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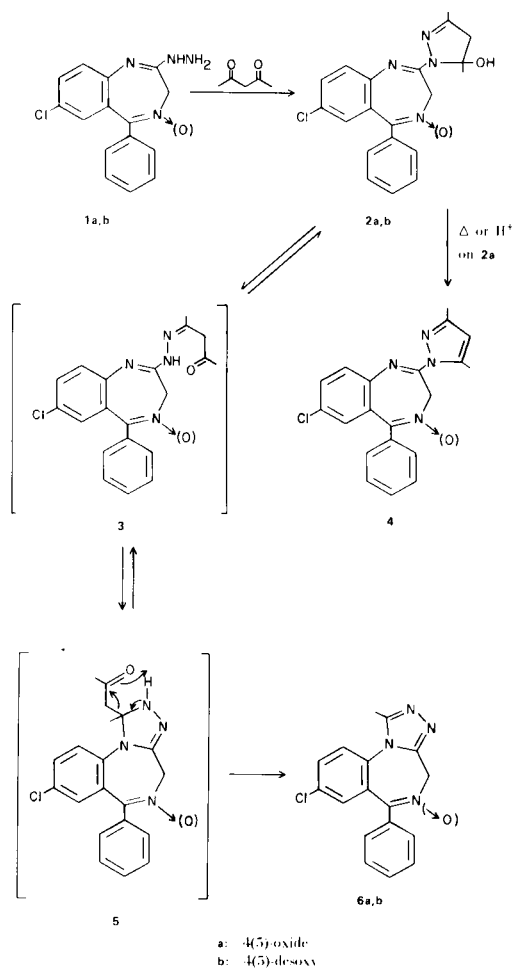
Received July 11, 1977

The 2-hydrazinobenzodiazepines **1** were reacted with acetylacetone to form the hydroxypyrazolines **2** which were converted to the triazolobenzodiazepines **6** and the 2-pyrazolylbenzodiazepine **4**. Ring cleavage of the hydrazone **8** obtained from cyclohexane-1,3-dione and **1a** led similarly to the 1-(4-oxopentyl)triazolobenzodiazepine **12**.

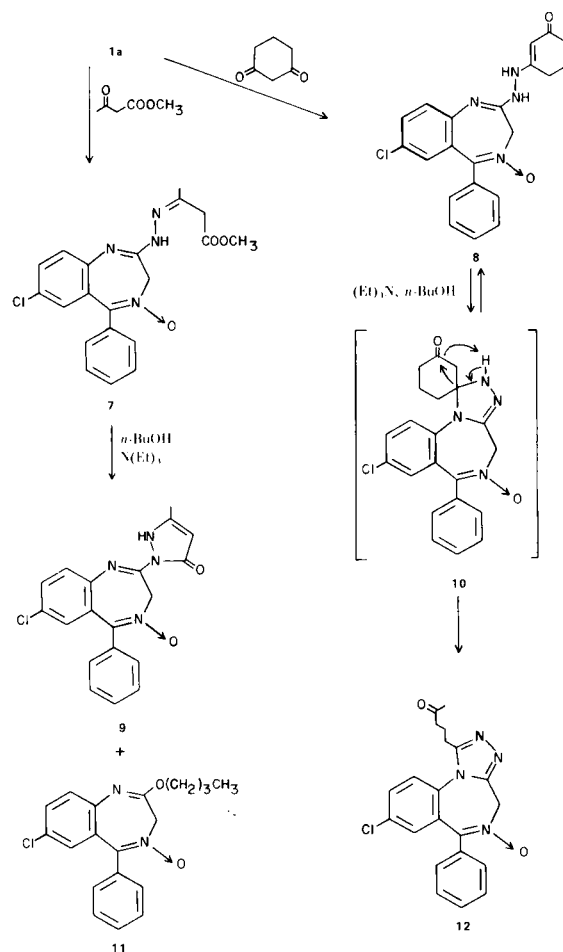
J. Heterocyclic Chem., **15**, 161 (1978)

We have found that the known 1-methyl-triazolo-[4,3-*a*][1,4]benzodiazepines **6a** (2) and **6b** (3) can be efficiently prepared by condensation of the 2-hydrazinobenzodiazepines **1** (4) with acetylacetone. The initially formed adducts **2** were isolated and characterized and assigned the structures of hydroxypyrazolines on the basis of spectral data. The lack of a carbonyl band in the ir and the absence of a vinylic proton in the nmr spectrum made the ring opened structure **3** or its enolized form less likely. The hydroxypyrazolines **2** were converted in good yield to the triazolobenzodiazepines **6** by heating in boiling 1-butanol in presence of triethylamine. This implies that under these conditions the hydroxypyrazoline

Scheme 1



Scheme 11



is not dehydrated but ring opened to **3** which should also exist in equilibrium with the triazoline **5**. Once formed, the triazoline **5** is perfectly set up for the transformation to the triazole **6** by elimination of acetone by the indicated cyclic mechanism.

