

Preparation of a 2-(Arylethynyl)benzimidazole and a  
2-Amino-4-aryl-3H-1,5-benzodiazepine from an  
Ethyl Arylpropiolimide Fluoroborate

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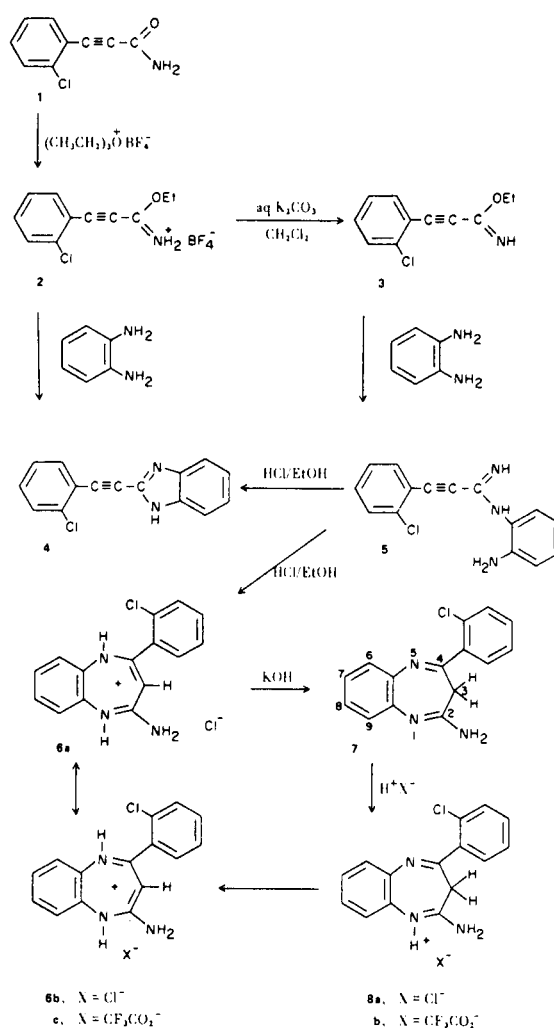
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In connection with a study of the reactions of acetylenic imidates with a variety of amines, we had occasion to examine reactions involving *o*-phenylenediamine. Starting from an ethyl arylpropiolimide fluoroborate (2) it proved to be possible to direct the course of reaction to produce either of two previously unreported types of products, a 2-(arylethynyl)benzimidazole (4) or a 2-amino-3H-1,5-benzodiazepine (7). Among the several methods for obtaining 1,5-benzodiazepine derivatives from *o*-phenylenediamine which have appeared in the literature (1,2,3,4), use of an acetylenic derivative has apparently not been included.

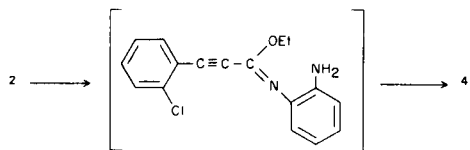
The acetylenic imidate salt, ethyl *o*-chlorophenylpropiolimide fluoroborate (2) resulted from treatment of *o*-chlorophenylpropiolamide (1) with triethyloxonium fluoroborate (Meerwein's Reagent). The free imidate base (3), although too unstable to be isolated, could be prepared in solution by reaction of the imidate salt (2) with aqueous potassium carbonate.

Reaction of 2 with *o*-phenylenediamine yielded a product corresponding to the elimination of the elements of ethanol and ammonium fluoroborate. The hydrochloride of this compound gave an elemental analysis and an infrared spectrum ( $\text{C}\equiv\text{C}$  stretch at  $2237\text{ cm}^{-1}$ ) consistent with the structure 2-(*o*-chlorophenylethynyl)benzimidazole (4). This structural assignment was also supported by the nmr spectrum of the free base, which showed only eight aromatic protons ( $\tau$  2.15-2.87) plus a single NH proton ( $\tau$  3.83-4.33, broad), and a mass spectrum having peaks at  $m/e$  values of 161 and 163 corresponding to fragmentation to an ion related to *o*-chlorophenylpropionitrile. On the other hand, the free imidate base 3 reacted to yield an *N*-substituted amidine 5. These results are in accord with the general precedent that imidate salts react with weakly basic amines to form *N*-substituted imidates while reaction of amines with free imidates often leads to amidines (5,6). An acetylenic *N*-substituted imidate can be postulated (7) as a labile intermediate in the formation of the benzimidazole 4 from 2.

