Synthesis of Some 2-Amino-4-phenyl-3*H*-1,5-benzodiazepines by Reaction of Aromatic Diamines and Acetylenic Imidates

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The reaction of several aromatic 1,2-diamines with conjugated acetylenic imidate salts is described. The use of hexamethylphosphoric triamide (HMPA) as the solvent allows preparation of 2-amino-4-phenyl-3*H*-1,5--benzodiazepines in a one-step reaction.

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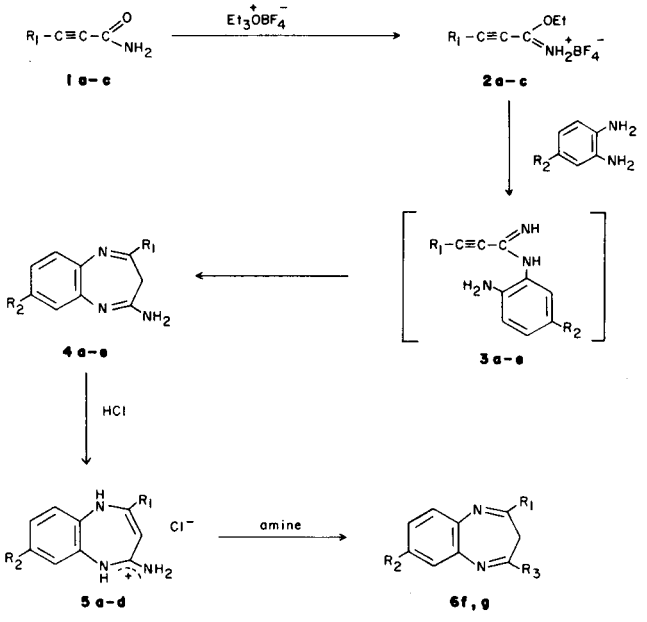
The 2-amino-4-phenyl-3*H*-1,5-benzodiazepines are of interest as analogues of the 1,4-benzodiazepine anti-anxiety agents (Valium® , Librium®), as well as certain neuroleptic agents (1,2). A number of 1,5-benzodiazepines are under clinical investigation for a variety of therapeutic applications (3).

Many 1,5-benzodiazepines have been prepared by condensation of an aromatic 1,2-diamine and β-dicarbonyl compounds, α,β-olefinic carbonyl compounds (4-6), ketoketeneacetals (7), ketoketenethioacetals (8), ketodithioacetic acids (1,9), or dichloromethyleniminium salts (10). Less common is the reaction of a 1,2-diamine and an ethynylcarbonyl compound (11-13).

We previously reported (14) the synthesis of the 2-ami-

Scheme I



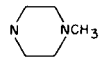
Compound Substituent	a	b	c	d	e	f	g
R_1	2-ClC_6H_4	4-ClC_6H_4	C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5
R_2	H	H	H	Cl	NO_2	H	H
R_3	NH_2	NH_2	NH_2	NH_2	NH_2		

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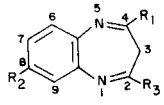
Table I

2-Amino-4-phenyl-3*H*-1,5-benzodiazepines



Compound (a)	Formula	% Yield (crude)	Anal. Calcd. (Found) % C	H	N
			66.79	4.48	15.58
4a	$C_{15}H_{12}ClN_3$	51 (b)	(66.87	4.99	15.64)
			66.79	4.48	15.58
4b	$C_{15}H_{12}ClN_3$	41 (c)	(66.53	4.42	15.45)
			64.27	4.32	19.99
4e	$C_{15}H_{12}N_4O_2$	36 (c)	(64.20	4.57	19.80)
			58.84	4.28	13.72
5b	$C_{15}H_{12}ClN_3 \cdot HCl$	41 (c)	(58.68	4.49	13.45)
			66.30	5.19	15.46
5c	$C_{15}H_{13}N_3 \cdot HCl$	56 (c)	(66.15	5.20	15.35)
			58.84	4.28	13.72
5d	$C_{15}H_{12}ClN_3 \cdot HCl$	34 (c)	(58.73	4.31	13.61)
			79.17	6.98	13.85
6f	$C_{20}H_{21}N_3$	49	(79.01	7.04	13.81)
			75.44	6.96	17.60
6g	$C_{20}H_{22}N_4$	68	(75.26	7.21	17.55)

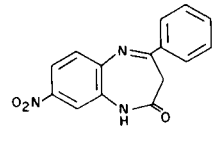
(a) Substituents are given in Scheme I. (b) Prepared from amidine **3a**. See reference (14). (c) Yield is that of the free base product calculated with the inclusion of one equivalent of HMPA.

no-1,5-benzodiazepine **4a** (Scheme I) by acid-catalyzed cyclization in ethanol of the stable acetylenic amidine **3a**. The amidine resulted from condensation of 2-aminoaniline (*o*-phenylenediamine) and the free imidate base derived from acetylenic imidate salt **2a**. We have now found that additional compounds analogous to **4a** can be prepared in one step from the imidates **2a-c** without prior neutralization of the imidate salts or isolation of the intermediate amidines **3a-e**. The key to this process appears to be the use of hexamethylphosphoric triamide ("HMPA") as the reaction solvent (17).

