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Reductive cyclization of 2-methylthio-1-(2-nitrobenzyl)-6-pyrimidones with stannous chloride and acetic acid in methanol gives 6,11-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4-ones, and, with trialkylphosphites, 6,11-dihydro-11-alkylpyrimido[2,1-*b*]quinazolin-4-ones.

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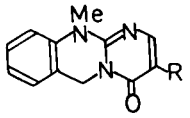
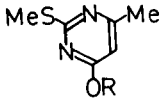
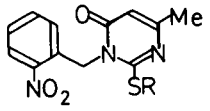
Although 6,11-dihydro-11-methylpyrimido[2,1-*b*]quinazolin-4-ones (**1-2**) were reported previously (1), the dependance of hypotensive activity on an NH-hydrogen in related heterotricyclic compounds (2) suggested that 11-unsubstituted dihydropyrimidoquinazolinones might be of interest. A series of such compounds is described (Table I), and was prepared by reductive cyclization of certain 2-methylthio-1-(2-nitrobenzyl)-6-pyrimidones.



1. R = H
2. R = CO_2Et



10. R = H
12. R = $CH_2C_6H_4NO_2$-*o*
13. R = Et



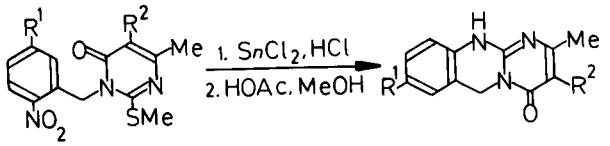
14. R = $CH_2C_6H_4NO_2$-*o*

While *N*-substituted pyrimidones result from alkylation of pyrimidols in ethanol containing potassium hydroxide (3), alkylation of the readily available 4-methyl-2-methylthio-6-pyrimidol (**10**) (4) with 2-nitrobenzyl bromide and sodium ethoxide in ethanol gave only 0.4% of the desired **11**. In contrast, alkylation occurred mostly at oxygen to give **12** (28%); also, 41% of **13** was obtained and a trace of **14** was detected by tlc. The lithium salt of the pyrimidol **10**, however, could be alkylated in hot dioxane by 2-nitrobenzyl bromide, 5-chloro-2-nitrobenzyl bromide (5), and by 5-methyl-2-nitrobenzyl chloride to give **11** (40%), **15** (54%), and **16** (31%), respectively. Exclusive N-1 alkylation may be due to the comparatively greater bulk of the transition state leading to the N-3 isomers. Compound **17** (90%) was prepared from **11** with *N*-bromosuccinimide in chloroform (6).

Reductions of **11** and **15-17** with stannous chloride in hydrochloric acid (7), and cyclization with acetic acid in methanol gave the expected dihydro[2,1-*b*]quinazolinones (Table II).

Table II

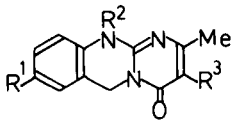
Reductive Cyclization of 4-Methyl-2-methylthio-1-(2-nitrobenzyl)-6-pyrimidones to 6,11-Dihydro-2-methyl-6*H*-pyrimido[2,1-*b*]quinazolin-4-ones.



No.	Substituents		No.	Yield (%)
	R^1	R^2		
11	H	H	**3**	70
15	Cl	H	**4**	56
16	Me	H	**5**	64
17	H	Br	**6**	66

Table I

6,11-Dihydro-2-methylpyrimido[2,1-*b*]quinazolin-4-ones.



No.	Substituents			M.p. (°C)	Mass Spectrum	Analysis							
						% Calcd.				% Found			
	R^1	R^2	R^3		m/e (M^+)	C	H	N	X	C	H	N	X
3	H	H	H	244-246	213	67.59	5.20	19.71	-----	67.51	5.44	19.50	-----
4	Cl	H	H	303-307	247	58.19	4.07	16.96	14.32 (a)	58.30	3.98	17.01	14.45 (a)
5	Me	H	H	257-260	227	68.70	5.76	18.49	-----	68.69	5.58	18.53	-----
6	H	H	Br	265 dec.	292	49.34	3.45	14.38	27.35 (b)	49.39	3.25	14.62	27.06 (b)
7	H	Me	H	144-147	227	68.70	5.76	18.49	-----	68.70	5.78	18.60	-----
8	H	Me	Br	201-203	306	50.99	3.95	13.73	26.10 (b)	51.10	3.97	13.70	25.79 (b)
9	H	Et	H	118-120	241	69.69	6.27	17.41	-----	69.65	5.97	17.54	-----

(a) X = Cl. (b) X = Br.

