74. *An Investigation of the Reactions of Phenyl-lithium with Some Methylpyrimidines.*

By T. D. Heyes and John C. Roberts.

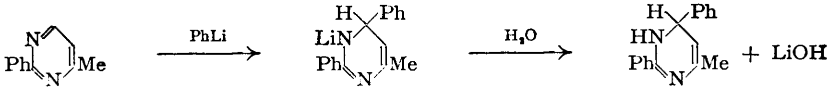
The reactions of phenyl-lithium with some 2- and 4-methylpyrimidines have been investigated. The broad mechanisms of the reactions have been deduced from the nature of the end-products. There were observed three main types of reaction involving, respectively, the initial formation of (i) an addition compound which, on hydrolysis, yielded a dihydro-phenyl derivative of the original pyrimidine; (ii) an addition compound which, under the experimental conditions, spontaneously split off lithium hydride to give a phenyl derivative; and (iii) a pyrimidylmethyl-lithium which reacted normally with an alkyl halide. In one case a dimerised pyrimidylmethyl was obtained, in poor yield, as the sole product.

Other work in progress in this laboratory necessitated the development of a synthesis for a pyrimidine containing a long-chain aliphatic substituent. This paper records investigations undertaken in the expectation that, by the reaction of phenyl-lithium with methylpyrimidines, pyrimidylmethyl-lithium compounds would be formed, which, on treatment with appropriate alkyl halides, would lead to the desired products.

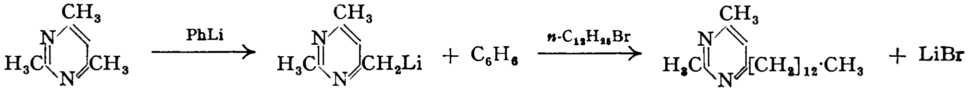
This expectation was based on the following considerations. A close similarity between the reactivity of methyl groups in the 2- and the 4-positions of the pyridine nucleus and of methyl groups in the 2- and the 4-positions of the pyrimidine nucleus is indicated by the ease with which both these types of compounds form styryl derivatives (Gabriel and Colman, *Ber.*, 1903, **36**, 3383; Ochiai and Yanai, *J. Pharm. Soc. Japan*, 1938, **58**, 76; *Chem. Zentr.*, 1938, II, 4242). Theoretical grounds for this similarity have been suggested previously by one of us (Roberts, *Chem. and Ind.*, 1947, **66**, 658). It seemed, therefore, reasonable to expect that, in reactions with phenyl-lithium, the methyl groups of 2- and 4-methylpyrimidines would behave similarly to those of 2-methyl-pyridine and -quinoline which are known to give 2-pyridyl- (Ziegler and Zeiser, *Annalen*, 1931, **485**, 174) and 2-quinolyl-methyl-lithium (Graef, Fredericksen, and Burger, *J. Org. Chem.*, 1946, **11**, 257). The last two compounds have been used as intermediates in chain-lengthening processes, as they react with alkyl halides in the normal manner (Bergmann and Rosenthal, *J. pr. Chem.*, 1932, **135**, 267; Graef *et al.*, *loc. cit.*).

Reactions between phenyl-lithium and 2-methyl-, 4-methyl-, 4-methyl-2-phenyl-, 4-methyl-2 : 6-diphenyl-, and 2 : 4 : 6-trimethyl-pyrimidine were carried out. When the initial reaction was complete, an alkyl halide (generally *n*-dodecyl bromide) was added to react with any pyrimidylmethyl-lithium compound which had been formed, and the final products were isolated and their structures established. In this connection a reaction due to Wolff (*Ber.*, 1892, **25**, 3033) and Byk (*ibid.*, 1903, **36**, 1923) proved particularly useful. Reduction of the pyrimidine or dihydropyrimidine by sodium and alcohol yielded a hexahydropyrimidine which, on acid hydrolysis, underwent ring fission, producing an aldehyde of which the alkyl or aryl group was the grouping originally attached to the 2-position.

