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Syntheses of 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)ones **2a-d** from 5-(*o*-aminophenyl)-tetrazoles **1a-d** and bromoacetyl bromide are described. Compounds **2a-d** are representatives of a novel tricyclic ring system. Several alternate methods for the synthesis of **2a-d** were attempted without success. Spectral evidence for structural assignments **2a-d** is presented. Chemical evidence for these assignments includes the transformation of **2a** to 6-(2,2-dimethylhydrazino)-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine (**19**) *via* the thione analog of **2a** (**18**).

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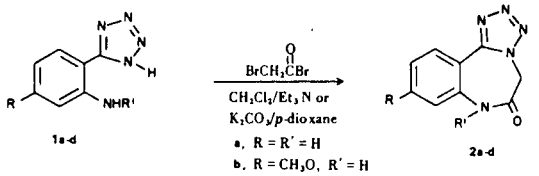
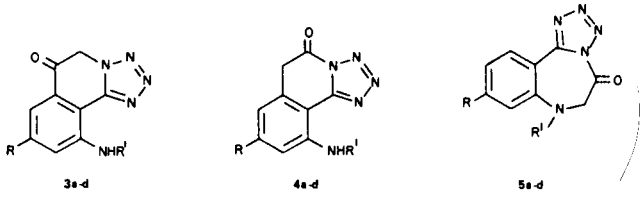
A great deal of synthetic work describing the preparation of nitrogen-containing five-membered rings fused to the benzodiazepine nucleus has appeared. The chemical literature is replete with pyrrolobenzodiazepines, imidazobenzodiazepines, and triazolobenzodiazepines, compound groups for which a variety of interesting pharmacological (central nervous system) activities are reported (1). There is, however, only one reported tetrazolobenzodiazepine, which is 8-chloro-6-phenyl-4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepine (2). In this report we wish to describe the synthesis of some 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)ones, and the chemistry which established these structural assignments.

Treatment of 5-(*o*-aminophenyl)tetrazole (**1a**) with bromoacetyl bromide, either in methylene chloride with excess triethylamine or in *p*-dioxane with potassium carbonate, yielded 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)one (**2a**). In similar fashion were prepared tetrazolobenzodiazepines **2b-d** from the respective tetrazoles **1b-d** (Scheme I).

Scheme I

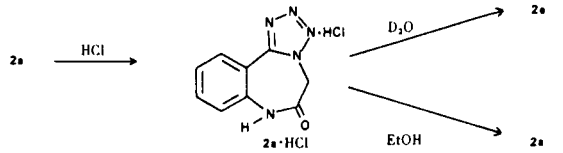


In establishing structural assignments for **2a-d**, it was necessary for us to rule out alternate, isomeric structures **3**, **4**, and **5**. It was relatively easy to eliminate structures **3** and **4** on the basis of spectral evidence. The most compelling evidence for discounting **3** and **4** from consideration came from nmr integrals of the aromatic protons. In each case (**a-d**) it was evident that the number of aromatic protons present was not consistent with structures **3** and **4**.



A more difficult problem was that of ruling out structures **5a-d**. We initially decided to compare spectral data gathered for **2a**, a representative which we chose for the series of tetrazolobenzodiazepines, with spectral data of model compounds chosen to mimic, to a certain extent, general structures **2** and **5**. These spectral data are summarized in Table I.

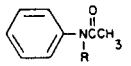
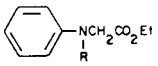
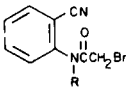
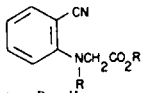
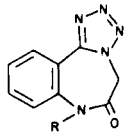
Model compounds chosen to mimic general structure **2** were acetanilide (**6a**) and 2-bromo-*N*-(2-cyanophenyl)acetamide (**8a**). Model compounds chosen to mimic general structure **5** were ethyl *N*-phenylglycinate (**7a**) and *N*-(2-cyanophenyl)glycine (**9a**). Deuterated derivatives **6b**, **7b**, and **8b** were prepared by shaking chloroform solutions of **6a**, **7a**, and **8a** with deuterium oxide. Compound **9b** was prepared by recrystallization of **9a** from deuterium oxide. Compound **2e** was prepared by dissolving the hydrochloride salt of **2a** (**2a**·HCl) in deuterium oxide and later collecting the resulting white, crystalline solid (**2e**). Recrystallization of **2a**·HCl from ethanol afforded **2a**. These preparations of **2e** and **2a** from **2a**·HCl (by disproportionation of a relatively unstable hydrochloride salt) argue against structure **5a**, which should form a stable hydrochloride salt, and indicate that **2a**·HCl must be a tetrazole salt. Compound **2a**·HCl, in turn, was prepared from **2a** by treatment with concentrated hydrochloric acid (4 hours at room temperature) followed by concentration of the solution and washing the residual white solid (**2a**·HCl) with acetone.



