515. *Substitution Reactions of Pyrimidine and its 2- and 4-Phenyl Derivatives.*

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Factors which may influence the course of catalytic dehalogenation of chloropyrimidines are considered and conditions for the preparation of pyrimidine itself on a half-molar scale from its 2 : 5-dichloro-compound are defined. Pyrimidine resisted attempted nitration; its 2-phenyl derivative underwent nitration *meta* in the benzene nucleus; its 4-phenyl derivative probably behaves similarly. The behaviour of pyrimidine with free *p*-nitrophenyl radical in the Gomberg–Hey reaction has been studied and compared with that of pyridine.

The present work was prompted by a wish to find out how far the analogy between pyrimidine and pyridine derivatives (compare Lythgoe, *Quart. Reviews*, 1949, **3**, 194) is valid for the parent compound pyrimidine and its alkyl and aryl derivatives. The behaviour of pyridine towards electrophilic, nucleophilic, and free-radical reagents is well known and highly characteristic; little more is known about pyrimidine in this connection than that the nucleophilic substitution of its 4-methyl derivative by sodamide parallels that of pyridine, giving a 2-amino- and a 2 : 6-diamino-compound (Ochiai and Karii, *J. Pharm. Soc. Japan*, 1939, **59**, 18). It therefore seemed of interest to study the effect of a free-radical substituting agent on pyrimidine and also to determine whether the nucleus is as resistant to electrophilic substitution as might be expected theoretically.

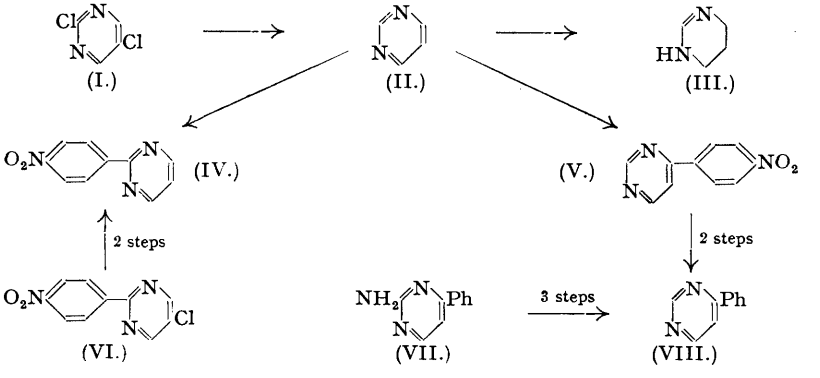
Pyrimidine was first prepared by reducing its 2 : 4 : 6-trichloro-derivative with zinc dust and water (Gabriel and Colman, *Ber.*, 1900, **33**, 3666), and more recently Cavalieri and Bendich (*J. Amer. Chem. Soc.*, 1950, **72**, 258) obtained it by desulphurising 2 : 6-dimercaptopyrimidine with Raney nickel. These and the other known methods give poor yields, and would probably not be suitable for its preparation in quantity. At the outset of this work a direct synthesis from formamidine and β-ethoxyacraldehyde acetal was contemplated, but in model experiments this acetal could not be condensed with benzamidine, and soon afterwards Price and Zomlefer (*J. Org. Chem.*, 1949, **14**, 210) reported that it did not condense with acetamidine. Attention was therefore given to the catalytic reductive dehalogenation of chloropyrimidines.

This method has been used to prepare many aminopyrimidine derivatives but is less successful in its application to true pyrimidines, *i.e.*, those carrying only alkyl or aryl substituents, where strict neutrality of the medium may be necessary to avoid both halogen replacement by solvent action and nuclear hydrogenation. Dihydroiminopyrimidines (2-, 4-, or 6-aminopyrimidines) are only difficultly hydrogenated in the nucleus; the reduction of 4-amino-6-chloro-2-methylpyrimidine stops at the stage of 4-amino-2-methylpyrimidine even when hydrochloric acid is present (Földi, Fodor, Demjen, Szekeres, and Halmos, *Ber.*, 1942, **75**, 755); on the other hand the halogen atoms in compounds such as 2-amino-4-chloropyrimidine are relatively unreactive, so that their reduction can usually be carried out

