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STUDY OF LACTAMS. VI*. SYNTHESIS OF 6-SUBSTITUTED PURINO[8, 9-1^1, 2^2]ISOINDOLINES

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It is shown with 1-ethoxyisoindolenine that the reaction of lactim ethers with α-amino-α-cyanoacetamide also extends to partly aromatized lactim ethers, although these react much less readily. Condensation of 1-ethoxyisoindolenine with α-amino-cyanoacetamide gives 4-carbamido-5-aminoimidazo[1, 2-1', 2']isoindoline, from which a new series of purinoisoindioline derivatives is synthesized.

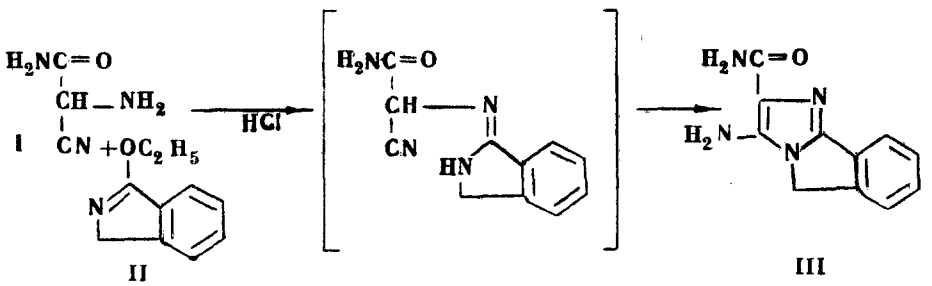
Information has previously been given [1] regarding the ability of the simplest lactim ethers, such as O-methylbutyro-, valero-, and caprolactims, to condense with α-amino-[α-cyanoacetamide (I) to give amides of 5-amino-]-1, 2-polymethyleneimidazole-4-carboxylic acids, and it has been shown that the reaction is catalyzed by hydrogen chloride [2]. The facility with which the lactim ethers condense with α-amino-α-cyanoacetamide is not governed by chance, but is conditioned by the properties of the components, so that formation of cyclic derivatives of 5-aminoimidazole-4-carboxylic acids from lactim ethers must be a general type of reaction applying to a wide range of cyclic systems containing the grouping

$$-C(OR)=N-.$$

The present communication is the first of a series of papers to determine how general this reaction is, and, in connection therewith, to ascertain the effect of various substituents, as well as of the degree of aromatization of the lactim ethers, on their reactivities with respect to various nucleophilic reagents.

For this purpose a study was made of the condensation of I with 1-ethoxyisoindolenine (II), which latter is readily formed on alkylating phthalimide with triethyloxoniumfluoroborate [3]. In previous attempts to condense I with II by heating them together in ethylcellosolve or alcohol, analogous to the corresponding reaction of O-methylcaprolactim with I [4], only the starting materials were isolated. Comparison of these results with those obtained in condensing the 5-membered lactim ether, O-methylbutyrolactim, showed that additional aromatization of the lactam ring due to condensing it with a benzene ring considerably cuts the reactivity of II in nucleophilic substitutions. Obviously, this is due to the reduced electrophilic character of the C=N bond in II.

This hypothesis found support in the results of a series of experiments on condensing I with II in the presence of catalytic amounts of hydrogen chloride. This gave 4-carbamido-5-aminoimidazo[1, 2-2', 1']isoindoline (III), though the yield did not exceed 46%



Structure III finds support in a qualitative reaction characteristic of aminoimidazoles, viz., the appearance of a purple color when III is diazotized and then coupled with α-naphthol.

Treatment of III with a mixture of orthoformic ester and acetic anhydride gave isoindolinohypoxanthine (IV). Comparison of the UV spectrum of IV and those of polymethylenehypoxanthines [2] revealed an essential difference, for the latter have only one maximum at 250 mμ, while IV has two (λ_{max} 228 mμ, log ε 4.203, and λ_{max} 304 mμ, log ε 4.350), though the UV spectrum of IV appeared to resemble that of 8-phenylpurine [5].