A number of different mechanisms were found. 4-Methyl-2-phenylpyrimidine gave 1 : 6-dihydro-4-methyl-2 : 6-diphenylpyrimidine in good yield as the sole product. The structure of this compound follows from the following facts : (i) it yielded a positive Liebermann reaction, indicating the presence of a secondary amino-group, and (ii) on oxidation with potassium permanganate in acetone solution it gave the known 4-methyl-2 : 6-diphenylpyrimidine. It was concluded that the reaction had occurred thus :



Pyridine is known to undergo an analogous reaction (Ziegler and Zeiser, *Ber.*, 1930, **63**, 1847; *Annalen*, 1931, **485**, 174). 4-Methylpyrimidine yielded a mixture of 4-methyl-2-phenylpyrimidine and 4-methyl-6-phenylpyrimidine, as shown by (i) analysis, (ii) separation and identification of the 6-phenyl isomer, and (iii) reduction of the mixture with sodium and alcohol, followed by acid hydrolysis, whereupon formaldehyde and benzaldehyde were obtained. It was not possible to separate the 2-phenyl isomer in a pure state. The nature of the products of this reaction indicates that addition of phenyl-lithium to the 1 : 6 or 1 : 2 positions of the pyrimidine nucleus takes place initially and that this is then followed by fission of lithium hydride from the adduct. [The pyridine–phenyl-lithium addition product undergoes a similar reaction when heated (Ziegler and Zeiser, *locc. cit.*)]. Owing to the difficulties of the single available synthesis, only a small quantity of 2-methylpyrimidine was prepared. This gave a product, insufficient in quantity for purification as such, which yielded with picric acid the picrate of either 2-methyl-4-phenyl-, 3 : 4-dihydro-2-methyl-4-phenyl-, or 1 : 2-dihydro-2 methyl-2-phenyl-pyrimidine. The mechanism of this reaction is therefore similar to one or other of the two reactions mentioned above. Treatment of 2 : 4 : 6-trimethylpyrimidine with phenyl-lithium followed by *n*-dodecyl bromide gave a good yield of 2 : 6-dimethyl-4-*n*-tridecylpyrimidine, thus indicating the production of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium as an intermediate product :



That the 2-methyl group had not been attacked was shown by the production of acetaldehyde alone when the product was reduced and hydrolysed. A much smaller quantity of 2-methyl-4 : 6-di-*n*-tridecylpyrimidine was obtained as a by-product. When, however, 4-methyl-2 : 6-diphenylpyrimidine was similarly treated, a large amount of unchanged starting material was obtained together with a very small quantity of *s*-di-(2 : 6-diphenyl-4-pyrimidyl)ethane which had possibly been produced by the dimerisation of two 2 : 6-diphenylpyrimidylmethyl radicals.

Hence of all the cases examined, the expected chain-lengthening process occurred only with 2 : 4 : 6-trimethylpyrimidine. In this instance it had been expected that the 2-methyl group would be attacked preferentially, since this group is more reactive than the 4- and the 6-methyl group towards benzaldehyde (Ochiai and Yanai, *loc. cit.*), whereas in fact the 4- or the 6-methyl group was attacked to the exclusion of the 2-methyl group. Finally, it is noteworthy that in those cases (except possibly that of 2-methylpyrimidine) in which the 2- or the 6-position in the pyrimidine ring was vacant, a phenyl group entered the ring at one of these points and the methyl group was not attacked. (The reactivity of the methyl groups of 4-methyl-2-phenyl- and 4-methyl-2 : 6-diphenyl-pyrimidine in an aldol type of reaction was confirmed by the preparation of 2-phenyl-4-styryl- and of 2 : 6-diphenyl-4-styryl-pyrimidine. Similar derivatives of the other methylpyrimidines mentioned in this paper, with the exception of 2-methylpyrimidine, have been prepared previously by other workers.)

EXPERIMENTAL.