safely in the presence of alkali (cf. Roblin, Williams, Winnek, and English, *J. Amer. Chem. Soc.*, 1940, **62**, 2002). Nuclear hydrogenation of true pyrimidines is catalysed by acids, as now shown for pyrimidine itself, so that for success in dehalogenation of their chloro-derivatives the presence of a base is desirable to neutralise the hydrogen chloride set free in the reaction. Thus 5-chloro-2-phenylpyrimidine absorbed 3 molar proportions of hydrogen in the presence of palladised barium sulphate, giving 1 : 4 : 5 : 6-tetrahydro-2-phenylpyrimidine, identical with the product obtained by Aspinall (*J. Amer. Chem. Soc.*, 1940, **62**, 2160), who cyclised monobenzoyltrimethylenediamine by heating it with calcium oxide. Davies and Piggott (*J.*, 1945, 348) observed a similar reduction of 4-chloro-5-phenylpyrimidine to a tetrahydro-5-phenylpyrimidine in the presence of palladised calcium carbonate; here the nuclear reduction appears to be promoted even by the weak carbonic acid, and a similar reduction encountered in the present work is recorded below. In view of these results it is rather surprising that Miyaki and Kataoka (*J. Pharm. Soc. Japan*, 1940, **60**, 367) were able to prepare 4-phenylpyrimidine and 4-methylpyrimidine by dehalogenating their 2 : 6-dichloro-compounds in the presence of palladised calcium carbonate; what yields were obtained is not known to us, as we were able to consult their paper only in abstract.

The suppression of nuclear reduction in the presence of aqueous sodium hydroxide was shown by the successful reduction of 5-chloro-2-phenylpyrimidine to 2-phenylpyrimidine and of 4-chloro-5-phenylpyrimidine to 5-phenylpyrimidine. Where the compound to be dehalogenated contains a halogen atom more reactive than those in the above examples, and especially when di- and tri-chloro-compounds are concerned, the presence of even quite dilute sodium hydroxide solution causes solvolytic replacement of chlorine, so that poor yields are obtained. The disparity between the hydrogen uptake and the amount of chloride ion liberated in earlier unsuccessful attempts in this laboratory to prepare pyrimidine by catalytic dehalogenation of its 2 : 4 : 6-trichloro- and its 2 : 6-dichloro-derivatives is one example of the incidence of this replacement reaction; another is mentioned below.

The above considerations dictated the preference for 2 : 5-dichloropyrimidine (I) rather than its 2 : 6-isomer as starting material for the preparation of pyrimidine; the chlorine atom at position 5 in (I) is quite stable and that at 2 not unduly reactive towards water and alcohols. The preparation of (I), although tedious, can be carried out in quantity; guanidine and tetrachloropropene condense to give 2-amino-5-chloropyrimidine (Roblin, Winnek, and English, *J. Amer. Chem. Soc.*, 1942, **64**, 567), the amino-group of which can then be replaced successively by hydroxyl and chlorine (English, Clark, Shepherd, Marson, Krapcho, and Roblin, *ibid.*, 1946, **68**, 1039).



Reduction of (I) with hydrogen and palladised barium sulphate in dilute sodium hydroxide solution was unsatisfactory, because some 5-chloro-2-hydroxypyrimidine was formed, and similarly the use of methanol containing suspended barium oxide gave 5-chloro-2-methoxypyridimidine. When water, alone or containing suspended calcium carbonate, was used as solvent 4 molar proportions of hydrogen were absorbed without any definite break in the hydrogenation curve, giving a tetrahydropyrimidine, characterised as its crystalline oxalate. It is formulated as 1 : 4 : 5 : 6-tetrahydropyrimidine (III) by analogy with the 1 : 4 : 5 : 6-tetrahydro-2-phenylpyrimidine mentioned above. Satisfactory results were obtained when (I) was hydrogenated in water containing suspended magnesium oxide. The rate of hydrogen uptake decreased after 2 molar proportions had been absorbed, and by stopping the reaction then

pyrimidine (II) was obtained as the main product, contaminated only by small amounts of 5-chloropyrimidine and of tetrahydropyrimidine. The latter was eliminated by precipitating the pyrimidine as its mercuric chloride complex in weakly acidic solution; the tetrahydro-compound forms a complex which is soluble below pH *ca.* 5. The pyrimidine was then regenerated and obtained pure in about 45% yield by fractional distillation. Pyrimidine should not be dried over potassium hydroxide, which slowly decomposes it; when heated with 30% potassium hydroxide solution it gave 1·8 mols. of volatile base (mainly ammonia).

As a way of determining which nuclear positions of pyrimidine are most susceptible to attack by free-radical reagents it was subjected to a Gomberg–Hey reaction, the mechanism of which has been established by Hey and his colleagues (for references, see " Organic Reactions," Vol. II, Chap. 6). To secure good yields and readily crystallising products diazotised *p*-nitroaniline was used as the second component, and because pyrimidine is neutral the reaction was carried out in the presence of sodium acetate (Elks, Haworth, and Hey, *J.*, 1940, 1285). Chromatography of the product on aluminium oxide gave two pure compounds, namely, 2-*p*-nitrophenylpyrimidine (IV) (yield, 10%) and 4-*p*-nitrophenylpyrimidine (V) (yield, 14%). The identification of (IV) was effected by an independent synthesis as follows. Chloromalondialdehyde and *p*-nitrobenzamidine condensed to give 5-chloro-2-*p*-nitrophenylpyrimidine (VI) which was reduced to 2-*p*-aminophenylpyrimidine; this was diazotised and converted into the corresponding nitro-compound (IV) by the method of Hodgson, Mahadevan, and Ward (*J.*, 1947, 1392).