The acetylenic amides **1a-c** were prepared by literature (14-16) procedures and were converted to the imidate salts **2a-c** by treatment with triethyloxonium tetrafluoroborate ("Meerwein's Reagent") in methylene chloride. When the salts **2b,c** were combined with an aromatic 1,2-diamine in HMPA and heated on the steam bath, benzodiazepines **4b-e** were obtained.

In most instances, the crude product was obtained as a 1:1 complex with HMPA. The ability of HMPA to catalyze nucleophilic addition reactions, as well as form stable addition complexes with amines is well known (18). The HMPA was removed by recrystallization and high-vacuum drying of the crystals or by converstion of the free base benzodiazepines to the hydrochloride salts (*e.g.*, **5b-d**). Hydrochloride salt **5c** was transaminated by heating with excess piperidine or 1-methylpiperazine to form benzodiazepines **6f,g**, two compounds prepared in the literature (1,19) by displacement of a benzodiazepine methylthioimino ether. The benzodiazepines obtained are listed in Table I.

The assignment of the R_2 substituent of **4e** and **5d** (Table I) to the #8 position in the aromatic ring (rather than the #7 position) presupposes the probable formation of amidines **3d** and **3e** as transient intermediates in the formation of **4e** and **5d**. In addition, a comparison of the ultraviolet spectra (20) of the known 1,5-benzodiazepin-2-ones **7** and **8** as model compounds, indicates the spectrum of nitrobenzodiazepine **4e** is clearly quite similar to that of



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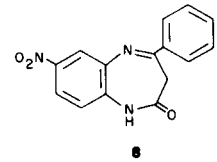

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7, while substantially dissimilar to that of the alternate isomer **8**.

We have described the preparation of several 2-amino-1,5-benzodiazepines by a simple, one-step reaction of aromatic 1,2-diamines with acetylenic imidate salts.

EXPERIMENTAL

Melting points were determined in a Mel-Temp capillary apparatus and are uncorrected. Nmr spectra were recorded on a Varian EM-390 spectrometer at 90 MHz, or a Perkin-Elmer R-12B spectrometer at 60 MHz, with tetramethylsilane as an internal standard in both cases. Infrared spectra were recorded on a Beckman DK-I spectrophotometer or a Digilab FTS-14 pulsed Fourier-transform spectrophotometer. All uv spectra were determined in 95% ethanol on a Cary Model 118 spectrophotometer.

Ethyl 3-Phenyl-2-propynimidate Tetrafluoroborate (**2c**).

A suspension of 32.0 g (0.22 mole) of 3-phenyl-2-propynamide **1c** (15) in 450 ml of dry dichloromethane was cooled in ice and treated over 2.0 hours with a solution of 42.1 g (0.22 mole) of triethyloxonium tetrafluoroborate. The ice bath was removed, and the mixture was stirred at room temperature for 3 days. The imidate salt product **2c** was filtered, and the filtrate was condensed to 75 ml and treated with ether to precipitate additional product. After being washed several times with fresh ether, the combined crops yielded white solid of mp 117-120° (49 g, 85% yield). A sample recrystallized from dichloromethane had mp 121-123°; ir (chloroform): ν 3300, 3140 (NH), 2220 (C≡C), 1676 (C=N), 1100 (broad, BF_4) cm^{-1}; nmr (DMSO-d_6): δ 1.41 (t, 3H, J = 7.5 Hz, CH_2CH_3), 4.67 (q, 2H, J = 7.5 Hz, CH_2-CH_3), 7.25-7.87 (m, 5H, Ar*H*), 10.50 (broad s, 2H, NH_2).

Anal. Calcd. for $C_{11}H_{12}BF_4NO$: C, 50.62; H, 4.63; N, 5.37; F, 29.11. Found: C, 50.48; H, 4.61; N, 5.44; F, 29.08.

Ethyl 3-(4-Chlorophenyl)-2-propynimidate Tetrafluoroborate (**2b**).

