Barriers to Rotation in Dialkylaminopyrimidines

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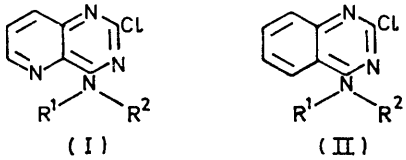
A number of 4-dialkylamino-pyrimidines (III), -quinazolines (II), and pyrido[3,2-*d*]pyrimidines (I), have been prepared, and their n.m.r. spectra studied in various solvents at room and at low temperatures. The barrier to rotation about the exocyclic C–N bond is not affected when the parent pyrimidine system (III) is annelated to a pyridine ring (I), but is substantially changed upon fusion to benzene (II). This finding is discussed in terms of a quantum-chemical all-valence electron approach.

In a communication [1] we reported that the barrier to rotation about the exocyclic C–N bond in 2-chloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine (Ia) is *ca.* 14 kcal mol^{-1}. We have now found that the rotational barrier about the corresponding bond in 2-chloro-4-dimethylaminoquinazoline (IIa) is significantly lower ($\Delta G \leqslant 8{\cdot}3$ kcal mol^{-1}). In an attempt to identify the factors that are responsible for this difference, a number of 4-dialkylamino-2-chloro-pyrido[3,2-*d*]pyrimidines (Ib—e), -quinazolines (IIb—e) and -pyrimidines (IIIa and b) were prepared, the temperature-dependence of their n.m.r. spectra was examined, and free energies



(I) (II) (III)

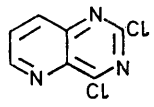
a; $R^1 = R^2 = Me$
b; $R^1 = R^2 = Et$
c; $R^1 = R^2 = CH_2Ph$
d; $R^1R^2 = [CH_2]_4$
e; $R^1 = R^2 = CH_2C_6H_4{\cdot}OMe(p)$

a; $R^1 = R^2 = Me$
b; $R^1R^2 = [CH_2]_4$

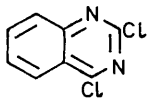
[1] J. Almog, A. Y. Meyer, and E. D. Bergmann, *Chem. Comm.*, 1970, 1011.

of activation were derived at the coalescence temperature of the relevant signals.

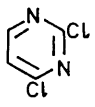
Synthesis and Structural Proof.—All compounds were prepared by treating the 2,4-dichloro-parent molecules (IV), (V), and (VI) with 1 mol. equiv. of the



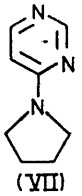
(IV)



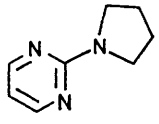
(V)



(VI)



(VII)



(VIII)

appropriate amine. By our procedure (see Experimental section) and contrary to another report,[2] monosubstituted products were obtained in good yield. Two of these (IIb and d) are known [3-5] and their structures were proved by independent syntheses. For compounds of types (IV) and (V) it is known [6-8] that the chlorine atom at C-4 is more liable to nucleophilic displacement than that at C-2. Reports conflict, however, on the reactivity of the monocyclic molecule (VI). Some authors [9] claim that the reaction with ammonia produces a mixture of the two possible monoamino-products, while others maintain [10] that, under conditions described as ' delicate ', only the diaminated derivative is obtained. Yet, the chlorine atom at C-4, which is considered to be more liable to substitution [9] than that at C-2, is apparently replaced first by secondary amines.[11]

In our hands, compound (V) produced, on treatment with dimethylamine, a single isomer, identical with the known 2-chloro-4-dimethylaminopyrimidine (m.p. 81°), previously synthesised [10,11] by an unambiguous route. The other isomer,[12] 4-chloro-2-dimethylamino-pyrimidine (m.p. 41°), could not be detected. In the reaction of pyrrolidine with compound (IV), a single isomer was obtained, which was dechlorinated to a compound showing an ABX pattern ($J_{AX} \neq J_{BX}$) in the aromatic n.m.r. spectral region. This establishes that its structure is (VII) [and therefore (Id)]; the alternative isomer (VIII) would exhibit an A_2X pattern.

The n.m.r. spectra of the dimethylamino- and pyrrolidino-derivatives at room temperature are shown in Figures 1 and 2. The chemical shifts of hydrogen atoms α to the amino nitrogen atom are significantly affected by varying the molecular structure. Chemical shifts differ thus in compounds (I), (II), and (III), α-hydrogen atoms (methyl or methylene) in the pyrido-pyrimidines (I) always absorbing at lower field, probably because of deshieldimg due to N-5. In the low-temperature spectra of compounds (I), two groups of non-equivalent α-hydrogen atoms may be identified, and the lower-field signals assigned to protons *cis* to N-5.