Table III

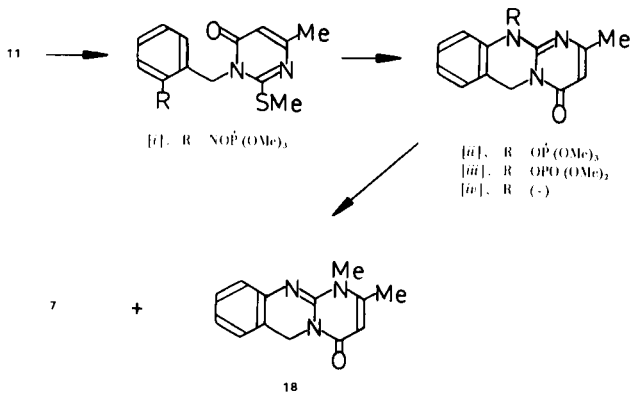
Spectral Data for 6,11-Dihydro-2-methylpyrimido[2,1-*b*]quinazolin-4-ones.

No.	Ir (λ CO, μ)	Uv λ max (methanol) (log ε) nm	Nmr (δ TFA, ppm)	
			H_3 (s)	$2H_6$ (s)
3	6.02 (a)	257 (4.10), 312 (4.10)	6.20	5.30
4	6.02 (a)	260 (4.20), 313 (4.19)	6.29	5.34
5	5.95 (a)	258 (4.14), 314 (4.09)	6.18	5.23
6	6.02 (a)	263 (4.12), 327 (4.20)	-----	5.42
7	5.99 (b)	255 (4.09), 310 (4.10)	6.42	5.37
8	6.01 (b)	260 (4.12), 323 (4.16)	-----	5.46
9	5.99 (b)	258 (4.10), 315 (4.14)	5.93	5.06 (c)

(a) In potassium bromide disks. (b) In dichloromethane solution. (c) In deuteriochloroform solution.

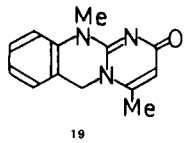
For comparisons, both *N*-methyl isomers of **3** were needed, and these (**7**, 38%; **18**, 23%) were obtained by treatment of **11** with trimethylphosphite. Similarly, trimethylphosphite in boiling *t*-butylbenzene converted **17** to **8** (37%), and triethylphosphite in boiling xylenes slowly changed **11** to **9** (45%) (8).

Deoxygenation of the nitro compounds **11** and **17** may lead, *via* the corresponding nitroso derivatives, to a dipolar intermediate [*i*] (9) which cyclizes to [*ii*] by elimination of methylmercaptide. Sequential dealkylation of [*ii*], cleavage of the O-N bond of the derived [*iii*] (both by phosphite), and alkylation of the resulting anion [*iv*] by trialkyl-



phosphate (10) may account for the observed products.

The structures of the tricyclic compounds **3-9**, and, therefore, of **11** and **15-17**, were established by comparisons of the uv spectra (Table III) of the former to that of the model compound **1** (1); it may be noted that reaction of the N-3 isomer of **11** with trimethylphosphite would have given the known compound **19** (1). The similarity of the uv spectra of **3** and **10** suggests that, in solution, the predominant form of **3** is as illustrated (11).



EXPERIMENTAL (12)

Lithium 4-Methyl-2-methylthio-6-pyrimidinolate.

4-Methyl-2-methylthio-6-pyrimidol (10) (25.9 g., 0.166 mole) was dissolved in a solution of lithium hydroxide (3.97 g., 0.166 mole) and water (275 ml.); after 2 hours at 25°, the solution was filtered and evaporated to dryness. Two 250-ml. portions of benzene were distilled from the residue, which was dried to give 24.6 g. (92%) of the salt as a white solid. N.E. Calcd. for C_6H_7LiNOS: 162.1. Found: 160.6 and 161.1.