Characterisation of the Substituent in the 2-Position of the Pyrimidine or Dihydropyrimidine Nucleus.—A solution of the base (0·2 g.) in dry ethanol (5 c.c.) was boiled under reflux on the water-bath. Small pieces of sodium (1·0 g. in all) were added rapidly through the condenser. When the reaction abated, more dry ethanol (10 c.c.) was added and heating continued until all the solid had dissolved. Concentrated hydrochloric acid (10 c.c.), diluted with water (30 c.c.), was then added and the resulting solution steam-distilled. The distillate was mixed with an excess of a 0·33% solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and the precipitated 2 : 4-dinitrophenylhydrazone was recrystallised from a suitable solvent and identified by its m. p., alone and after admixture with an authentic specimen.

Reaction between 4-Methyl-2-phenylpyrimidine and Phenyl-lithium. 1 : 6-*Dihydro*-4-*methyl*-2 : 6-*diphenylpyrimidine.*—A phenyl-lithium solution was prepared from bromobenzene (4·7 g., 1·0 mol.), lithium chips (0·43 g., 2·03 atoms), and dry ether (50 c.c.) under nitrogen. 4-Methyl-2-phenylpyrimidine (5·12 g., 1·06 mols.), prepared by Schmidt's method (*Ber.*, 1902, **35**, 1575), dissolved in dry ether (20 c.c.), was added slowly and with stirring. After 15 minutes, a solution of *n*-dodecyl bromide (6·97 g., 0·94 mol.) in dry ether (20 c.c.) was added alowly. The mixture was heated under reflux, with stirring, for 1 hour and was then cooled and shaken with water. The separated ethereal layer was extracted with N-hydrochloric acid, the extract was made alkaline, and the resulting yellow crystalline precipitate filtered off, washed with water, dried (2·8 g.), and recrystallised from acetone. 1 : 6-*Dihydro*-4-*methyl*-2 : 6-*diphenylpyrimidine* forms pale-yellow irregular plates, m. p. 142° (Found : C, 82·9; H, 6·45; N, 11·2. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%).

Oxidation of 1 : 6-*Dihydro*-4-*methyl*-2 : 6-*diphenylpyrimidine to* 4-*Methyl*-2 : 6-*diphenylpyrimidine*.—The base (0·4 g.) was dissolved in acetone (10 c.c.) and finely powdered potassium permanganate (0·17 g.) was added slowly with shaking and cooling, the temperature being kept below 30°. The precipitated manganese dioxide was filtered off and washed well with acetone. The acetone was evaporated from the combined filtrate and washings; the residual oil (0·35 g.), when scratched. solidified. The solid, after crystallisation from ethanol, formed hexagonal prisms, m. p. 93—94° alone or mixed with an authentic specimen of 4-methyl-2 : 6-diphenylpyrimidine, prepared by Asahina and Kuroda's method (*Ber.*, 1914, **47**, 1818).

Reaction between 4-*Methylpyrimidine and Phenyl-lithium*. 4-*Methyl*-2-*phenyl*- *and* 4-*Methyl*-6-*phenyl-pyrimidine*.—4-Methylpyrimidine (9·6 g., 1·02 mols.) [prepared by Gabriel and Coleman's method (*Ber.*, 1899, **32**, 1534)], dissolved in dry ether (20 c.c.), was added slowly and with stirring to a solution of phenyl-lithium (8·4 g., 1·0 mol.) in dry ether (100 c.c.). After 15 minutes, *n*-dodecyl bromide (21·7 g., 0·9 mol.) was added and the reaction carried out as before. The reaction mixture was shaken with water and the ethereal layer was separated. This was extracted with N-hydrochloric acid, the extract made alkaline, and the resulting emulsion extracted with ether; the extract was dried (KOH) and filtered, the solvent removed, and the residue was distilled *in vacuo*, the fraction, b. p. 142—150°/11 mm. (2·0 g.), being collected (Found : C, 77·8; H, 5·8; N, 16·2. Calc. for $C_{11}H_{10}N_2$: C, 77·6; H, 5·9; N, 16·5%). Reduction and hydrolysis of this material gave a mixture of benzaldehyde and formaldehyde (the 2 : 4-dinitrophenylhydrazones of these aldehydes were separated by fractional crystallisation from absolute ethanol and identified in the usual way). The distillate, after 2 days at room temperature, had partially solidified. The solid was filtered off and crystallised from light petroleum (b. p. 40—60°) giving colourless, hexagonal plates (1 g.), m. p. 48° alone or when mixed with an authentic specimen of 4-methyl-6-phenylpyrimidine, prepared by Merkatz's method (*Ber.*, 1919, **52**, 880). Thus, the mixture contained the two isomers, 4-methyl-2-phenyl- and 4-methyl-6-phenyl-pyrimidine.

