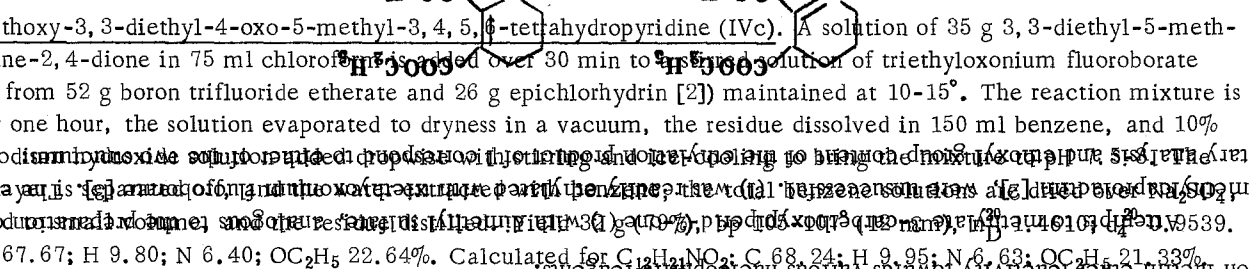


LS1 Attempts to condense V with IVc also failed. So it can be assumed that reaction of V with IIa and IVb is stopped by steric hindrance due to substituents at position 3, and not as a result of electron-donor (in compound IVb) or electron-acceptor (in compound IIa) effects of these substituents. Since α -amino- α -cyanoacetamide is a feebly nucleophilic reagent, an attempt was made to condense IIa with hydrazine hydrate, but this also failed. The reaction of IIa with hydrazine hydrate (VI) was also tried, but the reaction did not proceed. The reaction of IVc with hydrazine hydrate, which was expected to give the desired 4-chloro-2,3-dihydropyridino[2,3-d]pyrimidine (VII), from which a number of 4-substituted piperidino[2,3-d]pyrimidines was synthesized.

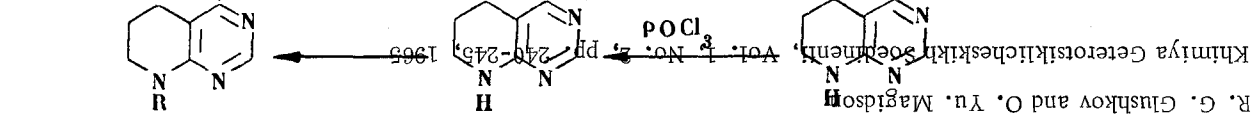
Initial attempts to prepare the desired 4-chloropiperidino[2,3-d]pyrimidine (IX) by reacting VIII with $POCl_3$ were unsuccessful. It was assumed that when VIII reacts with $POCl_3$, not only is OH substituted by Cl, but a phosphamide derivative is formed at the NH group of the piperidine ring. To check this view, the oily product formed by reacting VIII with $POCl_3$ was submitted to acid hydrolysis, and after neutralizing the solution with a dilute NaOH solution, IX was obtained in high yield. Investigation of the properties of IX showed that they fully correspond to the similarly substituted 4-amino-6-chloropyrimidines. In particular, because of the presence of a NH group at position 8 in IX, the mobility of the chlorine atom at position 4 is considerably diminished. Because of this, all attempts to effect reaction of IX with thiourea or sodium sulfide, to obtain 4-mercapto-4,5,6,7-tetrahydropyridino[2,3-d]pyrimidine, failed to give positive results. To decrease the electron-donor effect of NH on the chlorine atom at position 4 by reacting IX with $(CH_3CO)_2O$, 4-chloro-8-acetyl-piperidino[2,3-d]pyrimidine (XIII) was prepared, but here, too, attempts to effect reaction with thiourea were unsuccessful. Equally unsuccessful were experiments on the condensation of IX with monoethanolamine at 130° , and with alcoholic ammonia at $180-190^\circ$, the starting materials XIII and IX being used.