Examination of the NH and ND infrared stretching frequencies for **2a** and **2e**, respectively, shows them to be more typical of amide than amine frequencies. Although

Table I

Spectral Data for Tetrazolobenzodiazepine **2a** and Model Compounds

Compound	Infrared (cm^{-1}) C=O (R = H)	C=O (R = D)	NH	ND	Nmr (δ) NH
 **6a**, R = H **b**, R = D	1670	1640	3300	2420	8.66 ($CDCl_3$)
 **7a**, R = H **b**, R = D	1715	1715	3395	2520	4.20 ($CDCl_3$)
 **8a**, R = H **b**, R = D	1700	1655	3330	2355	8.77 ($CDCl_3$)
 **9a**, R = H **b**, R = D	1720	1710	3415	2510	5.20 ($CDCl_3$ + DMSO-d_6)
 **2a**, R = H **e**, R = D	1680	1670	3220 3150	2340	10.82 ($CDCl_3$ + DMSO-d_6)

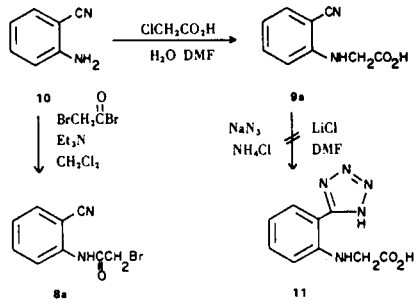
these frequencies are more consistent with the amide NH and ND frequencies of **6** and **8**, respectively, than with those of the respective amine NH and ND frequencies of **7** and **9**, it is perhaps apparent that cyclic amide and amine models would be most appropriate for this particular comparison. It is instructive, however, to notice that deuterated amides **6b** and **8b** suffer a decrease in their carbonyl stretching frequencies (30 cm^{-1} and 45 cm^{-1}, respectively) with respect to **6a** and **8a**, as does **2e** (10 cm^{-1} with respect to **2a**). The carbonyl frequency for deuterated amine **7b**, however, is unchanged with respect to **7a**. Infrared spectra of model compounds from the literature also lent support to structure **2a**. 1-Acetyltetrazole displays a carbonyl stretching frequency at *ca.* 1780 cm^{-1} (3). 8-Methyltetrazolo[1,5-*c*]pyrimidin-5(6*H*)one and tetrazolo[1,5-*c*]quinazolin-5(6*H*)one, systems in which the carbonyl group is attached to the 1-position of the tetrazole moiety, both display carbonyl stretching frequencies at 1770 cm^{-1} (4). Thus, the carbonyl stretching frequency of 1680 cm^{-1} was not compatible with structure **5a** and was indicative of **2a**.

In addition to the infrared data in Table I, which support the structural assignment for **2a**, are listed the nmr chemical shifts for the NH protons in compounds **6a**, **7a**, **8a**, **9a**, and **2a**. The low-field value for the NH proton of **2a** is clearly most consistent with those of the amide NH protons of **6a** and **8a**.

In addition to the spectral evidence we had accumulated which indicated that general structure **2** was, indeed, the correct structural assignment for out tetrazolobenzodiazepinones, we felt it was necessary to supply some chemical evidence. Model compounds **8a** and **9a**, in fact, were chosen with this thought in mind, as we envisioned them as possible precursors to **2a** and **5a**, respectively. Both compounds are novel and their syntheses are shown in Scheme II.