Reaction between 2-*Methylpyrimidine and Phenyl-lithium*.—The faintly yellow gum (0·26 g.) obtained from 2-methylpyrimidine (0·4 g.) in a manner analogous to that described for the 4-methyl isomer could not be crystallised. A solution of the gum in a little 2N-hydrochloric acid was mixed with an excess of a saturated aqueous solution of picric acid. The picrate, which was immediately precipitated, was filtered off and extracted with hot benzene, leaving a tarry residue. When the benzene solution was cooled, crystals formed which were recrystallised from 2-ethoxyethanol; the *picrate* of 2-methyl-4-phenyl-, or 3 : 4-dihydro-2-methyl-4-phenyl- or 1 : 2-dihydro-2-methyl-2-phenyl-pyrimidine crystallised in yellow needles, m. p. 205° (decomp.) (Found : N, 17·6. $C_{17}H_{13}O_7N_5$ requires N, 17·54. $C_{17}H_{15}N_5O_7$ requires N, 17·46%).

Reaction between 2 : 4 : 6-*Trimethylpyrimidine and Phenyl-lithium*. 2 : 6-*Dimethyl*-4-n-*tridecyl-pyrimidine and* 2-*Methyl*-4 : 6-*di*-n-*tridecylpyrimidine*.—2 : 4 : 6-Trimethylpyrimidine (14·64 g., 1·0 mol.) [prepared by Bowman's method (*J.*, 1937, 494)], in dry ether (25 c.c.), was added slowly, with stirring and cooling, to a solution of phenyl-lithium (10·28 g., 1·0 mol.) in dry ether (80 c.c.). After being heated under reflux and stirred for 15 minutes, the mixture, which contained a sticky mass of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium, was cooled. *n*-Dodecyl bromide (28·6 g., 0·99 mol.) was added slowly, with stirring and cooling, whereupon all the solid dissolved. The rest of the reaction was carried out and the product extracted as before. The crude product (15 g.) was distilled *in vacuo*; two fractions were obtained [(i) b. p. 144°/0·1 mm., and (ii) b. p. 194°/0·05 mm.] and both solidified on cooling. The first fraction was dissolved in light petroleum (b. p. 60—80°), and the solution saturated with hydrogen chloride. The precipitated hydrochloride was recrystallised from light petroleum (b. p. 60—80°) and formed needles, m. p. 80°. It was dissolved in water, the aqueous solution made alkaline, the emulsion so formed extracted with ether, the extract dried ($MgSO_4$), the ether distilled off, and the residue distilled under reduced pressure (b. p. 144°/0·1 mm.), giving 2 : 6-*dimethyl*-4-n-*tridecylpyrimidine* (11 g.), which crystallised in needles, m. p. 23° (Found : C, 78·4; H, 12·0; N, 9·4. $C_{18}H_{34}N_2$ requires C, 78·7; H, 11·8; N, 9·65%).

The second fraction was recrystallised from absolute ethanol; 2-*methyl*-4 : 6-*di*-n-*tridecylpyrimidine* (1 g.) was obtained in needles, m. p. 29—30° (Found : C, 81·1; H, 12·8; N, 6·2. $C_{31}H_{58}N_2$ requires C, 81·1; H, 12·7; N, 6·1%).

