The Dimroth Rearrangement. Part VI.[1] The Abnormal Behaviour of 5-Cyano-1,2-dihydro-2-imino-1-methylpyrimidine

By D. J. Brown and M. N. Paddon-Row

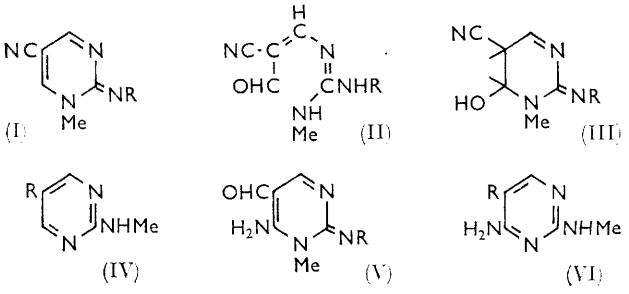
5-Cyano-1,2-dihydro-2-imino-1-methylpyrimidine rapidly undergoes normal or abnormal Dimroth rearrangements according to the conditions. At room temperature, a mildly alkaline solution yields the acyclic intermediate, *N*-(2-cyano-2-formylvinyl)-*N'*-methylguanidine, which can be variously cyclised. By warming the intermediate or the original pyrimidine in dilute aqueous ammonia, the normal product, 5-cyano-2-methylaminopyrimidine, is formed; in aqueous sodium hydroxide, an abnormal product, 4-amino-5-formyl-1,2-dihydro-2-imino-1-methylpyrimidine, results from the addition of the methylamino-group to the cyano-group at the intermediate stage. This iminopyrimidine slowly undergoes a second abnormal Dimroth rearrangement to 5-carbamoyl-2-methylaminopyrimidine.

Substituents remote from the site of reaction have been shown to affect profoundly the rate of Dimroth rearrangement by electron release or withdrawal.[2] We now describe the first cases in which the less remote substituents also become directly involved in the rearrangement, thereby leading to abnormal products.

As would be expected,[2] 5-cyano-1,2-dihydro-2-imino-1-methylpyrimidine (I; R = H) rapidly underwent ring-fission in alkaline solution at room temperature, to yield initially the acylic guanidine (II; R = H, and/or tautomer). The structure followed from the microanalytical results for carbon, hydrogen, and nitrogen, its reconversion into the imine (I; R = H) by acid ($t_{\frac{1}{2}}$ = 3 sec. at 20° and pH 2), its conversion into rearranged pyrimidines (see below) by alkali, and its unmistakable CN (2200 cm.$^{-1}$) and CO (1650) bands in the infrared spectrum. A contribution from the isomeric carbinolamine (III; R = H) cannot be precluded, especially in solution.

When either the imine (I; R = H) or the intermediate (II; R = H) was treated with warm aqueous ammonia, it was rapidly converted into the normal Dimroth product, 5-cyano-2-methylaminopyrimidine (IV; R = CN), which was also made unambiguously from its 5-bromo-analogue with cuprous cyanide. When alkali was substituted for ammonia, an isomer of the intermediate (II; R = H) was quickly precipitated. Since it was stable to cold alkali and acid, showed a CO band at 1660 cm.$^{-1}$, and formed a dinitrophenylhydrazone, it could be the pyrimidine (V; R = H) or (VI; R = CHO), produced from the intermediate (II; R = H) by addition to the nitrile grouping of the methylamino- or amino-group, respectively. Its pK_a value (8·5) was inconsistent with the second formulation because the basic strength of 4-amino-2-methylaminopyrimidine[3] (pK_a 7·5) must be appreciably reduced by 5-formylation. On the other hand, nuclear-*N*-methylated derivatives of 2,4-diaminopyrimidines are known[3,4] to have pK_a values upward of 10·6, so that the first formulation (V; R = H, or tautomer) was consistent with the measured value.

Being an α-*N*-methylated imine, the pyrimidine (V; R = H) should be capable of undergoing a second Dimroth rearrangement (either normal or abnormal) which would be slow because of electron-release by the amino-group. On prolonged treatment with alkali, the expected abnormal product, 5-carbamoyl-2-methylaminopyrimidine (IV; R = CO·NH$_2$), was indeed formed; it was identified by paper chromatography and ultraviolet spectra with material made unambiguously by acid hydrolysis of 5-cyano-2-methylaminopyrimidine (IV; R = CN). A small amount of 5-carboxy-2-methylaminopyrimidine (IV; R = CO$_2$H) was also formed during the second rearrangement, and it was chromatographically identical with authentic material made by alkaline hydrolysis of the cyano-analogue.