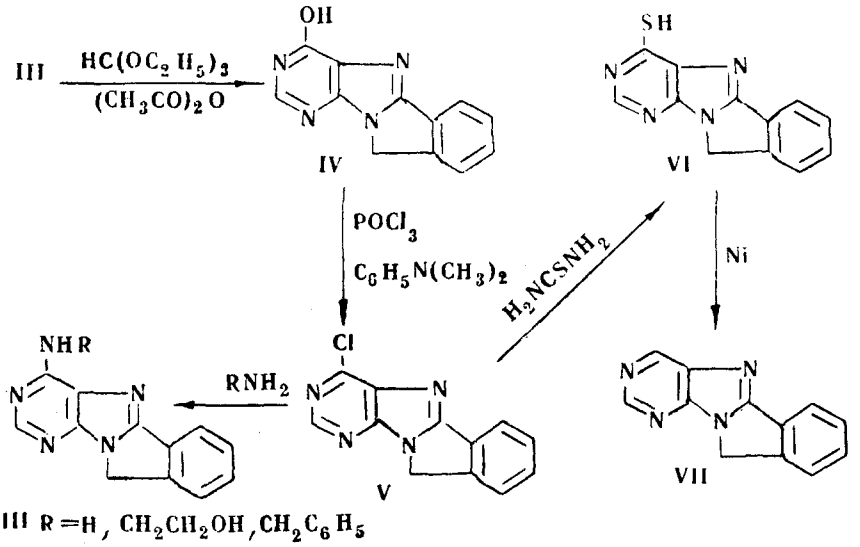
The isoindolinohypoxanthine was the starting material for preparing representatives of a new series of heterocyclic compounds, the isoindolinopurines, the synthesis of which was effected as follows.

EXPERIMENTAL

4-Carbamido-5-aminoamidazo[1, 2-1', 2']isoindoline (III). A mixture of 9.1 g compound II, 5.8 g α-amino-α-cyanoacetamide, 40 ml anhydrous methanol, and 0.2 ml 20% HCl in absolute alcohol was boiled and stirred for 3 hr. Solution was complete 15-20 min after commencement of boiling. A small crystal of II was added to the reaction mixture,

*For part V see [2].

and a fresh precipitate started to appear in 20-30 min. The reaction mixture was allowed to cool to room temperature, and then cooled further with ice. The precipitate was filtered off, washed with alcohol (twice with 5 ml), suspended in water, and a saturated solution of soda added to bring the pH to 7.5-8; the solution was filtered, and the precipitate washed with 10 ml water, then with 10 ml alcohol, and dried. Yield 46% of theoretical, m.p. 293-296° (decomp.); it is soluble with difficulty in most organic solvents, readily soluble in methanol and water, insoluble in solutions of alkalies, but soluble in acids.



For analysis it was crystallized from water (1:150), and then from methanol. Cubic crystals, m.p. 295-297° (decomp.). Found: C 61.97; H 4.60; N 25.90%. Calculated for $C_{11}H_{10}N_4O$: C 61.68; H 4.67; N 26.16%.

6-Hydroxypurino[1, 2-1'2']isoindoline (IV). 5.57 g compound III, 30 ml orthoformic ester and 50 ml acetic anhydride were refluxed and stirred for three and one half hr. During heating the boiling point fell from 120° to 103°, and after about one half hour the solution again contained solid. The product was evaporated to dryness, and the residue heated with 60 ml 50% aqueous methanol; the mixture was then concentrated to 20 ml and cooled in ice. The resultant precipitate was filtered off, washed with water, then with alcohol, and dried. Yield 5.3 g (91%), m.p. above 365°; soluble with difficulty in water, most organic solvents, and acids, readily soluble in dilute alkalies. Found: N 25.11%, calculated for $C_{12}H_8N_4O$: N 25.00%.

6-Chloropurino[1, 2-1'2']isoindoline (V). 2 g IV, 60 ml freshly distilled phosphorus oxychloride, and 5 ml dimethylaniline were refluxed for 2 hr. When boiling was ended, the light yellow solution was taken to dryness in a vacuum, 15 g crushed ice were added, and the mixture extracted with chloroform-methanol (10:2). After drying over sodium sulfate the extract was evaporated to dryness, and the residue triturated with 10 ml methanol, filtered, the undissolved material washed twice with 3 ml methanol, and then dried. Yield 1.93 g (90%), m.p. 263-265°; rather difficultly soluble in most organic solvents, water, and dilute alkalies; soluble in acids. For analysis it was twice crystallized from methanol. Pale yellow needles, m.p. 264-266°. Found: C 59.36, 59.30; H 3.40, 3.34; N 23.17; Cl 14.82%. Calculated for $C_{12}H_7ClN_4$: C 59.38; H 2.88; N 23.09; Cl 14.63%.