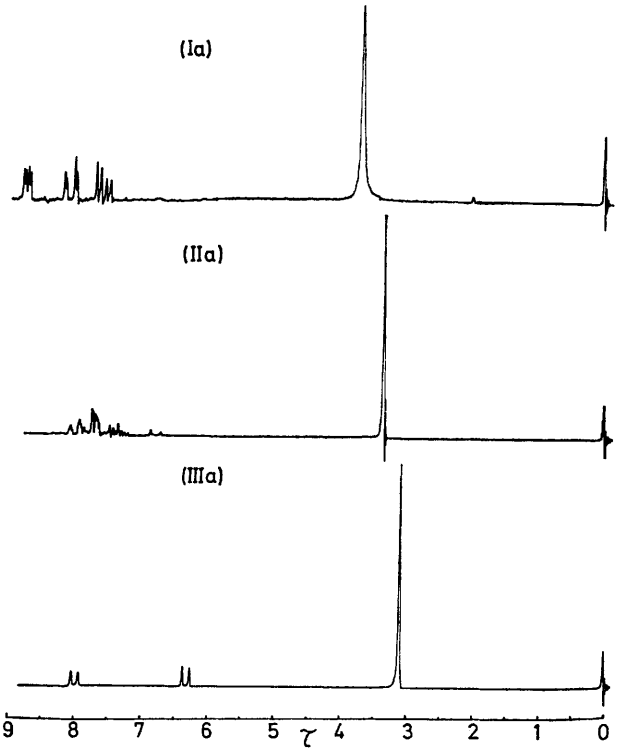


FIGURE 1 N.m.r. spectra of 2-chloro-4-dimethylamino-pyrido-[3,2-*d*]pyrimidine (Ia), -quinazoline (IIa), and -pyrimidine (IIIa) at room temperature

Rotational Barriers.—At low temperature, the α-amino-groups of all compounds, except compounds (IIa—c and e), exhibit two n.m.r. signals of equal intensity. When the temperature is raised, a reversible broadening, coalescence, and sharpening takes place (Table 1). Nitrogen inversion cannot account for this behaviour (see later), which must therefore be related to rotation about the exocyclic C–N bond. The free energies of activation ($\Delta G^{\ddagger}$) were determined, at the coalescence temperature, from the Gutowsky–

[2] R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 973.
[3] H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton, *J. Org. Chem.*, 1962, **27**, 957.
[4] A. G. Geigy, B.P. 822,069/1959 (*Chem. Abs.*, 1961, **55**, 2005e).
[5] I. Ya. Postovskii and I. N. Goncharova, *Zhur. obshchei Khim.*, 1962, **82**, 3323.
[6] V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.*, 1956, 1045.
[7] V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 1956, 4433.
[8] F. H. Curd, J. K. Landquist, and F. L. Rose, *J. Chem. Soc.*, 1947, 775.
[9] G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1152.
[10] W. Pfleiderer and H. Mosthalf, *Chem. Ber.*, 1957, **90**, 728.
[11] K. Westphal, U.S.P. 2,219,858/1941 (*Chem. Abs.*, 1941, **35**, 1805).
[12] C. G. Overberger and I. C. Kogon, *J. Amer. Chem. Soc.*, 1954, **76**, 1065.

Holm relationship [13] ($1/2T = \Pi\Delta\nu/\sqrt{2}$) and the Eyring activation function, with transmission coefficient taken as 1.*

While the dimethylamino-compound (Ia) undergoes thermal rotation about the exocyclic C–N bond on the

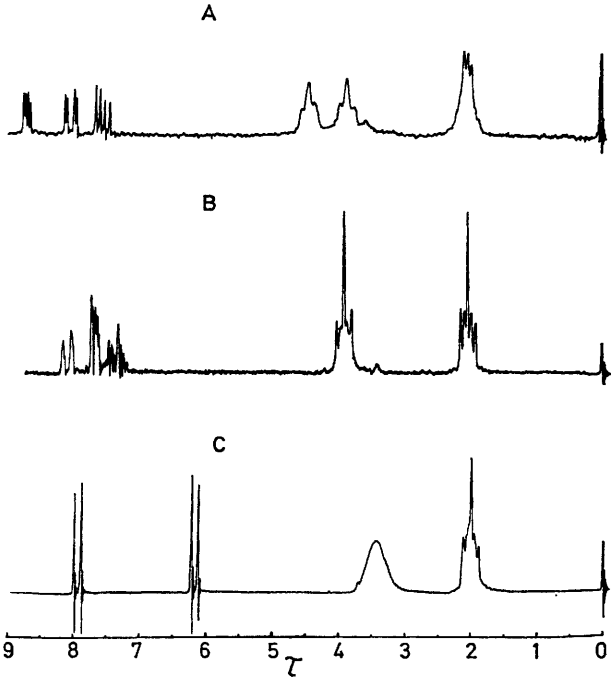


FIGURE 2 N.m.r. spectra of A, 2-chloro-4-pyrrolidino-pyrido-[3,2-*d*]pyrimidine; B, -quinazoline; and C, -pyrimidine at room temperature

