CCCXXIX.—*The Tautomerism of Amidines. Part VI. Methylation of 4-Anilino-2-phenyl-6-methylpyrimidine.*

By Robert Forsyth and Frank Lee Pyman.

In previous parts of this series it has been shown that methylation of glyoxalines (wholly cyclic amidines) and of open-chain amidines, by methyl salts, yields mixtures of the isomeric *N*-methyl derivatives, in which the relative amounts of the two isomerides produced vary from case to case. In some cases, the amount of one of the isomerides produced is very small; for example, benzenylphenylamidine (I or II) gave phenylmethylamidobenzenylimidine (III) in 82·7% yield, and benzenylphenylmethylamidine (IV) in 0·55% yield (Pyman, J., 1923, **123**, 3359).

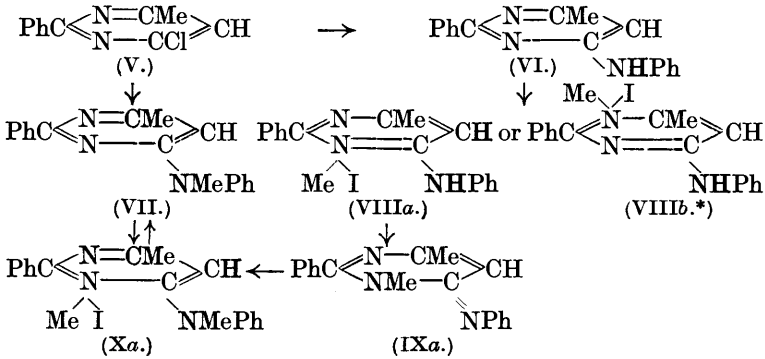
$CPh(:NPh)\cdot NH_2$ (I.) or $CPh(:NH)\cdot NHPh$ (II.) $\longrightarrow$ $CPh(:NH)\cdot NMePh$ (III.) and $CPh(:NMe)\cdot NHPh$ (IV.)

Here the formation of (IV) had escaped the notice of von Pechmann (*Ber.*, 1897, **30**, 1782), who regarded (III) as the sole product of the methylation of (I) or (II). In other cases also, one of us was able to show that the supposed homogeneous methylation of open-chain amidines was incorrect.

It seemed to us, therefore, of interest to re-examine some of the cases of alleged homogeneous methylation of partly cyclic amidines, and this paper deals with a re-investigation of the methylation of 2-phenyl-6-methyl-4-anilinopyrimidine (VI). Wheeler (*Amer. Chem. J.*, 1898, **20**, 481) states that when this base is heated with methyl iodide and methyl alcohol at 100°, it yields a methiodide (m. p. 210—213°; containing $2H_2O$) in which methyl iodide has been added to one of the tertiary nitrogen atoms of the ring, and not to the anilino-group, since this salt yields with alkali not 2-phenyl-6-methyl-4-methylanilinopyrimidine (VII), but the starting material, 2-phenyl-6-methyl-4-anilinopyrimidine. Our results show that on carrying out the reaction by the above method, *i.e.*, in the presence of methyl alcohol, the main product (79%) is the hydriodide (m. p. 238—239°; anhyd.) of unchanged 2-phenyl-6-methyl-4-anilinopyrimidine, whilst the only other product which could be isolated (yield 15%) was a methiodide, m. p. 220°, containing $2H_2O$. This separated first and is presumably identical with Wheeler's salt. On treatment with alkali, however, it does not give the original anilinopyrimidine, but loses hydriodic acid, giving a base, m. p. 193—194°, which is a methyl homologue of the anilinopyrimidine. Wheeler's recovery of the anilino-base is clearly due to the presence of its hydriodide in the product which he basified. Since the formation of the iodide of the original base was presumably due to the removal of hydriodic acid from methyl iodide and methyl alcohol, with the formation of dimethyl ether, we next heated the base with methyl iodide in the absence of methyl alcohol, and in this case obtained the methiodide, m. p. 220°, as the main product (77%), accompanied by a quantity of the starting material (11%) and an iodide B, m. p. 182—183° (7·1%). No other product could be isolated from the mixture.