Although *N*-(3-cyanophenyl)glycine (**5a**) and *N*-(4-cyanophenyl)glycine (**5b**) are known, the isomeric **9a** has not been reported. We were able to produce **9a** in 47% yield when anthranilonitrile (**10**) and chloroacetic acid

Scheme II



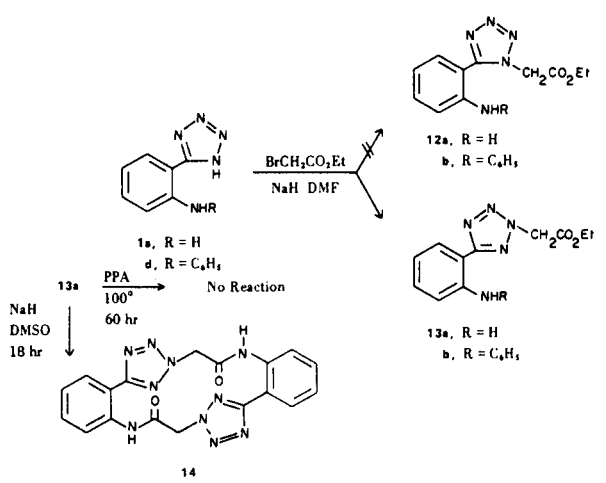
were heated at reflux for five days in water-dimethoxyethane (DME). However, our attempt to convert **9a** to **11**, a possible precursor to tetrazolobenzodiazepine **5a**, was not successful. Treatment of **9a** with sodium azide, ammonium chloride and lithium chloride (catalytic amount) in dimethylformamide (DMF) according to literature procedures (4,6,7) led only to recovered **9a**.

Amide **8a** was prepared by treating **10** with ethyl bromoacetate and triethylamine in methylene chloride. Since the attempted conversion of **9a** to **11** was unsuccessful, we did not pursue the preparation of **2a** from **8a**.

At this point we attempted to introduce the bridging unit into tetrazoles of general structure **1** in stepwise fashion. Accordingly, we treated **1a** and **1d** with sodium hydride and ethyl bromoacetate in dimethylformamide. It is known that alkylation of 5-substituted tetrazoles produces a mixture of 1- and 2-alkylated products (8), although the 2-alkyl derivatives are generally the major products (7,9,10). Hayao (11) has disclosed alkylation procedures for the preparation of 2-substituted-5-aryltetrazoles, one of which involves treating a 5-aryltetrazole with ethyl chloroacetate and sodium ethoxide in ethanol (12). Thus, the literature indicated that our alkylations had proceeded to yield the 2-alkyl derivatives **13a** and **13b** rather than the 1-alkyl derivatives **12a** and **12b**, which were the desired isomers for the stepwise syntheses of **2a** and **2d**, respectively.

Chemical observations also lent support to structures **13a** and **13b** as the correct assignments for our alkylated products. Treatment of the alkylated product derived from **2a** (**13a**) with polyphosphoric acid (PPA) at 100° for 60 hours led only to recovered **13a**. Had the alkylated product indeed been **12a**, one might have expected the formation of tricyclic compound **3a** from this reaction. Also, treatment of **13a** with sodium hydride in dimethyl sulfoxide at room temperature led to a small amount of new product which was observed by tlc only after an extended period of time (18 hours). We assigned to this product, which was isolated by chromatography, the sixteen-membered ring structure **14**. Infrared and nmr spectral data were consistent with structure **14**, and a mass spectrum displayed a molecular ion at m/e 402. See

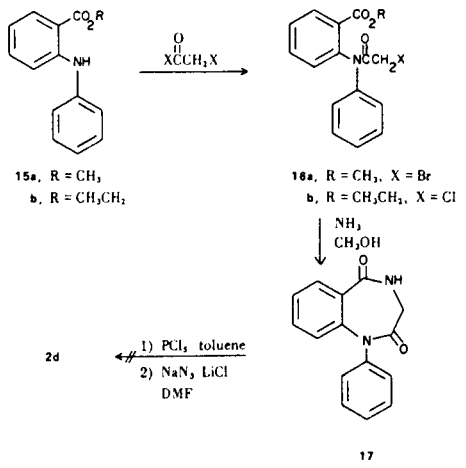
Scheme III



Scheme III.