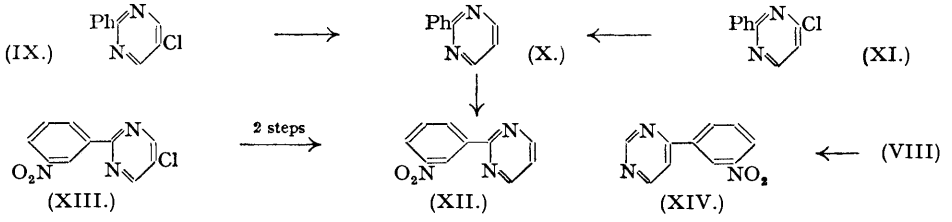
2-Amino-4-phenylpyrimidine (VII) can be made by condensing guanidine and benzoylacetaldehyde (Sprague, Kissinger, and Lincoln, *J. Amer. Chem. Soc.*, 1941, **63**, 3028) and, as shown below, can be used as starting material for a synthesis of 4-phenylpyrimidine. A similar synthesis of (VI) through 2-amino-4-*p*-nitrophenylpyrimidine from guanidine and *p*-nitrobenzoylacetaldehyde was projected, and to this end the latter compound was prepared from ethyl formate and *p*-nitroacetophenone, but it could not be caused to condense with guanidine. The structure of (VI) was therefore established by reducing it to 4-*p*-aminophenylpyrimidine, which when diazotised and treated with hypophosphorous acid gave 4-phenylpyrimidine (VIII). The latter has been described by Miyaki and Kataoka (*loc. cit.*), but for the present work it was obtained by exchanging the amino-group of (VII) successively by hydroxyl, chlorine, and hydrogen, which gave a product identical with that obtained from (V). The same compound was also obtained in low yield from the products of decomposition of *N*-nitrosoacetanilide in pyrimidine solution (cf. Haworth, Heilbron, and Hey, *J.*, 1940, 349, 373).

The reaction between pyridine and diazotised *p*-nitroaniline (Haworth, Heilbron, and Hey, *loc. cit.*) gave a product from which, by fractional crystallisation, *p*-nitrophenyl derivatives of pyridine were isolated in approximately the following yields: 2-isomer, 14·5%; 3-isomer, 5%; 4-isomer, 2·5%. The nuclear position adjacent to the nitrogen atom is here the most susceptible to attack, and on this basis the results obtained with pyrimidine are readily understood. Position 2 in the pyrimidine nucleus is adjacent to, and activated by, both nitrogen atoms, so that it is the most reactive position. Positions 4 and 6, each adjacent to one of the nitrogen atoms, are next in order of reactivity, and since substitution at either position gives the same product (V), this becomes the major product of the reaction. It would probably be unwise to attach too much significance to the failure to isolate any 5-*p*-nitrophenylpyrimidine, because of the small scale of the experiment, but it is clear that it cannot have been formed at all extensively.

Towards electrophilic substitution the pyrimidine nucleus should, theoretically, be even more resistant than that of pyridine, and it is probably significant that such substitutions have been carried out only on those pyrimidine derivatives which contain at least one activating hydroxyl, amino-, or similar group. The nitration of pyrimidine was attempted under conditions similar to those which have been used successfully for pyridine, but no nitro-compound could be isolated, so in order to secure more positive confirmation of the inertness of the nucleus the nitration of 2- and 4-phenylpyrimidines was investigated.

A compound described as 2-phenylpyrimidine was obtained by Cherbuliez and Stavritch (*Helv. Chim. Acta*, 1922, **5**, 267) who cyclised benzylideneasparagine with hypobromite to give 5-bromo-6-hydroxy-2-phenylpyrimidine and then replaced the substituents at positions 5 and 6 by hydrogen. As this method seemed inconvenient, alternatives were sought. Reductive deamination of 5-amino-2-phenylpyrimidine, obtained by reducing 5-nitro-2-phenylpyrimidine, was not found possible, since the amino-compound could not be diazotised to give a compound capable, for example, of coupling with β-naphthol. Instead, a satisfactory method was found in the catalytic reduction of 5-chloro-2-phenylpyrimidine (IX) obtained by condensing

benzamidine and chloromalondialdehyde. The 2-phenylpyrimidine (X) obtained in this way was different from that described by the Swiss workers, but its authenticity was shown by two further methods of synthesis, each of which gave the same product. In the first, the 1 : 4 : 5 : 6-tetrahydro-2-phenylpyrimidine mentioned earlier was dehydrogenated in good yield by heating



it with platinised charcoal in a current of carbon dioxide; in the second, 4-chloro-2-phenylpyrimidine was catalytically dehalogenated. Cherbuliez and Stavritch's compound cannot have the structure assigned to it, and the intermediates from which it was obtained must be regarded with some reserve.

