Synthesis of 5*H*-Tetrazolo[5,1-*c*][1,4]benzodiazepines

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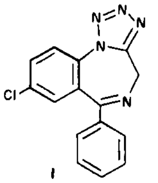
Received June 14, 1984

A three step synthesis of 5*H*-tetrazolo[5,1-*c*][1,4]benzodiazepin-11-ones **8a-d** *via* the reaction of a substituted benzyl azide and ethyl cyanoformate is described. The derived lactams are converted to the corresponding 11-thiones **9a-d** and, through the *S*-methylated derivatives, to the 11-amino analogs **11a-f**. All of the described compounds are representatives of a novel ring system.

J. Heterocyclic Chem., **22**, 333 (1985).

The potential central nervous system activity of heterocyclic fused benzodiazepines has generated considerable synthetic work in this area [2]. It has been previously noted [3], however, that there is a dearth of literature on the tetrazolobenzodiazepines. The only known examples are 8-chloro-6-phenyl-4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepine (**1**) [4], the 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6-ones (**2**) [3], and 6,7-dihydro-7-methyl-5*H*-tetrazolo[1,5-*d*][1,4]-benzodiazepine (**3**) [5].



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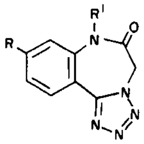

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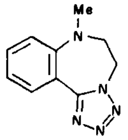

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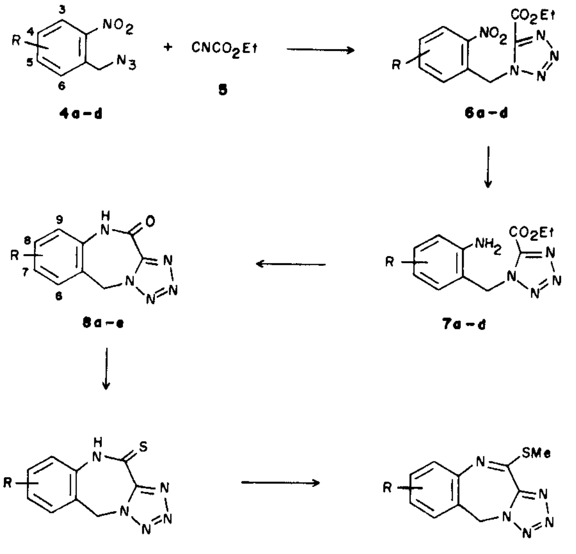
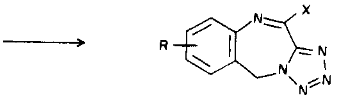
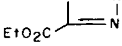
We wish to report a convenient synthesis of the related 5*H*-tetrazolo[5,1-*c*][1,4]benzodiazepin-11-ones **8a-e** and certain derivatives thereof. The synthetic sequence is outlined in Scheme I.

Scheme I





11a-f



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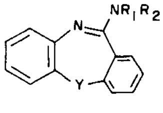

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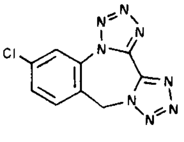

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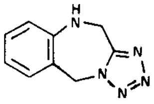

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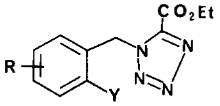
The azides **4a-d** were prepared by treatment of the corresponding benzyl chloride with sodium azide [6] in ethanol. The condensation of organic azides with nitriles has been achieved only when the reaction is intramolecular or the nitrile has a strongly electronegative substituent [7]. The use of perfluoroalkylnitriles by Carpenter [7] and ethyl cyanoformate (**5**) by Katner [8] are examples of such activated nitriles. Utilizing the latter methodology, we have found that the 2-nitrobenzyl azides **4a-d** readily condense with ethyl cyanoformate when heated neat in a Teflon® lined bomb at 100-140° [9].