TABLE 1

Compd.	$\Delta\nu$ [a]/Hz	T_C/°C	$\Delta G^{\ddagger}$/ kcal mol^{-1}	Solvent
(Ia)	57	+5	13·5	$CDCl_3$
(Ib)	57	+18·5	14·3 [e]	$CDCl_3$
(Ic)	83·3	+37	14·6	$CDCl_3$
(Id)	33 [b]	+70	17·2	$CDCl_3$
(Ie)	54 [b]	+20	14·3	$(CD_3)_2CO$
(IIa)	57 [b,c]	−100 [d]	8·3	$(CD_3)_2CO$
		−60 [d]		$CDCl_3$
(IIb)		−60 [d]		$CDCl_3$
(IIc)		−60 [d]		$CDCl_3$
(IId)	35	−28	12·1 [e]	$CDCl_3$–$(CD_3)_2CO$ (2 : 1)
(IIe)		−60 [d]		$CDCl_3(CD_3)_2CO$– (2 : 1)
(IIIa)	15·6	−9	13·5	CH_2Cl_2–$CDCl_3$ (1 : 2)
(IIIb)	24·4	+24·4	15·6 [e]	CH_2Cl_2–$CDCl_3$ (1 : 2)

[a] Measured at 100 MHz. [b] Measured at 60 MHz. [c] Assumed by comparing (IId) with (Id). [d] At lower temperature the compound separates. [e] Approximated by the Gutowsky–Holm relationship for an equal doublet.

n.m.r. time scale ($\Delta G^{\ddagger} = 13{\cdot}5$ kcal mol^{-1}), the corresponding quinazoline (IIa) shows, even at −100 °C, only one N–Me signal. In order to eliminate the possibility of an accidental coincidence of the chemical shifts of the two diastereotopic N–Me groups in compound (IIa), we have measured the n.m.r. spectra in a variety of solvents [15] [C_5H_5N (−20), CH_2Cl_2 (−80), $CDCl_3$ (−70), $(CD_3)_2CO$ (−100), CD_3CN (−50 °C) †]; no change in the line shape was observed, and we conclude that a rapid exchange takes place between the two sites. Assuming $\Delta\nu = 57$ Hz, as in compound (Ia), and $T_C = -100$ °C, an upper limit of 8·3 kcal mol^{-1} is obtained for $\Delta G^{\ddagger}$ in compound (IIa).

The rotational process under consideration can be described as an exchange between two conformations, and is depicted schematically in Figure 3. In the ground conformations A and B, which in our case are enantiomeric ($R^1 = R^2$), the angle α between the mean R–N–R plane and the plane of the fused-ring system can assume any value between 0 and 90°; its actual magnitude is determined by a combination of resonance and steric effects. The exchange between the two identical R groups implies necessarily the passage through a conformation in which the R–N–R plane is perpendicular ($\alpha = 90°$) to the plane of the rings. This conformation is considered to constitute the transition state (TS_1) for the rotational process. The exchange of the two R groups does not require transition through the planar conformation ($\alpha = 0°$), but this may be considered as another transition state (TS_2) for the rotational process.

In order to examine whether transition through TS_2 also occurs on the n.m.r. time scale we have studied

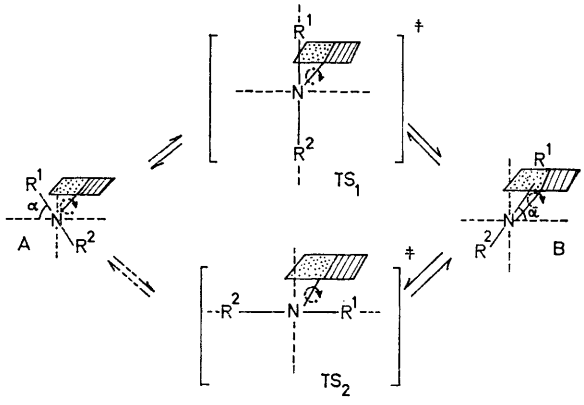


FIGURE 3 Conformations and transition states for compounds (I)—(III)

the spectra of some dibenzyl-, diethyl- and bis-*p*-methoxybenzyl-amino-derivatives [(Ib), (Ic), (IIb), (IIc), (Ie), and (IIe)]. Here the two methylene or benzylic α-hydrogen atoms are diastereotopic, except in the planar conformation TS_2, and their n.m.r. spectra should show an AB system if transition through TS_2 is sufficiently slow Neither at low nor at high temperature

* Although the Gutowsky–Holm equation is derived for equal doublets, it may be used [14] as an approximation also in the case of equal intensity multiplets [(Ib and d), (IIb and d), (IIIb)].

† The materials separate at lower temperatures.

[13] H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219.
[14] F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, 1967, **89**, 352.
[15] Y. Shvo and H. Shanan-Atidi, *J. Amer. Chem. Soc.*, 1969, **91**, 6683.

was an AB pattern observable in the n.m.r. spectra of these compounds.*

These results lead us to the conclusion that in both series (I) and (II) the energy of TS_2 is lower than that of TS_1 and therefore that the exchange A $\rightleftharpoons$ TS_2 $\rightleftharpoons$ B is fast on the n.m.r. time scale. The mechanism which governs the exchange of the two R groups is thus associated with a rotation of 180° around the exocyclic C–N bond, as depicted in Figure 3. It also follows that the inversion of the nitrogen pyramid is fast in any conformation and cannot account alone for the experimental findings; in any conformation (except TS_2) the benzylic protons are diastereotopic and inversion of the nitrogen pyramid should lead to diastereomeric conformers. We conclude therefore that transition through TS_2 and nitrogen inversion are both fast, and the kinetically slow process is the transition through TS_1.