Only one pure compound could be isolated from the product of nitration of (X); it was identified as 2-*m*-nitrophenylpyrimidine (XII) by an independent synthesis. Chloromalondialdehyde and *m*-nitrobenzamidine condensed to give 5-chloro-2-*m*-nitrophenylpyrimidine (XIII) which was reduced to 2-*m*-aminophenylpyrimidine and the amino-group was replaced by a nitro-group. The formation of (XII) from (X) made it likely that the unidentified nitro-compound which Ochiai *et al.* (*J. Pharm. Soc. Japan*, 1939, **59**, 462) obtained by nitrating 4 : 6-dimethyl-2-phenylpyrimidine would prove to be 4 : 6-dimethyl-2-*m*-nitrophenylpyrimidine, and not 4 : 6-dimethyl-5-nitro-2-phenylpyrimidine, under which name it is, for reasons which are not clear, indexed in *Chemical Abstracts* (1940, **34**, 102). This view was shown to be correct by a synthesis of the same compound from *m*-nitrobenzamidine and acetylacetone. Again only one pure compound could be isolated (and that in only moderate yield) from nitration of 4-phenylpyrimidine. Although its structure has not been proved completely it is almost certainly 4-*m*-nitrophenylpyrimidine (XIV); it differs from 4-*p*-nitrophenylpyrimidine and, in view of the results presented above, the possibility that the nitro-group entered the pyrimidine nucleus seems remote.

It is of interest to compare these results with those obtained when 2- and 4-phenylpyridines are nitrated (Forsyth and Pyman, *J.*, 1926, 2912; cf. Schofield, *Quart. Reviews*, 1950, **4**, 400). Substitution then occurs in the benzene, not the pyridine, nucleus and, although *op*-substitution predominates, considerable amounts (*ca.* 30%) of *m*-nitrophenyl derivatives are formed. The phenylpyrimidines also undergo substitution in the benzene nucleus preferentially, but apparently the deactivating effects of both nitrogen atoms are together strong enough to suppress *op*-substitution almost completely, and the *m*-nitrophenyl derivatives are the major products, just as happens with 2 : 4 : 6-triphenyl-1 : 3 : 5-triazine, which is nitrated to a tri-*m*-nitrophenyltriazine (Claus, *J. pr. Chem.*, 1895, [ii], **51**, 399).

Experimental.

5-Chloropyrimidines.—*2 : 5-Dichloropyrimidine.* Condensation of tetrachloropropene and guanidine in 20% fuming sulphuric acid (Roblin *et al.*, *loc. cit.*) gave 2-amino-5-chloropyrimidine (yield, 83%) which was converted into the dichloro-compound (yield, 50%) by a slight modification of the two-step method of English *et al.* (*loc. cit.*).

5-Chloro-2-phenylpyrimidine. After many trials, the following method was found to give the best results. Chloromalondialdehyde (5 g.; Cornforth *et al.*, *J.*, 1949, 1550) and benzamidine hydrochloride dihydrate (9·2 g.) were dissolved in methanol (50 c.c.) to which 6·2% aqueous sodium hydroxide was added (26·5 c.c.). The precipitate was collected after 16 hours; the filtrate was adjusted to pH 3·9 by addition of concentrated hydrochloric acid, kept for 15 minutes. and then adjusted to pH 10 by the addition of 10% aqueous sodium hydroxide. A further precipitate formed slowly; it was collected after 20 hours, and the filtrate retreated as before. This process was repeated four times. The combined precipitates (3·54 g.) crystallised from dilute methanol giving the pure chloro-compound, m. p. 96° (Found: C, 63·2; H, 4·1; N, 14·7. Calc. for $C_{10}H_7N_2Cl$: C, 63·0; H, 3·7; N, 14·7%).

5-Chloro-2-m-nitrophenylpyrimidine. Chloromalondialdehyde (2·44 g.) and *m*-nitrobenzamidine hydrochloride (4·61 g.) were condensed in the manner described above, and the crude product (yield, 40%) sublimed in a vacuum, giving *5-chloro-2-m-nitrophenylpyrimidine*, m. p. 172—173° (Found: C, 51·3; H, 2·5; N, 17·9. $C_{10}H_6O_2N_3Cl$ requires C, 51·0; H, 2·5; N, 17·8%).