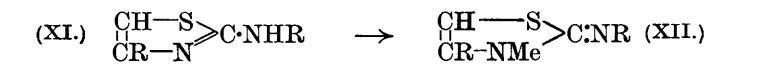
The methiodide, m. p. 220°, which is colourless, must be either 2-phenyl-3 : 6 (or 1 : 6)-dimethyl-4-anilinopyrimidinium iodide (VIII, *a* or *b*), since on treatment with alkali it does not yield the colourless base 2-phenyl-6-methyl-4-methylanilinopyrimidine (VII), but a yellow, unstable base (m. p. 193—194°) which must be either 4-*phenylimino*-2-*phenyl*-3 : 6-*dimethyl*-3 : 4-*dihydropyrimidine* (IX*a*) or 4-*phenylimino*-2-*phenyl*-1 : 6-*dimethyl*-1 : 4-*dihydropyrimidine* (IX*b*). Further methylation of this product with methyl iodide yields a salt identical with the methylation product of 2-phenyl-6-

methyl-4-methylanilinopyrimidine; it must therefore be **4-*methyl*-*anilino*-2-*phenyl*-3 : 6 (or 1 : 6)-*dimethylpyrimidinium iodide*** (X, *a* or *b*). The ***iodide B*** (m. p. 182—183°) proved to be a molecular compound of the quaternary iodide (X, *a* or *b*) with the original base (VI), and thus, whilst 95·1% of the material has been accounted for, no evidence of the formation of the methylanilino-base (VII) has been obtained.



It is interesting to note that the quaternary salt (X, *a* or *b*) loses methyl iodide on distillation, and yields the methylanilino-base (VII), that is the *N*-methyl derivative which is produced only in small quantity, if at all, on the methylation of (VI). This behaviour is similar to that of the methiodides of *N*-methyl-4(5)-nitro-(and bromo-) glyoxalines (J., 1925, **127**, 573, 1832). These also yield on distillation those tertiary bases which are produced in inferior quantity by methylation of the parent glyoxalines by methyl salts.

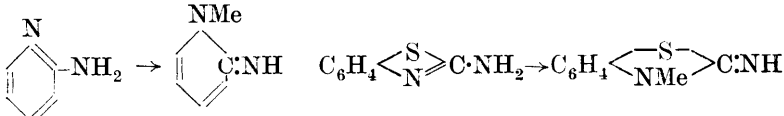
The formation of (VIII, *a* or *b*) as the main (or possibly sole) product of methylation of (VI) by methyl iodide falls into line with numerous other results of alkylation by methyl salts of those partly cyclic amidines which contain one of their nitrogen atoms as a member of an aromatic nucleus. Thus, the 2-amino-, -alkylamino-, and -anilino-thiazoles (XI) yield as main products the 3-methyl derivatives (XII) (Young and Crookes, J., 1906, **89**, 59; and previous investigators), and in these cases the isomerides methylated on the amino-group were not isolated; 2-aminopyridine (XIII) gives



1-methylpyridon-2-imide (XIV) with but little 2-methylaminopyridine (Tschitschibabin and Konowalowa, *Ber.*, 1921, **54**, 814);

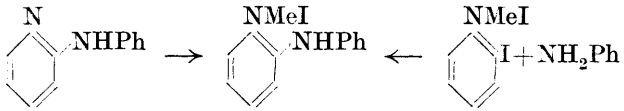
* Adoption of the formula (VIII*b*) would lead to corresponding formulæ (IX*b*) and (X*b*) with methyl attached to the 1- in place of the 3-nitrogen atom.

and 1-aminobenzthiazole (XV) gives 1-imino-2-methyl-1 : 2-dihydrobenzthiazole (XVI) with probably some 1-methylaminobenzthiazole (Hunter, this vol., p. 1385).



