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RESEARCHES ON LACTAMS

VIII. 3-Ethoxy-3,4-dehydromorpholine and its Condensation with Aminocyanoacetamide and Hydrazine*

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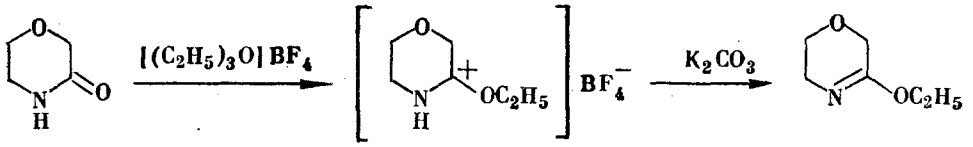
Replacement of the β-methylene group in O-alkylvalerolactim by an oxygen atom leaves the reactivity of the lactim group substantially unchanged. It is shown that the ability of simplest lactim ethers to undergo condensation with α-amino-α-cyanoacetamide and hydrazine hydrate also extends to 3-ethoxy-3, 4-dehydromorpholine, making it possible to synthesize new heterocyclic systems (morpholinoimidazole, morpholinopurine, and morpholinotetrazole). Replacement of a methylene group in derivatives of tetramethylenimidazole, purine, and tetrazole by an oxygen atom, markedly decreases the biological activities of these compounds.

In the course of work which we are carrying out on the synthesis of new heterocyclic compounds based on lactams [1], it was of interest to investigate the effect of a second heteroatom on the reactivities of the lactams and their O-alkyl derivatives.

In the present work the starting compound selected for this purpose was morpholin-3-one (I), formed by reaction of the Na derivative of monoethanolamine with chloroacetic ester [2].

The first stage in the work was study of the alkylation of I. As attempts to alkylate I with dimethylsulfate in benzene, similar to the methylation of caprolactam [3, 4], failed, we investigated the reaction of I with triethyloxonium-fluoroborate [5]. It was found that ethylation proceeded to give a high yield of 3-ethoxy-3, 4-dehydromorpholine (II). Judging by analysis and qualitative reaction for fluorine, an impurity (~ 10%) which cannot be separated by distillation is also formed. This is, apparently, the boron trifluoride etherate, reaction being carried out without isolating this intermediate complex (III).

