ON THE SYNTHESIS OF 4- AND 5-PYRIMIDINYL-DIPHENYL-(1-IMIDAZOLYL)METHANES AND THEIR ANTIFUNGAL ACTIVITY

Zdeněk BUDĚŠÍNSKÝ, Josef VAVŘINA, Leon LANGŠÁDL and Jiří HOLUBEK

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

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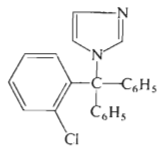
On reaction of phenylmagnesium bromide with ethyl ester of 5-chloro-2-methyl-, 5-chloro-2-methylthio-, 5-bromo-2-methylthio-4-pyrimidinecarboxylic acid and 2,4-dimethyl-5-pyrimidinecarboxylic acid (*IIa*, *IIb*, *IIc*, *V*) corresponding 4-pyrimidinyl- or 5-pyrimidinyl-diphenylmethanols (*IIIa*, *IIIb*, *IIIc*, *VI*) were obtained. On reaction of thionyl-bis-imidazole with these methanols (4- or 5-pyrimidinyl)-diphenyl-(1-imidazolyl)-methanes *IVa*, *IVb*, *IVc* and *VII* were prepared. Phenylmagnesium bromide reacted with ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate (*VIII*) under formation of dihydro derivative *IX*. We were unable to prepare Grignard's reagent from 5-bromo-2-methylthiopyrimidine and magnesium; it reacted with ethylmagnesium bromide under formation of dihydro derivative *I*. 5-Chloro-2-methylthio-4-pyrimidinecarboxylic acid when heated with NaOH in dimethyl sulfoxide gave 5-hydroxy-2-methylsulfinyl-4-pyrimidinecarboxylic acid. Compounds *IVb* and *IVc* prevented the growth of *Candida albicans in vitro* at almost the same concentrations as clotrimazole.

In our previous papers[1,2] we described the preparation and the antimycotic activity of pyrimidine analogues of haloprogine and miconazole. The subject of this paper is the investigation of pyrimidine analogues of another known antimycotic agent, clotrimazole[3] (*A*).

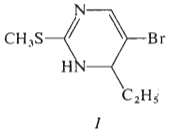


A

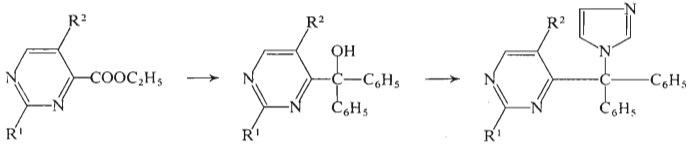
Intermediates for the synthesis of tetrasubstituted methane derivatives are the corresponding methanols. These can be obtainecd on reaction of alkyl- and arylmagnesium halogenides with corresponding esters or ketones. We were thus interested in the problem of the preparation of pyrimidinylmagnesium halogenides. While in the pyridine series Grignard's compounds are well known, for example of 2-bromo and 3-bromopyridine[4,5], analogous pyrimidine compounds are not yet known. There-

fore we tried to obtain Grignard's reagent from 5-bromo-2-methylthiopyrimidine that was prepared on decarboxylation of 5-bromo-2-methylthio-4-pyrimidinecarboxylic acid. However, this bromo derivative did not react with magnesium neither in ether nor in tetrahydrofuran. Therefore we applied the induction method[4]. After reaction with ethylmagnesium bromide and addition of benzophenone and working up of the reaction mixture we obtained 5-bromo-3,4-dihydro-4-ethyl-2-methylthiopyrimidine (*I*) instead of diphenyl-(2-methylthio-5-pyrimidinyl)methanol. Hence, the formation of Grignard's reagent did not take place, but ethylmagnesium bromide added to the —N=CH— group of the pyrimidine heterocycle instead. Ethyl 4-methyl-2-methylthio-5-pyrimidinecarboxylate (*VIII*) reacted in a similar manner. Instead of the corresponding methanol it gave with phenylmagnesium bromide ethyl 1,6-dihydro-6-phenyl-4-methyl-2-methylthio-5-pyrimidinecarboxylate (*IX*). This addition reaction of Grignard's reagents with nitrogen-containing heterocycles, such as pyridine, quinoline and others, is known from literature[6]; addition products are easily oxidized to corresponding substituted aromatic derivatives, while dihydro compounds *I* and *IX* are stable. The structure of both these compounds was proved by ^{1}H-NMR spectra.