CHART I

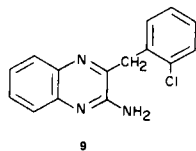


When the amidine 5 was treated with ethanolic hydrochloric acid for two hours at reflux it was converted into a red hydrochloride which afforded in 51% yield a free base isomeric with 5. A trace of the hydrochloride



of the benzimidazole **4** was formed simultaneously. The structure 2-amino-4-*o*-chlorophenyl-3*H*-1,5-benzodiazepine (**7**) has been assigned to the new isomer as the only formulation consistent with its infrared, ultraviolet and nmr spectra and with the nmr spectrum it yields following protonation with trifluoroacetic acid. The formation of **7** as a result of the action of the acid upon **5** is easily rationalized; it would be the product of an internal conjugate addition of the remaining primary amino function to the  $\beta$ -position of the acetylenic bond. Protonation of the imino nitrogen of **5** would be expected to enhance the susceptibility of the  $\beta$ -acetylenic carbon to nucleophilic attack.

The infrared spectrum of **7** failed to show the acetylenic stretching frequency observed for the precursor **5**. The ultraviolet spectrum of (**7**) ( $\lambda$  max (ethanol) 245 nm ( $\log \epsilon$  4.40); 320 nm (broad,  $\log \epsilon$  3.59)) was not consistent with the ultraviolet spectrum expected for the alternative possible structure **9**, since **9** should have a spectrum closely resembling that of 2-aminoquinoxaline



( $\lambda$  max (ethanol) 240 nm ( $\log \epsilon$  4.33); 352 nm ( $\log \epsilon$  3.80)) (**8**). (It is not apparent why a substance of structure **9** would not likewise have a long wavelength maximum near 350 nm.) The nmr spectrum of **7** in deuteriochloroform showed a sharp two-proton singlet at  $\tau$  6.73 assigned to the heterocyclic methylene group at position-3, a broad two-proton singlet for  $\text{NH}_2$  at  $\tau$  4.86 (removable by exchange with deuterium oxide) and an aromatic multiplet centered at  $\tau$  2.70. Addition of trifluoroacetic acid to the sample resulted in the disappearance of the peak at  $\tau$  6.73 (as well as that at  $\tau$  4.86), apparently as a result of transformation of the assumed initially formed salt **8b** to the tautomer represented by **6c**, in which the carbon at position-3 loses a proton and becomes  $\text{sp}^2$  hybridized as a part of the electronically delocalized cation represented in **6a**  $\leftrightarrow$  **6b** or **6c**. The nmr signal from the remaining proton at position-3 is apparently down-field far enough to be obscured by the complex aromatic multiplet, in agreement with a similar observation by Finar, Barry and Mooney (**9a**) regarding the

effect of trifluoroacetic acid on the tautomeric equilibrium and the nmr spectrum of 2,4-dimethyl-1,5-benzodiazepine. An nmr spectrum of the hydrochloride **6a** taken in dimethylsulfoxide- $\text{d}_6$  showed a one-proton singlet at  $\tau$  5.36, which may have arisen from a single hydrogen on a trigonal carbon at position 3, but the up-field position of the signal relative to that which must be assumed for the same proton in the spectrum taken in deuteriochloroform-trifluoroacetic acid suggests an important difference in the species under observation in the two instances. It is possible that deprotonation of the cation of **6a** in dimethylsulfoxide or a specific complexing of the cation with that solvent might provide an explanation.

