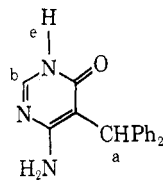
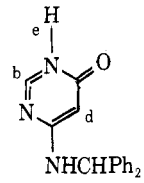
added to 80 ml of glacial acetic acid and heated under reflux for 16 hr. The product was precipitated with water and was crystallized from dilute alcohol. The C, H, and N analyses were correct for $C_{17}H_{15}N_3O$, but the nmr spectra indicated a 50:50 mixture of 4-amino-5-(diphenylmethyl)-6-hydroxypyrimidine and 4-[(diphenylmethyl)amino]-6-hydroxypyrimidine. The mixture was separated on a silica gel column with $CHCl_3$. Each compound was characterized by its nmr taken in dimethyl sulfoxide; the assignments are shown below.



δ, ppm
a, 5.66
b, 7.82
c, 5.97
e, 11.75



δ, ppm
a, 6.03
b, 7.87
c, 7.80
d, 5.22
e, 11.75

4-Amino-6-hydroxy-5-[2-methoxy(diphenylmethyl)]pyrimidine (26). 4-Amino-6-chloropyrimidine (0.1 mol, 13.0 g) and 2-methoxybenzhydrol (0.1 mol, 21.4 g) were added to 80 ml of acetic acid and heated under reflux for 16 hr. The product was precipitated by adding the mixture to 400 ml of water. It was purified by crystallization from EtOAc–petroleum ether, yield 14 g (43%), mp 293° dec.

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.29; H, 5.81; N, 13.88.

Acknowledgments. The authors are grateful for the able assistance of Dr. Harold E. Boaz (deceased) in interpreting nmr data, to Mr. Larry A. Spangle and coworkers for nmr data, and to Mr. George M. Maciak and coworkers for analytical results.

Registry No.—**1**, 50259-14-8; **2**, 50259-15-9; **3**, 50259-16-0; **4**, 50259-17-1; , 50259-18-2; **6**, 50259-19-3; **7**, 50259-20-6; **8**, 50259-21-7; **9**, 50259-22-8; **10**, 50259-23-9; **11**, 50259-24-0; **12**, 50430-99-4; **13**, 50259-25-1; **14**, 50259-26-2; **15**, 50259-27-3; **16**, 50259-28-4; **17**, 50259-29-5; **18**, 50431-00-0; **19**, 50259-30-8; **20**, 50259-31-9; **21**, 50259-32-0; **22**, 50259-33-1; **23**, 50259-34-2; **24**, 50259-35-3; **25**, 50259-36-4; **26**, 50259-37-5; 2-aminopyrimidine, 109-12-6; 2-amino-4,6-dimethylpyrimidine, 767-15-7; 4,6-diaminopyrimidine, 2434-56-2; 2-amino-4,6-dichloropyrimidine, 56-05-3; 2-amino-6-chloro-5-(diphenylmethyl)-4-hydroxypyrimidine, 50259-38-6; 6-chloro-5-(diphenylmethyl)-2,4-dihydroxypyrimidine, 50259-39-7; 4-amino-6-chloropyrimidine, 5305-59-9.

References and Notes

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(2) P. L. Thayer, D. H. Ford, and H. R. Hall, *Phytopathology*, **57**, 833 (1967).
(3) I. Tanaka and T. Sadatome, Japanese Patent 4146 (1962); *Chem. Abstr.*, **59** 2833a (1963).
(4) D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, pp 24, 311, 380.

Dimetalated Heterocycles as Synthetic Intermediates. V. Dianions Derived from Certain 2-Hydroxy-4-methylpyrimidines, 2-Amino-4-methylpyrimidines, and Related Compounds†[1]

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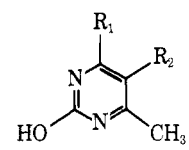
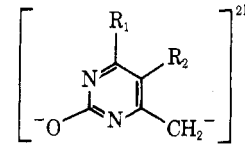
Received August 8, 1973

A convenient new method, involving dianion intermediates, has been developed for side-chain elaboration of 2-hydroxy-4-methylpyrimidines (**1a–c**), 2-anilino-4-methyl-6-phenylpyrimidine (**15a**), 2-amino-4-methylpyrimidine (**15b**), and 2-methyl-4(3*H*)-quinazolinone. The dianions, prepared by twofold metalation of the parent heterocycles with *n*-butyllithium in THF–hexane or sodium amide in liquid ammonia, reacted with benzyl chloride and carbonyl compounds to selectively establish exocyclic carbon–carbon bonds. Reaction of 4-hydroxy-2,6-dimethylpyrimidine (**8**) with 2 equiv of *n*-butyllithium produced a mixture of isomeric dianions (**9a–b**) in which **9a**, resulting from abstraction of a proton from the 4-methyl position, predominated.

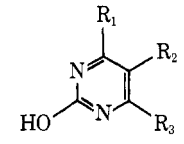
Although certain 2-hydroxy-, 2,4-dihydroxy-, 2-amino-, and 2,4-diaminopyrimidines containing a nuclear methyl substituent have been reported to undergo active hydrogen reactions such as aldol and Claisen condensations,[2] such processes generally appear to involve only low, equilibrium-controlled concentrations of carbanionic species. Recently, Klein and Fox[3] have used the Wittig reaction of phosphonium salt **4** with several aldehydes for the synthesis of 6-substituted uracils. We now describe a simple new method for elaboration of the methyl group of 2-hydroxypyrimidines (**1**) which avoids the necessity for hydroxyl masking or the preparation of phosphonium salts such as **4**. The procedure is based on initial generation of dianions (**2**), followed by treatment with various electrophilic reagents to form the appropriate C-substituted derivatives (**3**). Dianions derived from pyrimidines possessing other arrangements of hydroxyl and methyl, as well as those having suitably positioned mercapto and methyl, anilino and methyl, or amino and methyl groups, can be formed and utilized in a similar fashion.



1a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$



2a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = C_6H_5(CH_2)_2$; $R_2 = C_6H_5$



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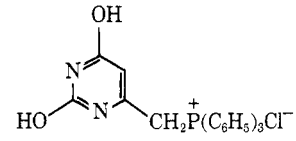


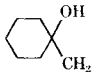
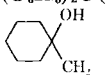
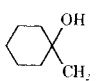
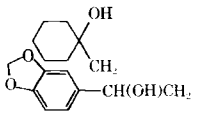
4

Results and Discussion

In an initial search for suitable basic reagents, the readily available 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine

Table I

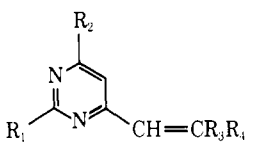
Reactions of Dianions with Electrophiles