5-Methyl-2-nitrobenzyl Chloride.

A solution of thionyl chloride (12.0 ml., 0.165 mole) in chloroform (38 ml.) was added dropwise to 5-methyl-2-nitrobenzyl alcohol (25 g., 0.150 mole) and pyridine (14.5 ml., 0.180 mole) in chloroform (125 ml.); an exothermic reaction occurred. The solution was boiled under reflux 2 hours, cooled, and combined with the corresponding solution from a similar preparation on 1/5th the scale. The solution was evaporated and the residue, in ether, was washed with water, aqueous cupric nitrate solution, water and brine. It was dried over sodium sulfate, filtered, concentrated, and crystallized to give 25.48 g. (76%) of brown needles of the desired product, pure to tlc. It was used without further purification. A sample showed ir: λ max 6.20, 6.28, 6.58, 7.48 μ; nmr: δ 8.17 (d, H_3, $J_o \approx 9$ Hz), 7.45 (br d, H_4, $J_o \approx 9$ Hz), 7.22 (br s, H_5), 4.97 (s, CH_2), 2.45 (s, Me) ppm; ms: m/e 185 (M^+).

Alkylation of **10** with 2-Nitrobenzyl Bromide and Sodium Ethoxide in Ethanol.

To a solution of sodium ethoxide (prepared from 0.230 g. (0.0100 mole) of sodium) and **10** (1.56 g., 0.0100 mole) in absolute ethanol (45 ml.) under nitrogen was added a solution of 2-nitrobenzyl bromide (2.16 g., 0.0100 mole) in ethanol (15 ml.). After 18 hours at 25°, tlc showed that two major products were forming. The mixture was boiled under reflux 2 hours, after which no more 2-nitrobenzyl bromide could be detected. It was cooled, evaporated, and partitioned between ether and water. The combined ether solutions were washed with 1 *N* sodium hydroxide, water, and brine. They were dried over sodium sulfate, filtered and evaporated. The residue was chromatographed with 20% ethyl acetate-hexane over a column of 470 g. of silica gel (Woelm), packed dry in a nylon tube. Three products were visualized under uv light, and were obtained by extracting the appropriate bands with ethyl acetate.

Ethyl 2-Nitrobenzyl Ether (**13**).

This compound (0.748 g., 41%) was obtained as a yellow liquid, pure to tlc; ir: λ max 6.19, 6.34, 6.56, 7.58, 9.64 μ; nmr: δ 8.25-7.25 (m, 4H), 4.87 (s, CH_2), 3.62 (q, J = 7 Hz, CH_2CH_3),

1.30 (t, J = 7 Hz, CH_2CH_3) ppm; ms: m/e 135 (M^+).

4-Methyl-2-methylthio-6-pyrimidine 2-Nitrobenzyl Ether (**12**).

This compound was obtained as a cream-colored solid (0.825 g., 28%), pure to tlc. Crystallization of a sample from ethyl acetate-hexane gave yellow prisms, m.p. 94.0-96.0°; ir: λ max 6.34, 6.45, 6.55, 7.46, 8.62 μ; nmr: δ 8.20-7.95 (m, 1H), 7.75-7.32 (m, 3H), 6.32 (s, 1H), 5.80 (s, 2H), 2.42 (s) and 2.37 (s) (6H) ppm; uv: λ max 250 (log ε = 3.28) nm; ms: m/e 291 (M^+).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.59; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.82; H, 4.69; N, 14.48; S, 10.47.

Impure **11** (0.163 g.) was obtained as a yellow solid. The material was rechromatographed with 50% ethyl acetate-hexane over two preparative layer plates of silica gel, and was crystallized from ethyl acetate-hexane to give 0.105 g. (0.4%) of pure **11**, m.p. 153.5-155.5°.

A fourth minor product, detected by tlc in this experiment, and isolated from another, was 4-methyl-2-(2-nitrobenzylthio)-1-(2-nitrobenzyl)-6-pyrimidone (**14**), m.p. 145.0-147.0°; ir: λ max 5.98 μ; nmr: δ 8.3-7.9 (m, 2H), 7.80-7.25 (m, 5H), 7.25-7.05 (m, 1H), 6.12 (s, 1H), 5.65 (s, NCH_2), 4.75 (s, SCH_2), 2.30 (s, Me) ppm; ms: m/e 412 (M^+).

