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CYCLIZATION OF THE HYDRAZIDES OF VICINAL PHENYLETHYNYL DERIVATIVES OF N-METHYLPYRAZOLE-5-CARBOXYLIC AND BENZOIC ACIDS

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Intramolecular cyclization of vicinal functionally substituted aromatic acetylenic compounds has recently become increasingly important as a method for synthesis of heterocyclic condensed systems [1]. This type of heterocyclization of acetylenic derivatives of aromatic carboxylic acid hydrazides is not known. It could be possible to prepare multinuclear heterocyclic compounds which are difficult to obtain by other methods with this reaction.

Intramolecular cyclization of 4-phenylethynyl-1-methyl-pyrazole-5-carboxylic (I) and tolan-2-carboxylic (II) acid hydrazides in the presence of Cu(I) salts yields products which were described as diazepinones (III) and (IV) [2] based on the PMR data, IR spectra, and elementary analysis. However, it was subsequently shown that the compounds obtained in heating with an acid or a base do not undergo the constriction of the ring characteristic of diazepinones [3, 4].

A supplementary study of the reaction and properties of the products, which were reliably identified as 6,7-dihydro-1-methyl-4-benzylpyrazolo[3,4-d]pyridazin-7-one (V) and 1,2-dihydro-4-benzyl-1-phthalazinone (VI), is reported in the present article.

The starting hydrazide (I) was prepared by boiling the methyl ester of 4-phenylethynyl-1-methylpyrazole-5-carboxylic acid (VII) with an excess of $NH_2NH_2 \cdot H_2O$ in EtOH for 7 h with a yield of 90%. In contrast to (I), the hydrazide of tolan-2-carboxylic acid (II) undergoes cyclization into 2-amino-3-benzylideneisoindolin-1-one (IX) (yield of 70%) as ester (VIII) is formed in similar conditions. It is possible to suppress the secondary process and to obtain (II) (yield of ~ 55%) together with (IX) (~ 35%) at ~ 20°C.

We found that cyclic hydrazides of type (IX) are easily deaminated in oxidation with air in the presence of CuCl in DMF. The transformation of (IX) into the described 3-benzylideneisoindolin-1-one (X) by this method [5] and the nonidentity of (IX) with the alternative product of cyclization, 1,2-dihydro-2-amino-3-phenylisoquinolin-1-one [3, 6], and (X) with the also well-known product of deamination, 1,2-dihydro-3-phenylisoquinolin-1-one [6, 7] confirms its structure sufficiently convincingly. There is one singlet with δ 6.72 and 6.54 ppm, respectively, in the PMR spectra of (IX) and (X), assigned to the ethylene proton, which indicates the formation of only one geometric isomer (the configuration has not been established) during cyclization. Pyrazolecarboxylic acid hydrazide (I) is cyclized in conditions of basic catalysis with more difficulty than (II), and is transformed into pyridopyrazole