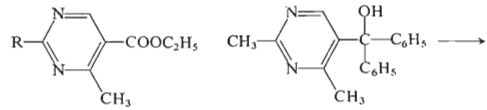
In further work we therefore used pyrimidines as passive components in the form of esters of pyrimidinecarboxylic acids and pyrimidinyl methyl ketones, which were allowed to react with phenylmagnesium bromide. In this manner we prepared trisubstituted methanols *IIIa*, *IIIb*, *IIIc*, *VI*, *XIa* and *XIb*. However, from the reaction of ester *VIII* with phenylmagnesium bromide we isolated the addition product *IX* only.



I

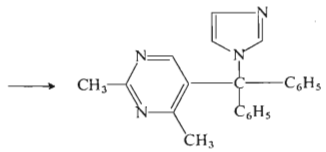


IIa, $R^1 = CH_3$, $R^2 = Cl$ *IIIa*, $R^1 = CH_3$, $R^2 = Cl$ *IVa*, $R^1 = CH_3$, $R^2 = Cl$
IIb, $R^1 = CH_3S$, $R^2 = Cl$ *IIIb*, $R^1 = CH_3S$, $R^2 = Cl$ *IVb*, $R^1 = CH_3S$, $R^2 = Cl$
IIc, $R^1 = CH_3S$, $R^2 = Br$ *IIIc*, $R^1 = CH_3S$, $R^2 = Br$ *IVc*, $R^1 = CH_3S$, $R^2 = Br$



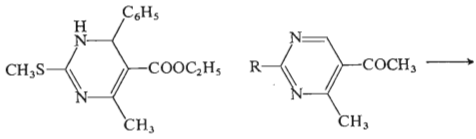
V, R = CH_3
VIII, R = CH_3S

VI



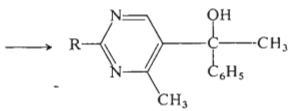
VII

When reacting with thionyl-bis-imidazole according to Büchel and coworkers[3] the trisubstituted methanols *IIIa*, *IIIb*, *IIIc* and *VI* gave diphenyl-imidazolyl-pyrimidinylmethanes *IVa*, *IVb*, *IVc* and *VII*. From other methanols we were unable to obtain corresponding tetrasubstituted methanes by this reaction. The working up of the reaction mixtures after imidazolylation was rather difficult, since the crude products



IX

Xa, R = CH_3
Xb, R = CH_3S



XIa, R = CH_3
XIb, R = CH_3S

which contained considerable amounts of starting methanols formed syrups which did not crystallize easily. The separation of these mixtures was possible by column chromatography on silica gel.

The trisubstituted methanols *IIIa*, *IIIb*, *IIIc*, *VI*, *XIa* and *XIb* and the tetrasubstituted methanes *IVa*, *IVb*, *IVc* and *VII* were tested for their antifungal activity *in vitro* against *Saccharomyces pasterianus*, *Trichophyton mentagrophytes*, *Candida albicans* and *Aspergillus niger*. All substances of the first group were inactive up to 50 μg/ml concentration. In the second group significant activity was found in substances *IVa*, *IVb* and *IVc* (Table I). In comparison with a methyl group the methylthio group had a favourable effect on the inhibitory activity (substances *IVa*, *IVb*). Chloro and bromo derivatives *IVb* and *IVc* were practically equally effective. None of these substances could equal the antifungal activity of clotrimazole which was used as standard.

EXPERIMENTAL

The melting points were determined on a Mettler FP 2 apparatus. The ^{1}H-NMR spectra were measured on a 80 MGHz instrument BS-487 C (Tesla, Brno); 10% of tetramethylsilane as internal standard.