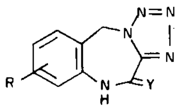
Surprisingly, the reduction of the nitro group in the resultant tetrazoles **6a-d** proved more troublesome than anticipated. The hydrogenolysis product **12** [10] was obtained by hydrogenation over palladium on charcoal. No reaction was observed in the reduction with the less active palladium on barium sulfate. Iron in acetic acid at reflux gave mixtures of **7a** and **8a**, although heating **7a** in acetic acid at reflux did not produce **8a**. Iron in aqueous ethanol-hydrochloric acid gave only poor yields of the desired **8a**, presumably because of hydrolysis of the ester and decarboxylation of the resultant acid. This latter possibility could be avoided by using non-aqueous conditions and, in fact, when the iron reduction was run in ethanol saturated with hydrogen chloride gas the only products isolated were the

Table I



Compound	R	Y	% Yield	Mp (°C)	Recrystallization Solvent	Formula	Analyses % Calculated			Analyses % Found		
							C	H	N	C	H	N
6a	H	NO_2	58	90-92	Benzene	$C_{11}H_{11}N_5O_4$	47.65	4.00	25.26	47.38	3.95	25.33
6b	5-Me	NO_2	49	110-112	EtOH	$C_{12}H_{13}N_5O_4$	49.48	4.50	24.05	49.77	4.23	24.16
6c	4-Cl	NO_2	57	95-97	EtOAc-hexane	$C_{11}H_{10}ClN_5O_4$	42.38	3.25	22.47	42.18	3.07	22.73
6d	5-Cl	NO_2	51	131-133	Ether	$C_{11}H_{10}ClN_5O_4$	42.38	3.25	22.47	42.21	3.17	22.68
7a	H	NH_2	83	76-78	Acetone-water	$C_{11}H_{13}N_5O_2$	53.43	5.30	28.32	53.05	5.33	28.23
7b	5-Me	NH_2	72	81-83	EtOAc-hexane	$C_{12}H_{15}N_5O_2$	55.16	5.78	26.81	54.96	5.73	27.04
7c	4-Cl	NH_2	71	135-137	Benzene-hexane	$C_{11}H_{12}ClN_5O_2$	46.89	4.30	24.86	46.51	4.27	24.79
7d	5-Cl	NH_2	73	125-129	EtOAc-hexane	$C_{11}H_{12}ClN_5O_2$	46.89	4.30	24.86	46.88	4.26	25.36

Table II



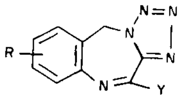
Compound	R	Y	% Yield	Mp (°C)	Recrystallization Solvent	Formula	Analyses % Calculated			Analyses % Found		
							C	H	N	C	H	N
8a	H	O	81	221-223	EtOAc-hexane	$C_9H_7N_5O$	53.73	3.51	34.81	53.33	3.39	35.17
8b	7-Me	O	80	244-247	EtOH	$C_{10}H_9N_5O$	55.81	4.21	32.54	55.70	4.35	32.89
8c	8-Cl	O	73	256-259	MeOH	$C_9H_6ClN_5O$	45.87	2.57	29.72	45.79	2.14	29.69
8d	7-Cl	O	77	260-263	Acetonitrile	$C_9H_6ClN_5O$	45.87	2.57	29.72	45.65	2.70	30.02
8e	7-NO_2	O	84	282-283	DMF-MeOH	$C_9H_6N_6O_3$	43.90	2.46	34.14	43.86	2.76	34.42
9a	H	S	80	275-277	HOAc	$C_9H_7N_5S$	49.75	3.25	32.24	49.95	3.30	32.55
9b	7-Me	S	86	293-296	HOAc	$C_9H_9N_5S$	51.93	3.92	30.28	51.83	3.77	30.60
9c	8-Cl	S	83	284-285	HOAc	$C_9H_6ClN_5S$	42.94	2.40	27.83	42.95	2.72	27.86
9d	7-Cl	S	75	289-290	HOAc	$C_9H_6ClN_5S$	42.94	2.40	27.83	42.02	2.54	28.00

anilines **7a-d**. Three methods of cyclization of these anilino esters were used. The poorest yield method consisted of heating the esters in a high boiling solvent such as diglyme. A better yield of the lactams **8a-d** was obtained by the addition of one equivalent of sodium hydride to a DMF solution of the ester, but the simplest and highest yield procedure consisted of treating a methylene chloride solution of the ester with one equivalent of trimethylaluminum in hexane [11].

