

The Chemistry of Aryltetramines. I. Benzobisdiazepines from  
1,2,4,5-Tetraminobenzene and 3,3',4,4'-Tetraminobiphenyl

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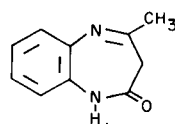
The condensation of aniline and ethyl acetoacetate (1) was reported to yield ethyl 3-phenylamino-2-butanoate. Under similar conditions the reaction of *o*-diaminobenzene and ethyl acetoacetate (2) gave ethyl 3-(2-aminophenylamino)-2-butanoate which was successfully ring closed to a benzodiazepine by Sexton (3) and more recently by Davoll (4).

We now wish to report our findings for the condensation of 1,2,4,5-tetraminobenzene with ethyl acetoacetate and acetylacetone under similar conditions. During our preliminary studies of this tetramine, it was necessary to re-examine the earlier work with *o*-diaminobenzene. Our findings are in agreement with those of Rossi *et al.*, (5) which indicate that the earlier assignment for the benzodiazepine from *o*-diaminobenzene was incorrect and that the compound is best represented as the  $\beta,\gamma$ -unsaturated amide (I) rather than the previously proposed  $\alpha,\beta$ -unsaturated system. This assignment is based on the analysis of its n.m.r. spectrum which shows the presence of a methylene singlet at 3.1 p.p.m. but is devoid of any vinyl absorption.

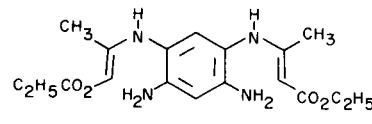
Condensation of 1,2,4,5-tetraminobenzene with excess ethyl acetoacetate in aqueous pyridine gave the corresponding 4,6-bis(1-carbethoxy-2-propenylamino)-1,3-diaminobenzene (II). Assignment of this structure was based upon the presence of two nonequivalent aromatic protons in the n.m.r. spectrum of (II). This is in good agreement with the suggested *meta* structure but is incompatible with the *para* isomer where both of the aromatic protons should be equivalent.

Treatment of (II) with two equivalents of sodium ethoxide from sodium metal in absolute ethanol (4) resulted in ring closure to give the corresponding 2,10-dimethyl-5,7-dihydrobenzobis[1,2-*b*:4,5-*b'*][1,5]diazepin-4,8-dione (III). Assignment of the  $\beta,\gamma$ -unsaturated structure to III is supported by the presence of only methylene absorption in the n.m.r. spectrum. Acid hydrolysis of III with 10% sulfuric acid gave the 2,6-dimethylbenzobis[1,2-*d*:4,5-*d'*]imidazole (IV).

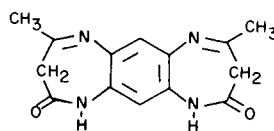
Condensation of 1,2,4,5-tetraminobenzene as well as 3,3',4,4'-tetraminobiphenyl with excess acetylacetone under acidic conditions (6) resulted in the direct formation of the corresponding 1,5-benzobisdiazepines (V) and (VI) respectively.



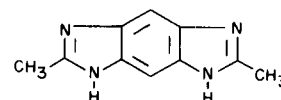
I



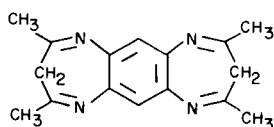
II



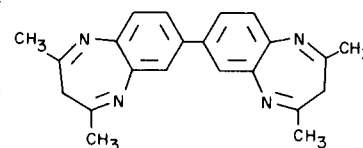
III



IV



V



VI

EXPERIMENTAL (7)

4-Methyl-1H-1,5-benzodiazepin-2-one (I) (4).

A 0.66 g. sample of ethyl-3-(2-aminophenylamino)-2-butanoate (3) was refluxed for two hours with two equivalents of sodium ethoxide from 0.069 g. of sodium metal in 3 ml. of absolute ethanol. The resulting mixture was concentrated *in vacuo* and diluted with 5 ml. of water. Neutralization with glacial acetic acid followed by filtration gave a tan solid. Recrystallization from ethanol/water gave fine needles, m.p. 145-146° (Lit. 147-148°);  $\nu$  max (potassium bromide, 3250 and 1695  $\text{cm}^{-1}$ ; n.m.r.  $\delta$  (deuteriochloroform) (8) 2.36 (s,3), 3.1 (s,2), 7.15 (m,4), 9.65 (s,1).

4,6-bis(1-Carbethoxy-2-propenylamino)-1,3-diaminobenzene (II).