6-Mercaptopurino[1, 2-1'2']isoindoline (VI). A suspension of 0.2 g compound V and 0.1 g thourea in 20 ml absolute alcohol was refluxed with stirring for 70 min. The precipitate slowly dissolved and new crystals appeared. The reaction mixture was cooled, the precipitate filtered off, washed with alcohol and dried, yield 0.19 g (100%), m.p. 340-350° (decomp.); soluble with difficulty in most organic solvents and dilute mineral acids, soluble in solutions of alkalies. For analysis it was reprecipitated from a hot conc. NH_4OH solution by adding acetic acid. M.p. 348-352° (decomp.). Found: C 59.69; H 3.62; N 23.18; S 13.34%, calculated for $C_{12}H_8N_4S$: C 60.00; H 3.33; N 23.33; S 13.33%.

6-(β-hydroxyethyl)aminopurino[1, 2-1'2']isoindoline (VIII, R = CH_2CH_2OH). A mixture of 1 g V, 1 ml $H_2NCH_2CH_2OH$, and 10 ml ethyl cellosolve is refluxed for one and one half hours with stirring. The resultant solution is evaporated to dryness in a vacuum, the residue triturated with 10 ml water and filtered, and the precipitate washed with water and dried. Yield 1 g (90%), m.p. 211-214°. It was soluble with difficulty in ether and benzene, and dissolves on heating in water, alcohol, acetone, and chloroform. For analysis it was crystallized from water (1:20). Needles, m.p. 213-215°. Found: C 62.90; H 5.11; N 26.08%. Calculated for $C_{14}H_{13}N_5O$: C 62.92; H 4.87; N 26.21%.

Adenino[1, 2-1', 2']isoindoline (VIII, R = H). A mixture of 1.2 g V and 30 ml 25% NH_3 in absolute alcohol was autoclaved for 6 hr, (temperature 160-170°). After cooling the reaction mixture was cooled, and the residue washed with methanol and dried. 1 g material was obtained, and a further 0.25 g on evaporating the mother liquors. The total material (1.25 g) was triturated with 20 ml water, filtered, and the residue washed twice with 5 ml water, then with 5 ml alcohol, and dried. Yield 1 g (87%), m.p. above 360°. It was soluble with difficulty in water and most organic solvents,

but soluble in hot acetic acid. For analysis it was reprecipitated from hot acetic acid solution by adding conc. NH_4OH; the resultant precipitate was filtered off, washed with water, then with alcohol, and dried, m.p. above 360°. Found: C 64.72, 64.67; H 4.41, 4.43; N 31.23, 31.60%. Calculated $C_{12}H_9N_5$: C 64.57; H 4.04; N 31.39%.

6-Benzylaminopurino[1,2-1',2']isoindoline (VIII, R = $C_6H_5CH_2$). A mixture of 1.25 g V, 1.5 ml benzylamine, and 10 ml ethyl cellosolve was refluxed for 1 hr with stirring, until everything went into solution. The reaction mixture was taken to dryness in a vacuum, the residue triturated with 10 ml water, filtered, and the precipitate washed with water and dried. Yield 1.7 g material which on recrystallization from 65 ml ethyl acetate gave 1.2 g (75%); m.p. 169-172°. After repeated crystallization from the same solvent, the m.p. was 171-173°. The compound dissolved on heating with most organic solvents, and was soluble only with difficulty in water. Found: C 72.95; H 5.07; N 22.60%. Calculated for $C_{19}H_{15}N_5$: C 72.84; H 4.79; N 22.36%.

Purino[1,2-1'2']isoindoline (VII). A mixture of 1.2 g VI, 3 g wet Ni catalyst, and 150 ml water was boiled together for 2 hr with stirring, the mixture filtered while hot, and the residue washed with 20 ml boiling water. The united filtrates were evaporated to dryness in a vacuum, the residue triturated with alcohol, and the mixture cooled in ice, filtered, washed with cold alcohol, and dried. Yield 0.8 g (77%), m.p. 270-272°; recrystallized from water, m.p. 271-273°. It was difficultly soluble in ether, soluble on heating in most organic solvents, readily soluble in dilute acids, but insoluble in solutions of alkalies. Found: C 69.00; H 3.69; N 26.60%. Calculated for $C_{12}H_8N_4$: C 69.23; H 3.84; N 26.92%.

REFERENCES

1. R. G. Glushkov, O. Yu. Magidson, DAN, 133, 585, 1960.
2. R. G. Glushkov, O. Yu. Magidson, ZhOKh, 31, 1906, 1961.
3. S. Petersen, E. Tietze, Ann., 623, 166, 1959.
4. R. G. Glushkov, O. Yu. Magidson, ZhOKh, 31, 1173, 1961.
5. S. F. Mason, J. Chem. Soc., 2071, 1954.

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