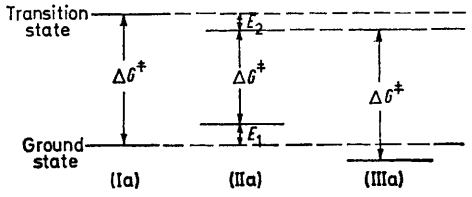
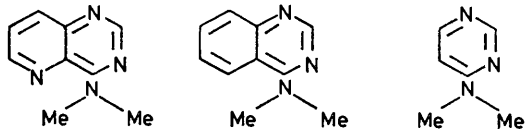


FIGURE 4 Conformational barriers for compounds (Ia)—(IIIa)

The fact that the activation energy for the rotational process in compound (IIa), which does not exceed 8·3 kcal mol^{-1} is so much lower than the value found for compound (Ia) (13·5 kcal mol^{-1}) may be explained as follows. The only structural difference between compounds (I) and (II) is the replacement of a trigonal nitrogen (N-5) by a carbon atom. The energy diagram (Figure 4) suggests that compound (IIa) is distinguished from compound (Ia) by ground-state raising (E_1), or transition-state lowering (E_2), or both. In our opinion, the decisive factor in the present case is E_1, which reflects the difference between the two steric interactions, Me–H-5 in (IIa), Me–N-5 in (Ia). This is tantamount to the proposition that the ' effective size ' of the non-bonding orbital of an sp^2 nitrogen atom is lower than that of a hydrogen atom. This factor, previously detected in the case of a pyramidal nitrogen structure,[16] would be even more pronounced in a trigonal N atom, of higher *s*-character and shorter bonds. The measured $\Delta G^{\ddagger}$ for the monocyclic compound (IIIa) (13·5 kcal mol^{-1}; Table 1) is identical with that of compound (Ia). In this case, the energy of the ground state must be even lower than that of compound (Ia), owing to the complete discharge of steric effects. It follows that the transition state of compound (IIIa) is also lower than that of compound (Ia), so that the N-5 atom brings about an increase in the energy of the transition state. Therefore E_2 in compound (IIa) is non-nul, as depicted in Figure 4.

Some additional varieties of steric interactions were investigated for compounds (Id), (IId), and (IIIb). For the pyrrolidino-compounds (IId) and (Id), $\Delta G^{\ddagger}$ is *ca.* 12 and 17 kcal mol^{-1}, respectively, both values being higher than the corresponding ones for their dimethylamino-analogues. This is expected, for the planar state of the former compounds should be lower in energy than that of the latter; the pyrrolidine ring gives less steric interaction and a higher resonance contribution.[17] One may also evaluate the upper limit for $\Delta G^{\ddagger}$ of compound (IIa), by assuming that the difference $\Delta G^{\ddagger}_{5d}$ (Id) — $\Delta G^{\ddagger}$ (Ia) equals $\Delta G^{\ddagger}$ (IId) — $\Delta G^{\ddagger}$ (IIa). This turns out to be 8·4 kcal mol^{-1}, in close agreement with the value (<8·3) estimated earlier on other grounds.

Quantum-chemical Results.—In order to derive general energy profiles in systems (I), (II), and (III), we have carried out calculations for the dimethylamino-derivatives (IX), (X), and (XI) which do not contain a



(IX) (X) (XI)

chlorine atom at C-2. In spite of this (made necessary by computer-programme limitations) the model is representative, because electronic factors, as well as the steric effects in the immediate vicinity of the amino-substituent, are accounted for appropriately. The dimethylamino-group serves as model for other amino-substituents (such as the pyrrolidino-radical) and contains hydrogen atoms which may be envisaged as approaching, by rotation about the C–N axis, an aza-nitrogen atom [(IX), *cf.* (I)] or a methine hydrogen atom [(X), *cf.* (II)], or may be considered to be devoid of neighbouring-ring effects [(XI), *cf.* (III)].

The molecular geometry of compounds (IX)—(XI) is not known, so that the calculations had to be performed in successive stages. Interatomic distances were first estimated by a parametrised Hückel treatment,[18] and this calculation was followed by a trigonometrical search for feasible interbond angles. The energy computation was then performed with PCILO,[19] the perturbational analogue of the all-valence-electron CNDO process.†

Hückel-type bond orders, π-electronic charges, and interatomic distances, derived with the parametrisation of Häfelinger,[18] are given in the molecular diagrams of (IX), (X), and (XI),‡ where a bond is depicted as

* To eliminate the possibility of coincidence of the chemical shifts, we have used a variety of solvents in these measurements.

† The variational SCF treatment [20] did not converge.

‡ These diagrams replace those in a previous report [1] which was based on a different parametrisation and where, in addition, some typographical errors had occurred.

[16] (*a*) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637; (*b*) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *Tetrahedron Letters*, 1964, **45**, 3345; (*c*) J. M. Bobbitt, A. R. Katritzky, P. D. Kennewell, and M. Snarey, *J. Chem. Soc.* (*B*), 1968, 550.

[17] (*a*) W. D. Weringa and M. J. Janssen, *Rec. Trav. chim.*, 1968, **87**, 1372; (*b*) R. T. C. Brownlee, R. E. J. Hutchinson A. R. Katritzky, T. T. Tidwell, and R. D. Topson, *J. Amer. Chem. Soc.*, 1968, **90**, 1757.