5-Bromo-3,4-dihydro-4-ethyl-2-methylthiopyrimidine (*I*)

Ethyl bromide (3·0 g) was added dropwise to a suspension of magnesium (9·6 g, 0·395 gat) in diethyl ether (20 ml) to induce the reaction. When this ceased a solution of ethyl bromide (30 g, 0·273 mol) and 5-bromo-2-methylthiopyrimidine (20·5 g, 0·1 mol) in diethyl ether (80 ml) was added dropwise in 1 h to the refluxing mixture and the refluxing was continued for another half-an-hour. The next day the major part of diethyl ether was distilled off and an equal amount of fresh diethyl ether was added and refluxed for 2 h. After cooling to 10°C a solution of benzo-

TABLE I

Antifungal *in vitro* Effect of Tetrasubstituted Methanes *IVa*, *IVb*, *IVc* and *VII*
Minimum inhibitory concentration in μg/ml.

Compound	*Saccharomyces pasterianus*	*Trychophyton mentagrophytes*	*Candida albicans*	*Aspergillus niger*
IVa	6·25	3·1	1·5	50
IVb	25	3·1	0·7	12·5
IVc	25	6·2	0·7	25
VII	50	50	50	50
Clotrimazole	3·1	0·03	0·3	3·1

phenone (72·8 g, 0·4 mol) in diethyl ether (100 ml) was added dropwise under stirring over 2 h and the mixture was allowed to stand overnight. It was then refluxed for 2 h and the mixture was decomposed with an aqueous ammonium chloride solution (42 g). The ethereal layer was separated and the aqueous layer extracted with diethyl ether (3× 100 ml). The combined ethereal extracts were extracted with 5M-HCl (3× 25 ml) and the acid extract was alkalized with ammonia. The separated oil solidified overnight. Yield, 19 g (80·8%) of the crude product which after two crystallizations from 50% ethanol had m.p. 111·3—112·7°C. ^{1}H-NMR ($CDCl_3$): δ 6·61 (s, 1 H, —CH=); 5·53 (s, 1 H, disappears after addition of D_2O, —NH—); 4·28 (dd, 1 H, —CH); 2·40 (s, 3 H, $—SCH_3$); 1·70 (m, 2 H, $—CH_2$); 0·98 (t, 3 H, $—CH_3$), J = 7·0 Hz. For $C_7H_{11}BrN_2S$ (235·1) calculated: 35·76% C, 4·72% H, 33·98% Br, 11·91% N, 13·63% S; found: 36·19% C, 4·93% H, 33·83% Br, 11·71% N, 13·61% S.

Ethyl 5-Chloro-2-methyl-4-pyrimidinecarboxylate (*IIa*)

This ester was prepared using the procedure described in ref.[7], now modified by us. A mixture of 5-chloro-2-methyl-4-pyrimidinecarboxylic acid[7] and ethanol (200 ml) was saturated with hydrogen chloride gas and heated at 60—70°C for 1 h. After evaporation of the solvent in a vacuum the oily residue was dissolved in chloroform, poured into a mixture of water and ice (100 ml) and neutralized with sodium carbonate. The chloroform layer was separated, washed with water and dried over calcium chloride. After evaporation of chloroform the crude ester was distilled *in vacuo*. Yield, 26·3 g (69%), b.p. 78—86°C/0·75 Torr (100 Pa). Repeated rectification gave a preparation boiling at 88°C/1·0 Torr (133 Pa), spec. density 1·2423 g/cm^3 at 20°C/4, n_D^{20} 1·5062.

α-(5-Chloro-2-methyl-4-pyrimidinyl)benzhydrol (*IIIa*)

A solution of phenylmagnesium bromide, prepared from bromobenzene (23·4 g, 150 mmol) and magnesium (3·4 g, 140 mmol) in diethyl ether was added dropwise at 30°C over half-an-hour into a solution of *IIa* (12 g, 60 mmol) in diethyl ether (200 ml). The separated salt was filtered off after 1 h standing, mixed with ice and acidified with 5M-HCl (20 ml). The separated oil was dissolved in chloroform and extracted with water. The chloroform layer was evaporated and the residue dissolved in ethanol (25 ml) and diluted with water (25 ml). The separated substance (2·4 g) had m.p. 127—129°C. The ethereal filtrate after the filtration off of the magnesium salt was extracted with 5M-HCl and water; ether was distilled off and the residue triturated with 50% ethanol (10 ml). The product obtained was identical according to its m.p. and R_F value (in benzene–light petroleum 1 : 1) with the above product. Total yield 6·4 g (34·2%). A sample for analysis was crystallized from ethanol and had m.p. 132—135°C. For $C_{18}H_{15}ClN_2O$ (310·8) calculated: 69·56% C, 4·86% H, 11·41% Cl, 9·01% N; found: 69·75% C, 5·06% H, 11·80% Cl, 9·04% N.