For confirmation, the above reaction sequences were repeated with the homologous methylimine (I; R = Me), prepared by methylating 5-cyano-2-methylaminopyrimidine. The acyclic intermediate (II; R = Me) was isolated and characterised (CN, 2200; CO, 1620 cm.$^{-1}$); it was reconverted into starting material by acid ($t_{\frac{1}{2}}$ = 1 sec. at 20° and pH 2). No normal rearranged pyrimidine corresponding to 5-cyano-2-methylaminopyrimidine is possible, but an abnormal product (V; R = Me) was prepared. It showed a CO band at 1660 cm.$^{-1}$, formed a dinitrophenylhydrazone, and corresponded to the lower homologue in pK_a and ultraviolet spectra (see Table). In addition, its n.m.r. spectrum showed three-proton peaks at τ 6·8 and 7·05 (pH 14 in D$_2$O/NaOD) and at τ 6·35 and 6·8 (pH 2 in D$_2$O/DCl), thus finally precluding representation of the abnormal product as its isomer (II; R = Me) which would have equivalent methyl groups and therefore show a single six-proton peak (cf. the bromo-analogue[1]). Because

[1] Part V, D. D. Perrin and I. H. Pitman, *J. Chem. Soc.*, 1965, 7071.

[2] D. J. Brown and J. S. Harper, in "Pteridine Chemistry," Pergamon Press, Oxford, 1964, p. 217; *J. Chem. Soc.*, 1965, 5542.

[3] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1962, 3172.

[4] D. J. Brown and T. Teitei, *J. Chem. Soc.*, 1965, 755.

of its progressive change in solution at 33°, measurement of the n.m.r. spectrum of the acyclic intermediate was unsatisfactory. The cation of the methylimine (I; R = Me) showed (in D_2O/DCl) three-proton signals at τ 6·1 and 6·75.

Like its cyano-analogous, 2-amino-5-carbamoylpyrimidine underwent nuclear methylation to 5-carbamoyl-1,2-dihydro-2-imino-1-methylpyrimidine. Rearrangement produced 5-carbamoyl-2-methylaminopyrimidine (IV; R = $CO{\cdot}NH_2$) quite rapidly [5] (at 20°, $t_{\frac{1}{2}}$ = 38 min. at pH 13; 14 min. at pH 14), but there was no trace of the possible abnormal products.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff; n.m.r. spectra are by Mr. S. Brown.

Ionisation and ultraviolet spectra

Pyrimidine derivative	pK_a [a]	$\lambda_{max.}$ (log ε) [b]	pH
2-Amino-5-cyano [c]		294(3·52), 254(4·41)	4·0
cation	0·66 ± 0·03(260)	307(3·36), 246(4·32) [d]	−0·4
di-cation	−1·48 ± 0·05(266)	—	
4-Amino-5-cyano [e]	2·54 ± 0·01(256)	—	
2-Amino-5-carbamoyl		*290(3·58)*, 255(4·32)	5·0
cation	2·06 ± 0·03(270)	305(3·53), 244(4·31)	−1·0
4-Amino-5-carbamoyl [f]	4·18 ± 0·03(256)	—	
5-Cyano-2-methylamino		303(3·54), 263(4·48)	5·0
cation	0·76 ± 0·02(263)	318(3·47), 254(4·41)	−1·2
5-Carbamoyl-2-methylamino		*305(3·62)*, 266(4·39)	5·0
cation	2·05 ± 0·02(266)	317(3·56), 253(4·33)	−0·5
5-Carboxy-2-methylamino (anion)	—	303(3·51), 260(4·38)	10·6
5-Cyano-1,2-dihydro-2-imino-1-methyl		— [g]	
cation	— [g]	308(3·56), *270(3·67)*, 246(4·31)	4·9
5-Carbamoyl-1,2-dihydro-2-imino-1-methyl		315(3·09), 266(4·36)	11·0
cation	9·13 ± 0·02 [h]	303(3·66), 244(4·28)	4·9
5-Cyano-1,2-dihydro-1-methyl-2-methylimino		— [g]	
cation	— [g]	323(3·47), 253(4·41) [i]	4·0
4-Amino-5-formyl-2,3-dihydro-2-imino-3-methyl		314(4·10), 243(3·95)	10·6
cation	8·47 ± 0·04(M/200)	303(4·28), 267(4·05)	6·0
4-Amino-5-formyl-2,3-dihydro-3-methyl-2-methylimino		328(4·13), 256(4·04)	11·0
cation	8·67 ± 0·02(M/1000)	308(4·32), 269(4·05)	4·0

