One-Pot Synthesis and Structure of 10-Heteroarylphenothiazines

Misa V. Jovanovic and Edward R. Biehl*

Department of Chemistry, Southern Methodist University,
Dallas, Texas 75275

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Novel 10-heteroarylphenothiazine compounds were prepared in high yields by Ullmann coupling of the appropriate iodoheterocycle, prepared *in situ*, with a series of phenothiazines. The ^{13}C nmr analysis of titled compounds predicts geometries which are in excellent agreement with available x-ray crystal structure data. The results also indicate significant π-interaction between the electron-rich phenothiazine ring and the π-deficient heterocycles.

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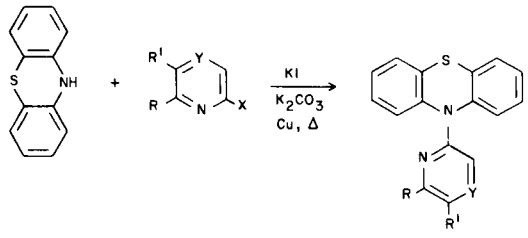
Although many 10-alkyl- and 10-aryl derivatives of phenothiazine have been prepared, the synthesis of 10-heteroaryl ones has not been reported. These derivatives, especially those containing nitrogen, might be valuable precursors of promazine analogs and other psychotherapeutic and anthelminitic agents [1-4]. Also, these compounds should be good models for studying electronic interactions between the electron-rich phenothiazine ring and π-deficient heteroaryl groups. This paper reports on the synthesis, ^{13}C nmr spectral properties, structure and X-ray data of several nitrogen-containing 10-heteroaryl derivatives of phenothiazine, **1**. The synthesis of 10-heteroaryl derivatives of 2-chlorophenothiazine, **5**, and 10*H*-pyrido[3,2-*b*][1,4]benzothiazines, **7**, is also described.

Results and Discussion.

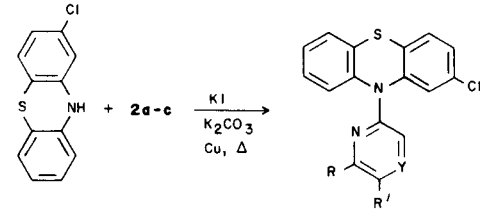
Compound **1** was converted in good yields (62-80%) to 10-heteroarylphenothiazines, **3**, using a one-pot synthesis in which **1**, appropriate chloroheterocycle, **2**, potassium iodide, potassium carbonate and activated copper were heated at 230-250° for 3-4 days. This reaction was preferred over the direct Ullmann coupling of phenothiazine with iodo- or bromoheterocycles because the latter decomposes faster than the chloro derivatives when heated excessively over prolonged periods. Decomposition of **2** was minimized by preparing iodo compounds *in situ*. Table 1 lists yields and physical properties of **3**.



1 **2a**, X = Cl, Y = CH, R = R' = H
2a', X = Br, Y = CH, R = R' = H
2a'', X = I, Y = CH, R = R' = H
2b, X = Cl, Y = N, R = R' = H
2c, X = Cl, Y = CH, R = R' = Benzo

3a, Y = CH, R = R' = H
3b, Y = N, R = R' = H
3c, Y = CH, R = R' = Benzo

Similarly, 2-chlorophenothiazine, **4**, was converted to 2-chloro-10-heteroarylphenothiazines, **5**; no 2-heteraryl-phenothiazines were detected. This is of particular importance since many drugs, such as chloropromazine, have halogen on the phenothiazine ring.

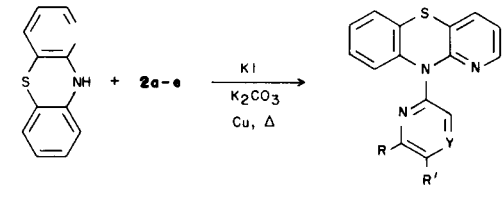


4

5a, Y = CH
5b, Y = N

The halogen substitution on the nitrogen heterocycle is expected to be much faster than that on the phenothiazine ring due to decreased electron density especially at the positions α and γ to the nitrogen atom/s of the π-deficient heterocycle as compared to the phenothiazine ring.

Finally, 10*H*-pyrido[3,2-*b*][1,4]benzothiazine, **6**, was coupled with **2a-e** to give 10-heteroarylpyrido[3,2-*b*][1,4]-benzothiazines, **7**.



6

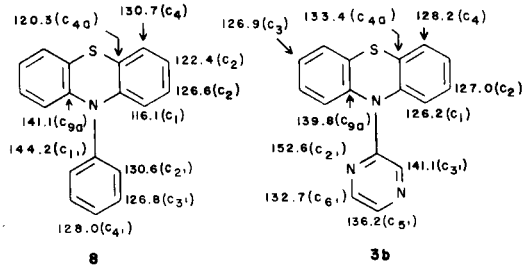
7a, Y = CH, R = R' = H
7b, Y = N, R = R' = H
7c, Y = CH, R = R' = Benzo

The incorporation of a 1-aza group into the phenothiazine ring increases the activity of phenothiazine drugs such

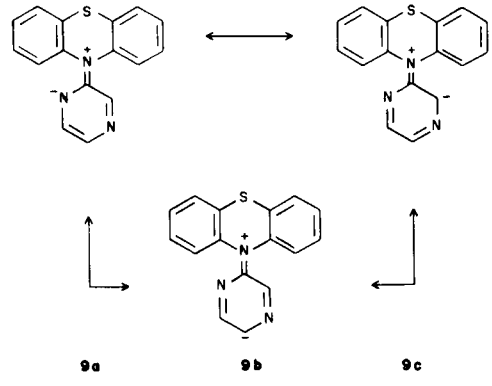
as prothipendyl, isothipendyl, pipazethate and perotral [5,6]. The pyridine "side ring" in this reaction is preserved as is the facile oxidation-reduction capability of phenothiazine nucleus.

The ^{13}C nmr spectra of these compounds indicate considerable electronic interactions between the phenothiazine ring and the 10-substituents. During this investigation, the structure of 10-(2′-pyrazyl)phenothiazine, **3b**, was determined by x-ray analysis [7]. Thus, we were able to evaluate the relationship between structure and ^{13}C nmr chemical shifts.

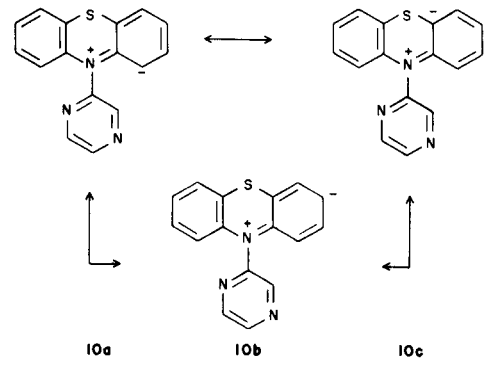
The carbon chemical shifts (in ppm) are given below together with those of 10-phenylphenothiazine, **8**. The carbon resonance frequencies ortho and para to N_{10} (phenothiazine nitrogen) in pyrazyl derivative **3b** are shifted downfield from those of the corresponding phenyl derivative, **8**; *i.e.* +10.1, +13.1 and +4.5 ppm for $C_{1(9)}$, $C_{4a(5a)}$ and $C_{3(7)}$, respectively. The plus sign represents the deshielding effect on the carbon atoms by the 10-pyrazyl group.

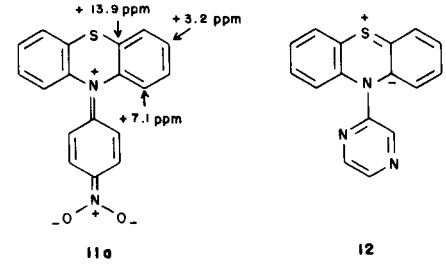


This suggests that a substantial decrease in ortho, para shielding ability of N_{10} results when substituted by the "π-deficient" heterocyclic pyrazine as compared to the 10-phenyl group, a "π-neutral" ring. Resonance structures **9a, 9b** and **9c** apparently contribute more to the resonance hybrid than **10a, 10b** and **10c** which indicates that the inductive effect of pyrazine takes precedence over mesomeric interactions of the N_{10} lone-pair electrons versus those with the side ortho-phenylene ring.



We have observed the same deshielding effect for other deactivated 10-arylphenothiazines [8]. For example 4′-nitro-10-phenylphenothiazine, **11**, shows similar deshielding effects indicating that the electronic contribution of structure such as **11a** is significant.





Electron-withdrawing substituents at position 10 should increase the resonance contribution of sulfur in the overall stabilization of the molecule. This is shown by the shielding of C_4 (−2.5 ppm) in **3b**. No such shielding is observed for C_2 and the evaluation of C_{9a} chemical shift changes is complicated since the deshielding influence of N_{10} would oppose any shielding caused by **12**. Similar conclusions have been reached also from esr studies on radical cations of 10-arylphenothiazines [9].

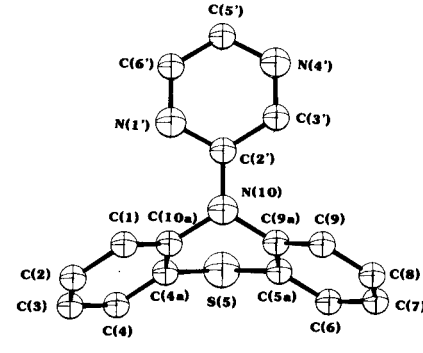
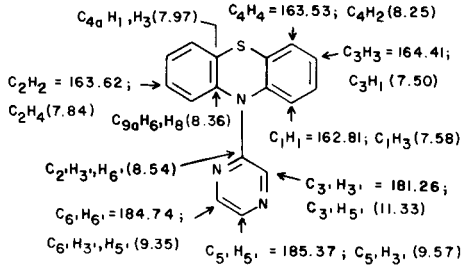


Figure 1. Computer drawing of 10-(2′-pyrazyl)phenothiazine from atomic position parameters determined by x-ray single crystal analysis. The size of the atoms shown is arbitrary.

These observations were supported by preliminary x-ray data [7]. The angle between the planes defined by S_5, N_{10}, $C_{5'}$, and the six atoms of the pyrazyl group is 88.7°, which shows the coplanarity of the pyrazine group with the C_{9a}, N_{10} and C_{10a} phenothiazine atoms. This shape would not be possible if the phenothiazine ring were planar (See Figure 1).

These parameters are supplemented by J_{CH} coupling constants which were analogous to equivalent couplings found for the other compounds in this series [8,10]. The J_{CH} *ipso* and three C-H allylic couplings (in parentheses) are given in Hz and reflect the bond order.



3b

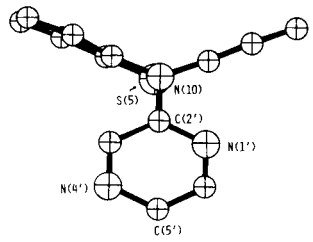


Figure 2a. Frontal view of **3b** showing the dihedral angle. The plane of the pyrazine ring is perpendicular to the plane (S_5, N_{10}, $C_{2'}$ and $C_{5'}$) bisecting the phenothiazine molecule. The interior angle between the two normals of the two phenothiazine phenyl rings (dihedral angle) is 133.0°.

The ^{13}C spectra of 10-heteroarylphenothiazines exhibited the same trends as those observed for other phenothiazines [10]; the magnitude of *ipso* C-H coupling is the same and follows the sequence $C_3H_3 > C_4H_4 > C_2H_2$. This trend was most useful in distinguishing pyrazine carbon resonances from those of the phenyl group; the former are of a much higher magnitude than those of the latter [11]. The C-H coupling across the heterocyclic nitrogen (allylic coupling) is the same size as the *ortho* J_{CH} couplings [12,14] and was the basis for the pyrazyl carbon assignments. For example, $C_{6'}$, is only a doublet of doublets whereas $C_{5'}$ carbon resonance in the coupled spectrum of **3b** appears as a doublet of triplets, due to the additional coupling to $H_{3'}$. The ortho J_{CH} coupling constants were too small to be detected for the phenyl carbon atoms. Only small couplings (allylic) for those carbons to meta hydrogens were observed.

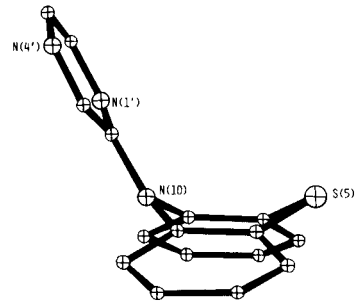


Figure 2b. Side view of **3b** showing the puckering of the molecule. The angle between planes C_{9a}, N_{10}, C_{10a} and C_{4a}, C_{5a}, C_{9a}, C_{10a} is 142.3°. The angle between planes C_{4a}, S_5, C_{5a} and C_{4a}, C_{5a}, C_{9a}, C_{10a} is 148.4°.

The $N_{1'}$-C_1 distance is 3.08 Å which indicates that hydrogen bonding between the lone-pair on pyrazyl nitrogen and H_1 is minimal and is not responsible for the puckered configuration of the pyrazyl group. The dihedral angle of the two phenothiazine phenyl rings in **3b** is 133.0° which is in agreement with other phenothiazine derivatives having electron-withdrawing groups at position 10 [15,16]. The boat portion of the phenothiazine section of **3b**, which contains the two heteroatoms inclusive with all tertiary carbon atoms (C_{4a}, C_{5a}, C_{9a}, and C_{10a}) indicates that the puckering at N_{10} is larger than expected (142.3°) (See Figures 2a and 2b). This geometric modification reflects the N-p and Aryl-π orbital overlap of N_{10} and the pyrazyl ring. This conformation is favored over that having a high twist angle between the planes of the aryl and phenothiazine ring systems as is the case with 2'-substituted-10-phenylphenothiazines [17]. In order to accomodate the geometric requirements of the coplanar pyrazyl ring, the phenothiazine ring is slightly more puckered and the pyrazyl group is lifted up in order to avoid peri interactions with $H_{1,9}$ phenylene hydrogens. The N_{10}-pyrazyl bond length compares favourably with the typical double-bond bond distance which is another indication that structures such as **13** contribute significantly to the overall stabilization of **3b**. On the basis of ^{13}C chemical shift changes, 4'-nitro-10-phenylphenothiazine, **11**, should have a structure similar to that of **3b**.

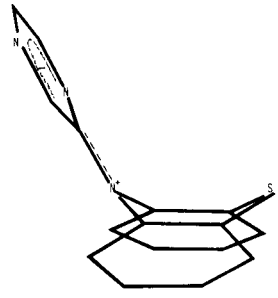


Table 1

Experimental Variables and Physical Properties of 10-Heteroarylphenothiazines

Compound No.	Molecular Formula	Synthetic Method [a]	Yield, %	Mp, °C [b]	Elemental Analysis % Calcd/Found C	H	N
3a	$C_{17}H_{12}N_2S$	A, B, C	62, 45, 27	109-110	73.88	4.39	10.14
					74.01	4.30	10.25
3b	$C_{16}H_{11}N_3S$	A	80	95-96.5	69.28	4.01	15.15
					69.50	4.12	15.26
3c	$C_{21}H_{14}N_2S$	A, B	69, 41	129-130	77.26	4.33	8.58
					77.52	4.50	8.63
5a	$C_{17}H_{11}ClN_2S$	A, C	72, 15	122-124	65.69	3.57	9.02
					65.87	3.76	8.90
5b	$C_{16}H_{10}ClN_3S$	A	78	127-128	61.63	3.24	13.48
					61.86	3.42	13.72
7a	$C_{16}H_{11}N_3S$	A, C	65, 18	136.5-138	69.28	4.01	15.15
					68.96	3.89	15.29
7b	$C_{15}H_{10}N_4S$	A	77	107-108	64.72	3.63	20.13
					64.98	3.79	19.95
7c	$C_{20}H_{13}N_3S$	A, B	73, 38	205-212 [c]	73.36	4.01	12.84
					73.56	4.24	12.75

[a] See experimental. [b] All melting points are uncorrected. [c] Listed as bp at 0.02 Torr.