Dianion (M)	Electrophile	Compd	R_1	R_2	R_3	Yield, %	Mp, °C
2a (Li)	Benzyl chloride	**3a**	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	76	198–202[a]
2a (Na)	Benzyl chloride	**3a**	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	75	202–204[a]
2a (Li)	Benzophenone	**3b**	CH_3	C_6H_5	$(C_6H_5)_2C(OH)CH_2$	89	144–146[b]
2a (Li)	Cyclohexanone	**3c**	CH_3	C_6H_5		52	148–150[c]
2a (Li)	Methyl benzoate	**3d**	CH_3	C_6H_5	$C_6H_5COCH_2$	69	324–327[b]
2d (Li)	Benzyl chloride	**3e**	$C_6H_5(CH_2)_2$	C_6H_5	$C_6H_5(CH_2)_2$	57	176–177[d]
2b (Li)	Benzyl chloride	**3f**	C_6H_5	H	$C_6H_5(CH_2)_2$	39	180–182[a]
2b (Na)	Benzyl chloride	**3f**	C_6H_5	H	$C_6H_5(CH_2)_2$	65	180–182[a]
2b (Li)	Benzophenone	**3g**	C_6H_5	H	$(C_6H_5)_2C(OH)CH_2$	79	166–167[e]
2b (Na)	Benzophenone	**3g**	C_6H_5	H	$(C_6H_5)_2C(OH)CH_2$	68	166–167[e]
2b (Li)	Cyclohexanone	**3h**	C_6H_5	H		44	183–184[b]
2b (Li)	Anisaldehyde	**3i**	C_6H_5	H	p-$CH_3OC_6H_4CH(OH)CH_2$	68	255–260[b]
2b (Li)	Heptaldehyde	**3j**	C_6H_5	H	$CH_3(CH_2)_5CH(OH)CH_2$	41	138–140[a]
2b (Li)	Methyl benzoate	**3k**	C_6H_5	H	$C_6H_5COCH_2$	64	233–234.5[b]
2b (Li)	Ethyl acetate	**3l**	C_6H_5	H	CH_3COCH_2	63	209–211[a]
2c (Li)	Benzophenone	**3m**	CH_3	H	$(C_6H_5)_2C(OH)CH_2$	21	98–103[a]
2c (Li)	3,4,5-Trimethoxybenzaldehyde	**3n**	CH_3	H	3,4,5-$(CH_3O)_3C_6H_2CH(OH)CH_2$	10	119–121[c]
12 (Li)	Benzyl chloride	**13a**	$C_6H_5(CH_2)_2$			58	208–210[b,f]
12 (Li)	Ethyl bromide	**13b**	$CH_3(CH_2)_2$			57	193.5–195[g,h]
12 (Li)	Acetophenone	**13c**	$C_6H_5C(OH)(CH_3)CH_2$			63	135–136[i]
12 (Li)	Benzophenone	**13d**	$(C_6H_5)_2C(OH)CH_2$			58	163–164[g]
12 (Li)	Anisaldehyde	**13e**	p-$CH_3OC_6H_4CH(OH)CH_2$			50	177.5–179[c]
16a (Li)	Benzyl chloride	**17a**	C_6H_5	C_6H_5	$C_6H_5(CH_2)_2$	70	90–92[a]
16a (Li)	Benzophenone	**17b**	C_6H_5	C_6H_5	$(C_6H_5)_2C(OH)CH_2$	90	149–152[b]
16a (Na)	Benzophenone	**17b**	C_6H_5	C_6H_5	$(C_6H_5)_2C(OH)CH_2$	38	149–152[b]
16a (Li)	3,4-Dichloro-4′-trifluoromethylbenzophenone	**17c**	C_6H_5	C_6H_5	3,4-$(Cl)_2C_6H_5C(OH)(4\text{-}CF_3C_6H_4)CH_2$	85	202–204[a,i]
16a (Li)	Cyclohexanone	**17d**	C_6H_5	C_6H_5		55	139–141[a]
16a (Li)	Anisaldehyde	**17e**	C_6H_5	C_6H_5	p-$CH_3OC_6H_4CH(OH)CH_2$	80	132–134[b]
16a (Li)	Heptaldehyde	**17f**	C_6H_5	C_6H_5	$CH_3(CH_2)_5CH(OH)CH_2$	40	175–177[c,j]
16b (Li)	Benzyl chloride	**17g**	H	H	$C_6H_5(CH_2)_2$	58	162–164[b,k]
16b (Na)	Benzyl chloride	**17g**	H	H	$C_6H_5(CH_2)_2$	11	162–164[b,k]
16b (Li)	Benzophenone	**17h**	H	H	$(C_6H_5)_2C(OH)CH_2$	70	193–195[a]
16b (Li)	Cyclohexanone	**17i**	H	H		54	197–199[a]
16b (Li)	Piperonal	**17j**	H	H		27	172–174[b]
16b (Li)	Heptaldehyde	**17k**	H	H	$CH_3(CH_2)_5CH(OH)CH_2$	37	103–104[a]

[a] Recrystallized from aqueous ethanol. [b] Recrystallized from ethanol. [c] Recrystallized from ethyl acetate. [d] Recrystallized from ethanol–2-propanol (1:1). [e] Crude product. [f] Lit. mp 209.5–210.5°: E. B. Marr and M. T. Bogert, *J. Amer. Chem. Soc.*, **57**, 729 (1935). [g] Recrystallized from ethyl acetate–hexane. [h] Lit. mp 200–201°: D. T. Zentmeyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949). [i] Recrystallized from acetone–hexane. [j] Characterized as the HCl salt. [k] Lit.[11] mp 162–164°.

(**1a**)[4] was used as a model substrate for dianion formation. Since alkali amides and organolithium reagents had previously[4,5] been reported to be suitable for lateral metalation of a few methylpyrimidines not possessing a second active-hydrogen substituent, sodium amide and *n*-butyllithium complexed with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[6] were tested for their ability to effect twofold deprotonation of **1a**. Treatment of **1a** with 2 molar equiv of *n*-butyllithium complexed with TMEDA in THF-hexane at 0° resulted in excellent conversion of **1a** into dianion **2a** (M = Li) as evidenced by deuteration and by alkylation with benzyl chloride to form **3a** (Table I). Dianion **2a** (M = Li) underwent carbonyl addition reactions with benzophenone and cyclohexanone to give carbinols **3b–c** in good yields, while acylation with methyl benzoate gave the highly enolic phenacylpyrimidine **3d**. Formation and benzylation of **2a** (M = Na) was also accomplished satisfactorily by means of 2 molar equiv of sodium amide in liquid ammonia. However, attempted condensation of disodio **2a** with cyclohexanone resulted mainly in enolization of the ketone. For this reason, the more covalent dilithio salts reported herein are recommended for reactions with aliphatic carbonyl compounds. Treatment of phenethylpyrimidine **3a** with 2 equiv of *n*-butyllithium–TMEDA afforded predominately dianion **2d** (M = Li) as shown by benzylation to form symmetrical derivative **3e**.

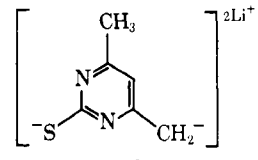
Next, it was demonstrated that a 5-phenyl substituent was not necessary for dianion formation and that TMEDA could also be eliminated without severely hampering the twofold ionization process. Thus, reaction of **1b** with 2 equiv of *n*-butyllithium followed by benzyl chloride afforded *C*-benzyl derivative **3f**. Further evidence for the presence of dianion **2b** (M = Li) was obtained by reactions with benzophenone, cyclohexanone, anisaldehyde, and heptaldehyde to form **3g–j**, respectively. Dehydration of carbinols **3g** and **3i** with *p*-toluenesulfonic acid (PTSA) in refluxing benzene afforded styryl derivatives **5a–b** in yields of 85 and 65%, respectively. Acylation of **2b** (M = Li) with methyl benzoate and ethyl acetate yielded pyrimidinyl ketones **3k–l**. Dianion **2b** (M = Na) could also be prepared by means of sodium amide in liquid ammonia, as shown by reactions with benzyl chloride and benzophenone to give **3f** and **3g** in yields comparable to those obtained with dilithio salt **2b**.



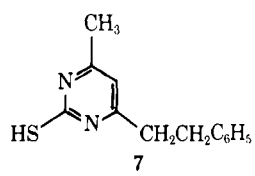
5a, R_1 = OH; R_2 = C_6H_5; R_3 = R_4 = C_6H_5
b, R_1 = OH; R_2 = C_6H_5; R_3 = *p*-$CH_3OC_6H_4$; R_4 = H
c, R_1 = OH; R_2 = CH_3; R_3 = R_4 = C_6H_5

While conversion of the hydrochloride salt of pyrimidine **1c** into dianion **2c** (M = Na) with 3 equiv of sodium amide in liquid ammonia was generally unsatisfactory, **2c** (M = Li) was generated, albeit in low concentrations, using 3 equiv of *n*-butyllithium complexed with TMEDA or 1,4-diazabicyclo[2.2.2]octane (Dabco).[7] Trapping experiments with benzophenone and 3,4,5-trimethoxybenzaldehyde in the presence of Dabco afforded adducts **3m–n**, the former of which was dehydrated with PTSA to give **5c**.