[a] Measured at 20° spectrometrically (analytical wavelength given), or potentiometrically (molarity given) by methods described by A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. [b] Inflexions in italics. [c] Prepn. from ref. 6. [d] Figures corrected for presence of 7·5% neutral molecule and 7·1% di-cation. [e] Prepn. from J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 1943, 386. [f] Prepn. from D. J. Brown and L. N. Short, *J. Chem. Soc.*, 1953, 331. [g] Free base too unstable for measurement even by rapid reaction techniques. [h] D. D. Perrin and I. H. Pitman, unpublished data. [i] Hydriodide used with appropriate I^- concentration in reference cell.

5-Cyano-1,2-dihydro-2-imino-1-methylpyrimidine.—2-Amino-5-cyanopyrimidine [6] (3·0 g.), methyl iodide (12 ml.), and 2-methoxyethanol (20 ml.) were rocked [7] at 98° in a sealed tube for 24 hr. The solid was removed, and the filtrate, reduced to small bulk and diluted with ether, gave a second crop. The *imine hydriodide* (83%) had m. p. 231° (from water) (Found: C, 27·4; H, 2·9; N, 21·1. $C_6H_7IN_4$ requires C, 27·5; H, 2·7; N, 21·4%). Treatment with silver chloride gave the *hydrochloride*, m. p. 228° (from methanol–ethyl acetate) (Found: C, 42·1; H, 4·3; N, 32·8. $C_6H_7ClN_4$ requires C, 42·2; H, 4·1; N, 32·8%).

4(2)-Amino-5-formyl-2,3(3,4)-dihydro-2(4)-imino-3-methylpyrimidine.—The above hydrochloride (1·0 g.) was stirred at room temperature with 1·4N-sodium hydroxide (4 ml.) until the yellow colour faded (*ca.* 8 min.). The solution, adjusted to pH 10, deposited the *formylpyrimidine* (75%), m. p. 202—203° (from propanol) (Found: C, 47·5; H, 5·3; N, 36·7. $C_6H_8N_4O$ requires C, 47·4; H, 5·3; N, 36·8%). When the imine hydriodide was used instead of the hydrochloride, and the solution was finally adjusted to *ca.* pH 4, the formyl pyrimidine *hydriodide* (70%) resulted, m. p. 248° (from methanol–ether) (Found: C, 25·7; H, 3·2; I, 45·4; N, 20·0. $C_6H_9IN_4O$ requires C, 25·7; H, 3·2; I, 45·3; N, 20·0%). The *picrate* (made from either free base or hydriodide) had m. p. 195° (from water) (Found: C, 37·7; H, 2·9. $C_{12}H_{11}N_7O_8$ requires C, 37·8; H, 2·9%). The formylpyrimidine hydriodide (0·2 g.), added to a hot solution of 2,4-dinitrophenylhydrazine (0·2 g.) in ethanol (5 ml.) and hydrochloric acid (1 ml.), furnished *4-amino-5-(2,4-dinitrophenylhydrazono)methyl-2,3-dihydro-2-imino-3-methylpyrimidine hydriodide* (0·2 g.), m. p. 262° (from water) (Found: C, 31·4; H, 3·0; I, 27·1; N, 24·0. $C_{12}H_{13}IN_8O_4$ requires C, 31·3; H, 2·85; I, 27·6; N, 24·35%).

N-(2-Cyano-2-formylvinyl)-N'-methylguanidine.—A solution of 5-cyano-1,2-dihydro-2-imino-1-methylpyrimidine hydrochloride (5·0 g.) in water (10 ml.) at 25° was slowly adjusted to pH 10 with 10N-sodium hydroxide. The precipitated *guanidine* (50%), washed with ethanol and dried *in vacuo*, had m. p. 190° (Found: C, 47·3; H, 5·0; N, 36·4. $C_6H_8N_4O$ requires C, 47·4; H, 5·3; N, 36·8%). An aqueous solution, adjusted to pH 3 with hydrochloric acid and evaporated to dryness, gave back the initial pyrimidine hydrochloride (mixed m. p. 228°), but when treated with sodium hydroxide it gave the formylpyrimidine (mixed m. p. 202°).