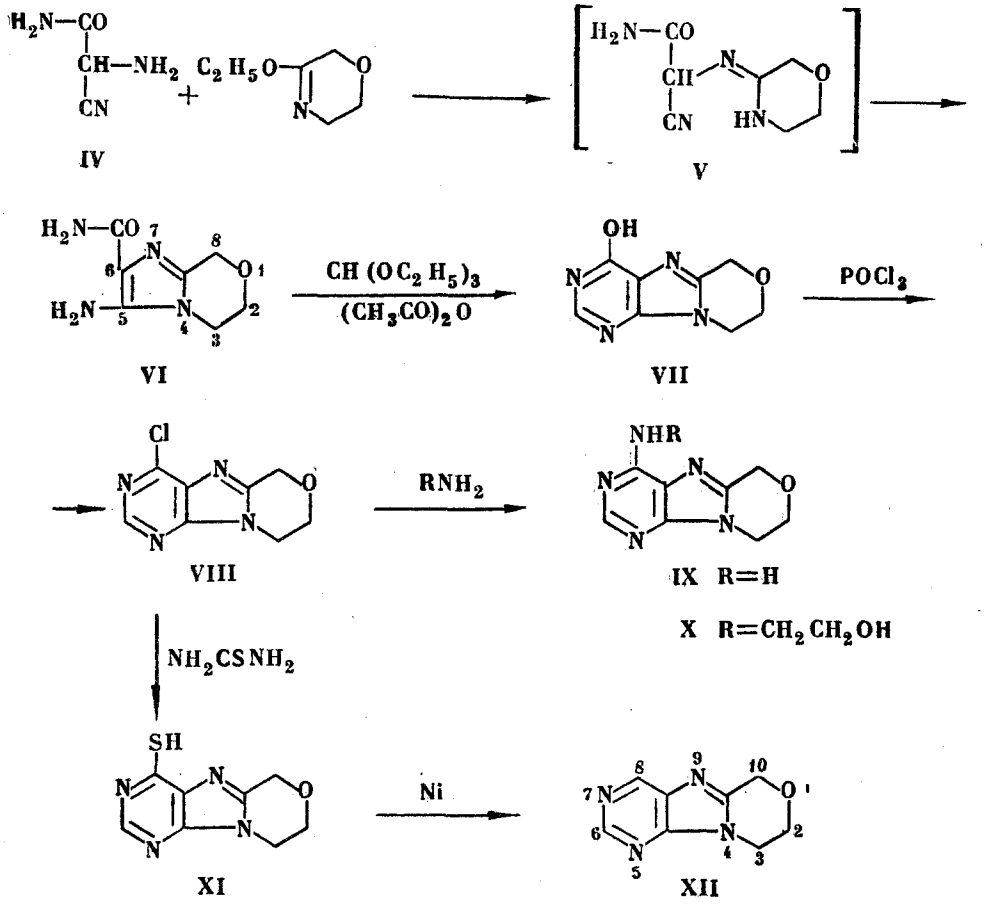


I III II

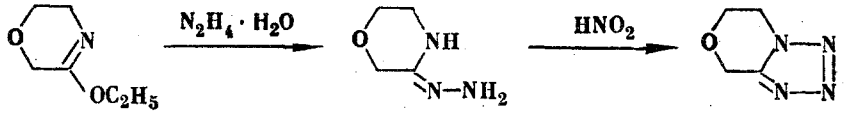
The structure of II was confirmed by its IR spectrum containing an absorption band at 1695 cm^{-1}, characteristic of the lactim bond C=N, as well as by its subsequent reactions.

The reactions of II with such nucleophilic reagents as hydrazine hydrate and α-amino-α-cyanoacetamide (IV), were studied, under the same conditions, that O-alkylcapro- and O-alkylvalero-(V) lactims react with them [6]. Comparisons of product yields established that replacement of the methylene group in V by an O atom β to the lactim group has no substantial effect on lactim group reactivity. II reacts smoothly with IV in the presence of catalytic amounts of hydrogen chloride to give 5-amino-6-carboxyamidoimidazo [1, 2-c] morpholine (VI). The structure of VI was confirmed by a qualitative reaction characteristic of aminoimidazoles (coupling of the diazonium salt of VI with α-naphthol, to give a purple dye), as well as by cyclization of VI with orthoformic ester in the presence of acetic anhydride to give hypoxanthino [8, 9-c] morpholine (VII), whose UV spectrum like the spectra [7] of 8, 9-polymethylenehypoxanthines, has one maximum at 252 mμ. Heating VII with $POCl_3$ in the presence of dimethylaniline gives 6-chloropurino [8, 9-c] morpholine (VIII), which, by reaction with ethanolic ammonia or ethanolamine gives, respectively, adenino [8, 9-c] morpholine (IX), and 8-(β-hydroxyethyl) aminopourino-[8, 9-c] morpholine (X). 8-Mercaptopurino [8, 9-c] morpholine (XI) is synthesized by reacting VIII with thiourea, and desulfurization of XI with Raney Ni gives purino [8, 9-c] morpholine (XII).

* For Part VII see [1].



Furthermore, 3-ethoxy-3, 4-dehydromorpholine is a starting material for preparing tetrazolo [1, 5-c] morpholine (XIII), an oxo analog of corazole (α, β-pentamethylenetetrazole) [7]. XIII was synthesized by condensing II with hydrazine hydrate, followed by cyclization of the intermediate hydrazine (XIV) with nitrous acid, to give XIII.



Comparison of the biological properties of the new synthesized heterocyclic compounds, with the properties of the corresponding polymethylene derivatives of imidazole, purine, and tetrazole, showed that replacement of a methylene group in the latter by an oxygen atom markedly lowered their physiological activity.