5-Chloro-2-p-nitrophenylpyrimidine. Prepared in a similar manner, the *5-chloro-2-p-nitrophenylpyrimidine* (yield, 35%) had m. p. 228° (Found: C, 51·0; H, 2·5; N, 17·8%).

Catalyst for Dehalogenation of Chloropyrimidines.—5% Palladised barium sulphate (Mozingo, *Org. Synth.*, **26**, 77) was used as the catalyst throughout.

Reduction of 2 : 5-Dichloropyrimidine in the Presence of Magnesium Oxide: Preparation of Pyrimidine.—The dichloro-compound (20·6 g.), magnesium oxide (6 g.), and catalyst (2 g.) in water (200 c.c.) were shaken with hydrogen at room temperature and pressure till 5·7 l. had been absorbed (*ca.* 12 hours). After removal of the catalyst the solution was treated with mercuric chloride solution containing enough hydrochloric acid to keep the pH at 3—5, and the precipitate collected, washed, and dried. Combined material (110 g.) from three such experiments was distilled with sodium sulphide (115 g. of nonahydrate), and the distillate saturated with potassium carbonate, giving an upper pyrimidine layer (24 c.c.) and a lower alkaline layer (108 c.c.). The latter was extracted with ether and the extract combined with the pyrimidine layer, dried ($CaSO_4$), and freed from ether. The residue was fractionally distilled through a small and efficient column (Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 299). Several fractions were collected in the b. p. range 121—123°; all solidified at room temperature (18°); the best fractions had m. p. 21·7°. The yield of substantially pure material was 42%. *Pyrimidine oxalate*, formed by mixing ethereal solutions of the two components, separated from alcohol as crystals, m. p. 160° (decomp.) and had the following light-absorption in water: $\lambda_{max.}$, 242·5 (ε, 2850); $\lambda_{min.}$, 221 (ε, 1015); $\lambda_{inflexion}$, 263—270 mμ. (ε, 415) (Found: C, 42·6; H, 3·7; N, 16·3. $C_4H_4N_2,C_2H_2O_4$ requires C, 42·4; H, 3·5; N, 16·5%).

Pyrimidine gave with aqueous solutions of copper sulphate and ammonium thiocyanate a green insoluble *complex*, analogous to that formed by pyridine [Found: N, 24·5. $(C_4H_4N_2)_2Cu(SCN)_2$ requires N, 24·7%). In solution in 0·1N-sodium hydroxide pyrimidine absorbed hydrogen in the presence of palladised barium sulphate only slowly; the rate of hydrogen uptake was increased 20-fold when the solution was made *ca.* 0·1N. with respect to hydrochloric acid.

In one experiment the hydrogenation of 2 : 5-dichloropyrimidine was stopped before the theoretical amount of hydrogen for replacement of both chlorine atoms had been absorbed. The product, isolated by fractional distillation, consisted of pyrimidine and a higher-boiling fraction from which a crystalline chloro-compound, m. p. 36·5°, was isolated. 2-Chloropyrimidine has m. p. 65° (see McOmie and Boarland, *Chem. and Ind.*, 1950, **31**, 602), so the compound must be *5-chloropyrimidine* (Found: C, 42·2; H, 2·4; N, 24·4. $C_4H_3N_2Cl$ requires C, 41·9; H, 2·6; N, 24·4%). It formed a white insoluble complex with mercuric chloride.

Attempted Reduction of 2 : 5-Dichloropyrimidine in the Presence of Alkali.—The dichloro-compound (1 g.), barium oxide (1 g.), and catalyst (1 g.) were shaken in methanol (35 c.c.) with hydrogen for 2 hours, but none was absorbed. Isolation in the usual way followed by sublimation in a vacuum gave *5-chloro-2-methoxypyrimidine*, m. p. 51·5° (Found: C, 41·9; H, 3·7; N, 19·6. $C_5H_5ON_2Cl$ requires C, 41·5; H, 3·5; N, 19·4%).

Reduction of 2 : 5-Dichloropyrimidine without Removal of Acid.—The dichloro-compound (5·2 g.), catalyst (1 g.), and water (100 c.c.) were shaken with hydrogen till no more was absorbed (uptake, 2·95 l.; 4 mols. of H_2 require 3·2 l.). The catalyst was removed, and the filtrate evaporated to small volume under reduced pressure, made alkaline, and extracted with ether. Treated with ethereal oxalic acid, the dried ethereal extract gave *tetrahydropyrimidine oxalate*, m. p. 151·5° (decomp.) (from alcohol), depressed on admixture with pyrimidine oxalate (Found: C, 41·5; H, 6·2; N, 16·1. $C_4H_8N_2,C_2H_2O_4$ requires C, 41·4; H, 5·8; N, 16·1%). The same material was obtained when the reduction was carried out in the presence of calcium carbonate.

