 15.958 (3) Å; b = 7.064 (2) Å; c = 13.637 (4) Å; β = 103.12 (2)°; space group $P2_1/c$; measured density by flotation = 1.38 g/cm^3; calculated density for four molecules per unit cell of the compound $C_{17}H_{13}N_4Cl$ (M_r = 308.5) = 1.38 g/cm^3.

The intensities of 1630 reflections were measured on a Syntex $P2_1$ four-circle diffractometer using Cu Kα radiation (1.5418 Å) and a graphite crystal monochromator. Of these, 1038 reflections had intensities greater than 3σ and were used in the analysis.

The chlorine atom was located on a Patterson map, and the other nonhydrogen atoms were located on subsequent Fourier electron density maps.

Least-squares refinement of coordinates and isotropic temperature factors gave an R factor of 0.113, and subsequent anisotropic temperature factors and coordinate refinement converged to a final R factor[21] of 0.10. No attempt was made to locate hydrogen atoms.

Acknowledgments. We wish to thank the Squibb analytical group under the direction of Dr. Allen Cohen for microanalysis and spectra. In addition, we wish to particularly thank Dr. Mohindar S. Puar for the ^{13}C NMR spectrum and assignments, Dr. Phillip T. Funke for the mass spectrum, and all of them for helpful discussions.

Registry No.—**6,** 3530-15-2; **8,** 66492-62-4; **9,** 66492-64-6; **10,** 66492-63-5; **13b,** 66492-61-3; **14c,** 67863-80-3; 4-chlorobenzonitrile, 623-03-0; benzonitrile, 100-47-0; hexamethylenetetraamine, 100-97-0; dimethoxymethane, 109-87-5.

Supplementary Material Available: ^1H NMR and IR spectra for **5, 6, 8, 9, 10, 13b,** and **14c,** ^{13}C NMR and mass spectra for **5**, and X-ray data for **5** consisting of fractional atomic coordinates and anisotropic temperature factors (10 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) U. Golik, *Tetrahedron Lett.*, 1327 (1975); (b) *J. Heterocycl. Chem.*, **12,** 903 (1975).
(2) U. Golik, *J. Heterocycl. Chem.*, **13,** 613 (1976).
(3) R. I. Fryer and J. V. Earley, *J. Heterocycl. Chem.*, **14,** 1435 (1977).
(4) B. Singh and J. C. Collins, *J. Chem. Soc. D*, 498 (1971).
(5) This is a modification of the procedure of H. Becker, W. Riediger, L. Krahnert, and K. Wehner, German (East) Patent 67 130, 1969; *Chem. Abstr.*, **71,** 124441e (1969).
(6) G. Heller, *J. Prakt. Chem.*, **120,** 49 (1929).
(7) E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 5149 (1962).
(8) S. Kubota and M. Uda, *Chem. Pharm. Bull.*, **23,** 955 (1975).
(9) Details will be published elsewhere.
(10) H. Watanabe, C. Mao, I. T. Barnish, and C. R. Hauser, *J. Org. Chem.*, **34,** 919 (1969).
(11) H. Breuer, *Tetrahedron Lett.*, 1935 (1976).
(12) L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, *J. Org. Chem.*, **41,** 3651 (1976).
(13) M. Tramontini, *Synthesis*, 703 (1973).
(14) G. deStevens and M. Dughi, *Trans. N.Y. Acad. Sci.*, **23,** 568 (1961).
(15) (a) Hexamethylenetetraamine has been used as a nitrogen source in benzodiazepine synthesis: N. Blazevic, V. Sunjic, I. Crvelin, D. Kolbah, and F. Kajfez, *J. Heterocycl. Chem.*, **9,** 531 (1972). (b) During preparation of the manuscript it was also reported to be a carbon source in the synthesis of benzodiazepines from isatins: M. Ogata and H. Matsumoto, *Chem. Ind. (London)*, 1067 (1976).
(16) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14,** 1078 (1971).
(17) A. W. Chow, R. J. Gyurik, and R. C. Parish, *J. Heterocycl. Chem.*, **13,** 163 (1976).
(18) B. R. Vogt, P. C. Wade, and M. S. Puar, *Tetrahedron Lett.*, 1931 (1976).
(19) Th. Curtius and G. M. Dedichen, *J. Prakt. Chem.*, **50,** 241 (1894) (structure given incorrectly as $[CH_3C(NH)NH-]_2$) "Beilstein's Handbuch der Organischen Chemie", 4th ed, Vol. 26, Springer-Verlag, West Berlin, 1936, p H29 (correct structure).
(20) (a) See Figure 1 for numbering. (b) Assignments other than for CH_3 and CH_2 are tentative and based on correlations: F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden, New York, 1976, p 47. (c) Total of 17 carbons.

(21) $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$. The minimized function was $\Sigma w||F_o|^2 - |F_c|^2|$, where w is the reciprocal of the sum of the background and total integrated reflection counts. The latter were measured using the θ–2θ variable scan rate technique; background counts were measured for half the scan time at each end of the scan range. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography", Vol. 3, C. H. MacGillavry and G. D. Riech, Ed., Kynoch Press, Birmingham, England, 1962.