Reaction of 2-mercapto-4,6-dimethylpyrimidine with 2 equiv of *n*-butyllithium followed by benzyl chloride afforded a complex mixture of products from which **7** was isolated in 29% yield, thereby providing evidence for the intermediacy of dianion **6**. Pmr analysis of the crude product mixture indicated the presence of S-benzylated products also.



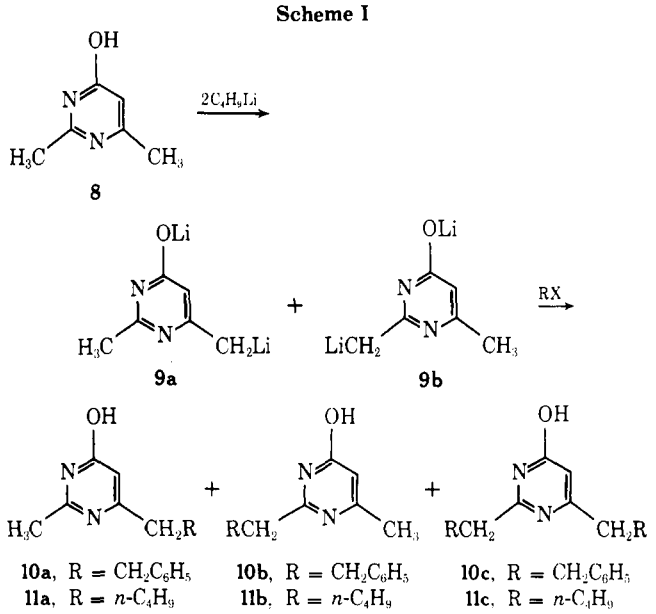
6



7

To ascertain if there was any preference for dianion formation at one or the other of two activated, but nonequivalent, methyl groups, 2,6-dimethyl-4-hydroxypyrimidine (**8**) was treated with 2 equiv of *n*-butyllithium and separate reaction mixtures were quenched with benzyl chloride and *n*-butyl bromide. Alkylation with benzyl chloride gave monoalkyl derivatives **10a–b** and dialkyl derivative **10c** in yields of 48, 13, and 7%, respectively, while alkylation with *n*-butyl bromide gave the corresponding mono- and dialkylation products **11a–c** in yields of 39, 18, and 8%, respectively (Scheme I). These results are consistent with predominant formation of dianion **9a**.[8] It seems unlikely that dialkylated products **10c** and **11c** arise through formation and alkylation of a dianion produced by ionization of both methyl groups but not the hydroxy function, or a trianion having both methyls and the hydroxyl ionized, since initial formation of such intermediates in the presence of 2 equiv of base should be cancelled by subsequent proton–metal exchange to form dianions **9a** and **9b**. Moreover, it was demonstrated that treatment of **8** with 3 equiv of *n*-butyllithium followed by benzyl chloride did not produce significantly higher yields of **10c** than those observed with 2 equiv of base. The most likely route to dialkylated products **10c** and **11c** therefore appears to involve initial C-alkylation of either **9a** or **9b** followed by proton–metal exchange between monoalkylated derivatives **10a–b** and **11a–b** (as the O-Li salts) and original dianions **9a–b** to form the isomeric dianions resulting from abstraction of methyl protons from **10a** or **10b** and **11a** or **11b**. Alkylation of these dianions then produces **10c** and **11c**.

Scheme I



8 **9a** **9b**

10a, R = $CH_2C_6H_5$ **10b**, R = $CH_2C_6H_5$ **10c**, R = $CH_2C_6H_5$
11a, R = *n*-C_4H_9 **11b**, R = *n*-C_4H_9 **11c**, R = *n*-C_4H_9

Although the foregoing results indicated that a 4- (or 6-) methyl substituent is more readily deprotonated than a 2-methyl group, we found that 2-methyl-4(3*H*)-quinazolinone, which may be regarded as analogous to a 4-hydroxy-2-methylpyrimidine, could be converted into dianion **12** by means of uncomplexed *n*-butyllithium. Subsequent condensations of **12** with benzyl chloride, ethyl bromide, acetophenone, benzophenone, and anisaldehyde resulted

JOC-32-1

EXPERIMENTAL SECTION

General. -- Melting points were obtained on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Infrared spectra were obtained on either a Beckman IR-5A or a Beckman IR 20A-X spectrophotometer. Pmr spectra were obtained on a Varian A-60 or a JEOL JNM-PS-100 instrument with chemical shifts expressed in parts per million downfield from TMS internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.; Weiler Laboratories, Garden City, Mich.; and this laboratory by T. E. Glass employing a Perkin Elmer 240 Elemental Analyser. Thin layer chromatography (tlc) was performed on Eastman 6060 precoated silica gel sheets, and spots were detected with ultraviolet light. All evaporations were carried out in vacuo.

Materials. -- Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. N,N,N',N'-Tetramethylethylenediamine (TMEDA) was distilled from calcium hydride and stored over "Linde" type 3A molecular sieves. n-Butyllithium (as a solution in hexane) was obtained from Foote Mineral Company, Exton, Pa., or Ventron Corporation, Beverly, Mass. All other commercial reagents were used without further purification.

2-Hydroxy-4,6-dimethyl-5-phenylpyrimidine (1a) and 2-hydroxy-4-methyl-6-phenylpyrimidine (1b) were prepared by the method of Hauser and Wanyik.[7] 2-Anilino-4-methyl-6-phenylpyrimidine (15a) was prepared by displacement of chlorine from 2-chloro-4-methyl-6-phenylpyrimidine by means of refluxing aniline and had mp 116-118°, after recrystallization from aqueous ethanol; ir ($CHCl_3$) 3400 cm^{-1} (NH); pmr (DMSO-d_6) δ 2.64 (s, 3, CH_3), 8.12 (m, 11, aromatic), and 10.40 (s, 1, NH).

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.03; H, 5.94; N, 15.78.

General Procedure for the Preparation and Reactions of Dianions 1a-b (M=Li). -- The following specific procedures involving dianion 1a (M=Li) are representative of those used to prepare other C-substituted derivatives of 1a-b via the appropriate dianions.

A. Preparation of Dianion 1a (M=Li). -- n-Butyllithium (51 ml of 1.6 M hexane solution) was added (via syringe) to a magnetically stirred suspension of 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine (1a) (8.00 g, 40 mmol) and TMEDA (9.30 g, 82 mmol) in 250 ml of THF at 0° under nitrogen. After 0.5 hr, the yellow solution was assumed to contain 40 mmol of dianion 1a (M=Li).

B. Deuteration. -- Deuterium oxide (15 ml) was added to a solution of 10 mmol of 1a (M=Li) in 150 ml of THF-hexane. The two-phase mixture was extracted with two 100 ml portions of ether, which were discarded. The deuterium oxide solution was neutralized with concentrated HCl; the precipitated pyrimidine (1a) was collected, washed with 100 ml of ether, 5 ml of deuterium oxide, and then dried. Integration of the pmr spectrum ($DMSO-d_6$) of this material revealed incorporation of 0.8D into the methyl group of 1a. [13]

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(13) Although neutralization of the reaction mixture with HCl may have effected some side-chain deuterium incorporation by acid-catalyzed H/D exchange, see T. J. Batterham, D. J. Brown, and H. N. Paddon-Row, J. Chem. Soc., B, 171 (1967), the extent of deuteration is consistent with the yields of condensation products and thus appears to provide a valid estimate of carbanion formation.

C. Benzylation. -- Benzyl chloride (5.3 g, 42 mmol), as a 50% w/v solution in THF, was added to a solution of 40 mmol of 2a (M=Li) in 150 ml of THF-hexane. The reaction was allowed to stir for 2 hr before being quenched with 150 ml of cold water. The organic phase was separated and discarded, and the aqueous phase was neutralized with 6N HCl. The resulting precipitate was collected, dried, and recrystallized from aqueous ethanol to afford 8.81 g (76%) of 2-hydroxy-4-methyl-5-phenyl-6-phenethylpyrimidine (3a).