A 25 g. sample of 1,2,4,5-tetraminobenzene tetrahydrochloride was dissolved in a nitrogen purged solution of 180 ml. of water and 50 ml. of pyridine and treated dropwise with stirring with 40 ml. of ethyl acetoacetate. The resulting heavy, crystalline mass was filtered and washed repeatedly with water and then with 0.05 N sodium hydroxide to yield 19.9 g. of (II), 95% yield. Recrystallization from methanol gave colorless needles, m.p. 185-190° dec.;

$\nu$  max (potassium bromide) 3420, 3320, 3250, 1670 and 1625  $\text{cm}^{-1}$ ; n.m.r.  $\delta$  (deuteriochloroform) (8) 1.25 (t,6,J=7 cps.), 1.73 (s,6), 3.74 [s,4(NH<sub>2</sub>-exchanges with deuterium oxide)], 4.11 (q,4,J=7 cps.), 4.48 (s,2), 6.06 (s each 1), 9.51 [s,2 (amine)].

*Anal.* Calcd. for C<sub>18</sub>H<sub>26</sub>N<sub>4</sub>: C, 59.65; H, 7.23; N, 15.46. Found: C, 60.12; H, 7.15; N, 15.24.

2,4,8,10-Tetramethyl-3,9-dihydro-benzobis[1,2-*b*:4,5-*b'*][1,5]-diazepine Hydrochloride (V).

A 10 g. sample of 1,2,4,5-tetraminobenzene tetrahydrochloride was dissolved in a nitrogen purged solution of 400 ml. of water and 50 ml. of pyridine and treated dropwise with 15 ml. of acetylacetone. The resulting black solid was filtered to give 5.25 g. (55%) of the hydrochloride of (V). Recrystallization from hot water gave fine, black needles m.p. > 350°;  $\nu$  max (potassium bromide), 3400-3300 Broad, 1640  $\text{cm}^{-1}$ .

Treatment of the hydrochloride of V with aqueous base gave the free base m.p. 270°;  $\nu$  max (chloroform), 3000, and 1640  $\text{cm}^{-1}$ .

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.21; H, 6.93; N, 21.00.

7,7'-bis(2,2',4,4'-Tetramethyl-3,3'-dihydro-1,5-benzodiazepinyl) (VI).

A 4.45 g. sample of 3,3'-diaminobenzidine in 20 ml. of 10% hydrochloric acid in 100 ml. of water was treated with 5 ml. of acetylacetone and stirred at room temperature for 20 minutes. Filtration of the heavy crystalline mass gave a fine, black solid characterized as the diazepine hydrochloride of (VI). Neutralization of this solid gave 9.58 g. of the diazepine free base, m.p. 185-190°.  $\nu$  max (potassium bromide), 1660  $\text{cm}^{-1}$ .

*Anal.* Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>: C, 77.16; H, 6.48; N, 16.36. Found: C, 76.99; H, 6.66; N, 16.54.

2,10-Dimethyl-5,7-dihydrobenzobis[1,2-*b*:4,5-*b'*][1,5]diazepin-4,8-dione (III).

A 40 g. sample of (II) was added in one portion to a solution of 5.36 g. of sodium in 2000 ml. of absolute ethanol and refluxed for three hours. The yellow-brown solution was concentrated *in vacuo* to approximately 800 ml. and diluted with 200 ml. of water.

The solution was neutralized with glacial acetic acid and the resulting solid filtered to give 13.9 g. (46.5%) of a cream colored solid (III). Recrystallization from ethanol gave colorless plates m.p. 255-258°;  $\nu$  max (Nujol), 3450, 3200, and 1690  $\text{cm}^{-1}$ ; n.m.r.  $\delta$  (D<sub>6</sub>MSO) (8), 2.23 (s,6), 3.05 (s,4), 6.91 (m,2), and 10.2 (s,2) (amide).

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.13; H, 5.28; N, 20.77.

2,6-Dimethylbenzobis[1,2-*d*:4,5-*d'*]imidazole (IV).

A 1.35 g. sample of (III) in 20 ml. of 2 N sulfuric acid was refluxed for one hour. The solution was cooled and made basic with aqueous potassium hydroxide to give a tan solid. Recrystallization from methanol water gave tan plates, m.p. > 300°;  $\nu$  max (Nujol), 3150 and 1595  $\text{cm}^{-1}$ .

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.36; H, 5.30; N, 30.23.

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- (7) The melting points were taken on a Mel-Temp, m.p. block and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Infracord 137.
- (8) N.m.r. spectra were recorded on a Varian model A-60 A spectrometer in either deuteriochloroform or deuterated dimethylsulfoxide using TMS as an internal standard ( $\delta=0$  p.p.m.). Interpretation of n.m.r. data: chemical shift p.p.m. (multiplicity, number of protons). s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet.

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