(5-Chloro-2-methyl-4-pyrimidinyl)-diphenyl-(1-imidazolyl)methane (*IVa*)

A mixture of thionyl chloride (3·6 g, 30 mmol) and acetonitrile (20 ml) was added dropwise into a solution of imidazole (8·2 g, 120 mmol) in acetonitrile (80 ml) and stirred for 1 h. The separated imidazole hydrochloride was filtered off under suction and the filtrate containing thionyl-bis-imidazole was mixed with a solution of *IIIa* (4·7 g, 15 mmol) in acetonitrile (160 ml). The next day acetonitrile was distilled off and the residue dissolved in chloroform (100 ml) and extracted with water (2× 25 ml). Chloroform was evaporated and the residue dissolved in hot ethanol (20 ml) and water was added until incipient turbidity (20 ml). The unreacted starting substance separated (0·5 g) by next day and it was filtered off. The filtrate was concentrated,

mixed with water and alkalized with a few drops of ammonia. A product separated (4·0 g) which was filtered off under suction and crystallized from ethanol. It contained solvent of crystallization which could be eliminated on heating at 100°C in a vacuum. M.p. 137—138·5°C. For $C_{21}H_{17}$. ClN_4 (360·9) calculated: 69·90% C, 4·75% H, 9·83% Cl, 15·52% N; found: 70·21% C, 4·82% H, 9·64% Cl, 15·69% N.

5-Chloro-2-methylthio-4-pyrimidinecarboxylic Acid

Triethylamine (152 g, 1·5 mol) was added dropwise at 5—10°C over half-an-hour into a mixture of S-methylisothiouronium sulfate (139 g, 0·5 mol), mucochloric acid (85 g, 0·5 mol) and water (750 ml) and allowed to stand for 2 days. The mixture was then acidified with concentrated hydrochloric acid (75 ml) and the separated product filtered off under suction and washed with water; yield, 67·4 g (65·9%). The crude acid was dissolved in water (500 ml), ammonia (50 ml) was added and the solution was decolorized with charcoal and precipitated with dilute hydrochloric acid at 60—70°C. M.p. 181·4—184·0°C (under decomp.), literature (ref.[8]) gives m.p. 169—170°C.

Ethyl 5-Chloro-2-methylthio-4-pyrimidinecarboxylate (*IIb*)

This ester was prepared analogously as *IIa*. From 5-chloro-2-methylthio-4-pyrimidinecarboxylic acid (70 g, 0·34 mol) and ethanol (450 ml) 57 g (68·6%) of the the ester was obtained. B.p. 120 to 122°C/0·5 Torr (70 Pa), n_D^{22} 1·5630.

α-(5-Chloro-2-methylthio-4-pyrimidinyl)benzhydrol (*IIIb*)

A solution of phenylmagnesium bromide, prepared from magnesium (6·8 g, 0·28 gat), bromobenzene (47·2 g, 0·3 mol) and diethyl ether (250 ml), was added dropwise at 30°C over 1·5 h into a solution of *IIb* (29·5 g, 0·12 mol) in diethyl ether (250 ml) and allowed to stand overnight. The separated substance was filtered off under suction, combined with the residue obtained on evaporation of the filtrate, and dissolved in water (50 ml), acidified with 5M-HCl to pH 1 to 2. The separated compound was suction-dried and washed with ethanol. Yield 22·8 g (55·4%) of a product melting at 108—110°C. An analytical sample had m.p. 111—112°C (ethanol). For $C_{18}H_{15}ClN_2OS$ (324·9) calculated: 63·06% C, 4·41% H, 10·34% Cl, 8·17% N, 9·35% S; found: 63·33% C, 4·34% H, 10·76% Cl, 8·57% N, 9·46% S.