Reduction of 4-Chloro-5-phenylpyrimidine.—The chloro-compound (0·5 g.; Davies and Piggott, *loc. cit.*) and catalyst (0·5 g.) were shaken in methanol (40 c.c.) containing 10% aqueous sodium hydroxide (1·5 c.c.) with hydrogen, of which 1·4 mols. were absorbed. The product was treated with picric acid, giving *5-phenylpyrimidine picrate*, m. p. 120° (from alcohol) (Found: C, 49·5; H, 3·2; N, 18·0. $C_{10}H_8N_2,C_6H_3O_7N_3$ requires C, 49·6; H, 2·9; N, 18·2%). Davies and Piggott record for 5-phenyltetrahydropyrimidine picrate m. p. 201—202°.

Reduction of 5-Chloro-2-phenylpyrimidine.—(*a*) The chloro-compound (5·52 g.), catalyst (1 g.), methanol (200 c.c.), and 10% aqueous sodium hydroxide (15 c.c.) were shaken together at 25° with hydrogen, of which 1 mol. was absorbed. The product was isolated in the usual way and sublimed in a vacuum, giving *2-phenylpyrimidine* (4·2 g.), m. p. 37—38° (Found: C, 76·9; H, 5·0; N, 18·3. $C_{10}H_8N_2$ requires C, 76·9; H, 5·1; N, 18·0%). Cherbuliez and Stavritch (*loc. cit.*) record m. p. 128° for a compound to which this structure was assigned.

(*b*) When the chloro-compound (0·84 g.), catalyst (1 g.), and methanol (20 c.c.) were shaken with hydrogen, 3 mols. were absorbed. Removal of catalyst and solvent, and crystallisation of the residue from alcohol, gave 1 : 4 : 5 : 6-*tetrahydro-2-phenylpyrimidine hydrochloride*, m. p. 243·5° (Found: C, 60·6; H, 6·3; N, 14·3. $C_{10}H_{12}N_2,HCl$ requires C, 61·1; H, 6·6; N, 14·2%). The free base had m. p. 86—87°, in agreement with Aspinall (*loc. cit.*), and the picrate, m. p. 180°.

The free base (100 mg.) and platinised charcoal (Linstead's catalyst-d; *J.*, 1940, 1127) were heated together at 260—270° in a current of carbon dioxide for 3 hours and the product (70 mg.; m. p. 34—36°) extracted from the cooled mixture with ether. Sublimation in a vacuum gave 2-phenylpyrimidine, m. p. 36·5°, undepressed on admixture with material obtained by method (*a*) above.

Reduction of 4-Chloro-2-phenylpyrimidine.—The chloro-compound (0·5 g.), catalyst (0·5 g.), and methanol (25 c.c.) containing 10% aqueous sodium hydroxide (1·5 c.c.) were shaken together with hydrogen, of which 1 mol. was absorbed in 2 hours. Isolation in the usual way gave 2-phenylpyrimidine, m. p. 36—37°.

Reduction of 2-Chloro-4-phenylpyrimidine.—The chloro-compound (1·07 g.; prepared as described below) was reduced just as described for 4-chloro-2-phenylpyrimidine. Crystallised from aqueous

alcohol, the 4-phenylpyrimidine had m. p. 61—62°. We were unable to duplicate the m. p. 66—67° recorded for this compound by Ochiai and Kataoka (*loc. cit.*).

Reduction of 5-Chloro-2-nitrophenylpyrimidines.—These reductions were carried out in the presence of aqueous sodium hydroxide in methanol, as described for the parent 5-chloro-2-phenylpyrimidine. The products were obtained in almost quantitative yield and were purified by sublimation in a vacuum.

2-m-*Aminophenylpyrimidine* had m. p. 100° (Found : C, 69·7; H, 5·2; N, 24·9. $C_{10}H_9N_3$ requires C, 70·2; H, 5·3; N, 24·6%).

2-p-*Aminophenylpyrimidine* had m. p. 145—146° (Found : C, 70·4; H, 5·3; N, 24·5%).

2-*Hydroxy*-4-*phenylpyrimidine.*—The 2-amino-4-phenylpyrimidine required for this preparation was obtained by the following modification of the method used by Sprague *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3028), who obtained a yield of only 10%. Guanidine nitrate (3·5 g.), sodiobenzoylacetaldehyde (4 g.), and pyridine (15 c.c.) were heated together under reflux for 4 hours. The pyridine was removed under reduced pressure, a little sodium hydroxide solution added to the residue, the insoluble material collected and dissolved in dilute hydrochloric acid, and the filtered solution made alkaline. The amino-compound (1·7 g., 42%) was collected and after recrystallisation from dilute alcohol had m. p. 165°.