[18] G. Häfelinger, *Chem. Ber.*, 1970, **103**, 2902.

[19] B. Pullman, B. Maigret, and D. Perahia, *Theor. Chim. Acta*, 1970, **18**, 44.

[20] P. A. Dobosh, CNINDO, QCPE 143, July 1968.

double whenever its order exceeds 0·68. In systems (IX) and (X), distances related to the pyrimidine ring, as well as the exocyclic bond order, are independent of the nature of the other ring; in the absence of ring fusion [the pyrimidine (XI)] there is, however, a marked change in bond orders and lengths.

The estimation of bond angles was carried out as follows. Literature data for similar compounds [21] were employed to fix acceptable ranges for angles α—ζ (Figure 5). Four of the angles (α, β, γ, and ζ) were then varied within their ranges and, for each set of these, five of the formerly-computed lengths (R, S, T, V, and W) were used to obtain U, as well as δ and ε. The number of solutions with U close to its Hückel value and with δ and ε within the permissible range, is very

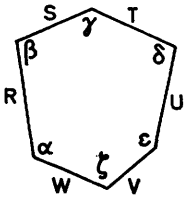


FIGURE 5 Bonds and angles in a six-membered ring

small; an extreme case is the pyrimidine ring of (X), with a unique solution. When necessary, a choice was based on the least-squares criterion. Substituents were assumed to be of ' standard ' structures [22] and to bisect angles.

The final geometries are shown in Figures 6—8. In the bicyclic systems, (IX) and (X), the permissible range was taken close (±3°) to the regular value of 120°; the similarity in the results for the two systems (Figures

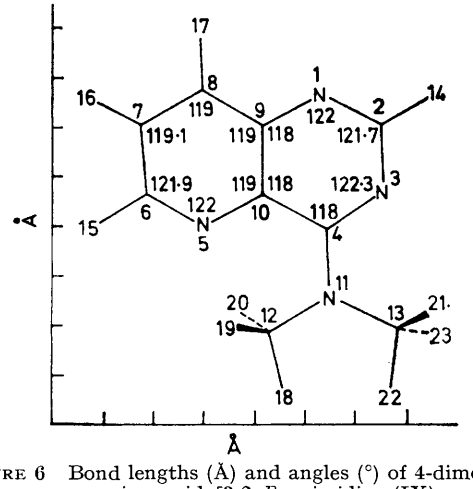


FIGURE 6 Bond lengths (Å) and angles (°) of 4-dimethylaminopyrido[3,2-*d*]pyrimidine (IX)

6 and 7) is noteworthy and suggests that the behavioural differences, cited earlier, between molecules of these two types, are not an outcome of differences in the overall geometry. In the monocyclic system (XI), on the other hand, there is no trigonometrical solution with angles close (±3°) to 120°. It has indeed been known experimentally [21] that such rings are deformed from the regular hexagonal structure; our procedure

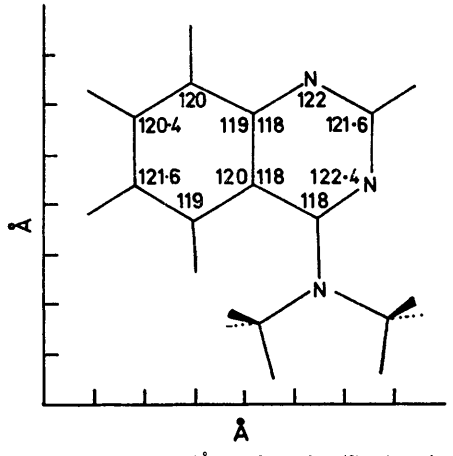


FIGURE 7 Bond lengths (Å) and angles (°) of 4-dimethylaminoquinazoline (X)

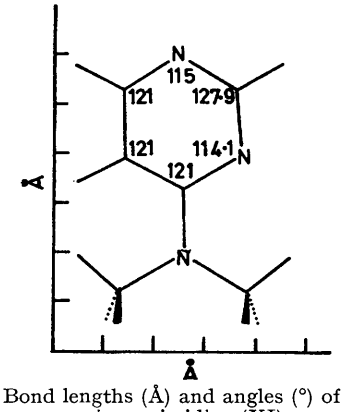


FIGURE 8 Bond lengths (Å) and angles (°) of 4-dimethylaminopyrimidine (XI)

shows now that these deviations can be detected by Hückel type approaches. By allowing angles to vary within a wider range (110—130°), a large number of solutions was obtained, of which we adopted the one (Figure 8) which fulfills $\beta > \alpha$, $\gamma < 120°$, $\delta > 120°$, and $\varepsilon < 120°$ (*cf.* the experimental examples).[21]

The number of sets of possible rotamers is quite large, for there are three axes of rotation (ring–N, N–Me[1], N–Me[2]), in addition to the hybridisational variety at the amino-nitrogen atoms. To simplify the discussion, we concentrate upon structures obtainable, by rotation about the ring–N axis, from the geometrical situations (' H-coplanar inside ', coplanar nitrogen) shown in Figure 6—8. Such rotamers may, in fact, represent other substituents (*e.g.* pyrrolidino) even better than alternative structures (*e.g.* ' H-coplanar outside ').