(XIII.) (XIV.) (XV.) (XVI.)

The main product in each case is the substance methylated on the ring nitrogen atom. The cause of this fact seems to us to lie in the structure of the molecule rather than in the relative basicity of the two nitrogen atoms. The latter explanation, which has been advanced by several previous investigators (for references, see Pyman, J., 1923, **123**, 367) to explain the results of methylating open-chain and partly cyclic amidines, seems to us unsatisfactory. It is true that in the methylation of open-chain amidines, when nitrogen atoms attached to aryl and alkyl groups are in competition, the main products are those in which the methyl group has attached itself to the arylamino-nitrogen atom, but this may be due, not to the feebler basicity of the arylamino-group, but to a tendency of the aryl group to attract the double linking into the $\alpha\beta$-position; thus the predominant formation of (III) on the methylation of (I) or (II) may be attributed to the reaction of this compound mainly in the form (I). The argument that the methylanilino-compounds are the main products because aniline is less basic than alkylamines is countered by the facts that whilst the bases NMePh·CPh:NR (R = H, CH_2Ph, Me) are the main products of methylation of NPh:CPh·NHR or NHPh·CPh:NR, proportions of the isomerides NPh:CPh·NMeR are produced which increase with the basicity of $R{\cdot}NH_2$, and further that in the methylation of NMe:CPh·NH_2 or NHMe·CPh:NH, the base NMe_2·CPh:NH, in which the more strongly basic amino-residue had become methylated, was produced in larger quantity than NHMe·CPh:NMe (Pyman, *loc. cit.*). A further argument against this view is found in the result of methylation of 2-anilinopyridine (XVII) with methyl iodide, when 2-anilinopyridine methiodide (XVIII), identical with the product of interaction of 2-iodopyridine methiodide (XIX) with aniline, is obtained, apparently

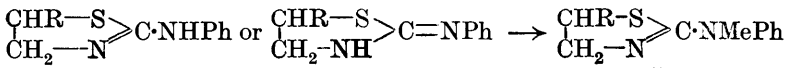


(XVII.) (XVIII.) (XIX.)

as the sole product (Steinhäuser and Diepolder, *J. pr. Chem.*, 1916, **93**, 387), for if the more feebly basic nitrogen atom had been

methylated preferentially, then 2-methylanilinopyridine should have been produced in greater quantity than (XVIII), since aniline ($K = 4{\cdot}6 \times 10^{-10}$) is a feebler base than pyridine ($K = 2{\cdot}4 \times 10^{-9}$).

Reference to the structure of the molecule, however, seems to us to give a more consistent systematisation of the results. It has been shown (compare Pyman, J., 1923, **123**, 3359) that the methylation of amidines by methyl salts leads to the attachment of the methyl group to the doubly-linked nitrogen atom in the case of open-chain and wholly cyclic amidines, and the methylation of (IX, *a* or *b*), resulting in the formation of (X, *a* or *b*) extends these proofs to a case of a partly cyclic amidine. It appears, then, that the reason why those partly cyclic amidines which contain one of their nitrogen atoms as a member of an aromatic nucleus yield with methyl salts mainly the isomerides methylated on the ring nitrogen atom, is because they tend to react mainly in the form in which the ring nitrogen atom is doubly-linked, that is, as amino-derivatives of aromatic compounds rather than as the isomeric iminodihydro-derivatives. Thus, for example, we attribute the formation of (XVI) as the main product of the methylation of 1-aminobenzthiazole to the reaction of this substance according to formula (XV) and not in the iminodihydro-form as Hunter (*loc. cit.*) believes. The common behaviour of the partly cyclic amidines derived from pyridine, pyrimidine, thiazole, and benzthiazole in yielding on methylation with methyl salts mainly compounds methylated on the ring nitrogen atom, no matter whether the side-chain nitrogen atom is present as an alkyl- or aryl-amino-group, is doubtless associated with their common feature, the aromatic character of their nuclei. Where, however, the ring is partly reduced and has lost its aromatic character, the phenyl group of an anilino-substituent can compete successfully for the proximity of the double linking, bringing it to the $\alpha\beta$-position, and thus the compounds (XX) or (XXI) yield as main products the substances (XXII), since they react mainly in the form (XXI) (Young and Crookes, *loc. cit.*).