The procedure described above for **2c** was employed in the preparation of **2b** except that after addition of triethyloxonium tetrafluoroborate solution, the reaction mixture was heated to reflux for 30 minutes (became one phase), filtered hot, and allowed to cool slowly. From 15.0 g (0.083 mole) of 3-(4-chlorophenyl-2-propynamide **1b** (15,16) there was obtained 17.2 g (70% yield) of imidate salt **2b**, white solid of mp 139-143°; ir (Nujol): ν 3320, 3180 (NH), 2230 (C≡C), 1690 (C=N), 1050 (broad, BF_4) cm^{-1}; nmr (DMSO-d_6): δ 1.47 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.70 (q, 2H, J = 7.0 Hz, CH_2CH_3), 7.20-8.20 (m, 4H, Ar*H*), 11.12 (broad s, 2H, NH_2). This material was used without further purification for the preparation of benzodiazepine **4b**.

4-(4-Chlorophenyl)-3*H*-1,5-benzodiazepin-2-amine (**4b**).

A mixture of 5.0 g (0.017 mole) of the imidate salt **2b** and 1.8 g (0.017 mole) of 1,2-benzenediamine (*o*-phenylenediamine) in 50 ml of hexamethylphosphoric triamide (HMPA) was stirred and heated on the steam bath for 3 hours. The cooled reaction mixture was added to 300 ml of 1% aqueous sodium hydroxide cooled in ice. After stirring for 30 minutes, the semi-solid product was extracted with chloroform (3 × 125 ml). The combined organic layers were back-washed with water (2 × 150 ml), dried (sodium sulfate), and evaporated under reduced pressure. The residue was treated with cold hexane (~350 ml) to form a yellow solid **4b**, which was filtered and washed several times with fresh cold hexane. Recrystallization of the crude product from benzene/hexane formed yellow cubes of mp 192-196° (3.1 g, 41% yield as •1 HMPA). The ir and nmr spectra of the recrystallized material indicated the incorporation of one equivalent of HMPA in the crystal. A second recrystallization of this material from ethanol/water followed by high-vacuum drying at 78° gave an analytical sample of **4b**, yellow solid of mp 198-200°, containing no solvent of crystallization; ir (Nujol): ν 3500, 3320 (NH), 1653 (C=N), 1590, 1306, 1002, 754 cm^{-1}; nmr (DMSO-d_6): δ 3.25 (s, 2H, CH_2), 6.95 (broad s, 2H, NH_2), 7.05-8.33 (m, 7H, Ar*H*); uv: λ max nm (ϵ) 214 (32,880), 254 (33,480), 345 (6920).

2-Amino-4-(4-chlorophenyl)-5*H*-1,5-benzodiazepinium Chloride (**5b**).

The hydrochloride **5b** was obtained by dissolving a sample of the crude HMPA-complex of **4b** in a minumum of chloroform, followed by ice cooling and the addition of excess gaseous hydrogen chloride to the solution. A volume of ether twice that of the original chloroform solution was added to precipitate the product. The crude hydrochloride was filtered, washed with fresh ether, and recrystallized twice from ethanol, to yield red solid **5b**, mp 305° dec, containing no incorporated solvent; ir (Nujol): ν 3238, 3088 (NH), 1642 (C=N), 1582, 1548, 1208, 1075, 758 cm^{-1}; nmr (DMSO-d_6): δ 3.82 (s, ~0.2-0.3 H, CH_2 tautomer), 4.80 (s, ~0.8 H, CH = tautomer), 6.68-7.71 (m, 8H, Ar*H*), 8.38 (broad s, 1H, N*H*), 9.06 (broad s, 2H, NH_2), 10.53 (broad s, 1H, N*H*); uv: λ max nm (ϵ) 206 (31,500), 264 (29,000), 335 (3500).

The procedures described above for **4b** and **5b** were also employed to prepare **4e**, **5c** and **5d**.

2-Amino-4-phenyl-5*H*-1,5-benzodiazepinium Chloride (**5c**).

There was obtained 54.7 g (56% yield) of the HMPA-complex of **4c** from reaction of 61.2 g (0.24 mole) of imidate **2c** and 25.8 g (0.24 mole) of 1,2-benzenediamine in 125 ml of HMPA. Conversion of **4c** to the hydrochloride **5c** yielded a red solid of mp 285° dec; ir (Nujol): ν 3270, 3120 (NH), 1662 (C=N), 1585, 1555 (broad), 1228, 758 cm^{-1} cm^{-1}; nmr (DMSO-d_6): δ 3.87 (s, ~0.2-0.3H, CH_2 tautomer) 4.84 (s, ~0.8-0.9H, CH = tautomer), 6.65-7.75 (m, 9H, Ar*H*), 8.39 (broad s, 1H, N*H*), 9.07 (broad s, 2H, NH_2), 10.58 (broad s, 1H, N*H*); uv: λ max nm (ϵ) 204 (29,800), 264 (26,900), 335 (2500).

2-Amino-8-chloro-4-phenyl-5*H*-1,5-benzodiazepinium Chloride (**5d**).