D. Condensation with Benzophenone. -- Benzophenone (7.3 g, 40 mmol), as a 50% solution in THF, was added to a solution of 40 mmol of 2a (M=Li) in 250 ml of THF-hexane. After 2 hr, the reaction mixture was poured into 150 ml of cold water. The organic phase was separated and discarded. The aqueous phase was neutralized with 6N HCl to form a white precipitate, which was collected, dried, and recrystallized from ethanol to give 13.5 g (89%) of 2-hydroxy-4-methyl-5-phenyl-6-(2-hydroxy-2,2-diphenylathyl)-pyrimidine (3b).

E. Condensation with Methyl Benzoate. -- A solution of methyl benzoate (1.36 g, 10 mmol) in 10 ml of THF was added dropwise to a solution of 20 mmol of 2a (M=Li) in 75 ml of THF. The reaction mixture was stirred for 2 hr before being poured into 100 ml of cold water. The organic phase was separated and discarded. The aqueous phase was neutralized with concentrated HCl to produce a yellow solid which was collected, dried, and crystallized from ethanol to afford 2.10 g (69%) of 2-hydroxy-4-methyl-5-phenyl-6-phenacylpyrimidine (3d).

Preparation and Reactions of Dianion 2c (M=Li). -- n-Butyllithium (75 ml of a 1.6 M hexane solution) was added to a stirred slurry of 2-hydroxy-4,6-dimethylpyrimidine hydrochloride (4c) (6.4 g, 40 mmol) and DABCO (13.4 g, 120 mmol) in 250 ml of THF at 0° under nitrogen. After 0.5 hr., benzophenone (7.03 g, 40 mmol), as a 50% w/v solution in THF, was added. The resulting mixture was allowed to stir for 2 hr before being poured into 50 ml of cold, dilute HCl. The resulting precipitate was collected, washed with 100 ml of water followed by 100 ml of ether, dried, and recrystallized from ethyl acetate to afford 2.46 g (21%) of 2-hydroxy-4-methyl-6-(2-hydroxy-2,2-diphenylethyl)pyrimidine (3m).

Similarly, condensation of 2c (M=Li) with 3,4,5-trimethoxybenzaldehyde gave pyrimidine (3n) in 10% yield.

General Procedure for the Preparation and Reactions of Dianions 2a-b (M=Li). -- The following specific procedures involving dianion 2b (M=Na) are representative of those used to prepare other C-substituted derivatives of 1a-b by means of sodium amide in liquid ammonia.

A. Preparation of Dianion 2b (M=Na). -- 2-Hydroxy-4-methyl-6-phenylpyrimidine (1b) (5.43 g, 30 mmol) was added to 62 mmol of sodium amide (prepared from 62 mg-atom of sodium) in 300 ml of liquid ammonia containing a catalytic amount of ferric nitrate. After 0.5 hr, the resulting red solution was assumed to contain 30 mmol of 2b (M=Na).

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B. Benzylation. -- Benzyl chloride (4.05 g, 32 mmol), as a 50% w/v solution in anhydrous ether, was added to 30 mmol of 2b (M=Na) in 300 ml of liquid ammonia. After 2 hr, the reaction was quenched with 10 g of solid NH_4Cl, and the ammonia was evaporated (steam bath) while being replaced with an equal volume of ether. Addition of 150 ml of water resulted in formation of a solid at the interface, which was collected, dried, and crystallized from aqueous ethanol to afford 5.35 g (65%) of 2-hydroxy-4-phenethyl-6-phenylpyrimidine (3f).

C. Condensation with Benzophenone. -- An ethereal solution of benzophenone (5.45 g, 30 mmol) was added to 30 mmol of 2b (M=Na) in 300 ml of liquid ammonia, and the reaction mixture was stirred for 2 hr before the addition of 10 g of NH_4Cl. The ammonia was replaced with ether, and water (150 ml) was added to the ethereal suspension. The resulting solid was collected and dried to give 7.48 g (68%) of 2-hydroxy-4-phenyl-6-(2-hydroxy-2,2-diphenylethyl)pyridine (3g).

Preparation and Benzylation of Dianion 2d (M=Li). -- n-Butyllithium (26 ml of 1.6 M hexane solution) was added to a stirred suspension of 2-hydroxy-4-methyl-6-phenethylpyrimidine (3a) (5.56 g, 20 mmol) and TMEDA (4.75 g, 41 mmol) in 250 ml of THF at 0° under nitrogen. After 0.5 hr, the resulting brown solution was assumed to contain 20 mmol of dianion 2d (M=Li). A solution of benzyl chloride (2.70 g, 21 mmol) in 50 ml of THF was then added, and after 2 hr, the reaction was poured into 100 ml of cold water. The two-phase mixture was neutralized with 6N HCl, and the organic layer was separated. The aqueous layer was extracted with two 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to afford 4.33 g (57%) of 2-hydroxy-4,6-diphenethyl-5-phenylpyrimidine (3e).

Dehydration of Alcohols 3g, 3i, and 3m. -- The appropriate alcohol and a few crystals of p-toluenesulfonic acid were heated for 3-4 hr in refluxing benzene. After cooling, the crude styryl derivative was collected by filtration and dried.

Dehydration of carbinol 3g afforded, after recrystallization from ethanol, 2-hydroxy-4-phenyl-6-(2,2-diphenylethenyl)pyrimidine (5a) in 85% yield: mp 236-238°; ir ($CHCl_3$) 3000 (vinyl CH) and 1640 cm^{-1} (C=O); pmr (DMSO-d_6) δ 6.30 (s, 1, vinyl), 7.74 (m, 16, aromatic and py), and 12.50 (s, 1, NH or OH).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.17; H, 5.34; N, 8.25.

Dehydration of 3i gave, after recrystallization from ethanol, 2-hydroxy-4-phenyl-6-[4-methoxystyryl]pyrimidine (5b) in 65% yield: mp 273-275°; ir (KBr) 3440 (NH or OH), 3025 (vinyl CH), and 1630 cm^{-1} (C=O); pmr (DMSO-d_6) δ 3.96 (s, 3, OCH_3), 7.74 (m, 12, aromatic, py, and vinyl), and 12.42 (s, 1, NH or OH).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.22; H, 5.06; N, 8.95.

Similarly, dehydration of 3m afforded, after recrystallization from ethyl acetate, 2-hydroxy-4-methyl-6-(2,2-diphenylethenyl)pyrimidine (5c) in 44% yield: mp 244-247°; ir ($CHCl_3$) 2750 cm^{-1} (OH); pmr ($CDCl_3$) δ 2.24 (s, 3, CH_3), 5.76 (s, 1, vinyl), and 7.67 (m, 12, aromatic, py, and OH).

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Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.44; H, 5.75; N, 9.72.

Preparation and Benzylation of Dianion 8 (M=Li). -- n-Butyllithium (51 ml of 1.6 M hexane solution) was added to a stirred suspension of 2-mercapto-4,6-dimethylpyrimidine (5.60 g, 40 mmol) in 250 ml of THF at 0° under nitrogen. The resulting brown suspension was stirred for 0.5 hr before the addition of a solution of benzyl chloride (5.30 g, 42 mmol) in 50 ml of THF. After 2.5 hr, the reaction mixture was poured into 150 ml of cold water, and the layers were separated. The aqueous layer was washed with 100 ml of ether, and the combined organic extracts were discarded. The aqueous solution was neutralized with concentrated HCl. Tlc of the resulting oil indicated the presence of four products; while pmr analysis ($DMSO-d_6$) revealed the presence of S-benzylated products as evidenced by resonances at 4.26, 4.32, and 4.37 ppm characteristic of methylene adsorption of aromatic benzyl sulfides. Upon standing at 0°, the oil crystallized to afford 2.63 g (29%) of 2-mercapto-4-methyl-6-phenethylpyrimidine (7), which was recrystallized from ethanol: mp 165-166°; pmr (DMSO-d_6) δ 2.14 (s, 3, CH_3), 2.76 (s, 4, CH_2), 5.56 (s, 1, py), and 7.10 (s, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.83; H, 6.09; N, 12.17. Found: C, 68.13, H, 5.97; N, 11.89.