Another approach to the alternate preparation of a tetrazolobenzodiazepine of general structure **2** involved the attempted inclusion of the fused tetrazolo ring to a preformed benzodiazepine. For this approach we chose to synthesize 3,4-dihydro-1-phenyl-1*H*-(1,4)benzodiazepin-2,5-dione (**17**) as the nucleus for the attempted tetrazolofusion reaction. Using the general procedure of Iacobelli, Uskokovic and Wenner (14) we prepared **17** (Scheme IV) from methyl *N*-phenylanthranilate (**15a**). These authors acylated **15a** with bromoacetyl bromide in ether and pyridine. They did not characterize the resulting product, methyl 2-[(bromoacetyl)phenylamino]benzoate (**16a**), which was isolated as a syrup and used in the next reac-

Scheme IV



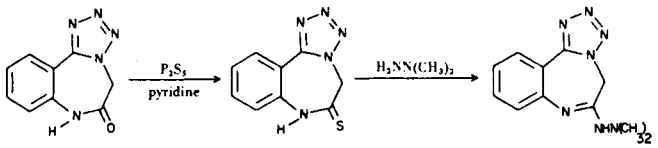
tion. By performing the acylation in toluene (15) we were able to produce **16a** as a crystalline solid. Treatment of **16a** with methanolic ammonia produced benzodiazepinedione **17**. We also prepared ethyl 2-[(chloroacetyl)phenylamino]benzoate (**16b**) from ester **15b**, but were unable to

cyclize it to **17** under the same conditions.

The conversion of lactams to tetrazole-fused systems directly, by treating first with phosphorous pentachloride in toluene and then with lithium azide in dimethylformamide, has recently been reported by Crawley and Safir (16). This method, however, when applied to **17** did not yield **2d**. The product mixture which we obtained was separated by chromatography into two unidentified components whose nmr spectra did not indicate the presence of methylene groups.

Since our attempts to prepare the tetrazolobenzodiazepines in Scheme I by alternate methods were not successful, we turned to derivatization in order to chemically confirm our assigned structures. Accordingly, we chose compound **2a** to represent the series and determined to functionalize the secondary amide. Scheme V shows the transformation which confirmed structural assignment **2a** and necessarily excluded structure **5a**. Treatment of **2a** with phosphorous pentasulfide in pyridine (17) yielded 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)thione (**18**). Thione **18** was then treated with 1,1-dimethylhydrazine to yield, after purification by chromatography, 6-(2,2-dimethylhydrazino)-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine (**19**). We feel that the structural assignments for tetrazolobenzodiazepines **2b-d** logically follow from the structure proof of **2a**.

Scheme V



2a **18** **19**

The reaction of 5-(*o*-aminophenyl)tetrazoles with bromoacetyl bromide provides an entry to 5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6-ones. The uniqueness of this method for preparing the novel tricyclic system is evidenced by our unsuccessful attempts to generate these compounds by alternate routes.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727 Spectrophotometer, nmr spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers, and mass spectra with a Finnigan gc/ms Model 3000D (electron impact and chemical ionization) at 70 eV. Combustion analyses for C, H, and N were performed by Dow Analytical Laboratories.

Materials.

5-(2-Aminophenyl)tetrazole (**1a**) [lit. (4) m.p. 143-144°], 5-(2-amino-4-methoxyphenyl)tetrazole (**1b**), m.p. 171-175° dec. and 5-(2-amino-4-trifluoromethylphenyl)tetrazole (**1c**), m.p. 207-209° dec. were prepared from the corresponding benzonitriles with sodium azide, ammonium chloride and lithium chloride in dimethylformamide (4,6,7). 5-(2-Phenylamino)tetrazole (**1d**), m.p. 212-213° [lit. (18) m.p. 210-211.5°] was prepared in five steps from *N*-phenylanthranilic acid using the procedure of Juby, Hudyma and Brown (18). Methyl *N*-phenylanthranilate (**15a**), b.p. 140° (0.10 mm), m.p. 53-56° [lit. (19a) m.p. 57-58°; lit. (19b) m.p. 58-59°] and ethyl *N*-phenylanthranilate (**15b**), b.p. 162° (2.5 mm) [lit. (20) b.p. 184-187° (6.0 mm)] were prepared from *N*-phenylanthranilic acid using standard esterification procedures.