Reaction of 16.7 g (0.064 mole) of imidate **2c** and 9.2 g (0.064 mole) of 4-chloro-1,2-benzenediamine in 30 ml of HMPA yielded 9.7 g (34% yield) of (**4d**) as the HMPA-complex. Conversion of **4d** to the hydrochloride **5d** gave an orange solid of mp 295° dec; ir (Nujol): ν 3390, 3175 (NH), 1662 (C=N), 1600, 1558 (broad), 1232, 1108, 762 cm^{-1}; nmr (DMSO-d_6): δ 3.97 (s, ~0.2-0.3H, CH_2 tautomer), 4.92 (s, ~0.8-0.9H, CH, CH = tautomer), 6.80-7.92 (m, 8H, Ar*H*), 8.53 (broad s, 1H, N*H*), 9.28 (broad s, 2H, NH_2), 10.92 (broad s, 1H, N*H*); uv: λ max nm (ϵ) 216 (25,000), 264 (29,400), 240 (3250).

8-Nitro-4-pheny-3*H*-1,5-benzodiazepin-2-amine (**4e**).

The procedure described in the prepartion of **4b** was employed to prepare 3.1 g (36% yield) of crude nitro-benzodiazepine **4e** from 8.0 g (0.03 mole) of imidate **2c** and 4.7 g (0.03 mole) of 4-nitro-1,2-benzenediamine in 20 ml of HMPA. When the initial reaction mixture was added to 400 ml of 1% aqueous sodium hydroxide and 125 ml of chloroform, a yellow precipitate formed. Filtration and recrystallization of a sample from acetone yielded **4e** as yellow needles of mp 280° dec, containing no incorporated solvent after high-vacuum drying at 78°; ir (Nujol): ν 3460, 3350 (NH), 1673 (C=N), 1558, 1508, 1330 (broad, NO_2), 1077, 760 cm^{-1}; nmr (DMSO-d_6): δ 3.35 (s, 2H, CH_2), 7.60 (broad s, 2H, NH_2), 7.18-8.58 (m, 8H, Ar*H*); uv: λ max nm (ϵ) 206 (30,320), 252 (17,720), 298 (16,200), 350 (15,280).

2-Phenyl-4-(1-piperidinyl)-3*H*-1,5-benzodiazepine (**6f**).

A suspension of 8.2 g (0.03 mole) of the hydrochloride **5c** in 80 ml of absolute ethanol was cooled in ice and treated dropwise over 30 minutes with a solution of 12.9 g (15.0 ml, 0.15 mole) of piperidine in 30 ml of ethanol. The ice bath was removed, and the mixture was stirred at reflux under nitrogen for 67 hours. The cooled reaction mixture was filtered and evaporated under vacuum.. The residue was partitioned between 300 ml of 0.3*N* sodium hydroxide solution and 100 ml of chloroform. The aqueous layer was separated and washed with fresh chloroform (2 × 100 ml). The combined organic layers were back-washed with water (1 × 150 ml), dried (sodium sulfate) and evaporated to an oil. Trituration with cold hexane yielded a yellow solid (4.5 g, 49% yeild). Recrystallization of a sample from ethanol/water yielded **6f** as yellow needles of mp 110-113°; literature (1,19) mp 115-118°, 119-121°; ir (Nujol): ν 1595, 1570 (broad), 1428, 1202, 959, 762 cm^{-1}; nmr (deuteriochloroform): δ 1.12-1.71 (m, 6H, piperidine CH_2), 3.22-3.82 (m, 6H, piperidine CH_2 and diazepine CH_2), 6.87-8.28 (m, 9H, Ar*H*); uv: λ max nm (ϵ) 210 (24,880), 261 (33,120), 350 (4440).

2-(4-Methyl-1-piperazinyl)-4-phenyl-3*H*-1,5-benzodiazepine (**6g**).

The procedure described in the preparation of **6f** was employed to prepare 4.0 g (68% yield) of crude piperazinylbenzodiazepine **6g** from

5.0 g (0.018 mole) of hydrochloride **5c** and 4.5 g (5.0 ml, 0.045 mole) of 1-methylpiperazine in 75 ml of absolute ethanol. Recrystallization of a sample from ethanol/ether yielded **6g** as yellow crystals of mp 151-154°, lit (1,19) mp 155-157°, 158°; ir (Nujol): ν 1601, 1573 (broad), 1412, 1210, 975, 782 cm^{-1}; nmr (deuteriochloroform): δ 2.08-2.54 (m, 7H, piperazinyl CH_2 and CH_3) 3.38 (s, 2H, diazepine CH_2), 3.48-3.86 (t, 4H, J = 5.0 Hz, piperazinyl CH_2), 6.91-8.18 (m, 9H, Ar*H*).

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(17) Caution: Hexamethylphosphoric triamide is a suspected carcinogen, and should be handled with appropriate precautions.

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