The nitro derivative **8e** was prepared by nitration of **8a** with nitric acid in sulfuric acid. The position of nitration was assumed from previous work on the nitration of benzodiazepines [12] as well as from comparison of the proton magnetic resonance spectrum with those of the two positional chlorine isomers **8c** and **8d**. The aromatic region of the 7-chloro isomer **8d** shows a one-proton doublet (J = 2 Hz) at δ 7.93 as the lowest aromatic peak. Similarly, the 8-chloro isomer **8c** shows a one-proton doublet (J = 9 Hz) at δ 7.75 as the lowest peak. From the coupling constants it is obvious that these peaks are due to H_6. In the nitro analog **8e**, the lowest peak, now at δ 8.7 shows a doublet (J = 2 Hz). Thus, if the relative positions of the three aromatic protons remain the same, H_6 shows only meta coupling and therefore the isomer is as shown. As an additional point, if the nitration occurred at the 8-position, then H_9 occurs upfield from its position in the 8-chloro analog which is highly unlikely, a downfield shift being expected.

Each of the lactams, **8a-d** was readily converted to the corresponding thiolactam **9a-d**, which were *S*-methylated with sodium hydroxide-methyl iodide to the thioimidates **10a-d**. These thioimidates reacted with various amines as expected [13] to form the amidines **11a-f**, which are strongly reminiscent of the neuroleptic dibenzoepines **13** [14]. In addition, treatment of the thioimidate **10c** with sodium azide-ammonium chloride-lithium chloride [15] resulted in the formation of the bis tetrazole **14**. Alternative-

Table III



Compound	R	Y	% Yield	Mp (°C)	Recrystallization Solvent	Formula	Analyses % Calculated C	H	N	Found C	H	N
10a	H	-SMe	89	105-108	EtOAc-hexane	$C_{10}H_9N_5S$	51.93	3.92	30.28	51.75	4.02	29.88
10b	7-Me	-SMe	87	157-160	EtOAc	$C_{11}H_{11}N_5S$	53.85	4.52	28.55	53.76	4.56	28.83
10c	8-Cl	-SMe	71	168-170	EtOAc-hexane	$C_{10}H_8ClN_5S$	45.20	3.03	26.36	45.08	3.30	26.22
10d	7-Cl	-SMe	77	131-133	EtOAc-hexane	$C_{10}H_8ClN_5S$	45.20	3.03	26.36	45.46	3.17	26.63
11a	H	*N*-methyl-4-piperidylamino	49	112-114	EtOH-ether	$C_{15}H_{19}N_7$	60.58	6.44	32.98	60.35	6.50	32.83
11b	H	$NH(CH_2)_3NMe_2$	78	145-150 [a]	Acetone-ether	$C_{14}H_{19}N_7 \cdot C_4H_4O_4$ (maleate)	53.85	5.77	24.43	53.83	5.76	24.72
11c	7-Cl	4-methyl-1-piperazyl	88	220-222	Ether	$C_{14}H_{16}ClN_7$	52.29	5.07	30.84	52.60	5.15	30.71
11d	8-Cl	4-methyl-1-piperazyl	84	228-230	Ether	$C_{14}H_{16}ClN_7$	52.29	5.07	30.84	52.43	5.12	30.76
11e	7-Me	4-methyl-1-piperazyl	65	280-282 [a]	*i*-PrOH-ether	$C_{15}H_{19}N_7$-1½HCl	51.17	5.86	27.85	50.67	5.84	28.06
11f	8-Cl	$NH(CH_2)_3NMe_2$	87	135 (dec) [a]	*i*-PrOH-ether	$C_{14}H_{18}ClN_7$-$2HCl \cdot H_2O$	40.93	5.40	23.87	40.95	5.72	24.08

[a] The mp is given for the salt indicated.

ly, the lactam **8a** was reduced to the amine **15** with lithium aluminum hydride.