EXPERIMENTAL

2-Ethoxy-3,3-diethyl-4-oxo-5-methyl-3,4,5,6-tetrahydropyridine (IVc). A solution of 35 g 3,3-diethyl-5-methylpiperidine-2,4-dione in 75 ml chloroform is added over 30 min to a solution of triethylxonium fluoroborate (prepared from 52 g boron trifluoride etherate and 26 g epichlorhydrin [2]) maintained at $10-15^\circ$. The reaction mixture is stirred for one hour, the solution evaporated to dryness in a vacuum, the residue dissolved in 150 ml benzene, and 10% aqueous sodium hydroxide solution added. The mixture is stirred for 15 min, the benzene layer is separated, and the water extract is added to the benzene. The total benzene solution is evaporated to dryness, the residue dissolved in 30 ml benzene, and the benzene solution is evaporated to dryness. Found: C 67.67; H 9.80; N 6.40; OC_2H_5 22.64%. Calculated for $C_{12}H_{19}NO_2$: C 68.24; H 9.95; N 6.63; OC_2H_5 21.33%.



It is shown that it is possible to use triethyl oxonium fluoroborate to prepare lactam ethers in cases where O-alkylation can be effected with dimethyl sulfate. The method is successfully used for preparing 2-ethoxy-3,3-diethyl-4-oxo-5-methyl-3,4,5,6-tetrahydropyridine and 2-ethoxy-3,3-diethyl-4-oxo-5-methyl-3,4,5,6-tetrahydropyridine. It is shown that 3,3-diethyl-5-methylpiperidine-2,4-dione reacts with dimethyl sulfate at the keto, and not at the lactam group. Reaction of 2-ethoxy-3,3-diethyl-4-oxo-5-methyl-3,4,5,6-tetrahydropyridine with thiourea gives 3-oxopyrazolo[3,4-b]piperidine, and 2-mercapto-4,5,6,7-tetrahydropyridino[2,3-d]pyrimidine, from which a number of 4-substituted piperidino[2,3-d]pyrimidines is obtained.



2-Ethoxy-3-carbethoxy-3, 4, 5, 6-tetrahydropyridine (IIa). A solution of 51.3 g 3-carbethoxypiperid-2-one in 50 ml chloroform is added in 30 min dropwise, with stirring, to a suspension of triethyloxonium fluoroborate (prepared from 62.4 g boron trifluoride etherate and 31.2 g epichlorhydrin) in 50 ml dry chloroform maintained at 10-15°. The reaction mixture is stirred for four hours at 5-10°, and 88 ml of 50% aqueous potash added to bring it to pH 8. The organic layer is separated, and the aqueous one extracted with chloroform. The total extracts are dried over Na₂SO₄, evaporated to small volume in a vacuum, and distilled. Distillation gives 5.2 g 3-carbethoxypiperid-2-one, bp 180-182° (5 mm), mp 76-78°. Yield 36 g (60.3%), bp 90-92° (5 mm), n_D²⁰ 1.4589. Found: C 60.02; H 8.60; N 7.10; OC₂H₅ 44.86%. Calculated for C₁₀H₁₇NO₃: C 60.30; H 8.54; N 7.03; OC₂H₅ 45.22%.

3-Oxopyrazolino[3, 4-b]piperidine (VI). A solution of 0.75 g hydrazine hydrate in 5 ml absolute alcohol is added to a solution of 2 g IIa in 10 ml absolute alcohol at 200 g, the mixture stirred for one hour, and the temperature raised to 28°. The mixture is boiled for 1 hr 30 min, when a precipitate forms. At the end of heating the reaction mixture is evaporated to dryness, the residue ground with 10 ml ether, filtered and dried. Yield 1.35 g (72.2%), mp 340-348°. The product is readily soluble in dilute acids and alkalis. For analysis it is crystallized from water. Prisms, mp 347-350° (Kofler). Found: C 51.65; H 6.53; N 30.77%. Calculated for C₆H₉N₃O: C 51.79; H 6.56; N 30.65%.

