

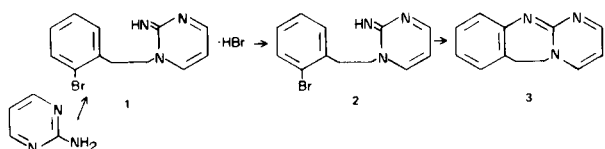
6,7-Dihydropyrimido[2,1-*b*][1,3]benzodiazepine

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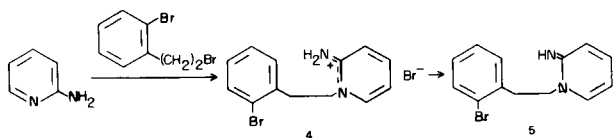
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We are reporting the preparation of **3** by the annulation of 2-aminopyrimidine with *o*-bromophenethyl bromide.



2-Aminopyrimidine forms quaternary derivatives with methyl iodide (2) and a variety of aralkyl halides (3); in these charged species, we have shown that the positive charge is not localized on either nitrogen atom, but is instead distributed between the two atoms as shown in **4** (3). From these quaternaries, the stable 1-substituted-2-pyrimidinimines, **5**, are obtained by treatment with base (4).



In contrast, the products obtained when 2-aminopyrimidine was reacted with alkyl and aralkyl halides have been assigned in the literature (5) the 1-substituted-2-pyrimidinimine hydrohalide structure, *e.g.*, **1**. In the literature, in addition, there have been numerous reports that while the latter class of compounds, when treated with base can yield the neutral species, **2**, these, in turn, readily undergo either hydrolysis to give a 1-substituted-2-pyrimidinone or a Dimroth rearrangement to form a 2-substituted-2-pyrimidinimine. The purposes of this Note are (a) to propose a more accurate designation for the quaternization products of 2-aminopyrimidine and (b) to show that neither of the side reactions of 1-substituted-2-pyrimidinimine mentioned in the literature, either one of which would have rendered our proposed synthesis inoperable, interfered significantly in the preparation of **3**.

Thus, treatment of 2-aminopyrimidine with *o*-bromophenethyl bromide in xylene, under reflux, gave **1** in 32% yield. Reaction of **1** with either potassium carbonate in anhydrous *n*-propanol or sodium methoxide in anhydrous methanol gave stable **2** in yields of 93 and 72%, respectively.

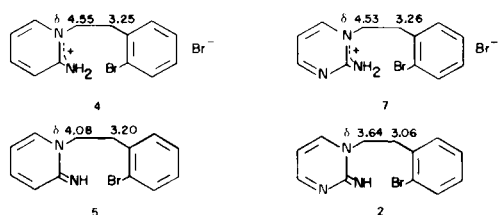
Finally, the copper bronze catalyzed annulation (3) of **2** gave **3** in 94% yield. Alternatively, the two steps could be combined and **1** was treated with potassium carbonate and copper bronze in anhydrous propanol to give **3** in 90% yield. The tricycle, **3**, was further characterized as its monohydrochloride, **6**.

## Pmr Spectra and Structure.

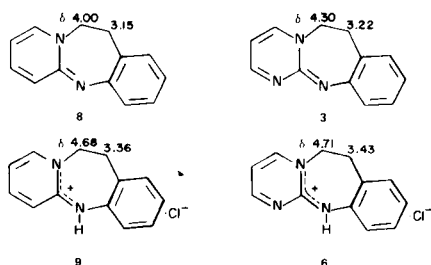
In the pmr spectrum of **1**, the resonances of the two pairs of methylene protons were almost identical with those of the quaternized 2-aminopyrimidine, **4**, where the positive charge has been shown to be distributed between the two nitrogen atoms (3). This coincidence of chemical shifts suggests strongly that structure **7** is a more accurate designation of the products obtained from 2-aminopyrimidine and *o*-bromophenethyl bromide rather than **1** as inferred in the earlier literature (5). The similarity between the "pyrido" and "pyrimido" derived structures is further emphasized by the almost identical chemical shifts of the two pairs of methylene protons in the pmr spectra of the protonated species, **9** and **6**.

In view of the almost identical chemical shifts for the methylene protons observed with the protonated species, it was unexpected to see rather curious dissimilarities in chemical shifts in the neutral compounds. Thus, while the chemical shifts for the methylene protons in the open and cyclized "pyrido" derivatives, **5** and **8**, were similar, being seen at  $\delta$  4.08 and 3.20 and 4.00 and 3.15, respectively, significant differences were found in the corresponding open and cyclized "pyrimido" derivatives, **2** and **3**, with the signals being seen at  $\delta$  3.64 and 3.06 and 4.30 and 3.22, respectively. These data, in addition, reveal that the resonances for **5** are *downfield* relative to those in **2** while in **8**, the signals are *upfield* relative to those in **3**.

