1 and 2 in this series, see ref 2a and 2b, respectively.
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Quinazolines and 1,4-Benzodiazepines. 81.[1] *s*-Triazolo[4,3-*a*][1,4]benzodiazepines by Oxidative Cyclization of Hydrazones

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s-Triazolo[4,3-*a*][1,4]benzodiazepines bearing various substituents in the 1 position were prepared by oxidative cyclization of the appropriate aldehyde hydrazones of 2-hydrazinobenzodiazepines. Diethyl azodicarboxylate and activated manganese dioxide were used as oxidizing agents. The new triazolo compounds were active in the CNS tests but none of them reached the potency of the known triazolobenzodiazepines.[2]

The conventional synthesis of the *s*-triazolo[4,3-*a*]-[1,4]benzodiazepines **8–10**[2] by dehydration–cyclization of the 2-(2-acylhydrazino)benzodiazepines **6** often requires vigorous reaction conditions and gives diminishing yields as the bulk of the substituent R in the 1 position increases. The steric hindrance affecting this ring closure can be avoided by employing the intermediate triazolines **7**. These triazolines should exist in equilibrium with the open hydrazones **2–5**. Once formed, the triazolines should be readily dehydrogenated to the triazoles by common oxidizing agents. A process using air as oxidant has been disclosed by Hester and Szmuszkovicz.[3]

We would like to report some of our results, in particular experiments which involved the use of diethyl azodicarboxylate or activated manganese dioxide as oxidizing agents, which led to both known and new triazolobenzodiazepines in good to excellent yields.

Thus, reaction of the known 2-hydrazinobenzodiazepines[4,5] with the appropriate aldehyde gave the corresponding hydrazones **2–5**. The spectral data of the characterized hydrazones were in agreement with the assigned structures. The NMR spectrum of **2a** in Me_2SO indicated the presence of only one form while an equilibrium of syn and anti forms was established in chloroform solution. The cyclic form **7a** was not detectable by NMR spectroscopy. When the acetaldehyde hydrazone **2a** was heated in boiling benzene in the presence of diethyl azodicarboxylate, the known triazolo compound **8a**[6] was obtained in 70% yield. Employing activated manganese dioxide in place of the azo reagent gave **8a** in about half this yield. As demonstrated for the preparation of **9a**,[4] **11d**, and **12**, it was not necessary to isolate the hydrazones prior to conversion to the triazole.

The methyl ester **10a** was obtained via the glyoxylic ester hydrazone **3a** and was reduced with PCl_3 to **10b** (Scheme I).

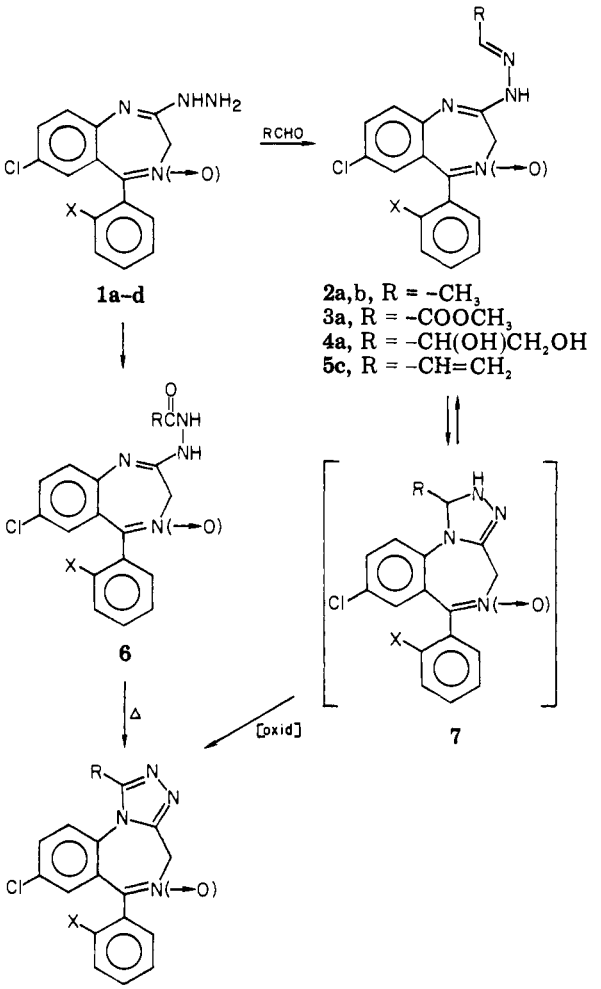
The dihydroxyethyl derivatives **11a,b,d** were accessible by the oxidative cyclization of the *dl*-glyceraldehyde hydrazones 4 and were of interest as possible stable, water-soluble triazolobenzodiazepines. However, their water solubility in relation to their pharmacological potency was not considered sufficient to pursue these compounds further.