5*H*-Tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)one (**2a**).

To a solution of 4.84 g. (30.0 mmoles) of **1a** and 6.58 g. (65.0 mmoles) of triethylamine in 40 ml. of methylene chloride was added 6.06 g. (30.0 mmoles) of bromoacetyl bromide (Aldrich). The addition was exothermic. After 3 days of stirring, the solution was washed with water, saturated sodium bicarbonate solution and again with water, dried (sodium sulfate) and concentrated to leave 1.76 g. (29%) of **2a** as a brown solid; m.p. 236-238° dec. (pale yellow needles from methylene chloride); ir (Nujol): 3220 and 3150 (NH), 1680 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 10.82 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.23-7.00 (m, 4H, aromatic), 5.28 (s, 2H, CH_2); mass spectrum (70 eV): m/e 201 (molecular ion).

Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.70; H, 3.61; N, 34.43.

9-Methoxy-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)one (**2b**).

To a solution of 9.56 g. (50.0 mmoles) of **1b** in 50 ml. of dimethoxyethane was added 7.60 g. (55.0 mmoles) of granular potassium carbonate. To this mixture, over a 5-minute period, was added 11.1 g. (55.0 mmoles) of bromoacetyl bromide. After 8 hours the mixture was filtered and the filtrate was concentrated to leave 4.92 g. of brown solid, whose tlc (silica gel, 9:1::chloroform:methanol) indicated one major product. The 4.92 g. of mateiral, which could not be purified by attempted recrystallization from a variety of solvents, was applied with a minimum quantity of dimethoxyethane to a 250-g. column of Silica Gel 60 (70-230 mesh, EM Reagents) and eluted with chloroform containing 2-5% (gradually increasing) quantities of methanol. Combination and concentration of the product-containing fractions yielded 2.32 g. (20%) of **2b**, m.p. 239-241° (clear rods from dimethoxyethane); ir (Nujol): 3240 and 3175 (NH), 1690 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 10.90 (broad s, 1H, NH), 7.88 (d, J = 8 Hz, 1H, H at 11-position), 7.07-6.67 (m, 2H, protons at 8- and 10-positions), 5.25 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3); mass spectrum (70 eV, chemical ionization, methane): m/e 232 (M^+ +1), 260 (M^+ + 29), 282 (M^+ + 41).

Anal. Calcd. for $C_{10}H_9N_5O_2$: C, 51.94; H, 3.92; N, 30.29. Found: C, 51.90; H, 4.18; N, 30.35.

9-(Trifluoromethyl)-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)-one (**2c**).

To a solution of 6.88 g. (30.0 mmoles) of **1c** in 100 ml. of dimethoxyethane was added 4.56 g. (33.0 mmoles) of granular potassium carbonate. To this mixture was added 6.66 g. (33.0 mmoles) of bromoacetyl bromide (exothermic addition). After 15 hours, tlc (silica gel, 9:1::chloroform:methanol) indicated that **1c** was substantially gone. The mixture was filtered and the precipitate was washed with water and air-dried to leave 2.00 g. (25%) of **2c** as a white solid, m.p. 266-277° dec. (dimethylformamide-methanol); ir (Nujol): 3280 (NH), 1665 (C=O) cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): δ 10.67 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.48 (d, J = 8 Hz, 1H, H at 11-position), 8.00 (s, 1H, H at 8-position), 7.86 (d, J = 8 Hz, 1H, H at 10-position), 5.83 (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_6F_3N_5O$: C, 44.62; H, 2.25; N, 26.02. Found: C, 44.60; H, 2.37; N, 26.11.

7-Phenyl-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)one (**2d**).