The condensation of 2-nitrobenzyl azides with ethyl cyanoformate has been shown to be a convenient method of preparation of tetrazolo[5,1-*c*][1,4]benzodiazepines, without any of the ambiguity [16] associated with the direct alkylation of tetrazole **12** with 2-nitrobenzyl halides. By a judicious choice of substituents on the azide, it is obvious that other interesting tricyclic tetrazole derivatives could be prepared just as readily.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover oil bath melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 299 spectrophotometer. The ^1H nmr spectra were measured on a Varian XL-100 or a Jeol Model C-60HL spectrometer. The spectra in all cases were consistent with the assigned structures. Combustion analyses were performed on a Perkin-Elmer Model 240 elemental analyzer.

2-Nitrobenzyl Azides **4a-d**.

Each of the benzyl azides **4a-d** was prepared by heating at reflux a 10% molar excess of sodium azide and corresponding benzyl chloride in ethanol for 6-8 hours. The insoluble salts were removed by filtration, the ethanol was evaporated, the resultant oil was dissolved in ether, and further insolubles were removed by filtration.

2-Nitrobenzyl azide (**4a**) was obtained as a pale yellow oil by removal of the ether.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.40; N, 31.45. Found: C, 47.56; H, 3.27; N, 31.16.

5-Methyl-2-nitrobenzyl azide (**4b**) was obtained as an oil that was used directly in the next step.

4-Chloro-2-nitrobenzyl azide (**4c**) was obtained as an oil used directly in the next step. A small aliquot was chromatographed on silica gel (50% methylene chloride-hexane) to give pure azide, mp 36-38° (from hexane).

Anal. Calcd. for $C_7H_5ClN_4O_2$: C, 39.54; H, 3.27; N, 26.35. Found: C, 39.55; H, 2.34; N, 26.16.

5-Chloro-2-nitrobenzyl azide (**4d**) was obtained as an oil that was purified on silica gel with methylene chloride and used directly.

Ethyl 1-(2-Nitrobenzyl)-5-tetrazolecarboxylates **6a-d**.

A mixture of 0.1 mole of ethyl cyanoformate and the appropriate 2-nitrobenzyl azide **4a-d** was heated in á Teflon® lined bomb for 5-6 hours at 145° [9]. The resultant semisold mass was chromatographed on silica gel with chloroform to give the desired products which were recrystallized from the solvent given in Table I.

Ethyl 1-(2-Aminobenzyl)-5-tetrazolecarboxylates **7a-d**.

To 0.3 mole of the nitro derivatives **6a-d** in 200 ml of ethanol saturated with hydrogen chloride gas was added an equal weight of iron powder in portions. The resulting exotherm raised the temperature to 60-70°, stirring was continued for 1 hour, the reaction mixture was evaporated to dryness and diluted with 200 ml of water. The desired product was extracted with methylene chloride and recrystallized (Table I).

Tetrazolo[5,1-*c*][1,4]benzodiazepin-11-ones **8a-d**.

a. To 75 mmoles of the amine **7a-d** in 500 ml of methylene chloride under nitrogen was slowly added 31 ml of trimethylaluminum in hexane (25%, 77 mmoles). After 1 hour, 80 ml of *N*-hydrochloric acid was added cautiously, the organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were dried, evaporated, and the desired product was recrystallized from the appropriate solvent (Table II).

b. Alternatively, to 8.0 g (0.03 mole) of **7a** in 200 ml of dimethylformamide was added 1.5 g (0.03 mole) of 50% sodium hydride in oil. The mixture was stirred overnight, poured into dilute hydrochloric acid and extracted into methylene chloride. Evaporation of the dried solvent gave a semi-solid that was triturated with hexane and recrystallized from acetonitrile, yield 3.7 g (56%), identical in all respects with **8a** prepared by the above method.

5,10-Dihydro-7-nitro-11*H*-tetrazolo[5,1-*c*][1,4]benzodiazepin-11-one (**8e**).