(XX.) (XXI.) (XXII.)

EXPERIMENTAL.

2-Phenyl-6-methyl-4-hydroxypyrimidine was prepared from benzamidine and ethyl acetoacetate by Pinner's method ("Die Imidoäther," 1892, p. 240), the average yield being 97% of the theoretical of the pure compound, m. p. 223—225° (corr.) (Pinner gives m. p. 216°). From this, 2-phenyl-6-methyl-4-chloropyrimidine (V) was prepared either by the action of phosphorus pentachloride

(Pinner, *op. cit.*, p. 246) or of phosphorus oxychloride (Schmidt, *Ber.*, 1902, **35**, 1575). In each case, the crude product was purified from phosphorus compounds by crystallisation from ether (these separating first) and gave the pure substance, m. p. 71° as stated by previous authors, in yields of 88 and 85% respectively.

2-Phenyl-6-methyl-4-anilinopyrimidine (VI) was prepared by a modification of Pinner's method (*op. cit.*, p. 248). Aniline (2 mols.) was added to an ethereal solution of 2-phenyl-6-methyl-4-chloropyrimidine (1 mol.), and the ether distilled off. On heating the mixture to 100°, an exothermic reaction took place, and the product solidified. After basifying and removing excess of aniline by distillation with steam, the anilino-base separated and was recrystallised from alcohol, from which it separates in coarse, colourless, prismatic needles, m. p. 161—162° (corr.), in 97% yield. (Pinner gives m. p. 150—153°, Wheeler 160—161°.)

The hydrochloride separates from warm dilute hydrochloric acid as a gelatinous mass, but crystallises from alcohol in fine, colourless needles, m. p. 258—259° (corr.), which are anhydrous (Found : Cl, 12·1. Calc. : Cl, 11·9%). (Pinner and Wheeler both give m. p. 240°.)

The hydriodide crystallises from water or alcohol in fine, colourless needles, m. p. 238—239° (corr.), which are anhydrous and sparingly soluble in water, but more readily soluble in alcohol (Found : I, 32·9. Calc. : I, 32·7%). (Wheeler gives m. p. 231°.)

The nitrate crystallises from dilute nitric acid in rosettes of fine, opaque needles, containing $1H_2O$, which is lost in a vacuum over sulphuric acid (Found : loss, 4·9; N, 16·6. $C_{17}H_{15}N_3,HNO_3,H_2O$ requires H_2O, 5·3; N, 16·4%). The air-dried salt sinters at 95—100° and finally melts sharply at 155—156° (corr.). The vacuum-dried salt melts at 158—159° (corr.). (Pinner gives m. p. 85—87°.)

The *hydrogen oxalate* crystallises from a large volume of alcohol in fine, feathery needles, m. p. 242—243° (decomp.; corr.), which are anhydrous (Found : C, 64·9; H, 5·0. $C_{17}H_{15}N_3,C_2H_2O_4$ requires C, 64·9; H, 4·8%).

The *picrate* crystallises from alcohol in clusters of yellow, prismatic needles, m. p. 195—196° (decomp.; corr.) (Found : N, 16·8. $C_{17}H_{15}N_3,C_6H_3O_7N_3$ requires N, 17·1%).