1,2,4-Triazolo- and 1,2,5-Triazino[4,3-*d*][1,4]benzodiazepinone Ring Systems: Synthesis and Barrier to Ring Inversion[1]

Peter C. Wade,* B. Richard Vogt, Barbara Toeplitz, and Mohindar S. Puar

The Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540

Jack Z. Gougoutas

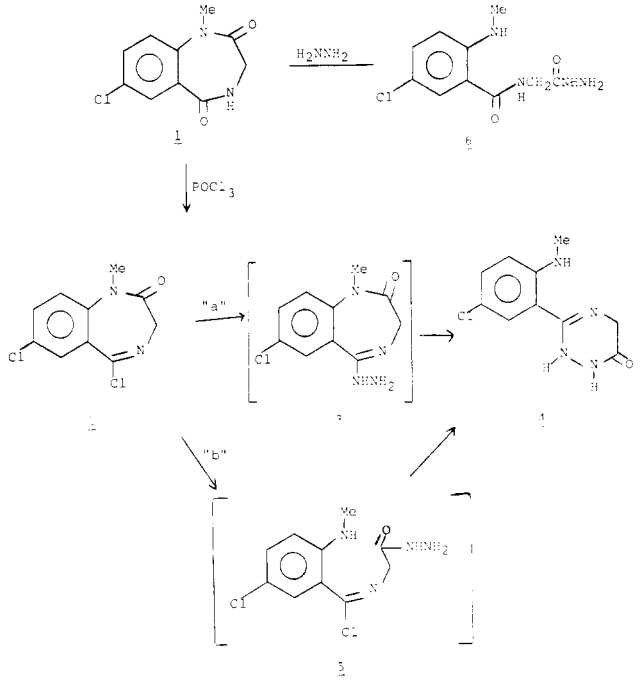
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received June 7, 1978

Reaction of the chloroimide 5,7-dichloro-1-methylbenzodiazepin-2-one with acylhydrazines produced annelated 3-substituted triazoles, and reaction with ethyl carbazate gave the analogous triazolone, which in turn could be alkylated on the 2 position via its thallous salt. Condensation of the chloroimide with 4-morpholineglyoxylic acid hydrazide gave the corresponding annelated triazinedione, which could also be alkylated via its thallous salt. The lactam moiety of the seven-membered ring proved labile to aminolysis by several cyclic secondary amines, yielding ring-opened amides. Temperature-dependent NMR studies revealed that the seven-membered rings of the triazolo derivatives were significantly less conformationally rigid (ΔF^* = 13.0–14.2 kcal/mol) than diazepam (ΔF^* = 18.1 kcal/mol), while the triazinedione derivatives were more rigid (ΔF^* = 19.9–20.7 kcal/mol). The solid state conformations (X-ray) of both annelated systems were distinctly nonplanar. Consistent with its higher ΔF^*, the triazinedione exhibited a greater degree of puckering than the triazolone.

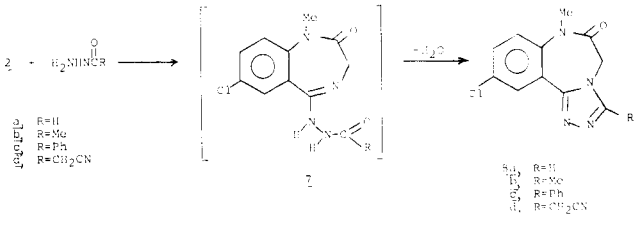
The benzodiazepines have been known as therapeutically important compounds for many years.[2] More recently, derivatives with heterocyclic groups annelated to the "a" face of the molecule have become of interest for their physical,[3] chemical,[4] and biological[5] properties. Some derivatives with the heterocycle fused to the "d" face are also known.[3b,6] We have prepared a series of compounds related to diazepam, where the 5-phenyl group has been replaced by a five- or six-membered nitrogen heterocycle fused to the "d" face. The nature of the heterocycle has been found to exert a profound influence on the conformational properties of the seven-membered ring.

Synthesis. Amidrazones are useful synthetic intermediates[7] that are frequently used to prepare triazoles via their condensation with carboxylic acid derivatives.[8] Thus it was our intention to prepare a suitable amidrazone in the benzodiazepine series from which a variety of substituted triazoles could be synthesized. To this end, the dilactam 1[9] was converted to the chloroimide **2** with phosphorus oxychloride under established conditions. Treatment of **2** with hydrazine under conditions that would be expected to form the amidrazone[10] **3** gave instead a compound that was identified as the dihydro[*as*]triazinone **4.** This product could arise from one of two possible routes. Pathway "a" involves initial displacement of the 5-chloro substituent to form **3** and subsequent attack of the NH_2 function of the amidrazone on the lactam carbonyl. Pathway "b" involves the reverse sequence, initial hydrazinolysis of the lactam followed by cyclization at the chloroimide. This reaction was initially not investigated further since an alternate triazole synthesis became available. However, **3** was prepared later by reacting 2 equiv of hydrazine with **2** in ethanol at room temperature, and it was subsequently shown that extended heating of **3** in either benzene or butanol gave no detectable conversion to **4.** The **4** obtained in the initial reaction must therefore have arisen via pathway "b". The ring opening of the dilactam **1** with hydrazine in refluxing butanol to the hydrazide **6** lends further support to the initial attack at the lactam carbonyl shown in pathway "b".



Allowing **2** to stand in excess neat hydrazine at room temperature was found to be a convenient synthetic procedure for the preparation of **4.**

Since the initial attempts to prepare **3** were unsuccessful, an alternate method for the synthesis of the annelated tria-



0022-3263/79/1944-0088$01.00/0