Experimental

3-Ethoxy-3, 4-dehydromorpholine (II). 62.2 g morpholin-3-one in 300 ml $CHCl_3$ was dropped into a stirred suspension of triethyloxoniumfluoroborate (prepared from 129 g BF_3 etherate and 65 g epichlorohydrin) in 50 ml $CHCl_3$ held at about 10°, the mixture was stirred for 5 hr, and then cooled to −3°, when a complex (III) separated. The suspension was vigorously stirred, and held at 5° while 50% potash solution (~ 150 ml) was added dropwise, to bring the pH to about 8, when the mass changed, and a precipitate of KBF_4 formed, which was filtered off on a cloth filter. The organic layer was separated off, and the aqueous layer extracted with $CHCl_3$. The bulked extracts were dried over calcined Na_2SO_4, evaporated, and the residue distilled under reduced pressure, to give 72 g (91%) II, 70–72° (22 mm), n_D^{24} 1.4488.

5-Amino-6-carbamidoimidazo [1, 2-c] morpholine (VI). 0.7 ml 20% ethanolic HCl was dropped, with stirring and ice cooling, into 2 g α-amino-α-cyanoacetamide and 3 g 2-ethoxy-3, 4-dehydromorpholine in 15 ml dry ethanol. The resultant suspension was refluxed and stirred for 45 min, when the nature of the precipitate changed. The reaction

products were cooled in ice, filtered, the precipitate washed with dry EtOH (3 × 5 ml), and then dried, yield of VI 3.1 g (84.9%), mp 289–291° (Kofler block). VI was sparingly soluble in most organic solvents, insoluble in alkalies, soluble in dilute acids. For analysis the substance was first recrystallized from water (1 : 15) and then from EtOH (1 : 35). Found: C 46.13; H 5.65; N 30.81, 30.85%. Calculated for $C_7H_{10}N_4O_2$: C 46.15; H 5.49; N 30.76.

5-Amino-6-carbamidoimidazo [1, 2-c] morpholine hydrochloride. This was prepared by adding 15% ethanolic HCl to a hot suspension of the base in 80% EtOH. For analysis the salt was recrystallized from 10% MeOH, prisms, decomp ~ 320°. Found: Cl 16.54, 16.63; N 24.96%. Calculated for $C_7H_{10}N_4O_2 \cdot HCl$: Cl 16.25; N 25.62%.

Hypoxanthino [8, 9-c] morpholine (VII). 15.35 g 5-amino-6-carbamidoimidazo [1, 2-c] morpholine, 65 ml orthoformic ester, and 120 ml Ac_2O were stirred and refluxed together for 3 hr 30 min. 10 min after the onset of boiling, the precipitate dissolved, after which fresh crystals separated.

At the end of the reaction the products were vacuum-dried, 150 ml water added to the residue, the whole heated on a boiling water bath for ~ 30 min, and evaporated to dryness, a further 100 ml water was added, then 50 ml Me_2CO, the whole heated for a further 30 min, then cooled in ice. The precipitate formed was filtered off, washed with cold water, and dried. Yield of VII, 14.29 g (88.2%); it did not melt below 360°. It was sparingly soluble in most organic solvents, soluble in dilute acids and alkalies. For analysis it was recrystallized from water. (1 : 400), when it formed needles, mp > 360°. Found: C 50.29; H 4.27; N 29.61%. Calculated for $C_8H_8N_4O_2$: C 50.00; H 4.16; N 29.16%.

8-Chloropurino [8, 9-c] morpholine (VIII). A mixture of 1 g VII, 2 ml dimethylaniline, and 20 ml $POCl_3$ was stirred and refluxed for 6 hr, when intensive darkening occurred. The reaction products were vacuum-dried, 20 g crushed ice added to the residue, and the whole stirred for about 15 min. A saturated soda solution was added to the dark solution to bring it to about pH 8, the solution then extracted with $CHCl_3$, the extracts dried over calcined Na_2SO_4, and evaporated to dryness. Recrystallization of the residue from 100 ml water gave 0.6 g (55%) VIII, mp 307–309°. The substance was readily soluble in $CHCl_3$, soluble in hot EtOH and hot water, sparingly soluble in Et_2O, benzene, EtOAc, and Me_2CO, readily soluble in acids, but sparingly soluble in dilute alkalies. Found: C 45.56; H 3.78; Cl 17.03; N 26.42%. Calculated for $C_8H_7ClN_4O$: C45.60; H 3.32; Cl 16.86; N 26.60%.