Benzylation of the Dilithio Salts of 2,6-Dimethyl-4-hydroxypyrimidine (8). -- n-Butyllithium (21.05 ml of 1.9M hexane solution was added to a stirred solution of 2,6-dimethyl-4-hydroxypyrimidine (1.24 g, 10 mmol) in 125 ml of THF at 0° under nitrogen, and the resulting yellow suspension was stirred for 1 hr before the addition of benzyl chloride (1.39 g, 11 mmol). After 2.5 hr, the reaction solution was poured into 100 ml of iced water, and the two-phase mixture was neutralized with concentrated HCl. The organic phase was separated, and the aqueous phase was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The resulting yellow oil was chromatographed on silica gel. Elution with benzene-acetone gave initially, 0.21 g(7%) of 2,6-diphenethyl-4-hydroxypyrimidine (10d), mp 158-161°, after recrystallization from acetone-hexane. Additional recrystallizations raised the mp to 161.5-163°: ir ($CHCl_3$) 3040 (NH) and 1645 cm^{-1} (C=O); pmr (DMSO-d_6) δ 2.76 (m, 8, CH_2), 5.94 (s, 1, py), and 7.10 (s, 10, aromatic).

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.91; H, 6.62; N, 9.21. Found: C, 78.69; H, 6.33; N, 9.05.

Continued elution with benzene-acetone afforded 0.26 g (13%) of 2-phenethyl-4-a-hydroxy-6-methylpyrimidine (10b), mp 166-168° after recrystallization from acetone-hexane. Two additional recrystallizations gave analytically pure material, mp 166-167°: ir (KBr) 1655 cm^{-1} (C=O); pmr (DMSO-d_6) δ 2.12 (s, 3, CH_3), 2.82 (m, 4, CH_2), 5.92 (s, 1, py), and 7.16 (s, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.04; H, 6.84; N, 13.13.

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Further elution with benzene-acetone gave 1.02 g (48%) of 2-methyl-4-hydroxy-6-phenethylpyrimidine (10a), mp 125.5-127° after recrystallization from acetone-hexane: ir ($CHCl_3$) 1665 cm^{-1} (C=O); pmr (DMSO-d_6) δ 2.22 (s, 3, CH_3), 2.72 (m, 4, CH_2), 5.88 (s, 1, py), and 7.12 (s, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.17; H, 6.62; N, 13.25.

Benzylation of 2,6-Dimethyl-4-hydroxypyrimidine in the Presence of 3 Equiv of n-Butyllithium. -- n-Butyllithium (5.80 ml of 1.9M hexane solution) was added to a solution of 2,6-dimethyl-4-hydroxypyrimidine (8) (0.62 g, 5 mmol) in 50 ml of THF at 0° under nitrogen. After 0.5 hr, a solution of TMEDA (1.64 g, 1.5 mmol) in 25 ml of THF was added, followed by n-butyllithium (2.90 ml of 1.9M hexane solution). The resulting yellow-orange slurry was stirred for 1.5 hr before the addition of benzyl chloride (1.46 g, 11.5 mmol). After 2 hr, the reaction solution was poured into 50 ml of iced water, and the aqueous mixture was neutralized with concentrated HCl. The organic phase was separated, and the aqueous phase was extracted with two 50 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the resulting oil (eluting with benzene-acetone) afforded 0.26 g (17%) of 10c, 0.04 g (4%) of 10b, and 0.35 g (33%) of 10a.

Butylation of the Dilithio Salts of 2,6-Dimethyl-4-hydroxypyrimidine (8). -- A solution of 1-bromobutane (3.01 g, 22 mmol) in 25 ml of THF was added dropwise to a stirred slurry of 20 mmol of the dilithio salt of 8 (prepared as described in the previous experiment) in 200 ml of THF-hexane at 0° under nitrogen. After 2 hr, the reaction solution was poured into 100 ml of iced water, and the aqueous mixture was neutralized with concentrated HCl. The organic phase was separated and the aqueous phase was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The resulting brown oil was chromatographed on silica gel. Elution with ether-hexane (1:1, v/v) gave, initially, 0.37 g (8%) of 2,6-dipentyl-4-hydroxypyrimidine (11c) as an oil, bp 182-185° (1 mm): ir (film) 1675 cm^{-1} (C=O); pmr (DMSO-d_6) δ 0.80 (t, 6, CH_3), 1.20 (m, 8, CH_2), 1.52 (m, 4, CH_2), 2.32 (m, 4, CH_2), and 5.82 (s, 1, py).

Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.16; H, 10.44; N, 11.63

Continued elution with ether-hexane afforded 0.65 g (18%) of 4-hydroxy-6-methyl-2-pentylpyrimidine (11b), mp 79-81° after two recrystallizations from pentane (lit.[14] mp 80-81°); pmr (DMSO-d_6) δ 0.84 (t, 3, CH_3), 1.30 (m, 4, CH_2), 1.67 (m, 2, CH_2), 2.16 (s, 3, CH_3), 2.52 (t, 2, CH_2), and 5.97 (s, 1, py).

(14) G. W. Miller and F. L. Rose, J. Chem. Soc., 3492 (1963).

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Further elution with ether-hexane gave 1.41 g (39%) of 4-hydroxy-2-methyl-6-pentylpyrimidine (11a), mp 87-88.5° after recrystallization from petroleum ether: ir ($CHCl_3$) 1655 cm^{-1} (C=O); pmr (DMSO-d_6) δ 0.82 (t, 3, CH_3), 1.22 (m, 4, CH_2), 1.48 (m, 2, CH_2), 2.16 (s, 3, CH_3), 2.31 (t, 2, CH_2), and 5.86 (s, 1, py).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.77; H, 9.01; N, 15.62.

Preparations and Reactions of Dianion 12. -- n-Butyllithium (11.1 ml of a 1.89 M hexane solution) was added to a stirred solution of 2-methyl-4(3H)-quinazolinone (1.60 g, 10 mmol) in 125 ml of THF at 0° under nitrogen. After 1 hr, the deep red solution was assumed to contain 10 mmol of dianion 12. A solution of the appropriate electrophile in 25 ml THF was then added dropwise. After 2 hr, the reaction mixture was poured into 100 ml of iced water, and the aqueous mixture was neutralized with concentrated HCl. The organic layer was separated, and the aqueous layer was extracted with two 100 ml portions of ether. The organic extracts were dried (Na_2SO_4), and the solvent was evaporated. Recrystallization of the crude products from appropriate solvents afforded 13a-e (Table I). Although the mp of 13b was somewhat lower than that reported by earlier investigators, the pmr spectrum of our material was completely consistent with the assigned structure: pmr (DMSO-d_6) δ 0.93 (t, 3, CH_3), 1.76 (m, 2, CH_2), 2.59 (t, 2, CH_2), and 7.74 (m, 4, aromatic).

Dehydration of Carbinol 11d. -- The alcohol (0.50 g, 1.46 mmol) was stirred in 25 ml of aqueous H_2SO_4 (3:2) for 2.5 hr at room temperature. The reaction mixture was poured into 100 ml of iced water and made alkaline with concentrated NH_4OH. The aqueous mixture was extracted with two 25 ml portions of chloroform. The organic solution was dried ($MgSO_4$), and the solvent was evaporated to give a light yellow solid. Recrystallization from ethyl acetate gave 0.37 g (79%) of 2-(2,2-diphenylethenyl)-4(3H)-quinazolinone (13f), mp 207-208°; pmr (DMSO-d_6) δ 6.83 (s, 1, vinyl), 7.41 (m, 13, aromatic), and 8.03 (d, 2, aromatic).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.64; H, 4.97; N, 8.64. Found: C, 81.96; H, 5.16; N, 8.93.