5-Cyano-2-methylaminopyrimidine.— (*a*) 5-Bromo-2-methylaminopyrimidine [8] (3·8 g.) and cuprous cyanide hydrate (2·2 g.) were heated in refluxing quinoline (8 ml.) for 40 min. The hot mixture was poured into boiling glacial acetic acid (115 ml.), immediately filtered, and diluted with water (250 ml.). Vacuum-distillation to

[5] D. D. Perrin and I. H. Pitman, personal communication.
[6] J. P. English, J. H. Clark, R. G. Shepherd, H. W. Marson, J. Krapcho, and R. O. Roblin, *J. Amer. Chem. Soc.*, 1946, **68**, 1039.
[7] S. Gabriel, *Ber.*, 1905, **38**, 630.
[8] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.

ca. 50 ml. gave a solid which was freed from copper by repeated dissolution in cold 10N-hydrochloric acid (15 ml.) and reprecipitation with an excess of aqueous ammonia. The *cyanopyrimidine* (42%) had m. p. 203° (from water) (Found: C, 53·9; H, 4·4; N, 41·9. $C_6H_6N_4$ requires C, 53·7; H, 4·5; N, 41·8%). Its *picrate* had m. p. 172° (from water) (Found: C, 39·6; H, 2·8. $C_{12}H_9N_7O_7$ requires C, 39·7; H, 2·5%).

(*b*) Aqueous ammonia was slowly added in excess to a boiling solution of 5-cyano-1,2-dihydro-2-amino-1-methylpyrimidine hydriodide (2·0 g.) dissolved in water (10 ml.). The resulting solid (83%) was identified with the above cyanopyrimidine by mixed m. p. Similar treatment of the guanidine (see above) gave the same product.

2-Amino-5-carbamoylpyrimidine.—2-Amino-5-cyanopyrimidine [6] (11·2 g.) was slowly dissolved in sulphuric acid (96%; 36 ml.) at 35—40° and set aside at room temperature for 24 hr. It was poured on to crushed ice and refrigerated. The sulphate was filtered off, and its solution in warm water (100 ml.) was made ammoniacal. Refrigeration gave the *carbamoylpyrimidine* (60%), m. p. 317° (from water) (Found, for material dried at 140°: C, 43·0; H, 4·5; N, 40·4. $C_5H_6N_4O$ requires C, 43·5; H, 4·4; N, 40·6%).

5-Carbamoyl-1,2-dihydro-2-imino-1-methylpyrimidine.—The above amide (3·0 g.), methyl iodide (6 ml.), and 2-methoxyethanol (37 ml.) were rocked [7] at 98° for 18 hr. Concentration *in vacuo* gave a crude product which was triturated with ether, and further purified by precipitation with ether from methanolic solution. The *imine hydriodide* (80%) had m. p. 240° (decomp.) (Found: C, 25·8; H, 3·3; N, 19·9. $C_6H_9IN_4O$ requires C, 25·7; H, 3·2; N, 20·0%) The *picrate* had m. p. 257° (from water) (Found: C, 37·7; H, 3·1. $C_{12}H_{11}N_7O_8$ requires C, 37·8; H, 2·9%), and the *hydrochloride* had m. p. 285—286° (from methanol–ether) (Found: C, 38·1; H, 5·0; N, 29·5. $C_6H_9ClN_4O$ requires C, 38·2; H, 4·8; N, 29·7%).

5-Carbamoyl-2-methylaminopyrimidine.—(*a*) The above imine hydriodide (4·0 g.) was warmed with N-sodium hydroxide (50 ml.) for 3 min. The cooled solution was adjusted to pH 7 and the *carbamoyl-methylaminopyrimidine* (80%) removed, m. p. 249—250° (from water) (Found: C, 47·6; H, 5·3; N, 36·8. $C_6H_8N_4O$ requires C, 47·4; H, 5·3; N, 36·8%). The *picrate* had m. p. 229° (from water) (Found: C, 37·8; H, 3·0. $C_{12}H_{11}N_7O_8$ requires C, 37·8; H, 2·9%).

(*b*) 5-Cyano-2-methylaminopyrimidine (3·0 g.) was slowly dissolved in sulphuric acid (96%; 9 ml.) at 30—35°. After 24 hr. at room temperature, the solution was added to crushed ice and adjusted to pH 6 with aqueous ammonia. The resulting carbamoylpyrimidine (55%) had mixed m. p. 249°.

(*c*) The cyanopyrimidine (0·3 g.) was heated at 96° with aqueous ammonia (*d* 0·91; 9 ml.) for 3 hr. Evaporation to small bulk gave the carbamoylpyrimidine (60%), mixed m. p. 249°.