Drieding models of **5** and **2** show no hindrance to free rotation about the tertiary nitrogen atom, and models of **8** and **3** are so similar as to be superimposable. In both cyclic structures, there appears to be a very similar degree of freedom of motion involving mutual interactions of the 6- and 7-membered heterocyclic rings, so that many conformations are possible. Finally, since molecular models appear



not to offer an explanation for these anomalies in the pmr spectra of the neutral compounds, and, since protonation leads in each instance to a striking coincidence of the chemical shifts of the methylene proton signals, the conclusion to be drawn is that there exist significant differences in the electron densities around the protons of the methylene groups in **5** and **2** conversely to those that exist in **8** and **3**, and, that these differences are significantly reduced in **5** and **8**.



#### EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected. The ir spectra were obtained on mineral oil mulls or on potassium bromide discs, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on deuteriochloroform or DMSO- $d_6$  solutions with a Perkin-Elmer R 12 B spectrometer. The mass spectra were obtained on an AEI-MS-902 spectrometer operating at 70 eV, using a direct insertion technique, with a probe temperature of 140-180°. The authors are indebted to Mrs. B. Toeplitz, Dr. M. S. Puar, and Dr. P. T. Funke of this Institute for these spectra. The microanalyses were carried out by Mr. J. F. Alicino and his associates of this Institute.

#### 2-Amino-1-[(*o*-bromophenethyl)]pyrimidinium Bromide, **1**.

A solution of 10.10 g. (0.107 mole) of 2-aminopyrimidine, 28.50 g. (0.107 mole) of *o*-bromophenethyl bromide, **10**, and 200 ml. of anhydrous xylene was heated under reflux in a nitrogen atmosphere for 24 hours; an additional 13.00 g. (0.05 mole) of **10** was added, and the heating under reflux continued for another 24 hours. The cooled reaction mixture was filtered to give 18.31 g. of crude **1**, m.p. 230-232°. Recrystallization from 65 ml. of methanol gave 12.40 g. (32% yield) of **1**, m.p. 231-232°; ir (potassium bromide):  $\nu$  3440 (broad, w), 1655 (s), 1615 (s), 1520 (m), 1470 (w), 1430 (m), 1415 (w)  $\text{cm}^{-1}$ ; pmr (DMSO- $d_6$ ):  $\delta$  3.26 [t (J = 6 Hz), 2H,  $\text{NCH}_2\text{CH}_2$ ], 4.53 [t (J = 6 Hz), 2H,  $\text{N-CH}_2\text{CH}_2$ ], 6.90-9.00 (m, 7H, 3 Py-H + 4 Ar-H), 9.24 (s, 2H,  $\text{NH}_2$ ); both equilibrate with deuterium oxide).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{N}_3\text{Br}_2$ : C, 40.13; H, 3.65; N, 11.71; Br, 44.51. Found: C, 40.11; H, 3.63; N, 12.00; Br, 44.24.

#### 1-(*o*-Bromophenethyl)-1,2-dihydro-2-iminopyrimidine, **2**

(a) A stirred suspension of 2.16 g. (0.006 mole) of **1**, 0.78 g. (0.006 mole) of anhydrous potassium carbonate, and 30 ml. of anhydrous 1-propanol was heated under reflux in a nitrogen atmo-

sphere for 2.5 hours and the whole concentrated to dryness *in vacuo*. The residue was distributed between 25 ml. of water and 50 ml. of ether, the ether layer was separated, the water layer was reextracted with 50 ml. of ether, the combined ether extracts were washed with 10 ml. of water, 25 ml. of saturated aqueous sodium chloride, dried, and concentrated. The residual solid was recrystallized from 20 ml. of cyclohexane to give 1.60 g. (93% yield) of **2**, m.p. 97-98°; ir (mull):  $\nu$  3250 (s), 1590 (s), 1580 (s), 1570 (s), 1530 (s), 1460 (s), 1405 (s), 1425 (m), 1410 (s)  $\text{cm}^{-1}$ ; pmr (deuteriochloroform):  $\delta$  3.06 [t (J = 6 Hz), 2H,  $\text{NCH}_2\text{CH}_2$ ], 3.64 [t (J = 6 Hz), 2H,  $\text{N-CH}_2\text{CH}_2$ ], 5.40 (broad s, 1H,  $\text{NH}$ ; equilibrates with deuterium oxide), 6.40-8.50 (m, 7H, 3 Py-H + 4 Ar-H).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{12}\text{N}_3\text{Br}$ : C, 51.81; H, 4.35; N, 15.11; Br, 28.73;  $M^+$ , 278. Found: C, 51.94; H, 4.40; N, 15.39; Br, 28.43;  $M^+$ , 278.