To a solution of 2.36 g. (10.0 mmoles) of **1d** and 2.20 g. (21.8 mmoles) of triethylamine in 40 ml. of methylene chloride was added, dropwise, 2.02 g. (10.0 mmoles) of bromoacetyl bromide (exothermic addition). After 2 days, the dark reaction mixture was washed with sodium carbonate solution, water, dried (sodium sulfate) and concentrated to leave a thick oil. The oil was crystallized from methanol-ether to yield 1.90 g. (68%) of **2d**, m.p. 176-179°; ir (Nujol): 1680 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.18-8.01 (m, 1H, aromatic), 7.60-6.97 (m, 8H, aromatic), 5.21 (s, 2H, CH_2); mass spectrum (70 eV, chemical ionization, methane): m/e 278 ($M^+ + 1$), 306 ($M^+ + 29$), 318 ($M^+ + 41$).

Anal. Calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26. Found: C, 64.70; H, 4.19; N, 25.20.

Preparation of **2a**·HCl and **2e**.

A 0.160-g. (0.795 mmole) quantity of **2a** was dissolved in 5 ml. of concentrated hydrochloric acid and stirred at room temperature for 4 hours. The solution was concentrated and the resulting white solid was slurried with acetone and collected to yield **2a**·HCl, m.p. 238-240°; ir (Nujol): 3250-2300 with NH spike at 3200, 1735 (broad C=O) cm^{-1}; nmr (deuterium oxide containing sodium 2,2-dimethyl-2-silapentane-5-sulfonate): δ 7.92-7.56 (m, 6H, aromatic), 5.52 (s, 2H, CH_2).

The nmr solution, upon standing, deposited **2e** as white needles, m.p. 238-239°; ir (Nujol): 2340 (ND), 1670 (C=O) cm^{-1}; mass spectrum (70 eV): m/e 202 (molecular ion). Recrystallization of **2a**·HCl from ethanol produced **2a**.

2-Bromo-*N*-(2-cyanophenyl)acetamide (**8a**).

To a solution of 23.6 g. (20.0 mmoles) of anthranilonitrile (Aldrich) and 20.2 g. (20.0 mmoles) of triethylamine in 40 ml. of methylene chloride was added 40.4 g. (20.0 mmoles) of bromoacetyl bromide, over a 20-minute period with icebath cooling. A voluminous precipitate was present. Water was added and the two clear phases were separated. The organic phase was dried (sodium sulfate) and concentrated to leave 44.6 g. (94%) of crude **8a**. Purification of this crude solid was best accomplished by extraction with hot benzene, followed by concentration of the extract and re-extraction with hot hexane. A tan crystalline solid could then be recovered by filtration. In this fashion was obtained 11.4 g. (24%) of **8a**, m.p. 108-113°, m.p. 119-120° (methylene chloride-hexane); ir (Nujol): 3330 (NH), 2240 (CN), 1700 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.77 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.44-8.23 (m, 1, aromatic), 7.78-7.40 (m, 2H, aromatic), 7.38-7.00 (m, 1H, aromatic), 4.03 (s, 2H, CH_2).

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; N, 11.72. Found: C, 45.00; H, 3.06; N, 11.82.

N-(2-Cyanophenyl)glycine (**9a**).

A mixture of 11.8 g. (10.0 mmoles) of anthranilonitrile, 4.72 g. (50.0 mmoles) of chloroacetic acid (Eastman) and 150 ml. of water was heated to reflux. Dimethoxyethane (50 ml.) was added until solution resulted. After 5 days at reflux, tlc (silica gel, 9:1::chloroform:methanol) on an ethyl acetate extract of an aliquot indicated a mixture of anthranilonitrile and a more polar material. The solution was cooled and the resulting mixture was extracted with methylene chloride. The organic extract was then extracted with 10% sodium hydroxide, and the aqueous layer was washed with methylene chloride. Acidification of the aqueous phase produced a tan solid which was collected and air-dried to yield 4.10 g. (47%) of **9a**, m.p. 157-161°, m.p. 162-164° (yellow needles from water); ir (Nujol): 3415 (NH), 3400-2300 (OH), 2210 (CN), 1720 (C=O) cm^{-1}; nmr (deuteriochloroform plus a small volume of DMSO-d_6): δ 9.40 (broad s, 1H, OH, deuterium oxide-exchangeable), 7.54-7.14 (m, 2H, aromatic), 6.84-6.40 (m, 2H, aromatic), 5.20 (very broad s, 1H, NH, deuterium oxide-exchangeable), 4.91 (s, 2H, CH_2).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.50; H, 4.69; N, 15.80.