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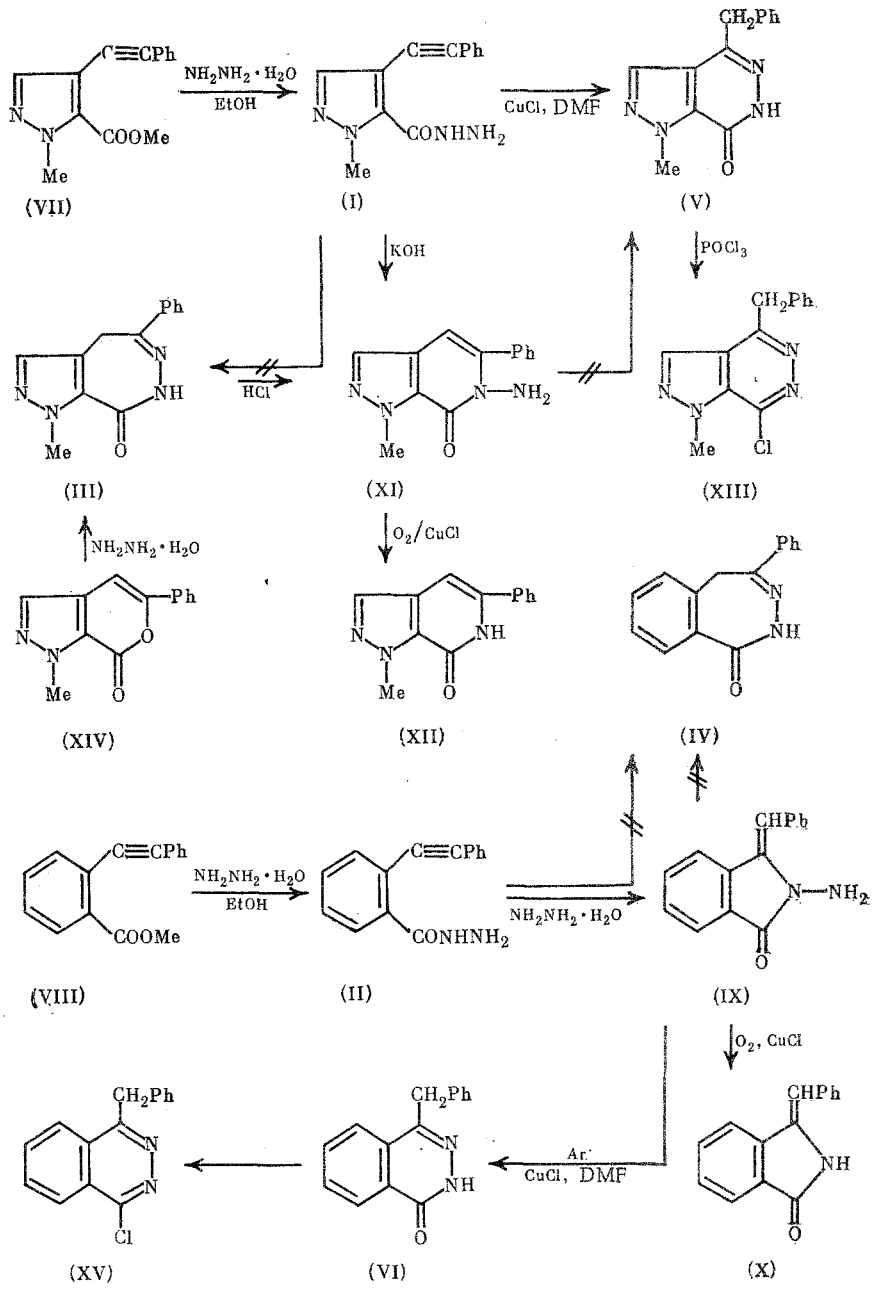

(XI) only on heating in an alcohol solution of KOH. The size of the heterocycle formed was established by contact synthesis of (XI) (see below). Deamination of (XI) results in δ-lactam (XII).

Compound (I) forms isomeric (XI) pyridazinone (V) with a yield of > 70% when boiled in DMF in the presence of CuCl. This compound was erroneously described as diazepinone (III) [2]. The noncorrespondence of the properties with the proposed structure was revealed by the incapacity of (V), in contrast to diazepines [4], for isomerization with constriction of the seven-membered ring in (XI) on prolonged heating in hydrochloric acid or in hydrocarbon solutions of $NH_2NH_2 \cdot H_2O$. Obtaining chloride (XIII) and not N-aminopyridone (XI) by the reaction of (V) with $POCl_3$ indicates its pyridazine structure [3, 8]. Finally, the structure of pyridazinone (V) was confirmed by independent synthesis of (III) from lactone (XIV). It was found that (III) and (V) actually have similar IR and PMR spectra, but different melting points. When heated in HCl, (III) is isomerized into (XI) with constriction of the diazepine ring. This makes the unambiguous selection of a diazepine structure possible for (V), and is evidence of the oxopyridopyrazole structure of (XI).