To 10.8 g (54 mmoles) of benzodiazepine **8a** in 135 ml of sulfuric acid at 0° was added 2.1 ml of 70% nitric acid. After 1½ hours at 0° the reaction mixture was poured into ice water, the product was collected, triturated with hot acetonitrile, then ether to give the crude product, mp 276-279°, 11.3 g (85%). An analytical sample was recrystallized from DMF-methanol, mp 283-284°.

Anal. Calcd. for $C_9H_6N_6O_3$: C, 43.90; H, 2.46; N, 34.14. Found: C, 43.86; H, 2.76; N, 34.42.

5,10-Dihydro-11*H*-tetrazolo[5,1-*c*][1,4]benzodiazepin-11-thione **9a-d**.

A solution of 50 mmoles of the lactams **8a-d** and 20 mmoles of phosphorus pentasulfide in 120 ml of pyridine was heated at 110° for 1 hour, poured into ice water, stirred for ½ hour and filtered. The resultant solid was washed well with water, then hexane. Recrystallization from acetic acid gave the desired products in the yields indicated (Table II).

11-Methylthio-5*H*-tetrazolo[5,1-*c*][1,4]benzodiazepines **10a-d**.

To 30 mmoles of the thiones **9a-d** in 300 ml of ethanol was added 33 ml of 1*N* sodium hydroxide followed by the slow addition of 34 mmoles of methyl iodide. After 2 hours the reaction mixture was evaporated to ¼ volume, 100 ml of water was added and the product was obtained by extraction into methylene chloride. The solid obtained after evaporation of the solvent was recrystallized as indicated (Table III).

Typical Preparation of the Amines **11a-f**. *N*-(1-Methyl-4-piperidinyl)-5*H*-tetrazolo[5,1-*c*][1,4]benzodiazepine-11-amine (**11a**).

A solution of 5.0 g (22 mmoles) of **10a** in 15 ml of 4-amino-1-methylpiperidine was heated at 115° for 18 hours. The excess amine was evaporated and the resultant solid was triturated with water. Recrystallization from ethanol-water gave the product. With slight modification the other amines (Table III) were prepared in an analogous manner. In some cases the free amine crude products were not purified but immediately converted to the acid salt (see Table).

11-Chloro-8*H*-ditetrazolo[1,5-*a*:5,1-*c*][1,4]benzodiazepine (**14**).

A mixture of 3.5 g (13 mmoles) of the thioether **10c**, 1.7 g (26 mmoles) of sodium azide, 1.3 g (25 mmoles) of ammonium chloride and 0.03 g of lithium chloride in 65 ml of DMF was heated at 100° for 3 hours, poured into ice water and the product was removed by filtration. Recrystallization from acetic acid gave 2.9 g (86%) of the bis tetrazole, mp 228-230°.

Anal. Calcd. for $C_9H_5ClN_8$: C, 41.47; H, 1.93; N, 42.99. Found: C, 41.54; H, 2.07; N, 43.10.

10,11-Dihydro-5*H*-tetrazolo[5,1-*c*][1,4]benzodiazepine (**15**).

To 1.9 g of lithium aluminum hydride in 250 ml of THF at reflux was added 10 g of **8a**. After 6 hours the mixture was cooled, 10 ml of sodium hydroxide was added, the mixture was filtered and the cake was washed with hot THF. The combined filtrates were evaporated. The resultant product was recrystallized from water, 3.6 g, mp 128-131°. This material was converted to the hydrochloride salt with *i*-propanolic hydrogen chloride-ether, mp 210-212°.

Anal. Calcd. for $C_9H_9N_5 \cdot HCl$: C, 48.32; H, 4.51; N, 31.31. Found: C, 48.38; H, 4.45; N, 31.71.

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[9] *Caution!* We have not had a problem with the 2-nitrobenzyl azides used in this report. However, in a reaction of 2.5 moles of ethyl cyanoformate and *p*-methoxybenzyl azide in a regular steel bomb a detonation occurred. The temperature control on the oil bath had failed and the last recorded temperature was 170°. A thermal stability study of *p*-methoxybenzyl azide showed a tendency for decomposition at 170-180° with vigorous evolution of nitrogen at 210°.

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