To a stirred solution of the amino-compound (13·4 g.) in 12% sulphuric acid (160 c.c.) containing a little octanol a solution of sodium nitrite (10 g.) in water (30 c.c.) was added slowly, whilst the temperature was kept below 10°. Stirring was then continued at room temperature for 6 hours, after which the solution was kept overnight, then filtered, and the filtrate adjusted to pH *ca.* 3, with concentrated aqueous ammonia. The precipitate, collected and recrystallised from alcohol, gave 2-*hydroxy*-4-*phenylpyrimidine* (6 g.), m. p. 240—241° (Found : N, 16·0. $C_{10}H_8ON_2$ requires N, 16·3%). Addition of more ammonia to the filtrate of pH 3 precipitated unchanged starting material (6 g.).

2-*Chloro*-4-*phenylpyrimidine.*—The above hydroxy-compound (2·83 g.) and phosphoryl chloride (15 c.c.) were heated together under reflux for 1½ hours and the solution kept overnight and then poured on crushed ice. The solid was collected and the filtrate made alkaline with aqueous sodium carbonate and extracted with ether. The ether was removed, and the residue combined with the solid referred to above and sublimed in a vacuum. The chloro-compound (1·4 g., 45%) so obtained had m. p. 88·5—89·5°; Matsukawa and Ohta (*J. Pharm. Soc. Japan*, 1950, **70**, 134) give m. p. 87—88° for this compound.

Reaction between Pyrimidine and Diazotised p-*Nitroaniline.*—A solution of *p*-nitrophenyldiazonium chloride (6 c.c.; prepared from 0·93 g. of *p*-nitroaniline) was added slowly with stirring to pyrimidine (3·4 g.); the solution was then diluted to 100 c.c., and filtered, and sodium acetate (2 g.) added to the filtrate, which was stirred for 5 hours and then kept for a further 2 days. The brown precipitate (0·77 g.) was collected and dried, and a portion (0·513 g.) was dissolved in benzene and filtered through a column of aluminium oxide. Development of the chromatogram with benzene gave two substantially pure fractions; that less strongly adsorbed (90 mg.; m. p. 196—198°) was sublimed in a vacuum giving 2-p-*nitrophenylpyrimidine*, m. p. 198—199° (Found : C, 59·9; H, 3·4; N, 21·1. $C_{10}H_7O_2N_3$ requires C, 59·7; H, 3·5; N, 20·9%). That more strongly adsorbed (130 mg.; m. p. 180—183°) gave on vacuum sublimation 4-p-*nitrophenylpyrimidine*, m. p. 184° (Found : C, 59·6; H, 3·4; N, 21·0%).

Identification of 2-p-*Nitrophenylpyrimidine by Synthesis.*—2-*p*-Aminophenylpyrimidine (102 mg.; prepared as described earlier) was dissolved in alcohol and diazotised at 0° by treatment with a little concentrated sulphuric acid and then with amyl nitrite. The diazonium compound was precipitated with ether, collected, and washed with more ether. Meanwhile, solutions of copper sulphate (0·5 g. of $CuSO_4,5H_2O$) and sodium sulphite (0·25 g.) were mixed and the precipitate collected, washed, and made into a sludge with sodium nitrite (1 g.) and water (4 c.c.); to this sludge the diazonium sulphate was added and the mixture was kept overnight. The solids were then filtered off and extracted with acetone: evaporation of the extract gave a crude product (78 mg.; m. p. 192°) which was sublimed under reduced pressure. The 2-*p*-nitrophenylpyrimidine so obtained separated from alcohol as needles, m. p. 199°, undepressed on admixture with the material obtained from the Gomberg reaction above.

p-*Nitrobenzoylacetaldehyde.*—Benzene (70 c.c.) containing ethyl formate (12·4 g.) and *p*-nitroacetophenone (18·6 g.) was kept in contact with sodium wire (2·6 g.) which, after 1 week, had all reacted to give a black mass. This was collected, washed with ether, and treated with water; the mixture was filtered and the filtrate acidified. The precipitate was collected, dried, and extracted with hot light petroleum (b. p. 60—80°); when cooled the extract gave yellow needles of p-*nitrobenzoylacetaldehyde* (*ω-formyl*-p-*nitroacetophenone*) (6·3 g.), m. p. 98—99° (Found : C, 56·3; H, 3·3; N, 7·0. $C_9H_7O_4N$ requires C, 56·0; H, 3·3; N, 7·2%). Attempts to condense this material with guanidine were unsuccessful.