Figures 9—11 show the relationship between the dihedral angle α (defined as 0° for the coplanar situations

[21] L. Pauling, ' The Nature of the Chemical Bond,' Cornell Univ. Press, Ithaca, New York, 2nd edn., 1940.

[22] J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, 1967, **89**, 4253.

shown in Figure 6—8) and the total energy E_T and its two components, namely, the all-valence-electron

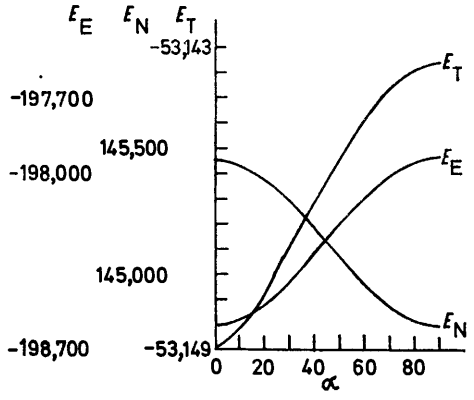


FIGURE 9 Relationship between dihedral angle (°) and total energy E_T, all-valence-electron stabilisation energy E_E, and the core–core repulsion energy E_N (all in cal mol^{-1}) for compound (XI)

stabilisation E_E and the sum E_N of the core–core repulsions (of these quantities, only E_T is comparable in magnitude and significance to the corresponding classical term, *e.g.* in the Westheimer approach [23]).

The case of 4-dimethylaminopyrimidine [(XI), Figure 9] is straight-forward. At $\alpha = 0°$, the molecular repulsions are maximal (large positive E_N), as is the electronic stabilisation (large negative E_E); the reverse

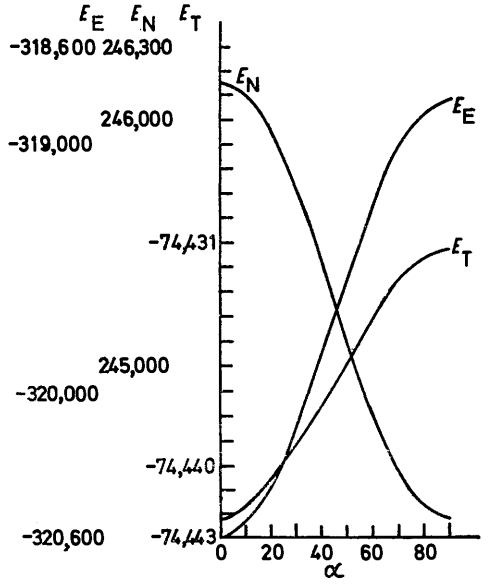


FIGURE 10 Relationship between dihedral angle (°) and total energy E_T, all-valence-electron stabilisation energy E_E, and the core–core repulsion energy E_N (all in cal mol^{-1}) for compound (IX)

is true at 90°. The energy components do not balance exactly, and E_T is lower in the coplanar than in other rotational states, the computed difference between the two rotational extremes being *ca.* 6 kcal mol^{-1} (the experimental value [24] for this particular compound is 10·7).

A similar situation is noted in the case of 4-dimethylaminopyrido[3,2-*d*]pyrimidine [(IX), Figure 10], except that here the computed ranges of change are wider than in the former case: ΔE_N *ca.* 1750 kcal mol^{-1} [as against 650 in (XI)], ΔE_E *ca.* 1800 kcal mol^{-1} (*vs.* 300), and ΔE_T *ca.* 12 kcal mol^{-1} (*vs.* 6). Thus, the augmented nuclear repulsions in a planar conformation for (IX) are more than compensated by an increased electronic stabilisation; in fact, the Hückel molecular diagrams indicate that the amino-nitrogen atom in compound

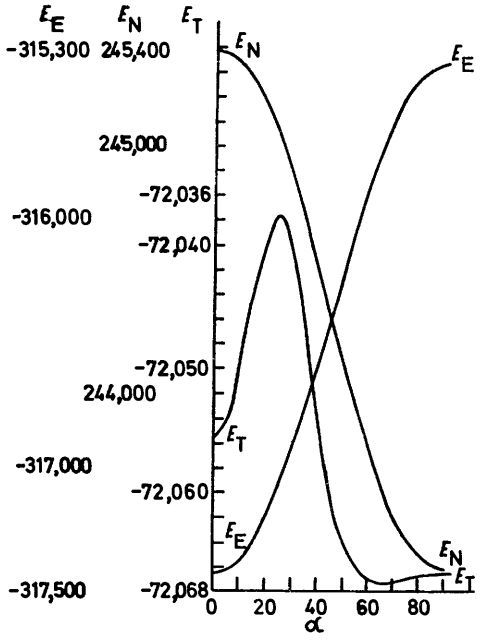


FIGURE 11 Relationship between dihedral angle (°) and total energy E_T, all-valence-electron stabilisation energy E_E, and the core–core repulsion energy E_N (all in cal mol^{-1}) for compound (X)

(IX) donates more π-charge to the rings than in compound (XI).