Methylation.—(*A*) *In the presence of methyl alcohol.* 2-Phenyl-6-methyl-4-anilinopyrimidine (6·525 g.), methyl alcohol (6 c.c.), and methyl iodide (3 c.c.) were heated for 7 hours at 100°. On cooling, pale yellow needles (4·9 g.; m. p. 207—210°) separated, and further crops of crystalline hydriodides were obtained on concentration. After prolonged fractional crystallisation from alcohol, these gave first 2-phenyl-3 : 6 (or 1 : 6)-dimethyl-4-anilinopyrimidinium

iodide (1·677 g.; m. p. 216°), then 2-phenyl-6-methyl-4-anilinopyrimidine hydriodide [5·087 g.; m. p. 235—236° (corr.)], which did not depress the m. p. of a known specimen. The bases in the mother-liquors were worked up first as hydrogen oxalates, and then as picrates, further quantities of the salts of the starting material being obtained [0·796 g. of hydrogen oxalate, m. p. 241—242° (corr.), and 2·12 g. of picrate, m. p. 195°, both identified by the mixed m. p. method]. The yield of 2-phenyl-6-methyl-4-anilinopyrimidine recovered is thus 78·77% and that of the methylated product 15·28%, the total material recovered being 94·05%.

(*B*) *In the absence of methyl alcohol.* 2-Phenyl-6-methyl-4-anilinopyrimidine (26·1 g.) and methyl iodide (6·8 c.c.) were heated for 3 hours at 100°. Fractional crystallisation of the products from alcohol gave first 2-phenyl-3 : 6 (or 1 : 6)-dimethyl-4-anilinopyrimidinium iodide (m. p. 220°; yield 33·854 g., 77·1%) and then iodide B (m. p. 182—183°; yield 2·393 g., 7·37%). The mother-liquors were evaporated to dryness and extracted with ether, which removed unchanged 2-phenyl-6-methyl-4-anilinopyrimidine as base (m. p. 157—159°; yield 0·81 g., 3·1%). The material undissolved in ether was dissolved in water and basified, when 2·52 g. of base, m. p. 147—152°, were precipitated, and a small quantity of oily base was collected by means of ether. Both fractions were converted into picrates, and gave 2-phenyl-6-methyl-4-anilinopyrimidine picrate (m. p. 195°; yield 3·883 g., 7·92%), which was identified by the mixed melting-point method.

4-*Anilino*-2-*phenyl*-3 : 6 (or 1 : 6)-*dimethylpyrimidinium iodide* (VIII, *a* or *b*) crystallises from moist alcohol in long, colourless needles containing $2H_2O$, which is lost at 110°, the dried salt then melting at 220° (corr.). It is sparingly soluble in water and organic solvents (Found, in air-dried salt: H_2O, 8·8, 8·4; I, 29·0. $C_{18}H_{17}N_3,HI,2H_2O$ requires H_2O, 8·2; I, 28·9%. Found, in dried salt: C, 53·7, 53·8; H, 4·5, 4·7. $C_{18}H_{17}N_3,HI$ requires C, 53·6; H, 4·5%).

The *chloride* was prepared by digesting the above salt in hot water with silver chloride. It crystallises from water in fine, colourless needles containing $1H_2O$, which is lost at 110°, the dried salt then melting at 231—232° (corr.). It is fairly readily soluble in water or alcohol (Found, in air-dried salt: H_2O, 4·7. $C_{18}H_{17}N_3,HCl,H_2O$ requires H_2O, 5·5%. Found, in dried salt: C, 69·5, 69·3; H, 5·8, 5·8. $C_{18}H_{17}N_3,HCl$ requires C, 69·3; H, 5·8%).