On reduction and hydrolysis both fractions gave acetaldehyde.

Reaction between 4-*Methyl*-2 : 6-*diphenylpyrimidine and Phenyl-lithium*. s-*Di*-(2 : 6-*diphenyl*-4-*pyrimidyl*)*ethane*.—4-Methyl-2 : 6-diphenylpyrimidine (5·0 g., 1·0 mol.), dissolved in dry ether (7·5 c.c.), was added slowly and with stirring to a solution of phenyl-lithium (1·68 g., 1·0 mol.) in dry ether (75 c.c.). After the reaction mixture had been stirred and heated under reflux for 30 minutes, *n*-hexyl bromide (3·35 g., 0·99 mol.) was added, slowly and with stirring. The rest of the procedure was as already described. When the reaction mixture was shaken with 2N-hydrochloric acid a white solid separated which was soluble in neither the acid nor the ether. This was filtered off and the filtrate treated as before. A crystalline material (2·3 g.) was obtained which melted at 93—94°, alone or when mixed with 4-methyl-2 : 6-diphenylpyrimidine and hence was unchanged starting material. The solid which was insoluble in hydrochloric acid and in ether was dissolved in hot pyridine from which, on cooling, s-*di*-(2 : 6-*diphenyl*-4-*pyrimidyl*)*ethane* crystallised as needles, m. p. 226° [Found: C, 82·9; H, 5·5; N, 11·6%; *M* (Micro-Rast), 415. $C_{34}H_{26}N_4$ requires C, 83·2; H, 5·3; N, 11·4%; *M*, 491].

2-*Phenyl*-4-*styrylpyrimidine*.—A mixture of 4-methyl-2-phenylpyrimidine (4 g., 1 mol.) and acetic anhydride (1·1 c.c.) was added slowly, during 10 minutes, to boiling benzaldehyde (4·9 c.c., 2 mols.) (cf. Shaw and Wagstaff, *J.*, 1933, 77). After 6 hours' heating, the product was distilled in steam, and the tarry residue was extracted with hot 5N-hydrochloric acid. After the hot solution had been filtered, crystals of the base hydrochloride were deposited. These were recrystallised from 2N-hydrochloric acid (charcoal) as long, fine needles, m. p. 201°. A hot solution of the hydrochloride in 2N-hydrochloric acid was made alkaline, and the emulsion, so formed, was extracted with ether, the extract dried (Na_2SO_4), the solvent evaporated, and the residual oil crystallised first from ethanol and then from 2-ethoxyethanol. 2-*Phenyl*-4-*styrylpyrimidine* (0·3 g.) crystallised as needles, m. p. 109° (Found: C, 83·9; H, 5·45; N, 11·2. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·5; N, 10·8%).

2 : 6-*Diphenyl*-4-*styrylpyrimidine*.—4-Methyl-2 : 6-diphenylpyrimidine (4·0 g., 1 mol.), suspended in an excess of acetic anhydride (10 c.c.), was allowed to react with benzaldehyde (3·5 g., 2 mols.) as before. The heating was continued for 12 hours and the reaction mixture distilled in steam. The residue was extracted with 5N-hydrochloric acid (to remove unchanged starting material) and was then dissolved in ethanol. The ethanolic solution was filtered, made alkaline with ethanolic potassium hydroxide solution, and again filtered, and the filtrate was evaporated to dryness. The residue was extracted with light petroleum (b. p. 60—80°), the petroleum solution was filtered and the filtrate evaporated to dryness. The residue was crystallised from ethanol (charcoal), giving 2 : 6-*diphenyl*-4-*styrylpyrimidine* (0·5 g.) in needles, m. p. 130° (Found: C, 86·2; H, 5·55; N, 8·4. $C_{24}H_{18}N_2$ requires C, 86·2; H, 5·4; N, 8·4%).

THE UNIVERSITY, NOTTINGHAM.

[*Received, October 27th,* 1950.]