Synthesis of 5*H*-Imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine

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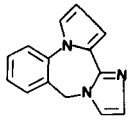
Received April 18, 1984

We have synthesized 5*H*-imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine **1** in five steps from 1-(2-aminomethylphenyl) pyrrole **4**. Amidino derivatives **11-12** have also been prepared.

J. Heterocyclic Chem., **21**, 1685 (1984).

As part of our efforts to synthesize tri- and tetracyclic systems where a pyrrole ring is incorporated, we have devised a synthesis for 5*H*-imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]-benzodiazepine **1** which is isomeric to 9*H*-imidazo[1,2-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepine **2** [3].



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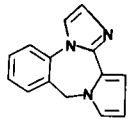
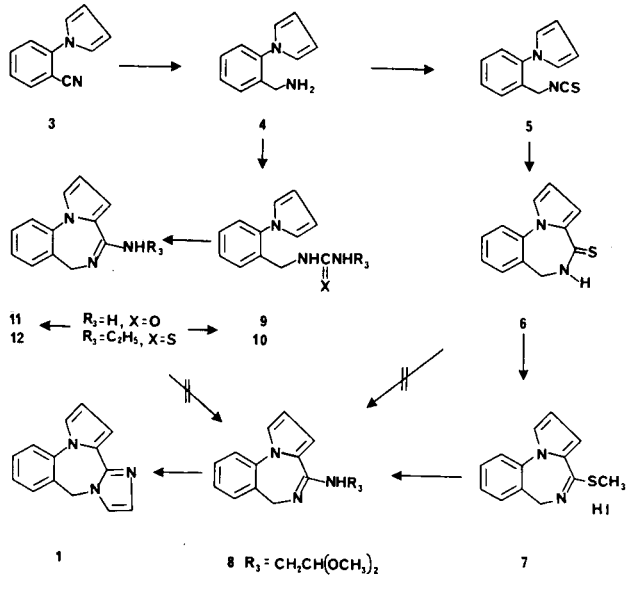


2

The title compound was synthesized as indicated (Scheme I). Reduction of 1-(2-cyanophenyl)pyrrole (**3**) with lithium aluminum hydride in dry THF gave 1-(2-aminomethylphenyl)pyrrole (**4**) in 97% yield [4]. The corresponding isocyanate **5** was obtained in 73% yield using carbon disulfide in methylene chloride at 0° in the presence of triethylamine followed by subsequent treatment with ethyl chloroformate and triethylamine under the same conditions. Thiolactam **6** was isolated in 54% yield by treatment with polyphosphoric acid (PPA) at 120° for 25 minutes. The corresponding methylthio derivative **7** was prepared from thiolactam **6** in acetone in the presence of methyl iodide. Amidinoketal **8** was prepared in 72% yield upon reaction with 2-aminoacetaldehyde dimethylacetal in toluene under reflux conditions. Amidines **11-12** were also prepared by another route involving urea **9** and thiourea **10**. The primary amine **4** was the substrate of choice in the preparation of urea **9** by reaction of sodium cyanate in aqueous methanol at 0° under acidic conditions. Thiourea **10** was formed from the same primary amine **4** by using ethyl isothiocyanate in methylene chloride under reflux conditions. The cyclization of urea **9** and thiourea **10** was best achieved in neat phosphoryl chloride under reflux for 18 hours to afford the corresponding amidines **11-12** in yields of 5% and 36% respectively. Attempts to convert thiolactam **6** and amidines **11-12** into the amidinoketal **8** using 2-aminoacetaldehyde dimethylacetal were unsuccessful. Finally, we subjected amidinoketal **8** to dilute mineral acid conditions under reflux and isolated the tetracyclic imidazole **1** in 98% yield.

Scheme I



EXPERIMENTAL

General.