5-(2-Aminophenyl)-2*H*-tetrazolo-2-acetic Acid Ethyl Ester (**13a**).

To a solution of 4.84 g. (30.0 mmoles) of **2a** and 7.60 g. (75.1 mmoles) of triethylamine in 40 ml. of methylene chloride was added 6.06 g. (30.0 mmoles) of ethyl bromoacetate (Aldrich). After 60 hours the reaction mixture was washed with sodium carbonate solution and water. The organic layer was dried (sodium sulfate) and concentrated to leave 3.40 g. (46%) of crude **13a**, m.p. 125° (ethanol); ir (Nujol): 3460 and 3340 (NH_2), 1740 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.30-8.10 (m, 1H, aromatic), 7.51-7.15 (m, 1H, aromatic), 7.04-6.71 (m, 2H, aromatic), 5.42 (s, 2H, NCH_2), 5.24 (broad s, 2H, NH_2), 4.38 (q, J = 7 Hz, 2H, OCH_2), 1.27 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.33. Found: C, 53.70; H, 5.47; N, 28.11.

5-[2-(Phenylamino)phenyl]-2*H*-tetrazole-2-acetic Acid Ethyl Ester (**13b**).

To a solution of 2.37 g. (10.0 mmoles) of **2d** and 1.20 g. (11.9 mmoles) of triethylamine in 40 ml. of methylene chloride was added 1.67 g. (10.0 mmoles) of ethyl bromoacetate. After 48 hours the reaction mixture was washed with sodium carbonate solution and water. The organic layer was dried (sodium sulfate) and concentrated to yield a thick oil, which was crystallized from methanol-ether to yield 2.06 g. (64%) of **13b**, m.p. 73-75°; ir (Nujol): 3330 (NH), 1745 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.83 (broad s, 1H, NH, deuterium oxide-exchangeable), 8.27-8.04 (m, 1H, aromatic), 7.48-6.54 (m, 8H, aromatic), 5.38 (s, 2H, NCH_2), 4.22 (q, J = 7 Hz, 2H, OCH_2), 1.25 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 63.40; H, 5.45; N, 21.93.

3,5,11,13-Tetrahydrodibenzo[*f*,*n*]ditetrazolo[5,1,2-*pa*:8,9,10-*hi*]-1,2,5,9,10,13-hexaazacyclohexadecine-4,12-dione (**14**).

To a 2.47-g. (10.0 mmoles) quantity of **13a** in 40 ml. of dry dimethyl sulfoxide, in a flame-dried reaction vessel under a nitrogen atmosphere, was added 0.300 g. (12.5 mmoles) of sodium hydride. After 15 minutes, a clear solution had resulted. The reaction was monitored by tlc (silica gel, 9:1::chloroform:methanol). After 15 hours, the reaction mixture was diluted with water, acidified with concentrated hydrochloric acid and extracted with methylene chloride. Tlc of the extract indicated **13a** (R_f = 0.8), a spot at R_f = 0.5, and a spot at the origin. The methylene chloride layer was then extracted with base and the organic layer, containing only **13a** (tlc), was discarded. The aqueous layer was acidified and extracted with methylene chloride. The methylene chloride extract, whose tlc indicated only a spot at the origin, was discarded. An insoluble material which remained in the aqueous phase was collected and applied, in a minimum volume of ethyl acetate, to a 30-g. column of Silica Gel 60 (70-230 mesh, EM Reagents) and eluted with 95:5::chloroform:methanol. The fractions containing, by tlc, the product of R_f = 0.5 were combined and concentrated to leave 0.700 g. (35%) of **14**; m.p. 237-239°; ir (Nujol): 3300 (NH), 1670 (C=O) cm^{-1}; nmr (deuteriochloroform plus a small volume of DMSO-d_6): δ 5.75 (both CH_2

groups); mass spectrum (70 eV): m/e 402 (molecular ion); mass spectrum (70 eV, chemical ionization, methane): m/e 403 ($M^+ + 1$), 431 ($M^+ + 29$).