By refluxing compound **2a** in xylene, both the 2-pyrazolylbenzodiazepine **4** and the triazole **6a** were formed. Treatment of the hydroxypyrazoline **2a** with trifluoroacetic acid gave the pyrazole **4**.

Reaction of the hydrazine **1a** with cyclohexane-1,3-dione yielded the corresponding hydrazone which on the basis of ir and nmr spectra exists as the enamine structure **8** (Scheme II). Compound **8** also underwent conversion to

the triazolobenzodiazepine **12** but in much lower yield than that described above for **6** indicating that in this case the formation and cleavage of the spirocyclic triazoline **10** is probably a less favorable process.

The condensation of the hydrazine **1a** with methyl acetoacetate gave the hydrazone **7** as a mixture of isomers, one of which was obtained pure by fractional crystallization. When this hydrazone was treated with triethylamine in boiling 1-butanol both the pyrazolone **9** and the iminoether **11** were obtained. Since the pyrazole moiety of **9** was not displaced by 1-butanol under the reaction conditions, the iminoether **11** must have been formed by displacement of a different species, possibly an azo moiety.

EXPERIMENTAL

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 TMS as internal standard. Ir spectra were determined on a Beckman Ir-9 spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-Chloro-2-[4,5-dihydro-3,5-dimethyl-5-hydroxypyrazol-1-yl]-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (**2a**).

A mixture of 15 g. (0.05 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**1a**) (4), 20 g. (0.2 mole) of acetylacetone and 400 ml. of methanol was warmed until solution was complete. After sitting overnight at room temperature the solvent was removed under reduced pressure and the residue was crystallized from ether to give 17.5 g. (91%) of yellow product. For analysis the product was purified by chromatography over silica gel using methylene chloride/ethyl acetate, 1:1 (v/v). Crystallization from methylene chloride/ether gave pale yellow crystals with m.p. 185-186°; uv: λ max 245 nm (ϵ , 21,600) 287 (42,000) inf 355 (3,400); ir (chloroform): 3350 cm^{-1} , OH, 1605, 1585; nmr (deuteriochloroform): δ 1.83 ppm (s, 3, -CH₃) 2.03 (s, 3, CH₃) 2.96 (s, 2, -CH₂-) 4.5-5.5 (broad s, 2, C₃-H) 5.92 (s, 1, OH) 6.9-7.8 (m, 8, aromatic H).

Anal. Calcd. for C₂₀H₁₉ClN₄O₂: C, 62.75; H, 5.00; N, 14.63. Found: C, 62.76; H, 4.90; N, 14.68.

7-Chloro-2-[4,5-dihydro-3,5-dimethyl-5-hydroxypyrazol-1-yl]-5-phenyl-3*H*-1,4-benzodiazepine (**2b**).

A mixture of 2 g. (0.007 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**1b**) (4), 2 ml. of acetylacetone and 20 ml. of ethanol was heated to reflux for 5 minutes. The solvent was evaporated and the residue was crystallized from methylene chloride/ether/hexane to yield 1.3 g. (50.5%) of product which was recrystallized twice from 2-propanol for analysis, m.p. 154-157°; uv: λ max 233 nm (ϵ , 24,600) sh 250 (21,000) 296 (24,100) 348 (5,250); ir (chloroform): 3350 cm^{-1} (OH) 1605, 1585; nmr (deuteriochloroform): δ 1.78 ppm (s, 3, CH₃) 2.03 (s, 3, CH₃) 2.92 (s, 2, -CH₂-) ca. 4.4 (very broad s, 2, C₃-H) 6.1 (broad s, 1, OH) 7.0-7.7 (m, 8, aromatic H); nmr (d-DMSO): δ 1.85 (s, 3, CH₃) 2.03 (s, 3, CH₃) 2.96 (s, 2, -CH₂-) ca. 4.3 (very broad s, 2, C₃-H) 6.35 (broad s, 1, OH, exchangeable with deuterium oxide) 7.1-7.8 (m, 8, aromatic H).

Anal. Calcd. for C₂₀H₁₉ClN₄O: C, 65.48; H, 5.22; N, 15.27. Found: C, 65.65; H, 5.17; N, 15.39.

7-Chloro-2-(3,5-dimethyl-1-pyrazolyl)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (**4**).