All experiments, with the exception of those in which water is used as the solvent, were carried out under nitrogen. The following solvents were distilled prior to use: tetrahydrofuran (from sodium metal), acetone (from potassium permanganate and toluene was stored over sieves (Linde 4A). Commercial starting materials were used without further purification. Elemental microanalyses were carried by Ayerst Laboratories in Montreal (Canada). The ir spectra were done on a Beckman Acculab II spectrophotometers, the nmr spectra were recorded on a Varian EM 360L apparatus and mass spectra on a Hitachi RMU 60 spectrometer. The melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

Organic extracts were dried over anhydrous magnesium sulfate and solvents were always removed under vacuum. Merck silica gel 60 (70-230) was used for column chromatography. All compounds gave satisfactory mass spectra. Thin layer chromatography (tlc) was carried out on silica gel plates using methanol-chloroform combinations in varying proportions. The chromatograms were developed in an iodine chamber or under the ultraviolet lamp (253.7 nm).

1-(2-Aminomethylphenyl)pyrrole (**4**).

A solution of 1-(2-cyanophenyl)pyrrole (**3**) [4] (20.00 g, 118.9 mmoles) in dry tetrahydrofuran (300 ml) was added dropwise to a mechanically stirred suspension of lithium aluminum hydride (5.00 g, 131.75 mmoles) in dry tetrahydrofuran (200 ml) under nitrogen. After, the reaction mixture was stirred at reflux for 3 hours. A saturated solution of ammonium chloride in water was very carefully added to the mixture maintained

under a nitrogen atmosphere in order to decompose excess reagent. The grey solid material thus obtained was filtered through celite and washed with diethylether. Solvents were stripped, the residue was basified and the mixture was extracted with diethyl ether. The organic phase was washed with brine, dried and concentrated to yield a yellow oil (19.01 g, 97%) homogeneous over silica gel plates; nmr (deuteriochloroform): δ ppm 1.50 (S, 2H, NH_2), 3.81 (S, 2H, CH_2), 6.31 (m, 2H, ArH), 6.80 (m, 2H, ArH) and 7.3-7.5 (m, 4H, ArH).

The hydrochloride salt of amine **4** was prepared in diethyl ether using dry hydrogen chloride to yield a crude powder which recrystallized readily from ethanol-diethyl ether to give a white solid mp 226-227° (lit [4] mp 226-227°).

[[2-(1-Pyrrolidinyl)phenyl]methyl]isothiocyanate (**5**).

A solution of carbon disulfide (1.75 ml, 29.10 mmoles) in methylene chloride (10 ml) was added dropwise during 15 minutes to a stirred mixture of 1-(2-aminomethylphenyl)pyrrole **4** (5.00 g, 29.03 mmoles), triethylamine (3.98 ml) in methylene chloride (5 ml) cooled at 0°. After the mixture was allowed to attain room temperature and upon further cooling at 0° before addition of ethyl chloroformate (2.78 ml, 3.16 g, 29.08 mmoles). The mixture was allowed to stir for 1.5 hours at room temperature and refluxed for 15 minutes. Water (60 ml) was added, the mixture was basified with 2*N* sodium hydroxide (30 ml) and extracted with methylene chloride (3 × 20 ml). The combined extracts were washed with water, brine, dried and concentrated. The dark oil thus obtained was purified by distillation to give a clear yellow oil (4.54 g, 73%) at 144°/0.8 torr; ir (chloroform): ν max 2070, 1485, 1315 cm^{-1}; nmr (deuteriochloroform): δ ppm 4.55 (S, 2H, CH_2), 6.40 (m, 2H, ArH), 6.81 (m, 2H, ArH) and 7.2-7.7 (m, 2H, ArH). Accurate Mass Calcd. for $C_{12}H_{10}N_2S$: 214.0564. Found: 214.0560.

5,6-Dihydro-4H-pyrrolo[1,2-*a*][1,4]benzodiazepin-4-thione (**6**).

A mixture of [[2-(1-pyrrolidinyl)phenyl]methyl]isothiocyanate **5** (8.17 g, 38.13 mmoles) in polyphosphoric acid (82.0 g) was dipped in a pre-heated bath at 120° for 25 minutes. The mixture was decomposed with ice and water by trituration. Several extractions with methylene chloride (3 × 40 ml), washing of the combined extracts with brine, drying and concentration gave a residue which upon trituration in hexane gave a yellow solid mp 215-216° (4.39 g, 54%). An analytical sample was obtained by recrystallization from ethylacetate-hexane to yield a pale yellow powder mp 220-221°; ir (chloroform): ν max 3360, 3130 cm^{-1}; nmr (deuteriochloroform): δ ppm 4.21 (d, J = 6 Hz, 2H, CH_2), 7.49 (S, 4H, ArH), 7.20 (m, 2H, ArH), 6.41 (m, 1H, ArH) and 10.50 (broad, 1H, NH).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.25; H, 4.70; N, 13.08. Found: C, 67.14; H, 4.78; N, 13.04.