Identification of 4-p-*Nitrophenylpyrimidine.*—The nitro-compound (100 mg.) of m. p. 184° from the Gomberg reaction was hydrogenated in methanol (40 c.c.) in the presence of 5% palladised barium sulphate (0·5 g.); the product, isolated as usual, was sublimed in a vacuum, giving 4-*p*-aminophenylpyrimidine (80 mg.), m. p. 196°. A portion (60 mg.) was diazotised at 0° with concentrated hydrochloric acid (0·25 c.c.) and sodium nitrite [29·4 mg. in water (0·2 c.c.)], and the mixture was kept at 0° for 24 hours with 30% hypophosphorous acid (1 c.c.), and then extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide and with water, then dried and evaporated. Sublimation of the residue in a vacuum gave 4-phenylpyrimidine, m. p. 61—62°, undepressed on admixture with material prepared as described earlier (Found : N, 18·5. Calc. for $C_{10}H_8N_2$: N, 18·0%).

5-*Amino*-2-*phenylpyrimidine.*—5-Nitro-2-phenylpyrimidine (2·11 g.; Hale and Brill, *J. Amer. Chem. Soc.*, 1912, **34**, 82) was hydrogenated in alcohol (200 c.c.) with palladised barium sulphate. The product was recrystallised from benzene, giving 5-*amino*-2-*phenylpyrimidine* (90%), m. p. 90—91° (Found : C, 70·1; H, 5·1; N, 24·4. $C_{10}H_9N_3$ requires C, 70·3; H, 5·3; N, 24·5%).

Nitration of 2-*Phenylpyrimidine.*—2-Phenylpyrimidine (4·18 g.) and nitric acid (2 c.c.; *d* 1·42) were mixed, cooled, and treated with concentrated sulphuric acid (12 c.c.). The solution was heated at 100°

for ½ hour, cooled, and poured into water (75 c.c.); a yellow crystalline solid (4·5 g.; m. p. 130—136°) separated and was collected. Recrystallisation from alcohol gave 2-m-*nitrophenylpyrimidine* as needles, m. p. 140—141° (Found: C, 59·9; H, 3·7; N, 20·9. $C_{10}H_7O_2N_3$ requires C, 59·7; H, 3·5; N, 20·9%). The same material was isolated by chromatography of the crude product on aluminium oxide with benzene as solvent. A trace of material, m. p. 159—161°, was also obtained, but could not be examined more closely.

Identification of 2-m-*Nitrophenylpyrimidine.*—2-*m*-Aminophenylpyrimidine (102 mg.; prepared as already described) was converted into the corresponding nitro-compound in a way similar to that described above for 2-*p*-aminophenylpyrimidine. The *m*-nitro-compound so obtained had m. p. 140—141°, undepressed on admixture with the product of nitration of 2-phenylpyrimidine.

4 : 6-*Dimethyl*-2-m-*nitrophenylpyrimidine.*—Acetylacetone (0·78 g.), *m*-nitrobenzamidine hydrochloride (1·58 g.), potassium carbonate (2·1 g.), and water (7·5 c.c.) were warmed together till a clear solution resulted; this was then kept for 20 hours. The crystalline precipitate was collected, washed with dilute hydrochloric acid and with water, dried, and sublimed under reduced pressure, which gave the nitro-compound, m. p. 154—155°, undepressed on admixture with material obtained by nitrating 4 : 6-dimethyl-2-phenylpyrimidine as described by Ochiai *et al.* (*loc. cit.*) (Found: C, 62·6; H, 5·0; N, 18·3. Calc. for $C_{12}H_{11}O_2N_3$: C, 62·9; H, 4·8; N, 18·3%).

Nitration of 4-*Phenylpyrimidine.*—4-Phenylpyrimidine (0·34 g.) was nitrated as described for 2-phenylpyrimidine, and the cooled reaction mixture diluted with water and aqueous ammonia added to pH *ca.* 4. The precipitate (100 mg.; m. p. 115—118°) was collected; further addition of ammonia to the filtrate gave a second crop of material (0·26 g.; m. p. 80—100°) from which, however, no pure substance could be isolated. The first crop was dissolved in benzene and the solution filtered through a column of aluminium oxide. Development of the chromatogram with benzene–alcohol gave an effluent which was evaporated; the residue sublimed in a vacuum. The pure material so obtained had m. p. 121—121·5° and was 4-m-*nitrophenylpyrimidine* (Found: C, 60·1; H, 3·5; N, 20·6%).

We thank the Department of Scientific and Industrial Research for a Maintenance Grant (to L. S. R.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 30th,* 1951.]