6-Methyl-2-methylthio-1-(2-nitrobenzyl)-4-pyrimidone (**11**).

A mixture of 2-nitrobenzyl bromide (43.2 g., 0.200 mole), lithium 4-methyl-2-methylthio-6-pyrimidinolate (45.4 g., 0.280 mole) and dioxane (500 ml.) was boiled under reflux in an atmosphere of nitrogen for 30 hours. It was cooled, filtered through Celite, and evaporated. A solution of the residue in dichloromethane was washed with water and brine, and was dried over sodium sulfate, filtered and evaporated. The residue was crystallized from dichloromethane-ether, and recrystallized from methanol (charcoal) to give 23.4 g. (40.4%) of **11**, m.p. 152-154°. The analytical sample had m.p. 153.5-155.5°; ir: λ max 5.97, 6.33, 6.53, 6.68 μ; uv: λ max 240sh (log ε = 3.96), 287 (log ε = 4.08) nm; nmr: δ 8.28-8.14 (m, 1H), 7.78-7.31 (m, 2H), 7.06-6.97 (m, 1H), 6.12 (br s, H_5), 5.74 (s, 2H), 2.52 (s, SMe), 2.29 (d, J = 1 Hz, CMe) ppm; ms: m/e 291 (M^+).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.59; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.89; H, 4.64; N, 14.67; S, 10.75.

4-Methyl-2-methylthio-1-(5-chloro-2-nitrobenzyl)-6-pyrimidone (**15**).

This compound (**15**) was prepared similarly to **11**; several recrystallizations of **15** from dichloromethane-diisopropyl ether and finally from methanol gave the analytical sample, m.p. 161.5-162.5°; ir: λ max 5.97 μ; uv: λ max 284 (log ε = 4.17) nm; nmr: δ 8.30 (d, H_3', J_o = 8 Hz), 7.43 (q, H_4', J_m = 2 Hz, J_o = 8 Hz), 6.80 (d, H_6', J_m = 2 Hz), 6.18 (s, H_3), 5.68 (s, $2H_6$), 2.53 (s, SMe), 2.30 (s, CMe) ppm; ms: m/e 325 (M^+).

Anal. Calcd. for $C_{13}H_{12}ClN_3O_3S$: C, 47.93; H, 3.71; Cl, 10.88; N, 12.90; S, 9.84. Found: C, 47.99; H, 3.84; Cl, 10.81; N, 12.85; S, 9.98.

4-Methyl-2-methylthio-1-(5-methyl-2-nitrobenzyl)-6-pyrimidone (**16**).

This compound (**16**) was prepared similarly to **11**; the analytical sample of **16**, m.p. 164.5-166°, was obtained by recrystallization from methanol; ir: λ max 5.95 μ; uv: λ max 285 (log ε = 4.15) nm; nmr: δ 8.07 (d, H_3', J_o = 8 Hz), 7.25 (br d, H_4', $J_o \approx$ 8 Hz), 6.75 (br s, H_6'), 6.15 (s, H_3), 5.65 (s, $2H_6$), 2.50 (s, SMe), 2.53 (s) and 2.32 (s) (2 CMe) ppm; ms: m/e 305 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 55.16; H, 4.89; N, 13.79; S, 10.39.

5-Bromo-4-methyl-2-methylthio-1-(2-nitrobenzyl)-6-pyrimidone (**17**).

A solution of **11** (20.0 g., 0.0684 mole), *N*-bromosuccinimide (12.2 g., 0.0684 mole) and chloroform (200 ml.) was boiled under reflux 3 hours, cooled, and washed with 1*M* sodium bisulfate, water, 1*M* sodium hydroxide, water, and brine. It was dried over sodium sulfate, filtered and evaporated. The residue was crystallized from dichloromethane-diisopropyl ether to give, after drying, 22.6 g. (90%) of light yellow prisms of **17**, m.p. 169-170°. Recrystallization from the same solvent pair gave the analytical sample, m.p. 168-171°; ir: λ max 5.98 μ; uv: λ max 250 (log ε = 4.09), 301 (log ε = 4.19) nm; nmr: δ 8.27-8.08 (m, 1H), 7.65-7.42 (m, 2H), 7.13-6.92 (m, 1H), 5.75 (s, 2H), 2.42 (s, 6H) ppm; ms: m/e 369 (M^+).