(5-Chloro-2-methylthio-4-pyrimidinyl)-diphenyl-(1-imidazolyl)methane (*IVb*)

A solution of thionyl-bis-imidazole in acetonitrile was prepared as in the preparation of *IVa* and it was mixed with a solution of *IIIb* (5·1 g, 15 mmol) in acetonitrile (100 ml). After two days' standing the mixture was evaporated and the residue dissolved in chloroform (65 ml) and extracted with water (20 ml). The chloroform solution was evaporated and the residue (8·0 g) dissolved in boiling ethanol (30 ml), decolorized with charcoal and the hot filtrate diluted with water until incipient turbidity (25 ml). The precipitated substance was filtered off with suction and washed with 50% ethanol. Yield, 3·0 g (51%) of product, m.p. 134—137°C. Another 1·8 g of a less pure substance was obtained from mother liquors. A sample for analysis was crystallized from 80% methanol, m.p. 130—132°C (crystallizes with 1 mol of H_2O). For $C_{21}H_{17}ClN_4S$ (392·9) calculated: 64·19% C, 4·36% H, 9·02% Cl, 14·26% N, 8·16% S; found: 63·61% C, 4·35% H, 9·43% Cl, 14·28% N, 8·08% S.

5-Bromo-2-methylthio-4-pyrimidinecarboxylic Acid

Triethylamine (150 g, 1·5 mol) was added dropwise and under stirring at 10—20°C over 3 h to a suspension of mucobromic acid (130 g, 0·5 mol) and S-methylisothiuronium sulfate (140 g, 0·5 mol) in water (1 000 ml). After one day's standing the mixture was decolorized with charcoal and the filtrate acidified with concentrated hydrochloric acid (50 ml). The separated product was filtered off with suction and washed with water. Yield, 79·6 g (63·9%). After reprecipitation with hydrochloric acid from ammoniacal solution the compound had m.p. 180—181°C (decomp.), lit.[9] gives 176—177°C (decomp.) and half the yield.

Ethyl 5-Bromo-2-methylthio-4-pyrimidinecarboxylate (*IIc*)

This ester was prepared from the above acid (79·6 g, 0·32 mol) in a manner analogous to that used for the preparation of *IIb*, with the difference that the evaporated mixture was dissolved in ethanol (200 ml) and resaturated with hydrogen chloride gas. Since the mixture solidified into crystals it was melted by heating at 60°C and evaporated in a vacuum. The oily residue was dissolved in chloroform (100 ml) and washed with a saturated sodium carbonate solution until neutral. The chloroform solution was washed with water (2× 25 ml), dried over calcium chloride and the residue fractionated in vacuo. On repeated crystallization 67·4 g (76%) of ester were obtained, b.p. 116—126°C/0·3 Torr (40 Pa). Pure ester had m.p. 33—34°C (pentane), b.p. 122 to 123°C/0·3 Torr (40 Pa). For $C_8H_9BrN_2O_2S$ (277·1) calculated: 34·68% C, 3·27% H, 28·83% Br, 10·11% N, 11·57% S; found: 34·75% C, 3·13% H, 29·00% Br, 10·32% N, 11·49% S.

α-(5-Bromo-2-methylthio-4-pyrimidinyl)benzhydrol (*IIIc*)

Phenylmagnesium bromide prepared from bromobenzene (91·5 g, 0·58 mol) and magnesium (14·2 g, 0·58 gat) was added dropwise at 30°C and over 2 h into a solution of *IIc* (67·4 g, 0·24 mol) in diethyl ether (200 ml) and the mixture allowed to stand overnight. The mixture was decomposed with water and 5M-HCl (140 ml). Evaporation of the ethereal layer gave a crude product which was crystallized from ethanol. Yield, 31·6 g (33·6%), m.p. 120·1—120·9°C. For $C_{18}H_{15}$·.BrN_2OS (387·3) calculated: 55·82% C, 3·90% H, 20·63% Br, 8·28% C; found: 56·12% C, 3·85% H, 19·69% Br, 8·67% S.

