SYNTHESIS OF DIPYRIDAZINO[3,4-b:4',5'-e]PYRAZINE

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As a continuation of our search amongst the substituted pyridazines [1, 2] and pyridazinoquinoxalines [3] for substances with antimicrobial activity, we have synthesized a new heterocyclic system, viz., dipyridazino[3,4-b:4',5'-e]pyrazine.

When 1-phenyl-4,5-diaminopyridazin-6-one is condensed with benzoylpyruvic acid, 3-phenacyl-2,5-dioxo-6-phenylpyrazino[2,3-d]pyridazine (I), which has not been described before, is obtained. The structure of I is confirmed by its IR spectrum, in which an amide carbonyl band is present (1660 cm^{-1}), the absorption band of the primary amino group (3395 cm^{-1}) observed in the spectrum of the initial diaminopyridazone is absent, and absorption bands corresponding to the NH (3150 cm^{-1}) and keto groups (1705 cm^{-1}) appear. The UV spectrum of I in formic acid shows an additional absorption maximum (at 415 nm) compared with the spectrum of the initial diaminopyridazone, in which there is only one maximum at 280 nm. In the condensation of diamino derivatives with dicarbonyl compounds when the reactants are asymmetric it is natural to expect isomers. However, a great deal of data [4] shows that one of the expected isomers is often formed exclusively or preferentially, the direction of the reaction depending on the basicity of the amino groups, the different reactivities of the carbonyl groups in the dicarbonyl component, the pH of the medium, etc. In the case of the preparation of substituted quinoxalines from pyruvic acid derivatives in a neutral medium, it has been shown [5] that the reactivity of the carbonyl groups of this carbonyl component decreases in the order carboxyl > ester > aldehyde > ketone.

In the present case, compound I is formed in good yield. It is known that the amino group in position 4 is the most basic in 1-phenyl-4,5-diaminopyridazin-6-one. On the basis of what has been said above, we may suppose that this amino group reacts with the carboxyl group of the benzoylpyruvic acid.

We attempted to prepare the condensation product of benzoylpyruvic acid with one of the amino groups of the disubstituted pyridazone. Under the conditions of synthesis of compound I, benzoylpyruvic acid does not react with 1-phenyl-4-nitro-5-aminopyridazin-6-one. We did succeed in obtaining such a product, however, in the case of 1-phenyl-4-amino-5-methylaminopyridazin-6-one (V). Compound V was synthesized by heating 1-phenyl-4-nitro-5-hydroxypyridazin-6-one with an aqueous solution of methylamine (analogously to the known method of preparing 1-phenyl-4-nitro-5-aminopyridazone by the action of ammonia [6]) and subsequently reducing the resulting 1-phenyl-4-nitro-5-methylaminopyridazin-6-one (IV) with stannous chloride in hydrochloric acid. In our case, however, the reaction gave a very low yield of the expected product IV, together with which the formation of 1-phenyl-3-nitropyrazole was observed. As is known from the literature [6], such contractions of the pyridazine ring are brought about by the action of mineral acids and alkalis.

The compound VI obtained by condensation of V with benzoylpyruvic acid is insoluble in sodium bicarbonate solution. In its IR spectrum the carboxyl group absorption bands are absent and the band of the primary amino group (3410 cm^{-1}) observed in the spectrum of the initial V disappears. Its UV spectrum is analogous to that of the initial V, with a bathochromic shift of 35 nm. On the basis of all these data, we can assign the N-(1-phenyl-5-methylamino-6-oxopyridazin-4-yl) benzoylpyruvamide structure to compound VI,

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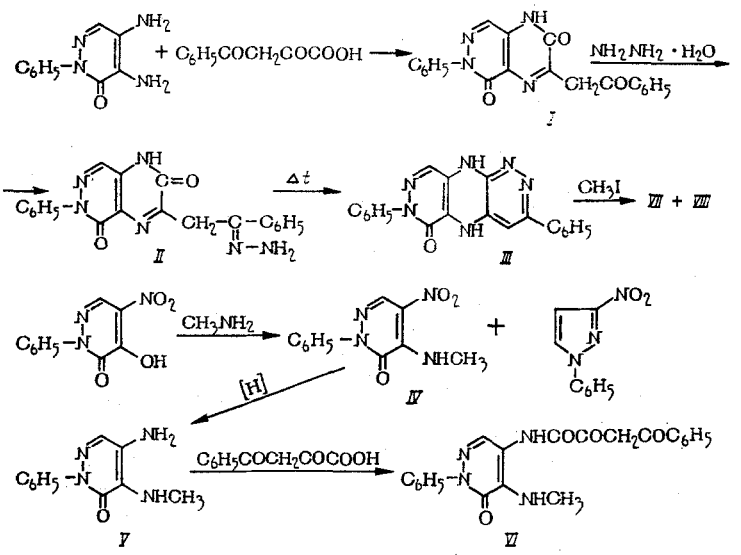
and from what has been said above, we can suppose that the phenacyl group in compound I is in the 3 position.