Anal. Calcd. for $C_{13}H_{12}BrN_3O_3S$: C, 42.17; H, 3.27; Br, 21.59; N, 11.35; S, 8.66. Found: C, 42.38; H, 3.34; Br, 21.51; N, 11.40; S, 8.26.

6,11-Dihydro-2-methyl-6*H*-pyrimido[2,1-*b*]quinazolin-4-one (**3**).

Ten g. (0.0344 mole) of **11** was added to a solution of stannous chloride (35.0 g 0.155 mole) in concentrated hydrochloric acid (175 ml.) at -10°. The suspension was mechanically stirred 2 hours; the temperature was allowed to rise to +5°. The mixture was filtered through a bed of sodium chloride on a sintered-glass funnel, and the paste was stirred 2 hours with 200 ml. of 2*M* sodium hydroxide (odor of methane thiol). It was heated on a steam bath 15 minutes, cooled in ice and filtered. The solid was crystallized (odor of thiol) from 700 ml. of boiling methanol containing 1 ml. of glacial acetic acid to give 4.97 g. (70%) of pure **3**, m.p. 244.5-246.5°.

Deoxygenation of **11** with Trimethylphosphite.

A solution of **11** (7.00 g., 0.0240 mole) and trimethylphosphite (8.5 ml., 0.0720 mole) in xylenes (700 ml.) was boiled under reflux in an atmosphere of nitrogen two weeks. The cooled solution was filtered and evaporated. A solution of the dark residue in dichloromethane was washed with water, dried over sodium sulfate, filtered and evaporated to give a dark solid which was chromatographed over silica gel. Elution with 40% ethyl acetate-hexane gave 2.12 g. (38%) of 6,11-dihydro-2,11-dimethylpyrimido[2,1-*b*]quinazolin-4-one (**7**) as a yellow solid, pure to tlc. Three crystallizations from dichloromethane-ether gave the anlytical sample, m.p. 144.5-147.0°.

Elution with 70% ethyl acetate-hexane gave 1.30 g. (23%) of yellow crystals of 1,6-dihydro-1,2-dimethylpyrimido[2,1-*b*]quinazolin-4-one (**18**), pure to tlc. Recrystallizations from dichloromethane-ether and from ethyl acetate gave the analytical sample, m.p. 180-184°; ir: λ max 5.96, 6.14, 6.22, 6.42 μ; uv: λ max 218 (log ε = 4.28), 290 (log ε = 4.20) nm; nmr: δ 7.16-6.92 (m, 4H), 5.45 (s, H_3), 5.12 (s, $2H_6$), 3.47 (s, NMe), 2.18 (s, CMe) ppm; δ (CF_3CO_2H) 7.43 (m, 4H), 6.48 (s, H_3), 5.42 (s, $2H_6$), 3.90 (s, NMe), 2.57 (s, CMe) ppm; ms: m/e 227 (M^+).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.70; N, 18.49. Found: C, 68.92; H, 5.82; N, 18.16.

Acknowledgement.

I thank the staff of Analytical Research Services of Schering-Plough Corporation for microanalyses, ir, nmr, uv, and mass spectra.

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(11) Compounds **3-8** lacked hypotensive activity.

(12) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer instruments, models 137 or 180. Ultraviolet spectra were measured on a Cary 118 spectrophotometer. Mass spectra were determined on a Varian CH5 spectrometer. Nuclear magnetic resonance spectra were recorded on Varian instruments, models A-60A, T-60, CFT-20, or XL-100; tetramethylsilane was used as an internal standard. Unless otherwise specified, ir, uv, and nmr spectra were determined as solutions in dichloromethane, methanol, and deuteriochloroform, respectively. E. Merck supplied F-254 silica gel plates for preparative and thin-layer chromatography, and ASTM silica gel for column chromatography. The preparations of **3**, **7**, and **11** are typical.