#### EXPERIMENTAL (10)

##### *o*-Chlorophenylpropiolamide (**1**).

To a solution of 100 g. (0.555 mole) of *o*-chlorophenylpropionic acid in 1100 ml. of dry benzene was added 133 g. (80.7 ml., 1.11 moles) of thionyl chloride, and the resulting solution was stirred and refluxed for two hours in an apparatus protected from moisture. After cooling, the solvent and excess thionyl chloride were removed under reduced pressure. The residual oily yellow-brown acid chloride was then slowly and cautiously poured into 640 ml. (9.6 moles) of previously chilled concentrated ammonium hydroxide. The receiving flask was packed in an ice bath, and the ammonia solution was stirred with a strong mechanical stirrer as addition of the acid chloride continued. The resulting mixture was refrigerated overnight, and the crude yellow precipitated amide was removed by filtration. The amide was slurried in a chilled aqueous sodium carbonate solution, filtered, and washed with water, yielding 100 g. of crude product, m.p. 114-119°. Recrystallization from water-95% ethanol (50:50 solution) gave 81.8 g. (82%) of light yellow plates of amide **1**, m.p. 121-122° (lit. (11) m.p. 120.5-121.5°); ir (Nujol), 3322, 3175 (NH), 2227 ( $\text{C}\equiv\text{C}$ ), 1647 ( $\text{C}=\text{O}$ ), 1610, 1057, 758, 736 (phenyl)  $\text{cm}^{-1}$ ; uv max (absolute ethanol), 249 nm ( $\log \epsilon$  4.09) (lit. (11) uv max, 250 nm ( $\log \epsilon$  4.16)); nmr ( $\text{d}_6$ -DMSO),  $\tau$  1.72 (s, 2,  $\text{NH}_2$ ), 2.00-2.80 (m, 4, aromatic).

##### Ethyl *o*-Chlorophenylpropiolimidate Fluoroborate (**2**).

A suspension of 16.0 g. (0.0891 mole) of **1** and 18.0 g. (0.0949 mole) of freshly prepared (12) triethyloxonium fluoroborate in 118 ml. of dry methylene chloride was heated under reflux until all of the amide had dissolved (30-45 minutes). The solution was filtered while warm and allowed to cool to room temperature. Upon cooling, white plates of the imidate fluoroborate precipitated. The precipitate was removed by filtration, ether was added to the filtrate until cloudiness developed, and the solution was refrigerated. Repeated removal of precipitated material by filtration followed by addition of ether to the filtrate and chilling yielded 20.2 g. (77%) of the imidate fluoroborate **2**, white plates of m.p. 142-144°. The product was hygroscopic and somewhat heat sensitive but could be recrystallized from methylene chloride, ir (Nujol), 3322, 3175 (NH), 2222 ( $\text{C}\equiv\text{C}$ ), 1681 ( $\text{C}=\text{N}$ ), 1351, 1224, 1053 (broad,  $\text{BF}_4$ ), 938, 769 (phenyl)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $C_{11}H_{11}BClF_4NO$ : C, 44.71; H, 3.75; N, 4.74. Found: C, 44.69; H, 3.71; N, 4.76.

2- $\beta$ -(2-Chlorophenyl)ethynylbenzimidazole (4).

To a solution of 8.00 g. (0.027 mole) of **2** in 400 ml. of methylene chloride was added 2.92 g. (0.027 mole) of *o*-phenylenediamine, and the resulting solution was heated under reflux for one hour. After standing in the refrigerator overnight, the precipitated ammonium fluoroborate was removed by filtration. Slight concentration and cooling of the filtrate caused precipitation of 2.00 g. of the crude benzimidazole, yellow needles of m.p. 170-173°. The crude product was removed by filtration, and the filtrate concentrated further and chilled, causing precipitation of additional product. The various crops were collected by filtration and recrystallized from acetone, yielding 3.66 g. (54%) of the acetylenic benzimidazole **4**, white needles of m.p. 172-173°; ir (potassium bromide): 1587, 1524, 1403, 1225, 1055, 1012, 756, 713 (phenyl)  $cm^{-1}$ ; uv max (absolute ethanol): 243 (shoulder, log  $\epsilon$  4.02), 248 (log  $\epsilon$  4.03), 256 (log  $\epsilon$  4.15), 305 (shoulder, log  $\epsilon$  4.42), 312 (log  $\epsilon$  4.45), 320 (shoulder, log  $\epsilon$  4.43), 333 (log  $\epsilon$  4.35) nm; nmr (acetone),  $\tau$  2.15-2.87 (m, 8, aromatic), 3.83-4.33 (broad s, 1, NH).