(5-Bromo-2-methylthio-4-pyrimidinyl)-diphenyl-(1-imidazolyl)-methane (*IVc*)

The procedure used for the preparation of this substance was the same as in the case of *IVa*. Since we were unable to induce crystallization of the evaporation residue and since thin-layer chromatography (Silufol, benzene–chloroform 3 : 7) showed that in addition to the required product it also contained the starting material, the crude product was dissolved in benzene and chromatographed on a column of silica gel (300 g, Lachema L 100/160). Elution was carried out with benzene and mixtures of benzene and chloroform. The regenerated *IIIc* weighed 2·64 g and the weight of the product was 6·32 g. After double crystallization from methanol it had m.p. 173·3—174·3°C. For $C_{21}H_{17}BrN_4S$ (437·4) calculated: 57·67% C, 3·92% H, 18·27% Br, 12·81% N, 7·33% S; found: 57·69% C, 4·04% H, 17·93% Br, 13·20% N, 7·68% S.

α-(2,4-Dimethyl-5-pyrimidinyl)benzhydrol (*VI*)

A solution of phenylmagnesium bromide, prepared from bromobenzene (33·0 g, 0·21 mol) and magnesium (5·1 g, 0·21 mol) in diethyl ether (150 ml), was added dropwise and under stirring at 3—5°C over 1 h into a solution of *V* (ref.[10]) (18·0 g, 0·1 mol) in diethyl ether (100 ml) and

allowed to stand overnight. After decomposition with water (110 ml) it was neutralized with conc. hydrochloric acid (22 ml). On standing, a small amount of a substance separated out from the ethereal layer, which was combined with the residue after evaporation and crystallized from 30% ethanol. Yield, 5·3 g (18·2%) of a product, m.p. 191·4—192·3°C. For $C_{19}H_{18}N_2O$ (290·4) calculated: 78·60% C, 6·25% H, 9·65% N; found: 78·66% C, 6·42% H, 9·48% N.

(2,4-Dimethyl-5-pyrimidinyl)diphenyl-(1-imidazolyl)methane (*VII*)

A solution of thionyl-bis-imidazole in acetonitrile was prepared as in the case of *IVa*, *i.e.* from imidazole (6·8 g, 0·1 mol) and thionyl chloride (3·0 g, 25 mmol). Compound *V* (4·95 g, 17 mmol) dissolved in a mixture of benzene (150 ml) and acetonitrile (50 ml) was added dropwise to it under stirring over 1 h. The next day the mixture was evaporated in a vacuum, the residue (10 g) dissolved in benzene (150 ml), washed with water (2× 20 ml) and then with 5M-HCl (25 ml). After one day's standing the starting compound *V* crystallized out from the acid extract. It was filtered off with suction and the filtrate alkalized with 5M-NaOH to pH 9—10. The separated gummy substance (3·8 g) was dissolved in ethanol (10 ml) and the solution diluted with hot water (25 ml) until incipient turbidity. On standing 3·4 g (58·5%) of a product with m.p. 58—60°C crystallized out, which was recrystallized from dilute ethanol. Yield, 1·4 g (21·7%), m.p. 61—63°C. For $C_{22}H_{20}N_4.2\,H_2O$ (376·5) calculated: 70·19% C, 6·43% H, 14·88% N; found: 70·46% C, 6·12% H, 15·35% N.

Hydrochloride of α-(2,4-Dimethyl-5-pyrimidinyl)-α-methylbenzyl Alcohol (*XIa*)

An ethereal solution of phenylmagnesium bromide, prepared from bromobenzene (17·2 g, 0·11 mol) and an equivalent amount of magnesium, was added dropwise at 8—10°C over half-an-hour into a solution of *Xa* (ref.[11]) (15·0 g, 0·1 mol) in diethyl ether (150 ml) and the mixture was stirred for another hour at the same temperature. After pouring onto ice the mixture was neutralized with 5M-HCl. The ethereal layer was separated and the aqueous layer extracted twice with ether (50 ml each time). The combined ethereal layers were evaporated, the residue dissolved in ethanol (30 ml) and an ethanolic solution of HCl was added. The precipitated substance was suction-dried and washed with benzene. Yield, 6·5 g (24·6%), m.p. (after crystallization from ethanol) 176—179°C. For $C_{14}H_{17}ClN_2O$ (264·8) calculated: 65·31% C, 6·47% H, 13·39% Cl, 10·58% N; found: 63·48% C, 6·54% H, 13·64% Cl, 10·54% N.