2-Mercapto-4-hydroxypiperidino[2, 3-d]pyrimidine (VII). 6 g IIa and 2.4 g thiourea are added to a solution of C₂H₅ONa (from 1.5 g Na and 60 ml absolute alcohol), the mixture refluxed for two hours, and the solution cooled in ice and acidified to pH 6-6.5 with glacial acetic acid. The precipitate formed is filtered off, washed with water (twice with 15 ml), then with alcohol (twice with 10 ml), and dried. Yield 4.4 g (80%), mp > 350°. The substance is soluble only with difficulty in most organic solvents, water, and acids, but readily soluble in dilute alkalis. For analysis it is crystallized from methanol (1:400). Long prisms, mp > 350°. Found: C 45.68; H 5.05; N 22.86; S 17.38%. Calculated for C₇H₉N₃OS: C 45.90; H 4.91; N 22.95; S 17.48%.

4-Hydroxypiperidino[2, 3-d]pyrimidine (VIII). 20 ml 25% NH₄OH are added to a suspension of 4.4 g VII in 250 ml water. 10 g Raney nickel paste are added to the resultant solution and the whole refluxed for one hour with stirring. When reaction is complete the hot mixture is filtered, the solution cooled, the precipitate filtered off, washed with cold alcohol, and dried. Yield 3.1 g (85.4%), mp 262-265°. It is soluble only with difficulty in most organic solvents, crystallizes from alcohol and water, is soluble in dilute acids and alkalis. For analysis it is recrystallized from water (1:14), mp 264-266°. Found: C 55.52, 56.76; H 6.17, 6.14; N 27.85%. Calculated for C₇H₉N₃O: C 55.63; H 5.96; N 27.81%.

4-Chloropiperidino[2, 3-d]pyrimidine (IX). A mixture of 1 g VIII and 25 ml phosphorus oxychloride is refluxed and stirred for 5 hr. The resultant light yellow solution is taken to dryness in a vacuum, 10 g cracked ice added to the oily residue, the solution boiled for 5-10 min, and cooled in ice. After neutralizing with 10% NaOH to pH 7.5-8, the mixture is extracted with chloroform, the extract dried over Na₂SO₄ and evaporated to dryness in a vacuum; the residue is triturated with 10 ml water, filtered, and dried. Yield 0.68 g (60.6%), mp 156-159°. Readily soluble in most organic solvents, also in dilute acids, soluble only with difficulty in alkalis. For analysis it is crystallized from water (1:50); needles, mp 162-164°. Found: C 49.34; H 4.77; N 24.96; Cl 21.09%. Calculated for C₇H₈ClN₃: C 49.55; H 4.72; N 24.77; Cl 20.94%.

4-Chloro-8-acetylpiperidino[2, 3-d]pyrimidine (XIII). A mixture of 1 g IX, 3 ml acetic anhydride, and 10 ml dry benzene is refluxed and stirred for 2.5 hr. The resultant solution is evaporated to dryness in a vacuum, stirred with 25 ml water at room temperature for 2.5 hr, and brought to pH 7.5-8 with a saturated soda solution. The precipitate is filtered off, washed with water, and dried. Yield 1.05 g (83%), mp 97-100°. Readily soluble in most organic solvents, soluble only with difficulty in water, dilute acids and alkalis. For analysis it is recrystallized from ether. Prismatic needles, mp 98-100°. Found: C 51.13; H 4.83; N 19.81; Cl 16.81%. Calculated for C₉H₁₀ClN₃O: C 51.06; H 4.72; N 19.85; Cl 16.87%.

4-Methoxypiperidino[2, 3-d]pyrimidine (XII). 1 g X is added to a solution of sodium methoxide (from 1 g Na in 25 ml absolute methanol), and the mixture refluxed and stirred for 2.5 hr, after which it is evaporated to dryness in a vacuum, and the residue ground with 20 ml water, filtered, and dried. Yield 0.6 g (61.8%), mp 105-107°. Readily soluble in most organic solvents and dilute acids, insoluble in alkalis. For analysis it is recrystallized from water. Prisms, mp 106-108°. Found: C 57.92; H 6.84; N 25.19%. Calculated for C₈H₁₁N₃O: C 58.18; H 6.66; N 25.45%.

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