4-*Phenylimino*-2-*phenyl*-3 : 6 (or 1 : 6)-*dimethyl*-3 : 4 (or 1 : 4)-*dihydropyrimidine* (IX, *a* or *b*) was prepared by basifying the aqueous solution of the above chloride with sodium carbonate, collecting the precipitated yellow base with chloroform and removing the solvent,

after drying the solution with potassium carbonate, under diminished pressure at room temperature. This course is necessary since the base decomposes when heated in chloroform solution. This base crystallises from acetone in canary-yellow, prismatic needles, m. p. 193—194° (corr.), which are insoluble in water, fairly readily soluble in acetone or chloroform, more readily soluble in alcohol, but sparingly soluble in ether (Found: C, 79·0, 78·6; H, 6·0, 6·1. $C_{18}H_{17}N_3$ requires C, 78·6; H, 6·2%).

Iodide B crystallises from alcohol in colourless needles, m. p. 182—183° (corr.), which are anhydrous and moderately soluble in hot alcohol, but sparingly soluble in water, acetone or cold alcohol (Found: C, 64·5, 64·2, 64·0, 63·2; H, 5·4, 5·4, 5·4, 5·2; N, 13·1, 13·5; I, 19·9, 20·0. $C_{17}H_{15}N_3,C_{19}H_{20}N_3I$ requires C, 63·7; H, 5·2; N, 12·4; I, 18·7%). It proved to be a compound of 2-phenyl-6-methyl-4-anilinopyrimidine and 2-phenyl-3 : 6 (or 1 : 6)-dimethyl-4-methylanilinopyrimidinium iodide in equimolecular proportions, and was prepared synthetically by crystallising equimolecular proportions of these compounds from alcohol, the specimen so obtained having m. p. 182—183° (corr.) alone or mixed with iodide B. When iodide B (0·385 g.) was digested with silver chloride and hot water for many hours and the product filtered, the insoluble matter gave on extraction with ether 0·148 g. of 2-phenyl-6-methyl-4-anilinopyrimidine as base (m. p. 159—160°, alone or mixed with a known specimen); the filtrate when basified gave only a trace of material to ether.

2-Phenyl-6-methyl-4-methylanilinopyrimidine (VII) was prepared from 2-phenyl-6-methyl-4-chloropyrimidine and methylaniline, in the same way as the anilino-base, in practically theoretical yield. It melted at 113° (corr.) (Wheeler gives 113°). The *hydrogen oxalate* crystallises from alcohol, in which it is fairly readily soluble, in small, colourless prisms, m. p. 182—183° (decomp.; corr.) (Found: C, 66·0; H, 5·1. $C_{18}H_{17}N_3,C_2H_2O_4$ requires C, 65·8; H, 5·2%). The *picrate* crystallises from alcohol in long, yellow needles, m. p. 174—175° (corr.). It is sparingly soluble in water and fairly readily soluble in alcohol (Found: N, 16·9. $C_{18}H_{17}N_3,C_6H_3O_7N_3$ requires N, 16·7%).

4-Methylanilino-2-phenyl-3 : 6 (or 1 : 6)-dimethylpyrimidinium iodide (X, *a* or *b*) was prepared both from 2-phenyl-3 : 6 (or 1 : 6)-dimethyl-4-phenylimino-3 : 4-dihydropyrimidine and from 2-phenyl-6-methyl-4-methylanilinopyrimidine by heating with excess of methyl iodide for 8 hours at 100°, the respective yields of pure salt isolated being 76 and 48% of the theoretical. The pure salt from either source and a mixture of the two specimens had m. p 215° (decomp.; corr.). It crystallised from acetone in colourless

anhydrous, prismatic needles. It is sparingly soluble in water, readily in alcohol, and fairly readily in acetone [Found (in salt from IX): I, 30·3; (in salt from VII): I, 30·5. $C_{19}H_{20}N_3I$ requires I, 30·5%].

Demethylation. The above salt, prepared from (IX), (0·5 g.) was heated to its m. p. under 15 mm. pressure, methyl iodide being thus removed. On crystallisation of the residue from acetone, 2-phenyl-6-methyl-4-methylanilinopyrimidine, m. p. 113°, was obtained, and recognised by the mixed melting-point method; yield 0·2 g., 60%.

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