A solution of 1 g. (2.6 mmoles) of **2a** in 10 ml. of trifluoroacetic acid was allowed to stand at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated. Crystallization of the residue from 2-propanol gave 0.65 g. (68%) of crude **4**. The analytical sample was purified by passing over a pad of silica gel with methylene chloride containing 10% of ethyl acetate and was crystallized from methylene chloride/petroleum ether to give 0.5 g. of colorless crystals with m.p. 221-224°; uv: λ sh 220 nm (ϵ , 20,600) max 250 (21,400) 290 (39,900) inf 325 (11,000); ir (chloroform): 1640 cm^{-1} ; nmr (deuteriochloroform): δ 2.25 ppm (s, 3, CH₃) 2.6 (s, 3, CH₃) 5.33 (broad s, 2, C₃-H) 6.0 (s, 1, =CH-) 7-7.8 (m, 8, aromatic H).

Anal. Calcd. for C₂₀H₁₇ClN₄O: C, 65.84; H, 4.70; N, 15.36. Found: C, 65.73; H, 4.62; N, 15.53.

8-Chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-*a*][1,4]benzodiazepine 5-Oxide (**6a**) (2).

A mixture of 3.8 g. (0.01 mole) of **2a**, 100 ml. of 1-butanol and 1 ml. of triethylamine was refluxed for 16 hours. The crystals separated upon cooling and were collected to yield 1.9 g. (59%) of **6a** (2) with m.p. 278-282° dec. (Lit. m.p. 273-274° dec.). Concentration of the filtrate left a residue which on crystallization from ether gave a second crop of 0.25 g., bringing the total yield to 66%.

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

A mixture of 0.37 g. (0.001 mole) of **2b**, 0.3 ml. of triethylamine and 20 ml. of 1-butanol was heated to reflux for 15 hours. The solvent was evaporated under reduced pressure and the residue was crystallized from methylene chloride/ethyl acetate/ether to yield 270 mg. (87%) of **6b** (3) with m.p. 225-227° (Lit. m.p. 228-228.5°).

8-Chloro-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-*a*][1,4]benzodiazepine 5-Oxide (**6a**) (2) and 7-Chloro-2-(3,5-dimethyl-1-pyrazolyl)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (**4**).

A mixture of 5.0 g. (0.013 mole) of **2a** and 50 ml. of xylene was refluxed for 15 hours. Part of the solvent (20 ml.) was distilled and collected in a Dean-Stark trap. Compound **6a** crystallized upon cooling to yield after filtration 1.7 g. (40%) of off-white product with m.p. 277-281° dec. A mixture melting point with an authentic sample was undepressed.

The mother liquor was evaporated under reduced pressure and the residue was chromatographed over 60 g. of silica gel using ethyl acetate/methylene chloride 1:1 (v/v). Compound **4** was crystallized from ether/petroleum ether and recrystallized from methylene chloride/petroleum ether to yield 0.9 g. (19%) of off-white crystals with m.p. 218-221°.

7-Chloro-2-[2-(carbomethoxyisopropylidene)hydrazino]-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (**7**).

A solution of 4.5 g. (0.015 mole) of **1a**, 1.5 ml. (0.014 mole) of methyl acetoacetate, 1.5 ml. of acetic acid, 75 ml. of methylene chloride and 45 ml. of 2-propanol was stirred at room temperature for 75 minutes. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated aqueous sodium bicarbonate solution. The methylene chloride layer was dried and evaporated. Crystallization of the residue from ether/petroleum ether yielded 4.6 g. of a mixture of two hydrazones according to nmr. The mixture was fractionally recrystallized from methylene chloride/ether/petroleum ether to yield 1.7 g. (30%) of one colorless crystalline isomer with m.p. 165-167°; uv: λ max 244 nm (ϵ , 23,500) 283 (30,200)

infl 350 (3,300); ir (chloroform): 3,350 cm^{-1} (NH) 1730 (COOMe) 1635, 1610; nmr (deuteriochloroform): δ 2.15 ppm (s, 3, CH_3) 3.38 (s, 2, $-\text{CH}_2-$) 3.73 (s, 3, COOCH_3) 4.73 (s, 2, $\text{C}_3\text{-H}$) 6.9-7.8 (m, 8, aromatic H) 8.47 (broad s, 1, NH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{ClN}_4\text{O}_3$: C, 60.23; H, 4.80; N, 14.05. Found: C, 60.14; H, 4.77; N, 14.09.

7-Chloro-2-[2-(3-oxocyclohexenyl)hydrazino]-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (**8**).