Preparation and Reactions of Dianion 16a (M=Li). -- n-Butyllithium (37.5 ml of 1.6 M hexane solution) was added (via syringe) to a stirred solution of 2-anilino-4-methyl-6-phenylpyrimidine (15a) (7.85 g, 30 mmol) in 150 ml of THF at 0° under nitrogen. After 0.5 hr, the deep red solution was assumed to contain 30 mmol of dianion 16a (M=Li).

A. Deuteration. -- A solution of 16a (M=Li) was quenched with 15 ml of deuterium oxide. After stirring for 0.5 hr, the layers were separated, and the deuterium oxide solution was extracted with two 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give deuterated 15a. Pmr analysis ($DMSO-d_6$) disclosed incorporation of 0.81D per methyl group.

B. Benzylation. -- Benzyl chloride (2.78 g, 22 mmol), as a 50% w/v solution in THF, was added to a stirred solution of 20 mmol of 16a (M=Li) in THF-hexane. After 2 hr, the reaction was quenched by the addition of 50 ml of cold, dilute HCl. The precipitate which formed was collected and neutralized with dilute NH_4OH. The resulting aqueous solution, containing an oil, was extracted with three 100 ml portions of ether. The ethereal extracts were dried (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized on standing. Recrystallization from aqueous ethanol gave 4.70 g (73%) of 2-anilino-4-phenyl-6-phenethylpyrimidine (17a).

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C. Condensation with Benzophenone. -- Benzophenone (4.00 g, 22 mmol), as a 50% w/v solution in THF, was added to a stirred solution of 20 mmol of 16a (M=Li) in THF-hexane, and the mixture was allowed to stir for 2 hr. The reaction mixture was poured into 100 ml of cold, dilute HCl. The resulting yellow precipitate was collected, washed with 100 ml of 5% $NaHCO_3$, followed by 100 ml of water, and then dried. Recrystallization from ethanol gave 7.81 g (90%) of 2-anilino-4-phenyl-6-(2-hydroxy-2,2-diphenylethyl)pyrimidine (17b).

D. Condensation with 3,4-Dichloro-4'-trifluoromethylbenzophenone. -- A 50% w/v solution of 3,4-dichloro-4'-trifluoromethylbenzophenone (17.24 g, 32 mmol) in THF was added to 30 mmol of 16a (M=Li) in THF-hexane, and the reaction was stirred for 2 hr. The mixture was poured into 100 ml of cold, dilute HCl, and the crude hydrochloride salt was collected and then neutralized with dilute NH_4OH. The free base was extracted into ether and the resulting ethereal solution was saturated with gaseous HCl to give a precipitate which was collected and dried. Crystallization from aqueous ethanol afforded 16.23 g (65%) of 2-anilino-5-phenyl-4-[2-hydroxy-2-(4-trifluoromethylphenyl)-2-(3,4-dichlorophenyl)ethyl]-pyrimidine hydrochloride (17c).

E. Condensation with Cyclohexanone. -- A solution of cyclohexanone (3.12 g, 32 mmol) in 10 ml of THF was added to 30 mmol of 16a (M=Li). After 2 hr, the reaction mixture was poured into 150 ml of cold water; the layers were separated, and the aqueous layer was extracted with three 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized on standing. Recrystallization from aqueous ethanol afforded 5.91 g (53%) of 2-anilino-4-phenyl-6-(1-hydroxycyclohexylmethyl)-pyrimidine (17d).

F. Condensation with Anisaldehyde. -- A 50% w/v solution of anisaldehyde (3.00 g, 22 mmol) in THF was added to 20 mmol of 16a (M=Li) in THF-hexane. After 2 hr, the reaction was poured into 50 ml of cold, dilute HCl; the resulting precipitate was collected, washed with water, dilute NH_4OH, and water once again. Crystallization from ethanol gave 6.20 g (80%) of 2-anilino-4-phenyl-6-[2-hydroxy-2-(4-methoxyphenyl)ethyl]pyrimidine (17e).

G. Condensation with Heptaldehyde. -- Heptaldehyde (2.51 g, 22 mmol), as a 50% w/v solution in THF, was added to 20 mmol of 16a (M=Li), and the resulting mixture was stirred for 2 hr before being hydrolyzed with 150 ml of cold water. The layers were separated, and the aqueous layer was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed. The resulting oil was dissolved in 200 ml of ether, and the ethereal solution was saturated with gaseous HCl. The resulting precipitate was collected and recrystallized from ethyl acetate to provide 3.28 g (40% of 2-anilino-4-phenyl-6-(2-hydroxyoctyl)pyrimidine hydrochloride (17f).

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Condensation of Dianion 16a (M=Na) with Benzophenone. -- 2-Anilino-4-methyl-6-phenyl-pyrimidine (15a) (3.32 g, 20 mmol) was added to a stirred suspension of 40 mmol of sodium amide (prepared from 40 mg-atom of sodium) in 200 ml of liquid ammonia. After, 0.5 hr, the deep red solution was assumed to contain 20 mmol of dianion 16a (M=Na). Benzophenone (3.64 g, 20 mmol) was then added. The mixture was allowed to stir for 2 hr before the addition of 10 g of solid NH_4Cl. The ammonia was evaporated while being replaced with an equal volume of ether, and then 100 ml of water was added. The layers were separated and the aqueous layer was extracted with two 100 ml portions of ether. The combined ethereal extracts were dried (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized slowly. Recrystallization from ethanol gave 3.32 g (38%) of 17b.

Benzylation of 15b in the Presence of 2 Mol Equiv of Sodium Amide. -- 2-Amino-4-methylpyrimidine (15b) (3.29 g, 30 mmol) was added to a stirred suspension of 62 mmol of sodium amide (prepared from 62 mg-atom of sodium) in 300 ml of liquid ammonia. After the light green solution had been stirred for 0.5 hr, benzyl chloride (4.05 g, 32 mmol), as a 50% w/v solution in anhydrous ether, was added. This addition caused the reaction mixture to assume the characteristic purple color associated with stilbene formation.[15] After 1 hr, the reaction was quenched by the addition of 10 g of solid NH_4Cl. Replacement of the ammonia by an equal volume of ether followed by addition of 100 ml of water caused the formation of a solid at the interface. The solid was collected, dried, and crystallized from ethanol to give 0.64 g (11%) of 2-amino-4-phenethylpyrimidine (17g), mp 162-164° (lit.[15] mp 162-164°). After removal of 17g by filtration, the ethereal layer was separated and dried (Na_2SO_4). Removal of the solvent and recrystallization of the resulting solid from ethanol afforded 1.04 g (61%) of stilbene, mp 122-124° (lit.[16] mp 124°).

(15) T. Matsukawa and K. Shirakawa, J. Pharm. Soc. Japan, 72, 909 (1952).

(16) T. W. J. Taylor and A. R. Murray, J. Chem. Soc., 2079 (1938).

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Benzylation of 15b in the Presence of 2 Mol Equiv of n-Butyllithium-TMEDA Complex. -- n-Butyllithium (51.3 ml of 1.6 M hexane solution) was added to a solution of 15b (4.26 g, 40 mmol) and TMEDA (9.51 g, 82 mmol) in 200 ml of THF at 0° under nitrogen. After 0.5 hr, benzyl chloride (5.30 g, 42 mmol), as a 50% w/v solution in THF, was added. The reaction mixture was allowed to stir 2 hr and was then worked up as in the preceeding experiment. Recrystallization from ethanol gave 2.83 g (36%) of phenethyl derivative 17g, mp 162-164°.

Benzylation of 15b in the Presence of 3 Mol Equiv of n-Butyllithium. -- n-Butyllithium (76 ml of a 1.6 M hexane solution) was added to a solution of 15b (4.36 g, 40 mmol) in 150 ml of THF at 0° under nitrogen. After 0.5 hr, benzyl chloride (5.30 g, 42 mmol) was added as an 0% v/v solution in THF. Workup of the reaction mixture after 2 hr afforded material whose pmr spectra possessed a methylene envelope characteristic of a n-butyl group, at δ.72-1.68 ppm. Recrystallization of this material gave 1.87 g (24%) of 17g, mp 162-164°.