The hydrochloride salt of **4** was prepared as follows: Anhydrous hydrogen chloride gas was bubbled through a stirred solution of 1.00 g. (0.00395 mole) of **4** in chloroform for  $\sim$  1 minute. Addition of anhydrous ether to the chloroform solution caused immediate precipitation of 1.08 g. (95%) of 2- $\beta$ -(2-chlorophenyl)ethynylbenzimidazole hydrochloride, fine white powder of m.p. 193° dec.; ir (potassium bromide): 2237 (C $\equiv$ C), 1613, 1555, 1225, 1059, 899, 769, 744 (phenyl)  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{15}H_{10}Cl_2N_2$ : C, 62.30; H, 3.49; N, 9.69. Found: C, 62.08; H, 3.31; N, 9.79.

*N*-(2-Aminophenyl)-*o*-chlorophenylpropiolamidine (5).

To a solution of 20.0 g. (0.0678 mole) of **2** in 1 liter of methylene chloride was added 12.9 g. (0.0466 mole) of a 50% aqueous potassium carbonate solution. Stirring was continued for 30 minutes as the gummy white potassium fluoroborate precipitated. The precipitate was removed by filtration and the filtrate dried (magnesium sulfate). The solution could be concentrated slightly for further synthetic use; however, attempts at distillation of the free imidate base under reduced pressure led to decomposition of the product, ethyl *o*-chlorophenylpropiolimidate (**3**), ir methylene chloride): 3390 (NH), 2227 (C $\equiv$ C), 1613 (C=N), 1321, 1081  $cm^{-1}$ ; nmr (methylene-chloride):  $\tau$  1.60-1.95 (broad s, 1, NH), 2.25-2.85 (m, 4, aromatic), 5.71 (q, 2,  $J = 7.5$  Hz,  $-O-CH_2-CH_3$ ), 8.65 (t, 3,  $J = 7.5$  Hz,  $-O-CH_2-CH_3$ ).

A solution of 3.00 g. (0.0101 mole) of **2** in 150 ml. of methylene chloride was neutralized with a 50% aqueous potassium carbonate solution, as described above. To the dried (magnesium sulfate) methylene chloride solution was added 1.10 g. (0.0102 mole) of *o*-phenylenediamine, and the resulting solution was heated under reflux for one hour. The solution was concentrated under reduced pressure to 10-15 ml. and chilled in an ice bath, causing precipitation of 0.89 g. of the yellow-brown crude aminoamidine. (In some cases, unreacted *o*-phenylenediamine was initially precipitated and was removed by filtration.) The precipitated crude product was removed by filtration and the filtrate concentrated and cooled, causing precipitation of additional product. The various crops of product were collected by filtration

and recrystallized several times from benzene, yielding 1.48 g. (54%) of light yellow needles of the amino-amidine **5**, m.p. 138-139°; ir (Nujol), 3413, 3205 (NH), 2247 (C $\equiv$ C), 1623 (C=N) 1575, 1279, 1056, 744 (phenyl)  $cm^{-1}$ ; uv max (absolute ethanol) 247 nm (log  $\epsilon$  4.37), 333 nm (shoulder, log  $\epsilon$  3.65) nmr (deuteriochloroform):  $\tau$  2.40-3.50 (m, 8, aromatic), 5.10-5.95 (broad s, 4, NH).

*Anal.* Calcd. for  $C_{15}H_{12}ClN_3$ : C, 66.79; H, 4.48; N, 15.58. Found: C, 66.83; H, 4.34; N, 15.88.

2-Amino-4-(*o*-chlorophenyl)-3*H*-(1,5)benzodiazepine (7).