Tolan-2-carboxylic acid hydrazide (II) reacts ambiguously in the presence of CuCl in DMF, yielding a complex mixture of products containing (VI) and (IX). Its isomer, isoindol-

inone (IX), is recyclized into phthalazone (VI) with a yield of 67% [it should be noted that in the same conditions, the six-membered cyclic hydrazide (XI) is not isomerized into diazinone (V)]. Phthalazone (VI) and diazepinone (IV) have similar physicochemical properties, including the melting point [3, 8, 9]. The structure of the product of recyclization of (VI) is unambiguously established by its transformation into 1-chloro-4-benzylphthalazine (XV) [8]; (VI) is stable on heating with HCl and $NH_2NH_2 \cdot H_2O$.

EXPERIMENTAL

The PMR spectra were made on a Varian XL-200 spectrometer in $CDCl_3$ and the IR spectra were made on a UR-20 spectrometer in $CHCl_3$.

4-Phenylethynyl-1-methylpyrazole-5-carboxylic Acid Hydrazide (I). Here 5.6 g of (VII) and 10 ml of 80% $NH_2NH_2 \cdot H_2O$ in 80 ml of EtOH were boiled for 6.5 h, cooled, and the (I) precipitated was filtered off; yield of 5.1 g (91.1%), bp 142-143°C (EtOH). Found: C 64.94, H 5.06, N 23.13%. $C_{13}H_{12}N_4O$. Calculated: C 64.99, H 5.03, N 23.32%. PMR spectrum (δ, ppm): 4.06 (NH_2), 4.28 (Me), 7.3-7.5 m (Ph), 7.57 (H^3), 8.46 (NH). IR spectrum (ν, cm^{-1}): 2225 (C≡C), 1675 (C=O), 3420, 3350 sh ($NHNH_2$).

In the same conditions (13 h), 5.4 g (65.1%) of (IX) were obtained from 8.3 g of (VIII), mp 102-103°C (EtOH). Found: C 76.27, H 5.15, N 11.83%. $C_{15}H_{12}N_2O$. Calculated: C 76.25, H 5.12, N 11.86%. PMR spectrum (δ, ppm): 4.28 (NH_2), 6.72 (CH=C), 7.3-7.5 m (Ph, $H^{4,5,6,7}$). IR spectrum (ν, cm^{-1}): 1710 (C=O), 3345 (NH_2).

In conducting the reaction of 5.4 g of (VIII) with 5.4 ml of 80% $NH_2NH_2 \cdot H_2O$ in 20 ml of EtOH at 20°C for 10 days, a mixture of (II) and (IX) (~ 1.5:1) was obtained; after cooling to −5-0°C, 2.5 g (46.3%) of (II), mp 127-128°C, was separated by filtration with subsequent crystallization from EtOH. Found: C 76.06, H 4.98, N 11.59%. $C_{15}H_{12}N_2O$. Calculated: C 76.25, H 5.12, N 11.86%. PMR spectrum (δ, ppm): 4.13 (NH_2), 7.3-8.0 m (Ph, $H^{3,4,5,6}$), 8.58 (NH). IR spectrum (ν, cm^{-1}): 2220 (C=C), 1675 (C=O), 3340, 3345 ($NHNH_2$).

6,7-Dihydro-6-amino-1-methyl-5-phenylpyrido[3,4-c]pyrazol-7-one (XI). Here 0.5 g of (I) and 0.2 g of KOH in 5 ml of EtOH were boiled for 5 h (TLC control: Silufol, ether), cooled, and the precipitated (XI) was filtered off, yield of 0.4 g (80%), mp 129.5-130.5°C (EtOH). Found: C 64.83, H 5.05, N 23.57%. $C_{13}H_{12}N_4O$. Calculated: C 64.99, H 5.04, N 23.32%. PMR spectrum (δ, ppm): 4.38 (Me), 4.99 (NH_2), 6.44 (H^4), 7.43 (Ph), 7.72 (H^3). IR spectrum (ν, cm^{-1}): 1660 (C=O), 3330 (NH_2).

3-Benzylideneisoindolin-1-one (X). