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MESOMERISM IN N,N-DIALKYL-N(HETEROARYL)AMINES

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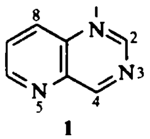
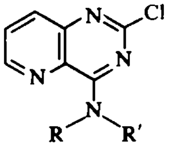
Abstract—The order in which dialkylamino groups release electrons to the pyrido[3,2-d]pyrimidine system was found to be, by the dynamic NMR method: pyrrolidino ≫ dibenzylamino > N-benzyl-N-methylamino ~ diethylamino > dimethylamino ≫ piperidino ~ morpholino ≫ aziridino. This order is discussed in terms of electronic and steric effects.

Several methods have been used to arrange dialkylamino groups according to their electron-releasing power to an unsaturated system (mesomeric effect): the strength of *p*-dialkylaminobenzoic acids,[1] the reactivity of N,N-dialkylanilines in the reaction with tricyanovinyl chloride,[2] the rate of hydrolysis of tertiary enamines in acidic medium,[3] the basic strength of N,N-dialkylanilines[4] and the σ_R^0 values for dialkylamino groups calculated from ν_{16} ring bands.[5]

We have studied the order of the electron-releasing ability of these groups to the pyrido[3,2-d]pyrimidine system (1), as deduced from the free energy of activation (ΔG^*) to rotation about the exocyclic C—N bond, in compounds 2. From the calculated geometry of this system,[6] one can conclude that 1 represents also other aromatic bicyclic systems of the same number of ring atoms.



1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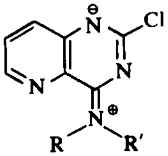
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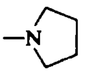
In a previous study[6] we reported ΔG^* values for several 2-chloro-4-dialkylaminopyrido[3,2-d]-pyrimidines (2), found by the dynamic NMR method. We are now adding ΔG^* values for some more compounds of type 2 (Table 1). Assuming that ΔG^* reflects the contribution of the zwitterionic form 3, namely the mesomeric effect of the -NRR′ group, the order of the ΔG^* values should give the order of the mesomeric effect.

The ΔG^* values reported in the previous study[6] were (Kcal mol^{-1}):  (17·2); $—N(CH_2\varphi)_2$ (14·6); $—NEt_2$ (14·3); $—NMe_2$ (13·5). Combining them with the values in Table 1, we arrive at the following order of the mesomeric effect: pyrrolidino ≫ dibenzylamino > N-benzyl-N-methylamino ~ diethylamino > dimethylamino ≫ piperidino ~ morpholino ≫ aziridino.

This order agrees very well with that of σ_R^0 in N,N-dialkylanilines[5] which was: pyrrolidino > diethylamino > dimethylamino > piperidino > aziridino.

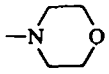
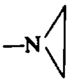
DISCUSSION

The interaction of a dialkylamino group with an unsaturated system is determined by two factors, the inductive effect (which depends primarily on the number of C atoms on the amine N) and the steric effect. The latter is responsible for the degree to which the dialkylamino group assumes the conformation most favorable for mesomerism. Most of the previous studies[1,2,4,5] dealt with systems in which the unsaturated center was a phenyl ring, whilst in our case it is a bicyclic system with larger steric requirements, due to interaction between the dialkylamino group and the N atom at 5.[6]

One could thus expect in the present case the steric effect to be more prominent, as compared with the electronic effect, than in the N,N-dialkylanilines; thus, the mesomeric effect in dialkylamino groups with small steric requirements will be even more outspoken than in these aniline derivatives.

Most surprising is at first sight the high ΔG^* value for the pyrrolidino group. However, Katritzky *et al.*[5] have already reported the fact that σ_R^0 is higher for this group than for all other basic groups, e.g. than for the diethylamino group (with the same number of C atoms) and have assumed for the case of N-phenylpyrrolidine that the steric interaction between the α-H atoms to the amine group and the o-H atoms of the phenyl ring causes a preferred conformation which is favorable for the interaction between the lone pair at the N atom and the aromatic ring. This explanation may well apply to our

Table 1[a]

Compd.	-NRR′	$\Delta\nu$/Hz[b]	Tc/C°	ΔG^* Kcal mol^{-1}
2a		47	−30	11·8[c]
2b		62	−30	11·7[c]
2c	—N(Me)$CH_2C_6H_5$	82[d,e]	18	14·3[f]
2d			< −70	< 10[g]
2e	—N(Me)C_6H_5		< −70[h]	

[a] All measurements in $CDCl_3$.

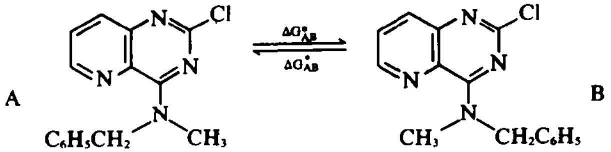
[b] Measured at 60 MHz.

[c] Approximated by the Gutowsky-Holm relationship for an equal doublet.

[d] Measured at 100 MHz.

[e] Refers to the separation of the signal of the benzylic protons.

[f] Average value between ΔG^*_{AB} (14·5) and ΔG^*_{BA} (14·05) in the process:



calculated according to Shanan-Atidi and Bar-Eli,[7] the rotamers population at low temp being A:B = 2:1, as found from the NMR spectrum.

[g] Approximated assuming Tc = −70°C and $\Delta\nu$ = 30 c/s.

[h] The lack of temp dependence of the spectra of N-phenyl-N-methyl compounds may be due either to a greater ΔG^* difference than 2 Kcal mol^{-1} between the two conformers or to a rotational barrier either too high or too low to be measured by NMR.[8]

case, with the modification that the interaction is not with the *ortho*-H atoms, but with the lone pairs at positions 3 and 5.

On the other end of the series we find the aziridino group which is known not to conjugate with unsaturated systems due to the strain engendered by an sp^2-hybridized atom in a 3-membered ring.[9] Next to the aziridino group we find the piperidino group with a very small interaction with the unsaturated system. This observation is in accord with that of Brown *et al.*[10] that the formation of an "exocyclic" double bond stabilizes a 5-membered and destabilizes a 6-membered ring. For N-phenylpiperidine, *e.g.*, the small σ^0_R value has been attributed to the interaction of the α- and the o-H atoms resulting in a conformation less favorable for the interaction lone pair-phenyl ring.[5]

The morpholino group effectively resembles the piperidino group, as the O atom would cause the same conformational effects as a methylene group.[10] The mesomeric effect of the diethylamino group is greater than that of the dimethylamino group because of the greater inductive effect, but the steric requirements of the two groups are expected to be practically identical. On the other hand, it is unexpected that the dibenzylamino group has a slightly larger mesomeric effect than the diethylamino group, as benzylamine is a weaker base than ethylamine.[11] One might assume that in our system (**2**) the dibenzylamine derivative tends more to a coplanar conformation than the diethylamino compound, because of the interaction of the benzylic phenyl group with the lone pair at nitrogen N_5. This assumption is strengthened by the observation that for the methyl-benzylamino derivative the form in which the benzyl is *syn* to N_5, is by 0·5 Kcal/mole more stable than the *anti*-conformer.

Thus it is clear that the order of interaction of dialkylamino groups with the pyrido[3,2-d]-pyrimidine system, as it expresses itself in the free energy of activation of the rotation around the exocyclic C—N bond, parallels the order of σ^0_R in N,N-dialkylanilines. There is a slightly larger weight of the steric as compared to the electronic effect.

Table 2

Compd.	Formula	Method[6]	M.p. (solvent)	Yield	Required (%)				Found (%)			
					C	H	Cl	N	C	H	Cl	N
2a	$C_{12}H_{13}ClN_4$	B	116° (benzene–pentane)	60	58·0	5·25	14·3	22·6	58·1	5·3	14·2	22·2
2b	$C_{11}H_{11}ClN_4O$	B	168–170° (C_6H_{12})	90	52·7	4·4	14·2		52·8	4·7	13·7	
2c	$C_{15}N_{13}ClN_4$	A	121–122° ($CHCl_3$)	48	63·3	4·6			63·2	4·5		
2d	$C_9H_7ClN_4$	A	138° (benzene–C_6H_{12})	95	52·3	3·4	17·2	27·1	52·2	3·7	17·6	26·9
2e	$C_{14}H_{11}ClN_4$	A	180–182° (EtOH)	95	62·1	4·1	13·1	20·6	61·9	4·2	13·9	20·5

EXPERIMENTAL

2 - Chloro - 4 - dialkylaminopyrido[3,2-d]pyrimidines **2** (Table 2) were prepared from the corresponding secondary amines and the 2,4-dichlorocompounds.[6]

REFERENCES

[1] W. D. Weringa and M. J. Janssen, *Rec. Trav. Chim.* **87**, 1372 (1968)

[2] Z. Rappoport, P. Greenzaid and A. Horowitz, *J. Chem. Soc.* 1334 (1964)

[3] W. Maas, M. J. Janssen, E. J. Stamhuis and H. Wynberg, *J. Org. Chem.* **32**, 1111 (1967)

[4] G. Baddeley, J. Chadwick and H. T. Taylor, *J. Chem. Soc.* 451 (1956)

[5] R. T. Brownlee, R. E. J. Hutchinson, A. R. Katritzky, T. T. Tidwell and R. D. Topsom, *J. Am. Chem. Soc.* **90**, 1757 (1968)

[6] J. Almog, A. Y. Meyer and H. Shanan-Atidi *J. Chem. Soc. Perkin II*, 45 1 (1972)

[7] H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.* **74**, 961 (1970)

[8a] Y. Shuo and H. Shanan-Atidi, *J. Am. Chem. Soc.* **91**, 6683 (1969); [b] Z. Rappoport and R. Ta-Shma, *Tetrahedron Letters*, 5281 (1972)

[9] F. A. L. Anet and J. M. Osyany, *J. Am. Chem. Soc.* **89**, 352 (1967)

[10] H. C. Brown, J. H. Brewster and H. Shechter, *Ibid.* **76**, 467 (1954)

[11] J. W. Smith, *The Chemistry of the Amino Group* (Edited by S. Patai), p. 178. Interscience (1968)