Adenino [8, 9-c] morpholine (IX). 1.1 g VIII and 40 ml 20% ethanolic NH_3 were autoclaved for 6 hr (bath temperature about 160°). When heating was finished, the reaction products were vacuum-dried, the residue triturated with 10 ml water, the mixture cooled in ice, filtered, the precipitate washed with 5 ml cold water and 5 ml EtOH, then dried. Yield of IX 0.8 g (84%), did not melt below 360°. Sparingly soluble in most organic solvents and alkalies, soluble in dilute acids. For analysis, it was recrystallized from water (1 : 25), prisms, mp > 360°. Found: C 49.80; H 4.91; N 36.58. Calculated for $C_8H_9N_5O$: C 50.26; H 4.71; N 36.65%.

8-(β-Hydroxyethyl) aminopurino [8, 9-c morpholine] (X). A mixture of 1 g VIII, 1 ml monoethanolamine, and 10 ml ethylcellosolve was refluxed and stirred for 1 hr 30 min. When the heating was ended, the reaction products were partly evaporated under reduced pressure, then cooled in ice, the precipitate formed filtered off, triturated with 10 ml cold water, filtered, and the solid washed with 5 ml cold EtOH, after which it was dried.

Yield of X 1 g (90%), mp 167–169°. The substance was soluble in most organic solvents, and water on heating. For analysis it was recrystallized from EtOh (1 : 20). Needles, mp 169–170°. Found: C 50.92; H 5.75; N 29.70%. Calculated for $C_{10}H_{13}N_5O_2$: C 51.06; H 5.53; N 29.78%.

8-Mercaptopurino [8, 9-c] morpholine (XI). 0.28 g thiourea was added to a suspension of 0.72 g VIII in 30 ml dry EtOH, the mixture stirred and refluxed for 1 hr, when, 30 min from the start of refluxing, a copious precipitate formed. At the end of the reaction the products were cooled in ice, the precipitate filtered off, washed with cold EtOH, and dried, yield of XI 0.7 g (about 100%), did not melt below 360°. It was sparingly soluble in most organic solvents and in acids, but readily soluble in dilute alkalies. For analysis it was recrystallized from water (1 : 1000), when it formed needles, mp > 360°. Found: C 45.80; H 3.84; N 27.09; S 15.45%. Calculated for $C_8H_8N_4OS$: C 46.15; H 3.84; N 26.92; S 15.38%.

Purino [8, 9-c] morpholine (XII). Concentrated aqueous ammonia was added to a suspension of 1.1 g XI in 30 ml water till solution was complete. 5 5 Raney Ni paste was added to the solution, followed by 70 ml water, and the mixture was refluxed and stirred for 1 hr, filtered hot, and the liquid evaporated to small volune under reduced pressure, then cooled in ice, filtered, and the solid washed with EtOAc and dried.

Yield of XII, 0.72 g (77.4%), mp 179–182°, soluble in water and most organic solvents. For analysis 0.2 g was recrystallized from a mixture of 10 ml EtOAc + 5 ml ether, to give prisms, mp 180–182°. Found: C 54.38; H 4.58; N 31.95%. Calculated for $C_8H_8N_4O$: C 54.54; H 4.54; N 31.87%.

Tetrazolo [1, 5-c] morpholine (XIII). 5 g II was added dropwise, with vigorous stirring, to 3.5 g 85% hydrazine hydrate, when the temperature rose to 28°. The mixture was stirred for 1 hr, when a precipitate of XIV formed. The reaction products were cooled to −5°, a solution of 6 g $NaNO_2$ in 20 ml H_2O added, and with the temperature kept the

same, about 25 ml 20% H_2SO_4 dropped in till starch-iodide paper gave a violet color. After standing for 12 hr, the reaction products were filtered, the filtrate extracted with $CHCl_3$ (6 × 15 ml), the extracts dried over calcined Na_2SO_4, and then vacuum-dried. Yield of XIII 3.25 g (66.6%), on the 3-ethoxy-3,4-dehydromorpholine). Readily soluble in water and most organic solvents. For analysis it was twice recrystallized from Et_2O, mp 121–123°. Found: C 37.95; H 4.88; N 44.81%. Calculated for $C_8H_6N_4O$: C 38.09; H 4.76; N 44.44%.

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