(b) To a solution of 0.36 (0.0066 mole) of 95% sodium methoxide in 20 ml. of anhydrous methanol was added 2.16 g. (0.006 mole) of **1** and the mixture heated under reflux in a nitrogen atmosphere for 2.5 hours. Workup as in (a) gave 1.24 g. (72% yield) of **2**, identical in all respects with the product obtained in (a).

#### 6,7-Dihydropyrimido[2,1-*b*][1,3]benzodiazepine, **3**.

(a) A stirred suspension of 7.20 g. (0.02 mole) of **1**, 6.20 g. (0.045 mole) of anhydrous potassium carbonate, 0.43 g. of copper bronze, and 200 ml. of anhydrous 1-propanol was stirred and heated under reflux for 7 days, filtered hot, and the filtrate concentrated to dryness *in vacuo*. The residue was recrystallized from 20 ml. of methanol to give 3.72 g. (94% yield) of **3**, m.p. 45-46°, ir (mull):  $\nu$  1575 (s), 1540 (s), 1490 (s), 1445 (s)  $\text{cm}^{-1}$ ; pmr (deuteriochloroform): 3.22 [t (J = 6 Hz), 2H,  $\text{NCH}_2\text{CH}_2$ ], 4.30 [t (J = 8 Hz), 2H,  $\text{N-CH}_2\text{CH}_2$ ], 6.72-8.70 (m, 7H, 3 Py-H + 4 Ar-H).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{11}\text{N}_3$ : C, 73.06; H, 5.62; N, 21.30. Found: C, 73.09; H, 5.46; N, 21.04.

(b) When a suspension of 2.30 g. (0.008 mole) of **2**, 2.10 g. (0.009 mole) of anhydrous potassium carbonate, 0.04 g. of copper bronze, and 100 ml. of anhydrous 1-propanol was stirred and heated in a nitrogen atmosphere as in (a) and then worked up, the yield of recrystallized **3** was 1.47 g. (90%), identical in all respects with the product obtained in (a).

#### 6,7-Dihydropyrimido[2,1-*b*][1,3]benzodiazepinium Chloride, **6**.

To a cooled solution of 1.04 g. (0.052 mole) of **3** in 10 ml. of anhydrous ether was added dropwise a total of 1.8 ml. of 3.3*N* ethereal hydrogen chloride. The yellow solid that separated was filtered to give 0.72 g. of crude **4**, m.p. 206-209°. Recrystallization from 25 ml. of methanol gave 0.55 g. (45% yield) of **4**, m.p. 209-210°; ir (potassium bromide):  $\nu$  3050-2300 (broad s), 1610 (s), 1600 (s), 1560 (s), 1520 (s), 1475 (s), 1455 (s), 1445 (s), 1435 (s), 1405 (m)  $\text{cm}^{-1}$ ; pmr (deuteriochloroform):  $\delta$  3.43 [t (J = 8 Hz), 2H,  $\text{NCH}_2\text{CH}_2$ ], 4.71 [t (J = 8 Hz), 2H,  $\text{N-CH}_2\text{CH}_2$ ], 6.70-9.00 [m, 8H, 3 Py-H + 4 Ar-H + NH (equilibrates with deuterium oxide)].

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{-HCl}$ : C, 61.66; H, 5.18; N, 17.98; Cl, 15.17. Found: C, 61.46; H, 5.26; N, 18.11; Cl, 15.19.

#### REFERENCES

- (1) To whom all correspondence should be addressed.
- (2) Only a few references can be found in the literature on the preparation of quaternary derivatives of 2-aminopyrimidine and the chemical reactions of that class of compounds.
- (3) R. B. Petigara and H. L. Yale, *J. Heterocyclic Chem.*, **11**, 331 (1974).
- (4) H. L. Yale and J. A. Bristol, *ibid.*, in press.
- (5) The literature has been reviewed most recently by D. J. Brown, "The Pyrimidines," Interscience Publishers, New York, 1962, pp. 365-368; D. J. Brown, "The Pyrimidines," Supplement 1, 1970, pp. 284-295.