Table I. Pharmacological Data for Triazolobenzodiazepines

Compd	Mouse (ED_{50}, mg/kg po)		
	Inclined screen	Footshock anti-fighting	Anti-pentyl-enetetra-zole
8a	>400	100	3.35
8b	2	2.5	0.3
9b	>400	0.5	1.1
10b	40	5	0.9
11a	>400	>100	620
11b	100	20	3.8
11d	200	5	1.5
12c	150	6.25	4.2
12d	150	2.5	1.3
13c	>400	>100	>800
14	500	50	2.8
15	300	100	50
Diazepam	25	10	1.4
Chlordiazepoxide	100	40	8

The 1-vinyl compounds **12c** and **12d** were isolated by chromatography in low yield due to the formation of polymeric by-products. The interesting adduct **13c** was isolated as a by-product and probably was formed by addition of diethyl hydrazodicarboxylate to the vinyl compound **12c**, followed by subsequent dehydrogenation to the unsaturated derivative with trans configuration. Reaction of the ester **10b** with hydrazine yielded the hydrazide 14 (Scheme II). Similarly, the basic amide **15** was obtained by heating the ester **10b** with 2-(dimethylamino)ethylamine. Hydrolysis of **10b** was accompanied by decarboxylation and afforded **9b**. The same

Scheme I



1a–d

2a,b, R = $-CH_3$
3a, R = $-COOCH_3$
4a, R = $-CH(OH)CH_2OH$
5c, R = $-CH=CH_2$

6

7

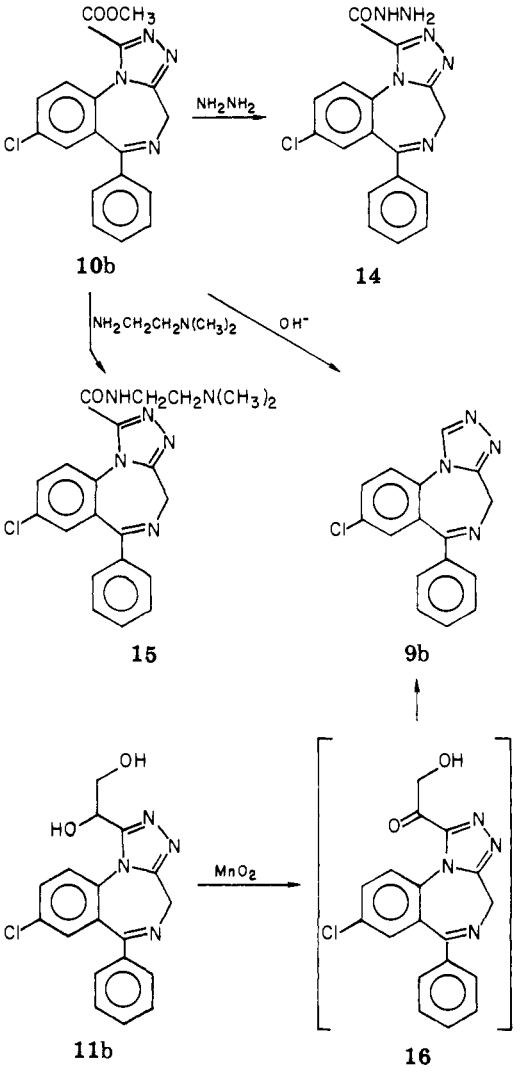
8a,b, R = CH_3
9a,b, R = H
10a,b, R = $COOCH_3$
11a,b,d, R = $-CH(OH)CH_2OH$
12c,d, R = $CH=CH_2$
13c, R = $-CH=CHNNHCOOEt$ (COOEt)

a, X = H [4(5)-oxide]
b, X = H
c, X = Cl
d, X = F

compound was formed by oxidation of the glycol **11b** with activated manganese dioxide, presumably via the hydroxy ketone **16**.

Biological Activity. The triazoles **8–15** were tested orally in mice for the CNS effects of benzodiazepines according to previously described procedures.[7,8] The results of the inclined screen test, the footshock test, and the antagonism against pentylenetetrazole are given in Table I. The reduction of the nitrone to the imine results in a large increase in activity as evident from the comparison of **8a** and **11a** vs. **8b** and **11b**. The methyl ester **10b** appears to be more active than the corresponding ethyl ester for which data (ip application) have been reported by Hester et al.[2] The hydrazide **14** and the basic amide **15** are less active than the methyl ester. The higher potency of the ester could be due to its faster metabolic conversion to the decarboxylated compound **9b**. However, comparison of the data of **9b** and the ester **10b** suggests that the ester has intrinsic activity with a different profile. The glycol **11b** is expectedly less potent than the 1-methyl derivative **8b**[2] and the introduction of an *o*-fluoro substituent in the 6-phenyl ring did not increase the activity significantly. The 1-vinyl compounds **12c** and **12d** show good activity but are also considerably weaker than the very potent 1-methyl analogues.[2] The adduct **13c** was inactive.

Scheme II



10b

14

15

9b

11b

16

Experimental Section

Melting points were determined in a capillary melting point apparatus. The UV spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. NMR spectra were recorded with a Varian T-60 instrument with Me_4Si as internal standard. IR spectra were determined on a Beckman IR-9 spectrometer. Merck silica gel (70–325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-Chloro-2-(2-ethylidenehydrazino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (2a). Acetaldehyde, 3 mL, was added to a solution of 12 g of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**1a**)[4,5] in 300 mL of THF, 50 mL of EtOH, and 3 drops of AcOH. After sitting at room temperature for 30 min, the reaction mixture was partially evaporated and crystallized by addition of Et_2O to yield 12.5 g (95%) of product with mp 194–196 °C dec. The analytical sample was recrystallized from MeOH: mp 198–200 °C dec; UV λ max 246–247 nm (ε 25 150), 282 (31 400), infl 350 (3500); NMR (Me_2SO) δ 2.05 (d, 3, J = 5.5 Hz, $-CH_3$), 4.67 (br s, 2, C_3-H), 6.9 (d, 1, J = 2 Hz, C_6-H), 7.2–7.8 (m, 7, aromatic H), 7.85 (q, 1, J = 5.5 Hz, $-CH=N$), 9.8 (br s, 1, NH). Anal. ($C_{17}H_{15}ClN_4O$) C, H, N.

7-Chloro-2-(2-ethylidenehydrazino)-5-phenyl-3*H*-1,4-benzodiazepine (2b).[3] Acetaldehyde, 0.3 mL, was added to a solution of 0.8 g of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**1b**)[4] in 20 mL of THF. After addition of 1 drop

of AcOH, the mixture was gently warmed on the steam bath for 5 min. The solvent was evaporated and the residue was crystallized from Et_2O to leave 0.75 g (85%) of product with mp 155–160 °C. For analysis it was recrystallized from CH_2Cl_2–Et_2O–hexane: mp 162–164 °C; UV λ infl 225 nm (ε 26 600), λ max 259 nm (ε 27 650), infl 280 (20 500), 334–336 (2500); NMR ($CDCl_3$) δ 2.02 (d, J = 5.5 Hz) and 2.05 (d, J = 5.5 Hz) (3, $-CH_3$, syn and anti isomers), 4.43 (s) and 4.48 (s) (2, C_3-H, syn and anti isomers), 6.8–7.6 (m, 8, aromatic H), 7.83 (q, 1, –CH=N), ~8.4 (br s, 1, NH). Anal. ($C_{17}H_{15}ClN_4$) C, H, N.

7-Chloro-2-[2-(carbomethoxymethylene)hydrazino]-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (3a). To a suspension of 15 g (0.05 mol) of **1a**[4,5] in 300 mL of CH_2Cl_2 was added a solution of 6 g (0.08 mol) of glyoxylic acid in 50 mL of MeOH. The mixture was heated to reflux on the steam bath and was concentrated under reduced pressure to 100 mL. 2-PrOH was added to the warm mixture. The precipitated product was collected after cooling and was washed with 2-PrOH and Et_2O to leave 15.5 g of light yellow crystals.