A stirred solution of 0.392 g. (0.00145 mole) of **5** and 0.24 ml. (0.00288 mole) of 12*N* hydrochloric acid in 25 ml. of absolute ethanol was heated under reflux for two hours. As heating continued, the initially yellow solution became bright red in color. The solution was concentrated slightly, and after the addition of ether until cloudiness appeared, the solution was placed in the freezer. There was precipitated 0.26 g. of the crude benzodiazepine hydrochloride, which was removed by filtration. The filtrate was concentrated further, ether added, and the solution chilled, causing precipitation of additional product, which was again removed by filtration. The above procedure was repeated several times to yield 0.42 g. (95%) of the benzodiazepine hydrochloride **6**, fine red needles of m.p. 285° dec., after recrystallization from absolute ethanol; ir (potassium bromide): 1664 (C=N), 1479, 1355, 1264, 1121, 955, 803, 770 (phenyl)  $cm^{-1}$ ; uv max (absolute ethanol): 268 (log  $\epsilon$  4.42), 305 (broad shoulder, log  $\epsilon$  3.44), 397 (log  $\epsilon$  3.06) nm.

There was also isolated 14.0 mg. of tan needles from the above filtrates, which was shown to be the hydrochloride salt of the acetylenic benzimidazole **4**.

The crude benzodiazepine hydrochloride was converted to the free compound as follows: A suspension of 0.40 g. (0.00131 mole) of **6** in 200 ml. of chloroform was extracted twice with 50 ml. of 2% aqueous potassium hydroxide solution, washed twice with water, and dried (magnesium sulfate). Concentration of the chloroform solution and chilling in the freezer for several days caused precipitation of a few milligrams of white needles, which proved to be the acetylenic benzimidazole **4**. The precipitate was removed by filtration and the filtrate evaporated to dryness. Recrystallization of the residue from methylene chloride yielded 0.20 g. (51% from the original amino-amidine **5**) of the benzodiazepine **7**, tan needles of m.p. 167-169°; ir (potassium bromide): 1661 (C=N), 1605, 1425, 1312, 1066, 876, 833, 758 (broad, phenyl)  $cm^{-1}$ ; uv max (absolute ethanol) 245 (log  $\epsilon$  4.40) 320 broad, (log  $\epsilon$  3.59) nm; nmr (deuteriochloroform):  $\tau$  2.41-3.00 (m, 8, aromatic), 4.63-5.09 (broad s, 2,  $NH_2$ ), 6.73 (s, 2,  $-CH_2$ ).

*Anal.* Calcd. for  $C_{15}H_{12}ClN_3$ : C, 66.79; H, 4.48; N, 15.58. Found: C, 66.87; H, 4.49; N, 15.64.

#### REFERENCES

- (1) G. Archer and L. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
- (2) J. Davoll, *J. Chem. Soc.*, 308 (1960).
- (3) W. Ried and G. Urlass, *Chem. Ber.*, **86**, 1101 (1953).
- (4) W. Ried and P. Stahlhofen, *ibid.*, **90**, 815 (1957).
- (5) E. Hand and W. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962).
- (6) L. Baiocchi and G. Palazzo, *Ann. Chim. (Rome)*, **58**, 609 (1968).

- (7) F. King and R. Acheson, *J. Chem. Soc.*, 1369 (1949).  
(8) G. Cheeseman, *ibid.*, 108 (1958).  
(9a) I. Finar, W. Barry, and E. Mooney, *Spectrochim. Acta*, **21**, 1095 (1965). (b) See also H. Staab and F. Vogtle, *Chem. Ber.* **98**, 2701 (1965).  
(10) Melting points were obtained on a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord Spectrometer and nmr spectra on a Varian A-60 nmr spectrometer. Ultraviolet spectra were obtained from absolute ethanol solutions in 1.0 cm cells on a Cary Model 11 recording spectrometer.  
(11) R. Mariella and T. Conway, *Can. J. Chem.*, **43**, 2426 (1965).  
(12) H. Meerwein, *Organic Syntheses*, **46**, 113 (1966).