REACTIONS OF 2-(BENZIMIDAZOL-2-YL)ACETONITRILE AND ITS N-ETHOXYCARBONYL DERIVATIVE WITH SOME AZOL-3-DIAZONIUM SALTS*

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Coupling of 2-(1-ethoxycarbonyl-benzimidazol-2-yl)acetonitrile (*II*) with 5-methylpyrazol-3-diazonium (*IIIa*) or indazol-3-diazonium salt (*IIIb*) does not give the corresponding derivatives *VIIa*, *VIIb* of pyrazolo[3,2-*c*]-1,2,4-triazine but, instead, gives the corresponding 2-(3-azolyl)-1-oxo-1,2-dihydro-1,2,4-triazino-[4,5-*a*]benzimidazole-4-carbonitriles *VIIIa*, *VIIIb*. Coupling of 2-(benzimidazol-2-yl)acetonitrile (*I*) with the diazonium salt *IIIa* gives 7-amino-6-(benzimidazol-2-yl)-2-methylpyrazolo[3,2-*c*]-1,2,4-triazine (*VIa*) which, on reaction with ethyl chloroformate, undergoes cyclization to 2-methyl-12,13-dihydropyrazolo[3″,2″:3′,4′]-1,2,4-triazino[5′,6′:6,5]-pyrimido[3,4-*a*]benzimidazol-12-one (*IXa*). The compound *VIa* and 1-amino-2-(benzimidazol-2-yl)-1,2,4-triazino[4,3-*b*]indazole (*VIb*) are also formed by recyclization of the compounds *VIIIa* and *VIIIb*, respectively, in boiling aqueous pyridine.

Among many various cyclization reactions of hydrazones there are also known reactions which proceed unusually easily. This type can be exemplified by the cyclizations of 3-pyrazolyl-[1-3] and 3-indazolylhydrazones of 2-ketonitriles[4,5] which give the corresponding azolo[3,2-*c*]1,2,4-triazines often spontaneously after being formed by coupling of the respective diazonium salts with the nitriles containing reactive methylene group. A quite different type of cyclization is observed with 2-arylhydrazono-2-(1-ethyoxycarbonylbenzimidazol-2-yl)acetonitriles which could not be trapped after the coupling of diazonium salts with 2-(1-ethoxycarbonylbenzimidazol-2-yl)-acetonitrile due to their rapid conversion into the corresponding 2-aryl-1-oxo-1,2-dihydro-1,2,4-triazino[4,5-*a*]benzimidazole-4-carbonitriles[6-8].

Therefore, we were very interested in the problem of what direction would take the cyclization of such hydrazones which contain the both said reactive groupings in the molecule – whether azolo[3,2-*c*]-1,2,4-triazine or 1,2,4-triazino[4,5-*a*]benzimidazole would be formed. The coupling reaction of 2-(1-ethoxycarbonylbenzimidazol-2-yl)acetonitrile (*II*) with 5-methylpyrazol-3-diazonium chloride (*IIIa*) or indazole-3-diazonium chloride (*IIIb*) was expected to give the reactive hydrazones

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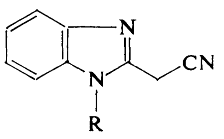
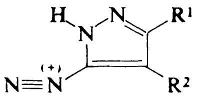
Va, *Vb* which can be easily cyclized to both the corresponding 6-(1-ethoxycarbonylbenzimidazol-2-yl)azolo[3,2-*c*]-1,2,4-triazines (*VIIa*, *VIIb*) and the respective 2-(azol-3-yl)-1-oxo-1,2-dihydro-1,2,4-triazino[4,5-*a*]benzimidazole-4-carbonitriles (*VIIIa*, *VIIIb*). The derivatives *VII*, if formed, were expected to undergo possibly a subsequent cyclization giving the condensed systems *IXa*, *IXb*.

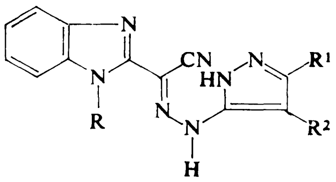
It was found experimentally that the hydrazones *V* preferred unambiguously the cyclization to give 1,2,4-triazino[4,5-*a*]benzimidazole, *i.e.*, the coupling reactions of nitrile *II* with diazonium salts *IIIa* and *IIIb* gave the corresponding 2-(5-methylpyrazol-3-yl)-1-oxo-1,2-dihydro-1,2,4-triazino[4,5-*a*]benzimidazole-4-carbonitrile (*VIIIa*) and the 2-(3-indazolyl) derivative *VIIIb*, respectively. IR spectra of the compounds prepared showed that the said reaction produced no isomeric derivatives *IX*: they contain typical band of vibration of nitrile group at 2 242 and 2 248 cm^{-1}, resp., as well as intensive band of valence vibration of the NH group bound to carbonyl group by intramolecular hydrogen bond at 3 250 and 3 252 cm^{-1}, respectively.



