Triazepinones I. Synthesis of 3-Benzyl-8-methyl-5*H*-*s*-triazolo-[4,3-*b*][1,2,4]-triazepin-6(9*H*)one

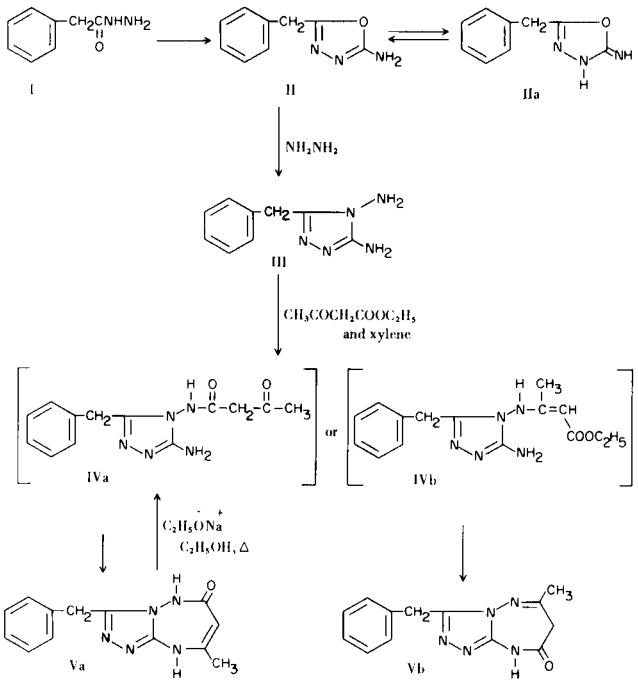
Man M. Kochhar

School of Pharmacy, Auburn University, Auburn, Alabama 36830

Received August 18, 1971

Since the introduction of chlordiazepoxide (1) as a potent tranquilizer, interest in the benzodiazepines as a class of pharmacologically active agents has rapidly increased. Recently, some pharmacologically active thiazolodiazepine (2,3,4) and oxazolodiazepine (5) derivatives have been synthesized. These reports led us to synthesize a triazolotriazepine, 3-benzyl-8-methyl-5*H*-*s*-triazolo[4,3-*b*][1,2,4]triazepin-6(9*H*)one (Va).

2-Amino-5-benzyl-1,3,4-oxadiazole (II) was prepared from phenylacetic acid hydrazide (I) and cyanogen bromide by modification of a method described in the literature (6,7,8). The ir data [λ max (potassium bromide) 3.2 (N-H), 6.0 and 6.35 (imino and C=N) and 9.75 (C-O) μ] indicated that compound II exists in equilibrium with the 2-imino form (IIa); this observation was further substantiated by uv absorption at 289 mμ. The ir and uv data support literature suggestions for dominance of the amino form (9,10).



3-Benzyl-4,5-diamino-1,2,4-triazole (III) was obtained by treating II with hydrazine hydrate (11,12). A minimum of 15 hours at reflux was essential for obtaining an optimum yield of 50% in this reaction; six to eight hours at reflux resulted in only 5 to 10% yield. Some of the semicarbazide of I was also recovered and hydrolysis of II might be responsible for the low yield of the final product III.

o-Phenylenediamine is known to react with crotonic acid to yield benzodiazepines (13,14,15). Diaminotriazoles resemble the *o*-aromatic diamines and should react with crotonic acid in the presence of hydrochloric acid to yield triazepines. However, reaction of III with crotonic acid gave a mixture from which only the hydrochloride salt of compound III and intractable tar could be obtained. The failure of crotonic acid to yield a triazepine with 3-benzyl-4,5-diamino-*s*-triazole (III) led us to try a β-ketoester as a possible cyclizing agent. Compound III and ethyl acetoacetate in anhydrous xylene was refluxed for six hours. The cyclization apparently proceeded *via* an intermediate 3-benzyl-4-acetoacetamido-5-amino-1,2,4-triazole (IVa). The identity of compound Va was established by its hydrolysis to compound IVa and by nmr. The methyl protons appeared at δ = 1.90 ppm as a doublet and vinyl proton at δ = 4.80 ppm as a poorly resolved multiplet. An alternate cyclization possibility involves the formation of a crotonate intermediate (IVb) which on cyclization would give 3-benzyl-6-methyl-7,8-dihydro-9*H*-*s*-triazolo[4,3-*b*][1,2,4]triazepin-8-one (Vb). Fractional crystallization gave 1% of Vb, which was confirmed by nuclear magnetic resonance spectrum. The methyl proton at δ = 2.2 ppm (3 proton) and methylene protons at δ = 3.25 ppm (2 proton). This was in accordance with the observations that when 4,5-diaminopyrimidine or 2,3-diaminopyridine reacted with ethyl acetoacetate, the compound obtained was pyrimidodiazepinone and pyridodiazepinone (16,17,18).

EXPERIMENTAL (19,20)

2-Amino-5-benzyl-1,3,4-oxadiazole (II).

A mixture of phenylacetic acid hydrazide (I) (4.5 g., 0.03

mole), potassium bicarbonate (3.6 g., 0.036 mole), cyanogen bromide (3.0 g., 0.03 mole) and water (150 ml.) was stirred at room temperature for 36 hours. The mixture was filtered, and the solid was washed with water, dried and crystallized from benzene; needles, m.p. 159-160°; yield 3.5 g. (67%). The ir spectrum showed λ max (potassium bromide) 3.2, 6.0, 6.35, and 9.75 μ; uv: λ max (ethanol) 289 mμ.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.17; N, 23.98. Found: C, 61.85; H, 5.19; N, 24.01.