This material was suspended in 1 L of CH_2Cl_2 and 200 mL of MeOH. Ethereal diazomethane was added until all material went into solution and TLC did not show any more acid remaining. The residue obtained after complete evaporation was dissolved in 100 mL of CH_2Cl_2. Some insoluble material was removed by filtration. The filtrate was again evaporated and the residue was crystallized from EtOAc to yield 13.5 g (73%) of light yellow crystals in two crops. For analysis it was recrystallized from CH_2Cl_2–2-PrOH: mp 190–192 °C dec; UV λ max 247 nm (ε 30 300), 306 (26 600), infl 350 (12 750); NMR ($CDCl_3$) δ 3.85 (s, 3, OCH_3), 4.8 (s, 2, $-CH_2-$), 6.9–8 (m, 9, aromatic H and CH=N), 9.27 (br s, 1, NH). Anal. ($C_{18}H_{15}ClN_4O_3$) C, H, N.

7-Chloro-2-[(2,3-dihydroxypropylidene)hydrazino]-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (4a). A mixture of 9.9 g (0.033 mol) of **1a**,[4,5] 11.0 g (0.122 mol) of *dl*-glyceraldehyde, 500 mL of MeOH, and 375 mL of CH_2Cl_2 was boiled on a steam bath for 0.5 h, cooled, diluted with Et_2O, and filtered. The solid obtained was triturated with a large volume of a boiling mixture of CH_2Cl_2 and MeOH. The filtrate was concentrated under reduced pressure to give an amorphous residue. Crystallization of the residue from CH_2Cl_2–Et_2O, followed by recrystallization from CH_2Cl_2–MeOH–Et_2O (charcoal), gave 8.9 g (72%) of **2d** as colorless crystals, mp 198–201 °C dec. The analytical sample prepared by recrystallization from the same solvent system had mp 201–203 °C dec: IR (KBr) 1650, 1620 cm^{-1} (C=N); UV λ max 245 nm (ε 22 500), 283 (31 400), infl ~355 (2600). Anal. ($C_{18}H_{17}ClN_4O_3$) C, H, N.

7-Chloro-5-(2-chlorophenyl)-2-(2-propenylidenehydrazino)-3*H*-1,4-benzodiazepine (5c). A solution of 39.5 g (0.12 mol) of **1c**,[6] 750 mL of CH_2Cl_2, 300 mL of MeOH, 20 mL of acetic acid, and 25 mL of acrolein was stirred at room temperature for 20 min, washed with $NaHCO_3$ solution, dried, and evaporated. Crystallization of the residue from Et_2O–petroleum ether yielded 22.8 g of tan product with mp 149–155 °C. Recrystallization from MeOH–H_2O (charcoal) and then from CH_2Cl_2–petroleum ether gave 9.5 g (22%) of colorless product with mp 157–159 °C: UV λ infl ~220 nm (ε 38 500), infl ~240 (24 750), max 306 (26 400); NMR ($CDCl_3$) δ 4.5 (s, 2, C_3-H), 5.5–6.8 (m, 3, $-CH=CH_2$), 6.9–7.6 (m, 8, aromatic H), 8.1 (d, 1, J = 9 Hz, –CH=N), 8.65 (br s, 1, NH). Anal. ($C_{18}H_{14}Cl_2N_4$) C, H, N.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine 5-Oxide (8a).[6] **(A)** A mixture of 1 g of **2a**, 1 mL of diethyl azodicarboxylate and 30 mL of C_6H_6 was refluxed for 4 h. The solvent was evaporated and the residue was crystallized from EtOAc. Recrystallization of the crude material from 2-PrOH–CH_2Cl_2 yielded 0.7 g (70%) of product with mp 265–270 °C. Further recrystallization raised the mp to 275–278 °C.

(B) A mixture of 1 g of **2a**, 5 g of activated MnO_2, and 100 mL of C_6H_6 was stirred and refluxed for 16 h. The MnO_2 was filtered off and the filtrate was evaporated. Crystallization of the residue from EtOAc yielded 0.34 g (34%) of product with mp 274–277 °C.