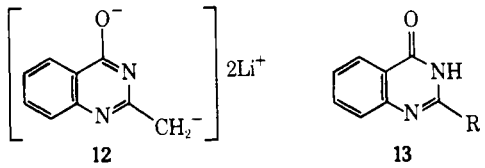
Preparation and Reactions of Dianion 16b (M=Li) Employing 3 Mol Equiv of n-Butyllithium-TMEDA Complex. -- n-Butyllithium (76 ml of a 1.6 M hexane solution) was added to a solution of 15b (4.36 g, 40 mmol) and TMEDA (13.92 g, 120 mmol) in 200 ml of THF at 0° under nitrogen, and the reaction mixture was stirred for 0.5 hr. The appropriate electrophile was added as a solution in THF, and the resulting reaction solution was stirred for 2 hr before workup.

Reactions of 16b (M=Li) with benzyl chloride, cyclohexanone, piperonal, and heptaldehyde were quenched by pouring into 100-200 ml of cold water. The products 17a and 17f-e were isolated by filtration or by extraction with ether, and then recrystallized from the appropriate solvent (Table I).

The condensation product of 16b (M=Li) with benzophenone was obtained by pouring the reaction mixture into 100 ml of cold dilute HCl, collection of the resulting mixture of HCl salts, washing with dilute NH_4OH, and drying. Recrystallization from aqueous ethanol afforded 17h.

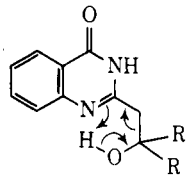
Deuteration was accomplished by adding 0.5 ml of deuterium oxide to a solution of 5 mmol of 16b (M=Li) in THF. After 5 min, the resulting slurry was filtered to remove the precipitated lithium deuteroxide. The filtrate was diluted with 100 ml of ether, dried ($MgSO_4$), concentrated, and the resulting deuterated product was dried overnight in vacuo. Pmr analysis ($DMSO-d_6$) of this material revealed incorporation of 0.74D/methyl group and 0.67D/amino group of 15b.

in selective modification of the original methyl group to form **13a–e** (Table I). These reactions apparently represent the first examples of a direct, general method for side-chain elaboration of 2-alkyl-4(3*H*)-quinazolinones.[9]



12 **13**

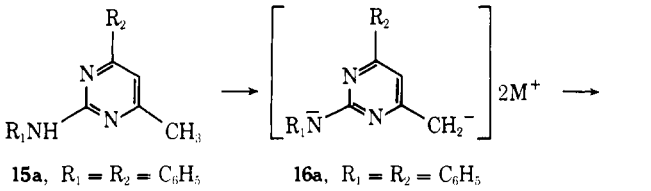
It should be noted that attempts to effect either thermal or PTSA-catalyzed dehydration of carbinols **13c** and **13d** resulted only in retroaldol reactions. Such lability is attributed to the fact that these compounds exist largely as the lactam tautomers (**14**) where the strategically positioned sp^2 ring nitrogen acts as an intramolecular catalytic center for retrocondensation.[10] However, dehydration of **13d** to form **13f** [R = CH=C(C_6H_5)$_2$], without concurrent retroaldol reaction, could be realized by means of aqueous sulfuric acid. In this more acidic medium, protonation of the ring nitrogen may prevent intramolecular degradation of **13d**, thereby allowing the normal mode of dehydration to become the major course of reaction.



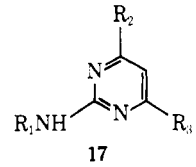
14

Turning next to several representative 2-amino-4-methylpyrimidines, it was found that 2-anilino-4-methyl-6-phenylpyrimidine (**15a**) underwent smooth twofold metalation with *n*-butyllithium complexed with TMEDA or sodium amide in liquid ammonia to yield dianion **16a** (M = Li or Na). Reactions of these dialkali salts with a representative series of electrophiles afforded methyl-substituted derivatives **17a–f** in good yields (Table I).

Conversion of 2-amino-4-methylpyrimidine (**15b**) into dianion **16b** (M = Na) by means of sodium amide in liquid ammonia was incomplete, as evidenced by stilbene formation[11] upon addition of benzyl chloride; the expected C-alkyl derivative **17g** was isolated in only 11% yield. Reactions of **15b** with *n*-butyllithium were characterized by some rather unexpected stoichiometry. Thus, treatment of **15b** with 2 equiv of the alkyllithium reagent, followed by benzyl chloride, afforded only a 5% yield of phenethyl derivative **17g**. Complexation of the organolithium reagent (2 equiv) with TMEDA effected an increase in metalation of the 4-methyl group as shown by the formation of **17g** in 36% yield upon addition of benzyl chloride. When 3 equiv of uncomplexed *n*-butyllithium was employed, the yield of **17g** was lowered to 24% owing to competition between metalation at the 4-methyl group and addition of the alkyllithium to the azomethine linkage. Subsequently it was found that 3 equiv of *n*-butyllithium–TMEDA complex effected metalation of the 4-methyl group of **15b** to an extent satisfactory for synthetically useful condensations with electrophiles. For example, deuteration produced **15b** containing 0.74 D/methyl group, while alkylation with benzyl chloride afforded **17g** in 58% yield. Similarly, reactions with benzophenone, cyclohexanone, piperonal, and heptaldehyde gave the anticipated products **17h–k** (Table I). Although we suspected that the metalated species involved in these reactions might be the trilithio salt resulting from abstraction of both amino protons and a methyl hydrogen from **15b**,[12] this premise was negated by the absence of N-alkylated products and by the finding that deuterium oxide quenches failed to incorporate more than one deuterium at the 2-amino group of **15b**. It is therefore assumed that the major reactive intermediate in the observed condensations employing 3 equiv of alkyllithium–TMEDA complex is dianion **16b** (M = Li).



15a, $R_1 = R_2 = C_6H_5$; b, $R_1 = R_2 = H$ **16a**, $R_1 = R_2 = C_6H_5$; b, $R_1 = R_2 = H$



17

In conclusion, it should be pointed out that the present dianion approach to pyrimidine structure modification offers a facile new route to numerous hydroxy- and aminopyrimidines from readily available starting materials without requiring construction of the heterocyclic ring from acyclic precursors.[2] In the interest of experimental convenience and ease of dianion formation the use of *n*-butyllithium to sodium amide as the metalating agent is preferred.

Registry No.—**1a**, 50324-02-2; **1b**, 6320-47-4; **1c** HCl, 34289-60-6; **2a** (Li), 50324-05-5; **2a** (Na), 50324-06-6; **2b** (Li), 50324-07-7; **2b** (Na), 50324-08-8; **2c** (Li), 50324-09-9; **2d** (Li), 50324-10-2; **3a**, 27433-90-5; **3b**, 27433-89-2; **3c**, 50324-13-5; **3d**, 50324-14-6; **3e**, 50324-15-7; **3f**, 27433-91-6; **3g**, 50324-17-9; **3h**, 27433-92-7; **3i**, 50324-19-1; **3j**, 50324-20-4; **3k**, 50324-21-5; **3l**, 50324-22-6; **3m**, 50324-23-7; **3n**, 50324-24-8; **5a**, 27433-93-8; **5b**, 50324-26-0; **5c**, 50324-27-1; **6** (Li), 50324-28-2; **7**, 50324-29-3; **8**, 6622-92-0; **9a**, 50324-31-7; **9b**, 50324-32-8; **10a**, 50324-33-9; **10b**, 50324-34-0; **10c**, 50324-35-1; **11a**, 50324-36-2; **11b**, 50324-37-3; **11c**, 50324-38-4; **12** (Li), 50324-39-5; **13a**, 4765-57-5; **13b**, 4765-54-2; **13c**, 50324-42-0; **13d**, 50324-43-1; **13e**, 50324-44-2; **13f**, 50324-45-3; **15a**, 50324-46-4; **15b**, 108-52-1; **16a** (Li), 50324-48-6; **16a** (Na), 50324-49-7; **16b** (Li), 50324-50-0; **16b** (Na), 50324-51-1; **17a**, 50324-52-2; **17b**, 50324-53-3; **17c** HCl, 50324-54-4; **17d**, 50324-55-5; **17e**, 50324-56-6; **17f** HCl, 50324-57-7; **17g**, 50324-58-8; **17h**, 50324-59-9; **17i**, 50324-60-2; **17j**, 50324-61-3; **17k**, 50324-62-4; benzyl chloride, 100-44-7; benzophenone, 119-61-9; cyclohexanone, 108-94-1; methyl benzoate, 93-58-3; anisaldehyde, 123-11-5; heptaldehyde, 111-71-7; ethyl acetate, 141-78-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; ethyl bromide, 74-96-4; acetophenone, 98-86-2; 3,4-dichloro-4′-trifluoromethylbenzophenone, 34328-34-2; piperonal, 120-57-0; 2-chloro-4-methyl-6-phenylpyrimidine, 32785-40-3; 2-mercapto-4,6-dimethylpyrimidine, 13139-97-4; 2-methyl-4(3*H*)-quinazolinone, 1769-24-0.