In the case of 4-dimethylaminoquinazoline (X), a hydrogen atom is present at C-5. By allowing the dimethylamino-group (in the 'H-inside' conformation of Figure 7) rotate about the ring–N axis, E_N and E_E behave as before (Figure 11), but E_T shows two maxima and two minima. The global maximum value for E_T is obtained at $\alpha = 25°$, close to the situation ($\alpha = 30°$) when one of the methyl hydrogen atoms is directed at 5-H. The global minimum is at 65° and, in addition, there is a local minimum at 0° and a shallow maximum at 90°. As this profile differs markedly from the former two, we found it desirable to carry out calculations for other rotamers, but could not detect structures of energy lower than that of the 'H-inside rotamer'. We also allowed the amino-nitrogen atom to assume a non-

[23] F. H. Westheimer, in 'Steric Effects in Organic Chemistry,' ed. S. Newman, Wiley, New York, 1956, p. 523.

[24] A. R. Katritzky and G. J. T. Tiddy, *Org. Magnetic Resonance*, 1969, **1**, 57.

planar conformation. Some stabilisation is noted with ' anti '-structures ($\alpha = 90°$, methyl groups farthest from benzene ring), but ' syn '-rotamers are markedly destabilised. The curve for the ' H-coplanar outside '

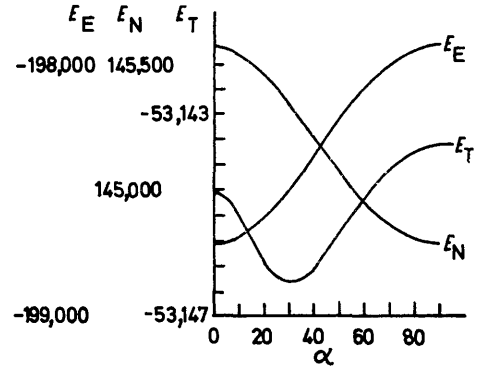


FIGURE 12 Energy relationships for the ' H-coplanar outside conformation for compound (XI)

situation is shown in Figure 12. We note that, at $\alpha = 0°$, the ' H-outside ' conformation is destabilised, in comparison with ' H-inside ', by *ca.* 4·5 kcal mol^{-1}. At 90°, however, the two conformers have similar values of E_N, E_E, and E_T. More important, while in ' H-inside ' the value of E_T is minimal at 0° and maximal at 90°, both rotational states correspond to maxima for ' H-outside '. This latter rotamer has minimum energy at 30°, when the hydrogen atom is just out of plane, and electronic stabilisation is still significant.

There is no point in trying to ' reconcile ' the profiles, computed for compound (X), with the spectral behaviour of compounds (II). A variety of conformational modifications is possible in the case of dimethylaminoquinazoline (IIa), and these may permit a tunnelling through the E_T maximum at $\alpha = 25°$. An alternative interpretation, namely, that the dialkylamino-substituent is trapped at $\alpha = 90 \pm 25°$, was shown above to be untenable.

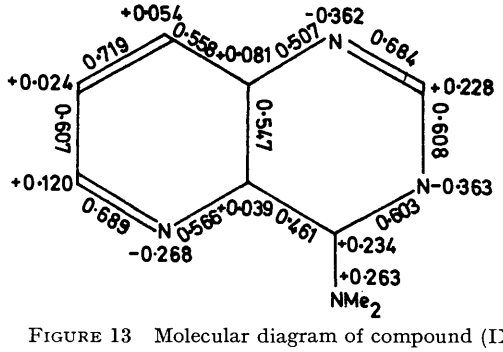


FIGURE 13 Molecular diagram of compound (IX)

Conclusions.—Annelation of a pyridine to a pyrimidine ring, as in the pyrido[3,2-*d*]pyrimidine system, does not significantly affect the barrier to rotation of a dialkylamino-substituent at C-4. Benzene fusion destabilises the planar confirmation, however, and leads to a net decrease in the rotational barriers.

In terms of ' effective sizes ', one may consider the lone pair of the pyridine nitrogen atom as smaller than an aromatic hydrogen atom.

Quantum-chemical calculations corroborate the hypothesis that in the pyrimidine and pyridopyrimidine derivatives, a conformation close to co-planarity is more feasible than a perpendicular one; the augmented nuclear repulsions are thus more than balanced by resonance stabilisation.

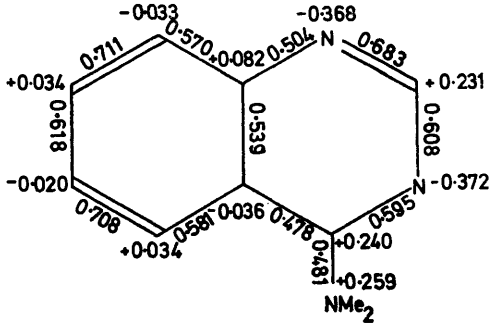


FIGURE 14 Molecular diagram of compound (X)

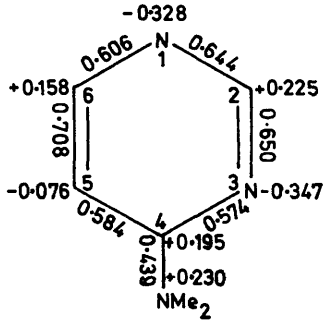


FIGURE 15 Molecular diagram of compound (XI)

In the case of the quinazoline compounds, computation is not in line with the experimental findings. This may be due to a deficiency of the quantum chemical approach,[25] but could also indicate the operation of a complex steric phenomenon.