8-Chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine (8b).[2] A mixture of 0.31 g of **2b**, 0.3 mL of diethyl azodicarboxylate, and 25 mL of C_6H_6 was refluxed for 16 h. The solvent was evaporated, and the residue was crystallized from 2-PrOH. The crude material was purified by chromatography on 8 g of silica gel with 5% (v/v) EtOH in CH_2Cl_2. Crystallization from CH_2Cl_2–hexane yielded 0.16 g (52%) of product with mp 224–226 °C.

8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 5-Oxide (9a).[4] A mixture of 1.5 g of **1a**, 0.5 mL of aqueous formaldehyde (30%), and 50 mL of C_6H_6 was refluxed for 10 min with separation of water. Diethyl azodicarboxylate, 2 mL, was added to the reaction mixture and refluxing was continued for 2 h. The crystals which separated from the cooled reaction mixture were collected (1.1 g). Recrystallization from CH_2Cl_2–EtOAc–MeOH yielded 0.75 g (48%) of product with mp 277–278 °C dec.

8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (9b).[4] **(A)** Activated MnO_2 (1.6 g) was added to a solution of 0.4 g (0.011 mol) of **11b** in 50 mL of $CHCl_3$. After stirring for 24 h at room temperature, an additional 2.4 g of MnO_2 was added and stirring continued for 24 h longer. The inorganic material was filtered off and the filtrate was evaporated. Crystallization of the residue from Et_2O yielded colorless crystals with mp 219–222 °C dec. A mixture melting point with an authentic sample was undepressed.

(B) A mixture of 0.35 g (1 mmol) of **10b**, 20 mL of MeOH, 0.2 g of KOH, and 1 mL of H_2O was heated to reflux under nitrogen for 2 h. The solvent was evaporated under reduced pressure and the residue was acidified with aqueous AcOH and extracted with CH_2Cl_2. The extracts were dried and evaporated, and the residue was crystallized from Et_2O to yield 0.23 g (78%) of product with mp 224–225 °C, identical with the above material.

Methyl 8-Chloro-5-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine-1-carboxylate 5-Oxide (10a). A mixture of 7.4 g of **3a**, 200 mL of DMF, and 10 mL of diethyl azodicarboxylate was heated to reflux for 2 h. After evaporation under reduced pressure, the product was precipitated by addition of H_2O. It was collected, washed with H_2O, and dissolved in CH_2Cl_2. The solution was dried over Na_2SO_4 and evaporated. Crystallization of the residue from EtOAc left 2.6 g (35%) of product. For analysis it was recrystallized from CH_2Cl_2–2-PrOH to leave colorless crystals with mp 240–242 °C dec: NMR (Me_2SO) δ 4.02 (s, 3, OCH_3), 5.15 (d, 1) and 5.45 (d, 1) (AB system, J = 14 Hz, C_4-H), 7–7.8 (m, 8, aromatic H). Anal. ($C_{18}H_{13}ClN_4O_3$) C, H, N.

Methyl 8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine-1-carboxylate (10b). PCl_3, 1 mL, was added to a solution of 1 g of **10a** in 30 mL of CH_2Cl_2. After sitting at room temperature for 5 h, the solution was washed with 10% aqueous Na_2CO_3 and H_2O. The organic layer was dried and evaporated. Crystallization of the residue from MeOH yielded 0.8 g (84%) of colorless product which, after recrystallization from CH_2Cl_2–MeOH, had mp 223–225 °C dec: UV λ infl 225 nm (ε 29 750), infl 250 (20 000), infl 290 (3200); NMR ($CDCl_3$) δ 4.0 (s, 3, OCH_3), 4.07 (d, 1) and 5.52 (d, 1) (AB system, J = 13 Hz, C_4-H), 7.2–7.8 ppm (m, 8, aromatic H). Anal. ($C_{18}H_{13}ClN_4O_2$) C, H, N.

8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-1-carboxylic Acid Hydrazide (14). A mixture of 1 g of **10b**, 1 mL of NH_2NH_2, and 20 mL of EtOH was refluxed for 10 min. The crystals which separated upon cooling were collected to leave 0.8 g (80%) of colorless product with mp 288–290 °C dec: UV λ max 224 nm (ε 31 900), sh 250 (21 600), infl 295 (3800). Anal. ($C_{17}H_{13}ClN_6O$) C, H, N.