4-(Methylhtio)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine Hydriodide (**7**).

A solution of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4-thione (**6**) (1.35 g, 6.30 mmoles) in alcohol free acetone (35 ml) was refluxed for 30 minutes in the presence of methyl iodide (3 ml). The warm mixture was saturated with diethyl ether to yield a brown precipitate mp 188-189° (1.80 g) upon cooling of the mixture in ice-water. Recrystallization of the material from methylene chloride-hexane gave a tan powder mp 190-191° (1.70 g, 76%) which decomposed on standing; nmr (DMSO-d_6): δ ppm 2.80 (S, 3H, CH_3), 4.71 (S, 2H, CH_2), 6.75 (m, 1H, ArH), 7.61 (m, 6H, ArH) and 8.05 (m, 1H, NH).

N-(2-Dimethoxyethyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepin-4-amine (**8**).

A mixture of 4-(methylthio)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine hydriodide (**7**) (400 mg, 1.12 mmoles) and 2-aminoacetaldehyde dimethylacetal (357 mg, 3.40 mmoles) was stirred for 15 hours in dry toluene (5.0 ml). The solvent was stripped; the brown oil was treated with concentrated ammonia and extracted with methylene chloride (3 × 5 ml). The organic extracts were washed with water, brine, treated with charcoal and concentrated. The brown oil thus obtained was filtered through a short silica gel column with a 1:1 methanol-chloroform combination to yield a main fraction giving a clear brown oil (230 mg, 72%) homogeneous over silica gel plates; ir (liquid film): ν max 3360, 1600, 1570, 1515 cm^{-1}; nmr (deuteriochloroform): δ ppm 3.31 (S, 6H, CH_3), 3.40 (d, J = 6 Hz, 2H, CH_2), 6.31 (m, 1H, ArH), 6.60 (m, 1H, ArH) and 7.33 (m, 5H, ArH).

Anal. Cacld. for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.73. Found: C, 67.29; H, 6.71; N, 14.67.

N-[[2-(1-Pyrrolidinyl)phenyl]methyl]urea (**9**).

Methanol (24 ml) and sodium cyanate (2.72 g, 41.8 mmoles) were added in portions to a solution of 1-(2-aminomethylphenyl)pyrrole (**4**) (3.00 g, 17.42 mmoles) in hydrochloric acid (0.2*N*, 36 ml) stirred at 0°. After 1 hour under these conditions, the mixture was kept for 2 hours at room temperature. The white powder which precipitated was recrystallized from ethyl acetate-hexane to yield a crop of white crystals (1.65 g, 44%) mp 152-153°; ir (chloroform): ν max 3480, 3380, 1660 cm^{-1}; nmr (DMSO-d_6): δ ppm 2.49 (broad, 1H, NH), 4.11 (d, J = 6 Hz, 2H, CH_2), 5.62 (S, 2H, NH_2), 6.28 (m, 2H, ArH), 6.95 (m, 2H, ArH) and 7.41 (m, 4H, ArH). Accurate Mass Calcd. for $C_{12}H_{13}NO_3$: 215.1058. Found: 215.1053.

N-Ethyl-*N*'-[[2-(1-pyrrolidinyl)phenyl]methyl]isothiourea (**10**).