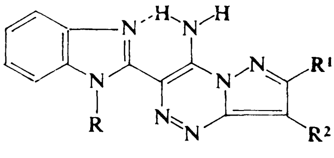
I, R = H
II, R = $COOC_2H_5$



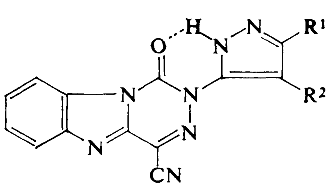
III



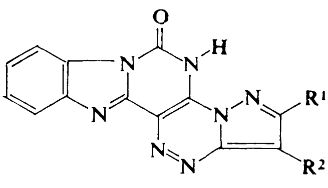
IV, R = H
V, R = $COOC_2H_5$



VI, R = H
VII, R = $COOC_2H_5$



VIII



IX

In formulas, *III*—*IX*: *a* $R^1 = CH_3$, $R^2 = H$; *b* $R^1 + R^2 = —CH{=}CH—CH{=}CH—$.

The most intensive band is that of valence vibration of carbonyl group at 1 733 and 1 746 cm^{-1}, resp.

For comparison we prepared 2-methyl-12,13-dihydropyrazolo[3″,2″:3′,4′]-1,2,4-triazino[5′,6′:6,5]pyrimido[3,4-*a*]benzimidazol-12-one (*IXa*) which is isomeric with compound *VIIIa*. The coupling reaction of 2-(benzimidazol-2-yl)acetonitrile (*I*) with diazonium salt *IIIa* gave directly good yields of 7-amino-6-(benzimidazol-2-yl)-2-methylpyrazolo[3,2-*c*]-1,2,4-triazine (*VIa*). The intermediate hydrazone *IVa* could not be trapped in this reaction. Its very easy cyclization is indicated by the fact that IR spectrum of the coupling product dried at room temperature is identical with that of the product recrystallized from ethanol. This spectrum does not contain the band of CN group but contains two intensive bands of valence vibration of N—H bond at 3 333 and 2 285 cm^{-1}. The band at lower wave number is probably due to valence vibration of the NH group bound by intramolecular hydrogen bond (in a six-membered cycle) to the N atom of imidazole cycle, the band at 3 333 cm^{-1} can be assigned to the NH group of imidazole which is bound by intramolecular hydrogen bond (in a five-membered cycle) to the N atom of 1,2,4-triazine cycle. The derivative *IXa* was prepared from *VIa* by acylation with ethyl chloroformate in pyridine medium and subsequent cyclization of the intermediate ethoxycarbonyl derivative at higher temperature. IR spectrum of compound *IXa* shows a band of valence vibration of carbonyl group at 1 660 cm^{-1}. The most intensive bands, however, are found at 1 535 and 1 628 cm^{-1} and are assigned to valence vibrations of C=N and C=C bonds. Compound *IXb* could not be prepared in analogous way due to slight solubility of the starting compound *VIb* in pyridine and other aprotic solvents.

Hydrolytic splitting of 1,2,4-triazino[4,5-*a*]benzimidazoles *VIIIa* and *VIIIb* gave interesting results. It was found that boiling of these substances in aqueous pyridine results in their recyclization to give *VIa* and *VIb*, respectively, which fully agrees with earlier findings[9] on hydrolytic splitting of 2-aryl-1-oxo-1,2-dihydro-1,2,4-triazino [4,5-*a*]benzimidazole-4-carbonitriles, if easy cyclization of the formed hydrazones *IVa* and *IVb* is also taken into account.

EXPERIMENTAL

The melting points were determined with a Boetius apparatus and are not corrected. The IR spectra were measured with an IR-75 spectrometer (Zeiss, Jena) by the KBr technique.

