UDC 547.836 + 542.953

STUDY OF LACTAMS. VII.* SYNTHESIS AND SOME REACTIONS OF LACTIM ETHERS OF 3,3-DIETHYL-5-METHYLPIPERIDINE-2,4-DIONE AND 3-CARBETHOXYPIPERID-2-ONE

R. G. Glushkov and O. Yu. Magidson

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 1, No. 2, pp. 240-245, 1965

It is shown that it is possible to use triethyl oxonium fluoroborate to prepare lactim ethers in cases where O-alkylation can be effected with dimethyl sulfate. The method is successfully used for preparing 2-ethoxy-3-carbethoxy-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-carbethoxy-3, 4, 5, 6-tetrahydropyridine with hydrazine hydrate and thiourea gives 3-oxopyrazolino[3, 4-b]piperidine, and 2-mercapto-4-hydroxypiperidino[2, 3-d]pyrimidine, from which a number of 4-substituted piperidino[2, 3-d]pyrimidines is obtained.

In connection with the synthesis and investigation of the reactivity of lactim ethers, attempts were made to prepare the lactim ether of 3-carbethoxypiperid-2-one, in order to explain the effect of the electron-accepting ester group on lactim ether reactivity towards various nucleophilic reagents.

Attempts to methylate 3-carbethoxypiperid-2-one (I) with dimethyl sulfate, analogous to the preparation of O-methylcaprolactim [2], were unsuccessful. (I) was readily ethylated with triethyloxonium fluoroborate [3]. The elementary analysis and ethoxyl group content of the ethylation product of I correspond to either of the two compounds:

Comparison of the ir spectrum of the ethylation product of I with that of O-methylcaprolactam showed that it had the same absorption band at 1680 cm^{-1}, characteristic of the C=N group, that the absorption band characteristic of the NH group was absent, and that it contained a band whose intensity was the same as that of the first absorption band, at 1735 cm^{-1}, corresponding to the group $COOC_2H_5$. Accordingly, it could be assumed to have structure IIa. Another subject for alkylation was 3, 3-diethyl-5-methylpiperidine-2, 4-dione (III) [4], dimerin. Methylation of III with dimethyl sulfate in benzene gave a substance, which analysis showed to contain 16.03% methoxyl and a double bond. Its structure could have been that of either of the two isomers IVa and IVb:

The ir absorption spectrum of IV revealed absorption bands characteristic of the group NH, and the absence of the 1680 cm^{-1} band characteristic of the C=N group, so that there was reason to assume that the methylation product III has structure IVa, i.e., that here the CO group enolizes more readily than the —CO—NH— group. To obtain the lactim ether IVc, experiments were undertaken on alkylation of III with triethyloxonium fluoroborate, and a substance was obtained which, judging by its ir spectrum (C=N absorption band at 1670 cm^{-1} and C=O absorption band at 1715 cm^{-1}) had structure IVc.

The present authors previously found that the simplest lactim ethers react with α-amino-α-cyanoacetamide (V) to give imidazole derivatives [5], and this motivated a study of the same reaction with 2-ethoxy-3-carbethoxy-3, 4, 5, 6-tetrahydropyridine (IIa). For this purpose a number of experiments were carried out on condensing IIa with V. However, in none of the experiments, some of them using catalytic amounts of HCl, could any condensation product be isolated, and in every case the starting substances were changed.

*For part VI see [1].

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 Na_2SO_4, 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_D^{20} 1.4589. Found: C 60.02; H 8.60; N 7.10; OC_2H_5 44.86%. Calculated for $C_{10}H_{17}NO_3$: C 60.30; H 8.54; N 7.03; OC_2H_5 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 alkalies. For analysis it is crystallized from water. Prisms, mp 347-350° (Kofler). Found: C 51.65; H 6.53; N 30.77%. Calculated for $C_6H_9N_3O$: 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 C_2H_5ONa (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 alkalies. 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 $C_7H_9N_3OS$: C 45.90; H 4.91; N 22.95; S 17.48%.

4-Hydroxypiperidino[2, 3-d]pyrimidine (VIII). 20 ml 25% NH_4OH 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 alkalies. 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 $C_7H_9N_3O$: 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 Na_2SO_4 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 alkalies. 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 $C_7H_8ClN_3$: 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 alkalies. 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 $C_9H_{10}ClN_3O$: 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 alkalies. For analysis it is recrystallized from water. Prisms, mp 106-108°. Found: C 57.92; H 6.84; N 25.19%. Calculated for $C_8H_{11}N_3O$: C 58.18; H 6.66; N 25.45%.

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30 November 1963

Ordzhonkidze All-Union Chemical-Pharmaceutical Scientific Research Institute, Moscow