2-[(Bromoacetyl)phenylamino]benzoic Acid Methyl Ester (**16a**).

To a solution of 48.2 g. (0.200 mole) of **15a** in 200 ml. of toluene was added 50.5 g. (0.250 mole) of bromoacetyl bromide. After a few minutes of stirring, a white precipitate (**15a**·HBr) began to form. The mixture was heated at reflux for 30 minutes, during which time a copious volume of hydrogen bromide was liberated. The solution was concentrated to a syrup which solidified upon trituration with ether to yield 69.6 g. (100%) of **16a**, m.p. 65-77°, m.p. 75.5-78° (clear prisms from hexane); ir (Nujol): 1720 (ester C=O), 1620 (amide C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.17-7.93 (m, 1H, H at 6-position), 7.84-7.04 (m, 8H, remaining aromatic), 3.87 (s, 2H, CH_2).

Anal. Calcd. for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; N, 4.02. Found: C, 55.00; H, 4.16; N, 4.17.

3,4-Dihydro-1-phenyl-1*H*-[1,4]benzodiazepine-2,5-dione (**17**).

A 40.0-g. (0.115 mole) quantity of **16a** in 1100 ml. of methanol was saturated with ammonia gas. After 4 days, the slightly cloudy solution was concentrated and the residue was slurried with ether and filtered. The precipitate was collected and recrystallized (methylene chloride-ether) to yield 15.6 g. (54%) of **17**, m.p. 222-223° [yellow plates, lit. (14) m.p. 221-224°]; ir (Nujol): 3180 (NH), 1690 (C=O), 1660 (C=O) cm^{-1}.

5*H*-Tetrazolo[1,5-*d*][1,4]benzodiazepin-6(7*H*)thione (**18**).

A solution of 0.800 g. (3.98 mmoles) of **2a** and 1.00 g. (4.44 mmoles) of phosphorous pentasulfide in 30 ml. of pyridine was heated at reflux for 3 hours. The solution was cooled, diluted with water and extracted with chloroform. The organic extracts were dried (sodium sulfate) and concentrated to leave 1.00 g. of yellow solid. An attempt to recrystallize this material from a small volume of chloroform left 480 mg. (56%) of **18** behind as an insoluble yellow solid, m.p. 193-194°; ir (Nujol): 3210 (NH), 1610 cm^{-1}; nmr (DMSO-d_6): δ 12.88 (broad s, 1H, NH), 8.30-7.17 (m, 4H, aromatic), 3.71 (s, 2H, CH_2); mass spectrum (70 eV, chemical ionization, methane): m/e 218 ($M^+ + 1$), 246 ($M^+ + 29$), 258 ($M^+ + 41$).

6-(2,2-Dimethylhydrazino)-5*H*-tetrazolo[1,5-*d*][1,4]benzodiazepine (**19**).

A 410-mg. (1.89 mmoles) quantity of **18** in 25 ml. of 1,1-dimethylhydrazine (Eastman) was heated at reflux for 2.5 hours. Concentration of the reaction solution left a purple oil which solidified upon standing. The solid was applied, in a minimum volume of chloroform, to a 100-g. column of Silica Gel 60 (70-230 mesh, EM Reagents) and eluted with chloroform. Combination and concentration of the product-containing fractions yielded 440 mg. (96%) of **19**, m.p. 94-96° (ethanol); ir (Nujol): 3240 (NH), 1630 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 7.97-7.77 (m, 1H, aromatic), 7.48-6.64 (m, 4H, aromatic and NH), 4.94 (s, 2H, CH_2), 2.24 [s, 6H, $N(CH_3)_2$]; mass spectrum (70 eV, chemical ionization, methane): m/e 226 ($M^+ + 1$), 254 ($M^+ + 29$), 266 ($M^+ + 41$).

Anal. Calcd. for $C_{11}H_{13}N_7$: C, 54.30; H, 5.39; N, 40.31. Found: C, 54.30; H, 5.45; N, 40.03.

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REFERENCES AND NOTES

(1) Due to the large number of literature references to these three general compound groups, and since a comprehensive review article on these "second generation benzodiazepines" has not yet appeared, the reader is referred to the general literature for information on these compound classes.

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