Ethyl isothiocyanate (1.52 g, 1.53 ml, 17.44 mmoles) was added dropwise to a solution of 1-(2-aminomethylphenyl)pyrrole (**4**) (3.00 g, 17.42 mmoles) in methylene chloride (40 ml). The mixture was refluxed for 8 hours, concentrated and the oil thus obtained was filtered through a short silica gel column using a 1:50 methanol-chloroform combination to afford a yellow oil (5.56 g, 67%); ir (chloroform): ν max 3400, 3260, 1530, 1485 cm^{-1}; nmr (deuteriochlorform): δ ppm 1.09 (t, J = 6 Hz, 3H, CH_3), 3.25 (q, J = 6 Hz, 2H, CH_2), 4.71 (d, J = 6 Hz, 2H, CH_2N), 5.80 (broad, 1H, NH), 6.41 (m, 2H, ArH), 6.79 (m, 2H, ArH), 7.3-7.5 (m, 4H, ArH) and 8.40 (S, 1H, NH). Accurate Mass Calcd. for $C_{14}H_{17}N_3S$: 259.1142. Found: 259.1127.

6*H*-Pyrrolo[1,2-*a*][1,4]benzodiazepin-4-amine (**11**).

N-[[2-(1-Pyrrolidinyl)phenyl]methyl]urea (**9**) (400 mg, 1.86 mmoles) was stirred in freshly distilled phosphoryl chloride (1.6 ml) under reflux conditions for 18 hours. Most of the solvent was stripped and the oily residue was basified with cold ammonium hydroxide and extracted thrice with methylene chloride. The combined extracts were washed with water, 1*N* acetic acid (3 × 10 ml) and the acidic solution was then basified with ammonium hydroxide. Finally the aqueous solution was extracted with several portions of methylene chloride; the combined extracts were then washed with brine, dried and concentrated to yield an oil which upon trituration in diethyl ether gave a tan powder mp 160-161° (20 mg, 5%); ir (chloroform): ν max 3380, 3120, 1590, 1470 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 72.99; H, 5.70; N, 21.41.

N-Ethyl-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepin-4-amine (**12**).

N-Ethyl *N*'-[[2-(1-pyrrolidinyl)phenyl]methyl]isothiourea (**10**) (2.53 g, 9.8 mmoles) was stirred in freshly distilled phosphoryl chloride (6.0 ml) under reflux conditions for 18 hours. Most of the solvent was stripped and the brown oil obtained was basified with cold ammonium hydroxide and extracted with several portions of methylene chloride. The combined extracts were washed with water, 1*N* acetic acid (3 × 15 ml) and the acidic solution was then basified with ammonium hydroxide. This solution was finally extracted with methylene chloride in the usual way followed by washing, drying and stripping of solvent to give a solid residue upon trituration in diethyl ether. Recrystallization of the material from ethyl acetate-hexane yielded a white powder (830 mg, 36%) mp 103-104°; ir (chloroform): ν max 3420, 1600, 1475 cm^{-1}; nmr (deuteriochloroform): δ ppm 1.21 (t, J = 6 Hz, 3H, CH_3), 3.29 (q, J = 6 Hz, 2H, CH_2), 4.30 (S, 1H, NH), 4.32 (S, 2H, CH_2), 6.31 (t, J = 3 Hz, 1H, ArH), 6.60 (m, 1H, ArH), 7.2-7.5 (m, 5H, ArH).

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.34; H, 6.79; N, 18.89.

5*H*-Imidazo[2,1-*c*]pyrrolo[1,2-*a*][1,4]benzodiazepine (**1**).

N-(2-Dimethoxyethyl)-6*H*-pyrrolo[1,2-*a*][1,4]benzodiazepin-4-amine (**8**) (1.73 g, 6.06 mmoles) was subjected to 2*N* hydrochloric acid (20 ml)

under reflux conditions for 2 hours. The cold solution was basified with ammonium hydroxide and extracted with several portions of methylene chloride. The combined organic fractions were washed with water brine, dried and concentrated to give a brown oil. Dissolution in ethylacetate and saturation with hexane afforded a pale yellow solid mp 123-124° (1.32 g, 98%) nmr (deuteriochloroform): δ ppm 4.91 (S, 2H, CH_2), 6.52 (t, J = 3 Hz, 1H, ArH), 6.8-7.5 (m, 8H, ArH).

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.78; H, 5.09; N, 18.92.

Acknowledgements.

We wish to thank professors A. Drweski and D. Vocelle for encouragement and support of this work. We are also thankful to professor M. Bertrand (University of Montreal) for high resolution mass spectra.

REFERENCES AND NOTES

[1] Taken in part from the master thesis of Jean Simon Duceppe.

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