8-Chloro-*N*-(2-dimethylaminoethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine-2-carboxamide (15). A mixture of 0.5 g of **10b** and 3 mL of 2-dimethylaminoethylamine was refluxed for 10 min. The excess reagent was evaporated under reduced pressure, at the end azeotropically with xylene. The residue was crystallized from Et_2O–hexane and recrystallized from Et_2O–MeOH to leave 0.42 g (72%) of colorless product with mp 173–175 °C: UV λ max 224 nm (ε 31 600), sh 251 (21 300), infl 300 (1600); NMR ($CDCl_3$) δ 2.25 [s, 6, $N(CH_3)_2$], 2.5 [t, 2, J = 6 Hz, $-CH_2N(CH_3)_2$], 3.48 (q, 2, J = 6 Hz, $-NHCH_2-$), 4.03 (d, 1) and 5.5 (d, 1) (AB system, J = 13 Hz, C_4-H), 7.2–7.8 (m, 8, aromatic H), 7.94 (br t, 1, NH). Anal. ($C_{21}H_{21}ClN_6O$) C, H, N.

8-Chloro-1-(1,2-dihydroxyethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine 5-Oxide (11a). A solution of 10.6 g (0.037 mol) of **4a**, 500 mL of 1-BuOH, and 7 mL (7.5 g or 0.043 mol) of diethyl azodicarboxylate was refluxed for 2.5 h. The reagents were evaporated under reduced pressure and the residue was crystallized from Et_2O. The product was collected and

recrystallized twice from CH_2Cl_2–EtOH to leave 7.5 g (55%) of colorless crystals with mp 245–247 °C dec: UV λ max 228 nm (ε 27 700), 258 (16 300), 309 (11 450). Anal. ($C_{18}H_{15}ClN_4O_3$) C, H, N.

8-Chloro-1-(1,2-dihydroxyethyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11b). A mixture of 4.5 g (0.012 mol) of **11a**, 200 mL of THF, 100 mL of MeOH, and 2 teaspoonfuls of Raney nickel was shaken under hydrogen at atmospheric pressure for 2 h. The catalyst was removed by filtration, the filtrate evaporated under reduced pressure, and the residue crystallized from EtOH. Recrystallization from CH_2Cl_2–EtOH yielded 3.2 g (76%) of pure colorless product with mp 211–214 °C dec: UV λ max 222 nm (ε 38 600), sh 245 (16 600), sh 290 (2900). Anal. ($C_{18}H_{15}ClN_4O_2$) C, H, N.

8-Chloro-1-(1,2-dihydroxyethyl)-6-(2-fluorophenyl)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (11d). A mixture of 10.5 g (0.035 mol) of **1d**,[9] 3.8 g (0.042 mol) of *dl*-glyceraldehyde, and 300 mL of MeOH was boiled on a steam bath for 10 min, allowed to sit at room temperature for 16 h, and filtered. The filtrate was evaporated under reduced pressure. The residue was treated with 400 mL of 1-BuOH and 12 mL (0.073 mol) of diethyl azodicarboxylate. After refluxing for 2 h, the reaction mixture was evaporated under reduced pressure. Crystallization of the residue from CH_2Cl_2–Et_2O gave 4.5 g (35%) of product with mp 203–206 °C. Recrystallization from MeOH–Et_2O yielded colorless crystals with mp 208–210 °C: UV λ max 222 nm (ε 36 450), infl 245 (15 700), sh 280 (2800). Anal. ($C_{18}H_{14}ClFN_4O_2$) C, H, N.

8-Chloro-6-(2-fluorophenyl)-1-vinyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12d). A solution of 5.3 g (0.017 mol) of **1d**,[9] 100 mL of CH_2Cl_2, 35 mL of MeOH, 2.5 mL of HOAc, and 3.0 mL of acrolein was stirred at room temperature for 25 min, washed with $NaHCO_3$ solution, dried, and concentrated under reduced pressure. The residue was treated with 2.5 mL (0.0155 mol) of diethyl azodicarboxylate and 125 mL of DMF and refluxed for 1.5 h. The reaction mixture was evaporated under reduced pressure. The residue was chromatographed over 150 g of silica gel using 3% (v/v) MeOH in CH_2Cl_2. Clean fractions were combined and evaporated. The product crystallized from Et_2O–petroleum ether and was recrystallized from CH_2Cl_2–petroleum ether to yield 0.5 g (8.7%) of off-white prisms with mp 176–179 °C dec: UV λ sh 211 nm (ε 45 500), sh 245 (24 000), sh 290 (2750); NMR ($CDCl_3$) δ 4.13 (d, 1) and 5.6 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.6–6.8 (m, 3, CH=CH_2), 6.8–7.9 (m, 7, aromatic H). Anal. ($C_{18}H_{12}ClFN_4$) C, H, N.