EXPERIMENTAL

2,4-Dichloropyrido[3,2-*d*]pyrimidine was prepared [2] from the dihydroxy-analogue. 2,4-Dichloroquinazoline [8] and 2,4-dichloropyrimidine [26] were prepared by treating phosphoryl chloride, in the presence of dimethylaniline, with 2,4-dihydroxyquinazoline and uracil, respectively. Compounds of types (I), (II), and (III), obtained by either of the following two methods, are listed in Table 2.

Method A.—To a stirred ethanolic suspension of the dichloro-compounds (1 g in 50 ml) a solution of the appropriate amine (1 mol. equiv.) and triethylamine (1 mol. equiv.) in ethanol (10 ml) was added dropwise. Stirring was continued for 1 h at room temperature; the mixture was heated for 10 min, then cooled, poured into ice–water (0·5 l), and extracted with chloroform. The extract was

[25] V. Galasso, G. de Alti, and A. Bigotto, *Tetrahedron*, 1971, **27**, 991.
[26] N. Whittaker, *J. Chem. Soc.*, 1951, 1565.

washed with water, dried, and evaporated, and the product was recrystallised.

Method B.—To a solution of the dichloro-compound in dry dioxan (1 g in 30 ml) was added a solution of the amine (2 mol. equiv.) in dioxan (10 ml). The mixture was stirred for 1 h, filtered, and evaporated to dryness; the product was recrystallised.

Reduction of 2-Chloro-4-pyrrolidinopyrimidine (IIIb) *to 4-Pyrrolidinopyrimidine* (VII).—To a solution of the pyrimidine (IIIb) (500 mg) and anhydrous sodium acetate (240 mg) in absolute methanol (40 ml) palladium–carbon (0·5 g; 10%) was added and the reduction was carried out under a pressure of 22 lb in^{-2}. When the required amount of hydrogen had been absorbed, the suspension was filtered, the filtrate was evaporated, and the solid residue was extracted with hexane. Work-up and purification by t.l.c. [silica gel, BuOH–$CHCl_3$ (1 : 9)] gave 400 mg (98%) of crystals, m.p. 103°.

TABLE 2

Compd.	Formula	Method	M.p. (°C) (solvent)	Yield (%)	Required (%)				Found (%)			
					C	H	Cl	N	C	H	Cl	N
(Ia)	$C_9H_4ClN_4$	A [a]	115—116 (light petroleum)	42	51·8	4·31	17·0		51·6	4·20	16·7	
(Ib)	$C_{11}H_{13}ClN_4$	A [b]	116 (light petroleum)	67	55·8	5·5	15·0		56·0	5·6	14·6	
(Ic)	$C_{21}H_{17}ClN_4$	B	133—134 (EtOH)	52	69·9	4·7	9·85	15·5	69·7	5·0	10·0	15·7
(Id)	$C_{11}H_{11}ClN_4$	B	169—170 (C_6H_{12})	44	56·3	4·69	15·1	23·8	57·0	4·78	15·2	23·5
(Ie)	$C_{23}H_{21}ClN_4O_2$	A	109—110 (EtOH)	55	65·6	5·0	8·4		65·3	5·3	8·7	
(IIa)	$C_{10}H_{10}ClN_3$	A [a]	104—106 (C_6H_{12})	72	57·8	4·82	17·1		58·0	4·88	17·9	
(IIb)	$C_{12}H_{14}ClN_3$	A [b]	75 (light petroleum)	93	61·2	5·9	15·05		61·4	6·0	15·1	
(IIc)	$C_{22}H_{18}ClN_3$	A	111—112 (C_6H_{12})	62	73·5	5·0	9·9		73·3	5·1	9·9	
(IId)	$C_{12}H_{12}ClN_3$	A	169 (EtOH)	79	61·7	5·14		18·0	61·7	5·05		17·9
(IIe)	$C_{24}H_{22}ClN_3O_2$	A	140 (EtOH)	55	68·6	5·25	8·5	10·0	68·5	4·95	8·3	9·9
(IIIa)	$C_6H_8ClN_3$	A [c]	81 (pentane)	50	45·9	5·1		26·6	45·9	5·1		26·4
(IIIb)	$C_8H_{10}ClN_3$	A	120 [(pentane–hexane (1 : 1)]	46	52·3	5·45	19·3	22·9	52·5	5·7	19·0	23·0

[a] Aqueous 33% dimethylamine. [b] Aqueous 20% diethylamine. [c] Alcoholic 33% dimethylamine.

Bis-(p-methoxybenzyl)amine.—This was prepared [27] from *p*-methoxybenzaldehyde and *p*-methoxybenzylamine.

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[27] R. Juday and H. Adkins, *J. Amer. Chem. Soc.*, 1955, **77**, 4559.

[1/1621 *Received*, 6*th September*, 1971]