Compound I was converted into the hydrazone of 3-phenacyl-2,5-dioxo-6-phenylpyrazino[2,3-d]pyridazine (II) by reaction with hydrazine hydrate in alcohol solution. The structure of II is confirmed by its IR spectrum, in which the absorption band corresponding to the keto group observed in the spectrum of I disappears and absorption bands appear for the azine C–N (1625 cm^{-1}) and the primary amino group of the hydrazone (3310 cm^{-1}).

On prolonged boiling in acetic acid solution, hydrazone II is cyclized to form 3,7-diphenyl-6-oxodipyridazino[3,4-b:4',5'-e]pyrazine (III). The absorption bands of the azine and primary amino groups observed in the spectrum of II disappear in the IR spectrum of III. A study of the UV and H^1 NMR spectra of II and III proved to be impossible owing to the very low solubility of the substances in solvents suitable for measuring these spectra.

Reaction of III with excess methyl iodide in a solution of sodium alcoholate leads, as shown by thin-layer chromatography on aluminum oxide, to a mixture of five products with R_f values of 0.78, 0.407, 0.295, 0.200, and 0.080.

The first two products (VII and VIII) are the main components of this mixture. They were separated by fractional crystallization: VII, mp 281-283°, R_f = 0.407; VIII, mp 235-237°, R_f = 0.78. According to elementary analysis data, both compounds are dimethyl derivatives of III.

The obtained compounds do not possess antimicrobial activity.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer in mineral oil and the UV spectra with an EPS-3 spectrophotometer. The H^1 NMR spectra were recorded on a C-60-HL instrument with a working frequency of 60 MHz using hexamethyldisiloxane as internal standard and deuteropyridine as solvent. Thin-layer chromatography was carried out on an unfixed layer of 2nd-degree activity aluminum oxide in the chloroform–methanol (98 : 2) system.

3-Phenacyl-6-phenylpyridazino[2,3-d]pyrazin-2,5-dione (I). A solution of 8.4 g 1-phenyl-4,5-diaminopyridazin-6-one in 150 ml alcohol is added to a solution of 8 g benzoylpyruvic acid in 60 ml alcohol. The mixture is heated to boiling for 15 min. After 5 min, a bright-yellow precipitate begins to be deposited, giving 12.7 g (85.6%) of I, mp 312-315° (from acetic acid). IR spectrum (cm^{-1}): 3150 (NH), 1705 (ketone CO), 1660 (amide CO). UV spectrum, λ_{max} nm (log ε), in formic acid: 260 (4.8), 415 (1.65). Found (%): C 66.78; H 4.21; N 15.44. $C_{20}H_{14}N_4O_3$. Calculated (%): C 67.04; H 3.94; N 15.64.

3-Phenacyl-6-phenylpyridazino[2,3-d] pyrazin-2,5-dione Hydrazone (II). A stirred suspension of 8.3 g I in 250 ml alcohol and 16 ml hydrazine hydrate is heated for 5 h. The precipitate of I is gradually converted into II, giving 6.5 g (75.4%) of II as yellow crystals, mp > 360° (from dimethylformamide). IR spec-

trum (cm^{-1}): 3310 (NH_2), 3140, 320* (NH), 1625 (azine C−N),1660 (amide CO). Found (%): C 64.28; H 4.50; N 22.83. $C_{20}H_{16}N_6O_2$. Calculated (%): C 64.50; H 4.33; N 22.57.