(*d*) 4-Amino-5-formyl-2,3-dihydro-2-imino-3-methylpyrimidine (0·23 g.) and 1·2N-sodium hydroxide (5 ml.) were allowed to react at 50° for 12 hr. and then at 25° for 48 hr. The solution was adjusted to pH 7 with hydrochloric acid and evaporated to dryness. The residue was extracted with boiling ethanol (3 ml.) and the clarified extract diluted with ether. The resulting solid consisted of at least four substances (paper chromatogram in 3% aqueous ammonium chloride). The spot corresponding to that of 5-carbamoyl-2-methylaminopyrimidine (R_F 70) was eluted. Its ultraviolet spectra (pH 5·0 and −0·5) corresponded to those of the neutral molecule and cation of authentic amide.

5-Carboxy-2-methylaminopyrimidine.—The above amide (2·0 g.) was heated with 3N-sodium hydroxide (20 ml.) at 98° for 1 hr. Adjustment to pH 3—4 gave the *carboxypyrimidine*, m. p. 308—309° (purified by reprecipitation from alkaline solution) (Found: C, 47·4; H, 4·6; N, 27·3. $C_6H_7N_3O_2$ requires C, 47·1; H, 4·6; N, 27·4%).

5-Cyano-1,2-dihydro-1-methyl-2-methyliminopyrimidine.—5-Cyano-2-methylaminopyrimidine (4·0 g.), methyl iodide (16 ml.), and methoxyethanol (30 ml.) were rocked at 98° for 24 hr. The cooled mixture was diluted with ether (600 ml.) to deposit the *methyliminopyrimidine hydriodide* (81%), m. p. 208—209° (from ethanol) (Found: C, 30·3; H, 3·4; N, 20·2. $C_7H_9IN_4$ requires C, 30·45; H, 3·3; N, 20·3%). The hygroscopic *hydrochloride* had m. p. 242° (from water or acetone–ether) (Found, for material dried at 60°/0·5 mm.: C, 44·2; H, 5·2; N, 29·5. $C_7H_9ClN_4,0·25H_2O$ requires C, 44·45; H, 5·1; N, 29·6%).

N-(2-Cyano-2-formylvinyl)-N′N″-dimethylguanidine.—1·2N-Sodium hydroxide was slowly added to the above hydrochloride (2·0 g.) dissolved in water (5 ml.) until pH 11 was reached. The *dimethylguanidine* (50%), washed with water and with acetone, had m. p. 143° (Found: C, 50·4; H, 6·0. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·1%). A specimen (0·5 g.), dissolved in hydrochloric acid (2 ml.), was diluted with a mixture of acetone and ether (1 : 1; 200 ml.). The crystalline precipitate (91%) was identified with the above methylimine hydrochloride by mixed m. p. 242°.

4-Amino-5-formyl-2,3-dihydro-3-methyl-2-methyliminopyrimidine (or tautomer).—(*a*) 5-Cyano-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydriodide (4·25 g.) was warmed with 1·2N-sodium hydroxide (15 ml.) until dissolved (*ca.* 3 min.). After a further 5 min. the solution was extracted with chloroform (6 × 100 ml.). The residue from evaporation of the extract recrystallised (−50°) from acetone–ether. The *formyl methylimine* (50%) had m. p. *ca.* 205° (decomp.) (Found: C, 50·6; H, 5·9; N, 33·2. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·1; N, 33·7%). Alternatively, the reaction mixture was acidified to pH 6 in order to precipitate the *hydriodide* (70%). It had m. p. 241° (from water) (Found: N, 19·0. $C_7H_9IN_4$ requires N, 19·1%).

(*b*) The dimethylguanidine (see above) (0·5 g.) was added to 1·2N-sodium hydroxide (5 ml.) at 50°. After 2 min. the formyl methylimine (52%) was extracted as above and identified by mixed m. p.

Formed similarly to its lower homologue (see above), *4-amino-5-(2,4-dinitrophenylhydrazono)methyl-2,3-dihydro-3-methyl-2-methyliminopyrimidine hydrochloride monohydrate* had m. p. 259° (from water) (Found: C, 39·0; H, 4·3. $C_{13}H_{15}ClN_8O_4·H_2O$ requires C, 39·0; H, 4·25%).

We thank Mr. B. Arantz for some assistance; M. N. P-R. thanks this University for supporting him as a Scholar.

Department of Medical Chemistry,
Australian National University,
Canberra. [5/935 *Received, September 1st*, 1965]