2-(5-Methyl-3-pyrazolyl)-1-oxo-1,2-dihydro-1,2,4-triazino[4,5-*a*]-benzimidazole-4-carbonitrile (*VIIIa*)

Solution of 200 mg (2·06 mmol) 3-amino-5-methylpyrazole in 5 ml ice water and 2·0 ml 37% HCl was treated with about 2 g crushed ice and solution of 140 mg (2·03 mmol) $NaNO_2$ in 2 ml ice water which was added portionwise with stirring and cooling in ice bath. The mixture was stirred in ice bath 10 min and added portionwise to solution of 500 mg (2·18 mmol) 2-(1-ethoxycarbonylbenzimidazol-2-yl)acetonitrile[6] (*II*) in 35 ml pyridine with cooling; then it was left to stand at 0—5°C 48 h and diluted with 200 ml ice water. After several hours the precipitated solid was collected by suction. washed with water, and dried. Yield 465 mg (78·7%). After recrystallization from ethanol m.p. 359—361°C. For $C_{14}H_9N_7O$ (291·3) calculated: 57·74% C, 3·11% H, 33·66% N; found: 57·71% C, 3·25% H, 33·58% N. IR spectrum (KBr, cm^{-1}): 3 252 s ν(NH), 2 242 w ν(CN), 1 733 s ν(CO).

2-(3-Indazolyl)-1-oxo-1,2-dihydro-1,2,4-triazino[4,5-*a*]benzimidazole-4-carbonitrile (*VIIIb*)

The substance was prepared similarly as *VIIIa* from 275 mg (2·07 mmol) 3-aminoindazole. Yield 644 mg (86·5%). After recrystallization from ethanol m.p. 310 to 312°C. For $C_{17}H_9N_7O$ (327·3) calculated: 62·38% C, 2·77% H, 29·96% N; found: 62·17% C, 2·97% H, 29·73% N. IR spectrum (KBr, cm^{-1}): 3 250 s ν(NH), 2 248 w ν(CN), 1 746 s ν(CO).

7-Amino-6-(2-benzimidazolyl)-2-methylpyrazolo[3,2-*c*]-1,2,4-triazine (*VIa*)

a) The diazonium salt solution prepared from 200 mg (2·06 mmol) 3-amino-5-methylpyrazole in the same way as in the preparation of *VIIIa* was added portionwise with stirring to a mixture obtained by dissolution of 350 mg (2·23 mmol) 2-(2-benzimidazolyl)acetonitrile in 160 ml hot water, cooling to 0—3°C, and subsequent addition of 6·0 g $CH_3COONa.3\,H_2O$ and crushed ice. The mixture was left to stand at 0—5°C 24 h, the separated solid was collected by suction, washed with water, and dried in air at room temperature. Yield 490 mg (91%), m.p. above 360°C. IR spectrum of the product was identical with that of the product obtained by recrystallization from ethanol. For $C_{13}H_{11}N_7$ (265·3) calculated: 58·86% C, 4·18% H, 36·96% N; found: 58·78% C, 4·23% H, 36·97% N. IR spectrum (KBr, cm^{-1}): 3 333 s ν(NH), 3 285 s (ν(NH), 1 650 s ν(CO).

b) Mixture of 150 mg (0·51 mmol) *VIIIa*, 35 ml water, and 4·0 ml pyridine was refluxed 5 h and cooled. The crystalline product was collected by suction, wahsed with water, and dried at 120°C. Yield 125 mg (91·5%). All properties inclusive of IR spectrum of the product are identical with those of the product prepared ad *a*).

1-Amino-2-(2-benzimidazolyl)-1,2,4-triazino[4,3-*b*]indazole (*VIb*)

The substance was prepared similarly as *VIa* from 170 mg (0·52 mmol) compound *VIIIb*, 35 ml water, and 10 ml pyridine; yield 148 mg (94·6%). All properties inclusive of IR spectrum of the product are identical with those of the compound prepared by the coupling reaction[5].

2-Methyl-12,13-dihydropyrazolo[3″,2″:3′,4′]-1,2,4-triazino[5′,6′:6,5]-pyrimido[3,4-*a*]-benzimidazol-12-one (*IXa*)

Mixture of 140 mg (0·53 mmol) derivative *VIa* and 20 ml pyridine was heated until dissolution, and the solution was cooled in ice bath to 3—5°C, whereupon 1·0 ml ethyl chloroformate was added drop by drop with stirring and cooling. The mixture was left to stand at 0—5°C 6 days with occasional shaking, diluted with 250 ml wat er (to decompose the excess N-ethoxycarbonylpyridinium chloride), filtered, and evaporated. The evaporation residue was mixed with 25 ml water, coollected by suction after several hours, washed with water, and dried at 140°C. Yield 124 mg (80·7%). M.p. above 360°C (after recrystallization from acetic acid and drying at 160°C). For $C_{14}H_9N_7O$ (291·3) calculated: 57·73% C, 3·11% H, 33·66% N; found: 57·49% C, 3·20% H, 33·37% N. IR spectrum (KBr, cm^{-1}): 1 660 s ν(CO), 1 628 s, 1 535 s ν(C=N), ν(C=C).

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