8-Chloro-6-(2-chlorophenyl)-1-vinyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (12c) and 8-Chloro-6-(2-chlorophenyl)-1-[2-[1,2-bis(ethoxycarbonyl)hydrazo]-*trans*-vinyl]-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (13c). A solution of 18.0 g (0.05 mol) of **5c**, 18 mL (0.11 mol) of diethyl azodicarboxylate, and 500 mL of DMF was refluxed for 45 min and concentrated under reduced pressure. The residue was treated with Et_2O and filtered. The filtrate was evaporated, leaving a mixture according to TLC. Chromatography on 300 g of silica gel with 10% (v/v) EtOH in EtOAc did not separate the products. Two successive chromatographies over silica gel H (according to Stahl for TLC) with 5% (v/v) EtOH in CH_2Cl_2 gave 1.5 g (8%) of **12c** and 1.15 g (4%) of **13c**.

Recrystallization of **12c** from CH_2Cl_2–Et_2O yielded colorless crystals with mp 216–220 °C dec: UV λ infl 218 nm (ε 41 000), infl 254 (15 800), infl ~300 (1700); NMR ($CDCl_3$) δ 4.15 (d, 1) and 5.55 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.6–6.8 (m, 3, CH=CH_2), 7–7.9 (m, 7, aromatic H). Anal. ($C_{18}H_{12}Cl_2N_4$) C, H, N.

Recrystallization of **13c** from CH_2Cl_2–hexane yielded colorless crystals with mp 199–201 °C dec: UV λ max 217 nm (ε 43 600), sh 245 (22 600), max 274 (18 450); IR (KBr) 1740 cm^{-1} (COOEt); NMR (Me_2SO) δ 1.25 (t, 6, J = 7 Hz, CH_3), 4.25 (m, 4, OCH_2), 4.25 (d, 1) and 5.25 (d, 1) (AB system, J = 13 Hz, C_4-H), 5.75 (d, 1) and 7.95 (d, 1) (AB system, J = 13.5 Hz, –CH=CH–), 7.14 (d, 1, J = 2 Hz, C_7-H), 7.3–7.9 ppm (m, 6, aromatic H). Anal. ($C_{24}H_{21}Cl_2N_6O_4$) C, H, N.

Acknowledgment. The authors wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Dr. F. Scheidl for the microanalyses, Mr. S. Traiman for the IR spectra, and Dr. V. Toome for the UV spectra. We are obliged to Dr. L. O. Randall and Dr. W. Pool and their respective staffs for the pharmacological data.

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Nitroimidazoles with Antibacterial Activity against *Neisseria gonorrhoeae*

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Nitroimidazoles have been prepared which show interesting activity against the bacterium, *Neisseria gonorrhoeae*, in addition to the activities usually shown by nitroimidazoles against protozoa and anaerobic bacteria. The compounds were prepared by alkylation of 1-methyl-2-mercaptoimidazole, followed by nitration. Optimum activity occurs with a 5-nitro group and a free carboxyl at the end of the group attached to the sulfur. The linkage between the sulfur atom and the carboxyl group can be alkylene or phenoxyalkylene. These compounds have only weak activity against other aerobic or facultative bacteria.

Gonorrhea is a serious public health problem in the world today.[1] Strains of the responsible organism, *Neisseria gonorrhoeae*, have arisen which are resistant to penicillin[2] and there is the possibility that resistance will also develop to alternative drugs. Thus, development of additional drugs with different structures is most desirable. An antigonococcal screening program in our laboratories uncovered interesting activity in some of the compounds reported in a previous paper.[3] A number of additional compounds were prepared to explore this activity.

Chemistry. The compounds were made by the methods described in our previous paper.[3] Yields of some of the 5-nitro compounds in Table I were low due in part to concurrent nitration of the benzene ring as seen in