A solution of hydrochloride (0·270 g, 1 mmol) in water (2·0 ml) was alkalized with 5M-NaOH (2·0 ml) and the precipitated oil was extracted with chloroform (4, 2, 2 ml). The combined extracts were evaporated and the residue dissolved in 25% ethanol (5·0 ml), decolorized with Norite and allowed to stand in a refrigerator for crystallization. The obtained base had m.p. 104·4 to 105·0°C. ^{1}H-NMR ($CDCl_3$): δ 8·70 (s, 1 H, —CH=); 7·31 (s, 5 H, monosubst. Ar); 4·10 (bs, 1 H, —OH); 2·60 (s, 3 H, $—CH_3$); 2·15 (s, 3 H, $—CH_3$); 1·91 (s, 3 H, $—CH_3$). In its IR spectrum the ν(C=O) band was absent.

Hydrochloride of α-Methyl-α-(4-methyl-2-methylthio-5-pyrimidinyl)benzyl Alcohol (*XIb*)

The preparation of this compound was carried out from ketone[12] *Xb* using a similar procedure as in the synthesis of *XIa*, with the difference that after decomposition of the reaction mixture with water the ethereal layer was evaporated and the residue dissolved in benzene (250 ml). The benzene solution was extracted with ammonia (30 ml) and then with 5M-HCl (50 ml), which caused the precipitation of hydrochloride. From 18·2 g (0·1 mol) of ketone *Xb* 20·0 g (67·5%) of the product were obtained, m.p. 158—165°C which after crystallization from ethanol had m.p. 162—165°C. Yield, 11·0 g (37·1%). For $C_{14}H_{17}ClN_2OS$ (296·8) calculated: 56·65% C,

5·77% H, 11·95% Cl, 9·44% N, 10·80% S; found: 56·98% C, 5·99% H, 12·15% Cl, 9·52% N, 10·83% S. The base was prepared as above and had m.p. 107—109°C (ethanol).

Ethyl 1,6-Dihydro-4-methyl-2-methylthio-6-phenyl-5-pyrimidinecarboxylate (*IX*)

An ethereal solution of phenylmagnesium bromide, prepared from bromobenzene (33·0 g, 0·21 mol) and an equivalent amount of magnesium, was added dropwise at 5—10°C over 1 h into a solution of *VIII* (ref.[13]) (21·2 g, 0·1 mol) in ether (130 ml) and the mixture allowed to stand for 2 h. After decomposition with ice and acidification with 5M-HCl to pH 2 the ethereal layer was separated and evaporated. The residue (27 g) was dissolved in benzene (150 ml) and extracted with 1M-NaOH (50 ml) and water. The benzene layer was evaporated and the residue dissolved in boiling ethanol (30 ml). After standing overnight 2·2 g of a compound separated, m. p. 168 to 170°C. A sample for analysis was crystallized from ethanol, m.p. 169—171°C. ^{1}H-NMR (hexadeuteriodimethyl sulfoxide) δ 9·50 (vbs, 1 H, NH); 7·19 (s, 5 H, monosubstituted Ar); 3·98 (q, 2 H, J = 7·0 Hz, —OCH_2—); 2·28 (s, 3 H, —CH_3); 2·20 (s, 3 H, —CH_3); 1·10 (t, 3 H, J = 7·0 Hz, —CH_2—CH_3). For $C_{15}H_{18}N_2O_2S$ (290·4) calculated: 62·04% C, 6·24% H, 9·65% N, 11·04% S; found: 62·95% C, 6·32% H, 9·84% N, 10·26% S.

5-Hydroxy-2-methylsulfinyl-4-pyrimidinecarboxylic Acid (*XIII*)

A mixture of 5-chloro-2-methylthio-4-pyrimidinecarboxylic acid (205 mg, 1 mmol), dimethyl sulfoxide (3·0 ml) and 0·20 ml of aqueous alkali (3 mmol of NaOH) was heated at 110°C for 2 h, neutralized with 5M-HCl and evaporated in a vacuum. The residue was dissolved in water (2 ml) and acidified with concentrated hydrochloric acid. The separated product was filtered off under suction and crystallized from 25% ethanol; m.p. 182—184°C (decomp.). For $C_6H_6N_2O_3S$ (186·2) calculated: 35·64% C, 2·99% H, 13·85% N, 15·80% S; found: 35·89% C, 2·75% H, 14·02% N, 16·09% S.

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