3-Benzyl-4,5-diamino-1,2,4-triazole (III).

A mixture of II (1.8 g., 0.01 mole) and 85% hydrazine hydrate (5 ml.) was refluxed overnight, cooled, and poured into ice. The solid was separated, washed with water, and dried. Crystallization from ethanol afforded small needles, m.p. 174-175°; yield 1.0 g. (50%); ir: λ max (potassium bromide) 2.95, 3.0, 3.2, 6.1, 6.4, and 9.8 μ.

Anal. Calcd. for $C_9H_{11}N_5$: C, 57.12; H, 5.86; N, 37.01. Found: C, 57.20; H, 5.74; N, 37.05.

3-Benzyl-8-methyl-5*H*-*s*-triazolo[4,3-*b*][1,2,4]triazepin-6(9*H*)one (Va).

A solution of 3-benzyl-4,5-diamino-1,2,4-triazole (III) (0.9 g., 5 mmoles), ethyl acetoacetate (1.0 g., 7.5 mmoles) and anhydrous xylene (10 ml.) was refluxed for six hours. The solution was reduced to 5 ml. under reduced pressure and left overnight in the refrigerator. The solid was crystallized from anhydrous benzene as light yellow needles; m.p. 231-232°; yield 0.3 g. (24%); ir: λ max (potassium bromide) 3.15, 3.3, 3.4, 5.9, 6.15, 6.3, 6.55, 6.9, 7.0, and 7.1 μ.

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.08; H, 5.09; N, 27.39.

From the mother liquor (benzene) another crop of greenish yellow crystals was collected; m.p. 223-224°; yield 0.015 g. (1%); ir: λ max (potassium bromide) 2.9, 3.0, 3.45, 5.95, 6.2, 6.4, 6.7, 6.95, and 7.01 μ. The solid gave a single spot on tlc and was assigned the structure 3-benzyl-6-methyl-7,8-dihydro-9*H*-*s*-triazolo[4,3-*b*][1,2,4]triazepin-8-one (Vb).

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43. Found: C, 61.25; H, 5.00; N, 27.25.

3-Benzyl-4-acetoacetamido-5-amino-1,2,4-triazole (IVa).

A solution of compound Vb (0.25 g., 1 mmoles) and sodium ethoxide (0.068 g., 1 mmoles) in absolute ethanol (25 ml.) was refluxed for 5 hours and evaporated to dryness under reduced pressure. The dried material was dissolved in water (20 ml.), and the solution was acidified with acetic acid to *p*H 6.5 and cooled in the refrigerator. Solid material on crystallization gave white needles; m.p. 214-215°; yield 0.2 g. (80%); ir: λ max (potassium bromide) 2.95, 3.1, 5.8, 6.1, 6.3, 6.55, 6.7, and 7.1 μ.

Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.62. Found: C, 57.20; H, 5.45; N, 25.75.

REFERENCES

(1) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(2) E. F. Elslager, J. R. McLean, S. C. Perricone, D. Potoczak, H. Veloso, D. F. Worth and R. H. Wheelock, *J. Med. Chem.*, **14**, 397 (1971).

(3) E. F. Elslager, D. F. Worth, Neil F. Haley, and S. C. Perricone, *J. Heterocyclic Chem.*, **5**, 609 (1968).

(4) E. F. Elslager, D. F. Worth and S. C. Perricone, *ibid.*, **6**, 491 (1969).

(5) T. Miyadera, A. Terada, M. Fukunaga, Y. Kawano, T. Kamioka, C. Tamura, H. Takagi and R. Tachikanea, *J. Med. Chem.*, **14**, 520 (1971).

(6) S. G. Boots and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 272 (1967).

(7) H. Gehlen, *Ann. Chem.*, **563**, 185 (1949).

(8) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(9) M. S. Gibson, *Tetrahedron*, **18**, 1377 (1962).

(10) H. Najer, J. Menin and J. F. Guidicelli, *Compt. Rend.*, **258**, 4579 (1964).

(11) H. Gehlen and G. Robisch, *Ann. Chem.*, **663**, 119 (1963).

(12) H. Gehlen and H. Elchlepp, *ibid.*, **594**, 14 (1955).

(13) J. Davoll, *J. Chem. Soc.*, 308 (1960).

(14) W. Ried and G. Urlass, *Chem. Ber.*, **86**, 1101 (1953).

(15) W. Ried and W. Hohne, *ibid.*, **87**, 1801 (1954).

(16) M. Israel, L. C. Jones and E. J. Modest, *J. Heterocyclic Chem.*, **4**, 659 (1967).

(17) W. H. Nyberg, C. W. Noell and C. C. Cheng, *ibid.*, **2**, 110 (1965).

(18) M. Israel, S. K. Tinfer, D. H. Trites and E. J. Modest, *ibid.*, **7**, 1029 (1970).

(19) I thank Dr. Kurt L. Leoning, Director of Nomenclature, Chemical Abstracts Service, for assistance in ascribing correct nomenclature to triazoletriazepinones described herein.

(20) Reported melting points are uncorrected. A Thomas-Hoover Uni-Melt apparatus was used for melting point determinations. Galbraith Laboratories, Inc., Knoxville, Tenn., conducted the elemental analyses.