Supplementary and Miniprint Material Available. Analytical and pmr spectral data for all new compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material and full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-595.

References and Notes

† This paper contains "miniprint." See Editorial regarding miniprint on p 8A of the Jan 11, 1974, issue.

(1) (a) For part IV of this series, see J. V. Hay, D. E. Portlock, and J. F. Wolfe, *J. Org. Chem.*, **38**, 4379 (1973). (b) A preliminary account of a portion of the present work has appeared: J. F. Wohe and T. P. Murray, *J. Chem. Soc., Chem. Commun.*, 1040 (1970). (c) This investigation was supported by Grants GM-14340 and NS-10197 from the National Institutes of Health and by Contract No. DA-49-193-MD-3024 from the U. S. Army Research and Development Command.

(2) See (a) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962. (b) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1970, Supplement I.
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(4) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).
(5) (a) T. D. Heys and J. C. Roberts, *J. Chem. Soc.*, 328 (1951); (b) J. C. Roberts, *ibid.*, 3065 (1952).
(6) (a) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965); (b) M. D. Raush and D. J. Ciappenelli, *J. Organometal. Chem.*, **10**, 127 (1967).
(7) (a) W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (b) E. J. Corey and D. Seebach, *ibid.*, **31**, 4097 (1966).
(8) 2,4,6-Trimethylpyrimidine has been shown to undergo metalation with phenyllithium exclusively at the 4-methyl group.[5]
(9) (a) 2-Methyl-4(3*H*)-quinazolinone has been shown to undergo condensation at the methyl group with chloral: P. Y. Kulkarni, *J. Indian Chem. Soc.*, **19**, 180 (1942). (b) The *N*-phenyl derivative also has been reported to undergo similar reactions with other aldehydes: B. D. Singh and D. N. Chaudbury, *ibid.*, **45**, 311 (1968). (c) Alkylation of 2-methyl-4(3*H*)-quinazolinone employing sodium hydride reportedly gives only N- and O-alkylated products: C. Bogentoft, L. Kronberg, and B. Danielsson, *Acta Pharm. Suecica*, **6**, 489 (1969).
(10) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. G. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(11) See R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967), and references cited therein.
(12) Related 1,1-dianions derived from aromatic, primary amines and 1,1-diarylhydrazines have recently been reported: R. West and H. F. Stewart, *J. Amer. Chem. Soc.*, **92**, 853 (1970).

Metallo Aldimines. A Masked Acyl Carbanion[1,2]

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Received September 10, 1973

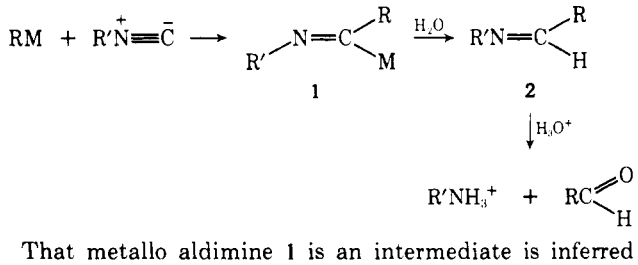
The addition of lithium and Grignard reagents to isocyanides not containing α hydrogens proceeds by an α addition to produce metallo aldimines. The lithium aldimines are versatile reagents which can be used as precursors for the preparation of aldehydes, ketones, α diketones, α-hydroxy ketones, α-keto acids, α- and β-hydroxy acids, and silyl ketones.

There has been a paucity of work on the reaction of organolithium and Grignard reagents with isocyanides. In 1904 Sachs and Loevy[3] added phenylmagnesium bromide to methyl isocyanide and detected benzaldehyde from the steam distillate. Gilman and Heckert[4] 24 years later verified this reaction and reported isolating a 2.5% yield of benzaldehyde; however, the use of ethyl isocyanide or *tert*-butyl isocyanide proved unsuccessful. In 1961, another attempt to use this reaction was made by Ugi,[5] who showed, under a variety of conditions, that the reaction of phenylmagnesium bromide with cyclohexyl isocyanide gave only a 1.5% yield of benzaldehyde.

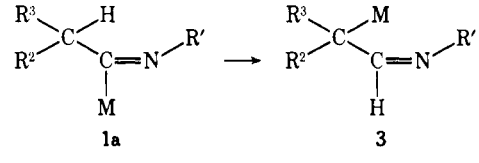
The recent discovery in our laboratory that organolithium reagents added to isocyanides[6] prompted a reinvestigation of this problem. This paper deals with the α addition of organolithium and Grignard reagents to isocyanides to yield metallo aldimines (**1**) and the use of these metallo aldimines as precursors for the synthesis of a variety of functional groups.

Results and Discussion

1-Metallo Aldimines. Metallo aldimines can be most simply prepared by the α addition of an organometallic reagent to an appropriate isocyanide.



That metallo aldimine **1** is an intermediate is inferred from the fact that addition of water to **1** yields the aldimine **2**, which can be isolated. Hydrolysis of **1** or **2** produces the corresponding aldehyde and amine salt. To resolve the question of whether **1** rearranges to give **3**, the metallo aldimine was quenched with D_2O (>99%) and then hydrolyzed. The deuterioaldehyde formed was shown by nmr analysis to have greater than 98% deuterium in the 1 position, which confirms the structural assignment as **1**.



1a **3**

M = Li, MgBr

However, during the deuterolysis of various halomagnesium aldimines, it was observed that less than 100% of the deuterium was incorporated into the C-1 position, and incorporation of some deuterium occurred at the C-2 position (Table III). Several explanations could be conjectured for the presence of deuterium at C-2. First, addition of Grignard reagents to isocyanides requires several hours at room temperature, in contrast to the rapid addition of lithium reagents, and the long reaction time may permit rearrangement of **1a** to the more thermodynamically stable **3**. Secondly, the metallo aldimine **1a** could abstract a proton from the ether solvent and finally a C-2 hydrogen could be abstracted by **1a** during deuterolysis.

To determine if the lithium aldimine was stable to rearrangement, two experiments were conducted. In the first experiment, ethyllithium was added to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) in diethyl ether at 0°. The mixture was stirred for 75 min, then quenched with a fivefold excess of D_2O. The aldimine was distilled, and from the nmr spectrum the relative deuterium content at C-1 and C-2 positions was determined (the methylene protons of the 1,1,3,3-tetramethylbutyl moiety at 1.51 ppm were used as an internal standard). Only 86% incorporation of the deuterium occurred at C-1 while 14% occurred at C-2. The observation that 100% of the deuterium was incorporated into the aldimine suggests[7] that **1a** is not abstracting a proton from the ether solvent, since if this were the case less than 100% deuterium would be incorporated.

The other experiment that was performed involved the addition of ethyllithium to TMBI in ether followed by stirring the reaction mixture at 0° for 6 hr. An inverse ad-