1,3-Cyclohexanedione, 1.0 g. (0.009 mole), dissolved in 15 ml. of methanol was added to a solution of 1.0 g. (0.0033 mole) of **1a** and 3 drops of acetic acid in 100 ml. of methylene chloride/methanol 1:1. The reaction mixture was stirred for 40 minutes under an atmosphere of nitrogen and the bulk of the solvent was evaporated under reduced pressure. The residue was treated with ether to yield 1.1 g. (85%) of yellow crystals with m.p. 216-220° dec. The analytical sample was recrystallized from methylene chloride/methanol/ether, m.p. 223-224° dec.; uv: λ max 219 nm (ϵ , 21,900) 239 (22,300) 330 (45,750); ir (potassium bromide): 1660 cm^{-1} conjug. ketone; nmr (DMSO): δ 1.6-2.6 ppm (m, 6, $-\text{CH}_2-$) 4.66 (broad s, 2, $\text{C}_3\text{-H}$) 5.46 (s, 1, $=\text{CH-}$) 6.86 (d, 1, $J = 2$ Hz, $\text{C}_6\text{-H}$) 7.2-7.7 (m, 7, aromatic H) 9.05 (s, 1, NH) 9.7 (s, 1, NH).

7-Chloro-2-[3-methyl-2,5-dihydro-1H-pyrazol-5-one-1-yl]-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (**9**) and 7-Chloro-2-butoxy-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (**11**).

A mixture of 9.0 g. (0.023 mole) of **7**, 50 ml. of triethylamine and 450 ml. of 1-butanol was heated to reflux for 2.5 hours. The solvent was evaporated under reduced pressure and the residue was triturated with methylene chloride. Filtration gave 2.4 g. of crude **9** which was recrystallized from methylene chloride/methanol (charcoal) to yield 1.0 g. (12%) of yellow crystals with m.p. 257-260° dec. The analytical sample was recrystallized from the same solvent mixture and had m.p. 260-261° dec.; uv: λ sh 220 nm (ϵ , 22,700) sh 237 (18,700) max 298 (29,100) 367 (15,600); ir (Nujol): 3150 cm^{-1} (NH) 1660 (CO) 1620 ($\text{C}=\text{N}$); nmr (DMSO): δ 2.41 (s, 3, CH_3) 5.08 (broad s, 2, $\text{C}_3\text{-H}$) 6.98 (s with fine structure, 1) and 7.2-7.8 (m, 8) (aromatic H and pyrazole-H) 11.29 (broad s, 1, NH).

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_2$: C, 62.21; H, 4.12; N, 15.27. Found: C, 62.23; H, 3.92; N, 15.14.

The filtrate was evaporated and the residue (8.0 g.) was chromatographed over 240 g. of silica gel using ethyl acetate. The least polar component was crystallized from petroleum ether to yield 2.4 g. (30%) of **11** with m.p. 87-90°. The analytical sample was recrystallized from methylene chloride/petroleum

ether and had m.p. 91-93°, uv: λ max 243 nm (ϵ , 25,800) 310 (10,250); ir (chloroform): 1630 cm^{-1} ; nmr (deuteriochloroform): δ 0.95 ppm (degenerated t, 3, CH_3) 1.2-2.2 (m, 4, $-\text{CH}_2-\text{CH}_2-$) 4.3 (t, 2, $-\text{OCH}_2-$) 4.48 (s, 2, $\text{C}_3\text{-H}$) 5.8-7.8 (m, 8, aromatic H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_2$: C, 66.56; H, 5.59; N, 8.17. Found: C, 66.65; H, 5.50; N, 8.20.

8-Chloro-1-(4-oxopentyl)-6-phenyl-4H-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine 5-Oxide (**12**).

A solution of 11.6 g. (0.03 mole) of **8**, 25 ml. of triethylamine and 500 ml. of 1-butanol was stirred under reflux for 16 hours under an atmosphere of nitrogen. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed over 300 g. of silica gel using ethanol/methylene chloride 1:20 (v/v). The fractions containing **12** were combined and evaporated. The residue was crystallized from ethyl acetate and recrystallized from acetone/petroleum ether to yield 1.3 g. (11%) of colorless crystals with m.p. 192-195°. The analytical sample was recrystallized from the same solvent mixture, m.p. 194-196°; uv: λ max 227 nm (ϵ , 26,800) 258 (15,400) 308 (11,000); ir (chloroform): 1700 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.1 ppm (s, 3, COCH_3), 1.9-3.3 (m, 6, $-\text{CH}_2)_3$), 4.97 (d, 1) and 5.45 (d, 1) (AB-system, $J = 14$ Hz, $\text{C}_4\text{-H}$) 7.1-7.8 (m, 8, aromatic H).

Anal. Calcd. for $\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_2$: C, 63.67; H, 4.85; N, 14.19. Found: C, 63.78; H, 4.74; N, 14.27.

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.

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