EXPERIMENTAL

In general, phenothiazine, **1**, was treated with 6 equivalents of chloroheterocycle, **2**, and 4 equivalents of potassium iodide without solvent.

Method A. 10-(2'-Pyrazyl)phenothiazine.

This description is typical of most of the compounds synthesized in this study. In 100 ml round-bottom flask were mixed 10 g (10 mmoles) of phenothiazine, **1**, 34.4 g (300 mmoles) of 2-chloropyrazine, **2a**, 33.2 g (200 mmoles) of potassium iodide, 7.0 g of potassium carbonate and 800 mg of copper bronze powder and this mixture heated at 230-250° for 4 days. The mixture was cooled to room temperature, extracted with five 100-ml portions of methylene chloride, the combined extracts filtered and evaporated under reduced pressure. The oily residue was chromatographed on a 20 cm, 1 cm o.d. alumina column with 95% pet ether/5% methylene chloride as the eluent. The yellow band was collected and evaporated to dryness to yield a reddish-orange resin which was redissolved in hexane and crystallized upon standing. Second recrystallization from 50:50 mixture of acetone/hexane gave white transparent crystals, mp 95-96.5° (See Table 1).

Alternatively, 90:5:5 ethanol:water:methylene chloride mixture can be used for recrystallization. Most compounds listed in Table 1 were recrystallized from this ternary solvent mixture.

Method B.

The same procedure was used as described in method A except that the crude reaction mixture was distilled under reduced pressure (20-50 Torr).

Method C.

The same procedure was used as described in method A except that bromo- and iodo-heterocycles, **2a'** and **2a''**, were used in place of chloro, **2a**, and the reaction mixture heated for 36 hours.

Acknowledgements.

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REFERENCES AND NOTES

[1] C. Bodea and T. Silberg, "Advances in Heterocyclic Chemistry", Vol 9, A. R. Katritzky and A. J. Boulton, eds, Accademic Press, New York, NY, 1968, p 322.

[2] G. R. Ramage, E. H. Rodd and J. K Landqist, "Chemitry of Carbon Comounds IVc, Heterocyclic Compounds", E. H. Rodd, ed, Elsevier, New York, NY, 1957, Ch XVI.

[3] D. E. Pearson, "Heterocyclic Compounds", Vol 6 (R. C. Elderfield, ed, Wiley, New York, NY, 1957, Ch XIV.

[4] J. A. Board, A. Ledwith and H. J. Shine, "Advances in Physical Organic Chemistry", Vol 13, V. Gold, ed, Academic Press, New York, NY, 1976, p 155.

[5] F. M. Pasutto and E. E. Knaus, *Can. J. Chem.*, **57**, 2371 (1979).

[6] C. O. Okafor, *Int. J. Sulfur Chem. B*, **6** 237 (1971).

[7] S. S. Chu and R. R. Rosenstein, private communication.

[8] M. V. Jovanovic and E. R. Biehl, *Org. Magn. Reson.*, accepted (1983).

[9] V. D. Clarke, B. C. Gilbert and P. Hanson, *J. Chem. Soc., Perkin Trans. II*, 1078 (1975).

[10] Ref 8 and references cited therein.

[11] C. G. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley, New York, NY, 1972, Ch 14.

[12] C. J. Turner and C. W. H. Cheeseman, *Org. Magn. Reson.*, **8**, 357 (1976).

[13] G. W. H. Cheesemen, C. J. Turner and D. J. Brown, *ibid.*, **12**, 212 (1979).

[14] M. Mattsuo, S. Matsumoto, T. Kurihara, Y. Akita, T. Watanabe and A. Ohta, *ibid.*, **13**, 172 (1980).

[15] S. S. Chu and D. Van der Helm, *Acta Cryst.*, **B30**, 2489 (1974).

[16] S. S. Chu and D. Va der Helm, *ibid.*, **B31**, 1179 (1975).

[17] S. S. Chu and H. T. Yang, *ibid.*, **B32**, 2567 (1976).