3,7-Diphenyldipyridazino[3,4-b:4',5'-e]pyrazin-6-one (III). A mixture of 6.5 g II and 150 ml glacial acetic acid is boiled for 6-8 h. A bluish-white precipitate is gradually deposited from solution. This is filtered off, washed with alcohol, boiling dimethylformamide, and alcohol again, to give 5.3 g (85.8%) of III, mp > 360°. IR spectrum (cm^{-1}): 3120 (NH), 1665 (CO). Found (%): C 67.49; H 4.14; N 23.11. $C_{20}H_{14}N_6O$. Calculated (%): C 67.79; H 4.00; N 23.84.

1-Phenyl-4-nitro-5-methylaminopyridazin-6-one (IV) and 1-Phenyl-3-nitropyrazole. A mixture of 10 g 1-phenyl-4-nitro-5-hydroxypyridazin-6-one and 300 ml of a 25% aqueous solution of methylamine is boiled for 16 h while periodically saturating with methylamine from a cylinder. The precipitate formed on cooling is filtered off to give 1.8 g (32.8%) of 1-phenyl-3-nitropyrazole, mp 126-128° (from alcohol). Found (%): C 57.21; H 3.64; N 22.22. $C_9H_7N_3O_2$. Calculated (%): C 57.20; H 3.70; N 22.80.

On cooling the mother liquor, 3.3 g of the starting material is precipitated. The mother liquor is then evaporated to dryness, and the residue recrystallized from water and alcohol, to give 2.3 g (32.5%) of IV, mp 158-159°. Found (%): C 53.38; H 3.90; N 22.96. $C_{11}H_{10}N_4O_3$. Calculated (%): C 53.00; H 4.05; N 22.80.

1-Phenyl-4-amino-5-methylaminopyridazin-6-one (V). A solution of 6.4 g stannous chloride in 50 ml concentrated hydrochloric acid is added to a stirred solution of 2.3 g IV in 50 ml ethanol. The mixture is heated for 30 min; the alcohol is distilled off; the residue is diluted with 50 ml water, made alkaline with a solution of caustic soda, and extracted with chloroform. After evaporating off the chloroform, the residue is triturated with petroleum ether, giving 1.2 g (59.5%) of V, mp 110-111° (from benzene). IR spectrum (cm^{-1}): 3410 (NH_2), 3200 (NH), 1665 (CO). Found (%): C 61.25; H 5.86; N 25.89. $C_{11}H_{12}N_4O$. Calculated (%): C 61.12; H 5.59; N 25.92.

N-(1-phenyl-5-methylamino-6-oxo-4-pyridazinyl) benzoylpyruvamide (VI). A mixture of 1.2 g V and 1.07 g benzoylpyruvic acid in 20 ml ethanol is boiled for 1 h. The yellow precipitate formed on cooling is filtered off to give 1.8 g (82.8%) of VI, mp 187-188° (from alcohol). IR spectrum (cm^{-1}): 3230(NH), 1707 (ketone CO), 1650 (amide CO). UV spectrum, γ_{max} nm (log ε), in formic acid: 315 (2.6). Found (%): C 64.28; H 4.90; N 14.36. $C_{21}H_{18}N_4O_4$. Calculated (%): C 64.60; H 4.62; N 14.40.

Methylation of III. A mixture of 3.4 g III, 150 ml of a solution of sodium alcoholate obtained from 0.75 g metallic sodium, and 13.6 g methyl iodide is heated to boiling and left to stand for 6 days. The white precipitate is filtered off and washed with water to give 1.5 g of precipitate (A), mp 205-290°, R_f 0.78, 0.407, 0.295. The alcoholic mother liquor is evaporated to dryness, and the residue treated with water to give 3.5 g of a precipitate (B), mp 150-275°, R_f 0.78, 0.407, 0.295, 0.20, 0.08.

Precipitates A and B are recrystallized from alcohol to give 2.2 g of a mixture of substances with R_f values of 0.78 and 0.407. After repeated crystallization from alcohol, 0.3 g of VII, mp 281-283°, R_f = 0.407, is obtained from this mixture. Found (%): C 68.87; H 4.82; N 21.80. $C_{22}H_{18}N_6O$. Calculated (%): C 69.10; H 4.74; N 21.98.

The mother liquors from VII are evaporated and repeatedly recrystallized from benzene to give 0.1 g of VIII, mp 235-237°, R_f = 0.78. Found (%): C 69.54; H 4.78; N 22.06. $C_{22}H_{18}N_6O$. Calculated (%): C 69.10; H 4.74; N 21.98.

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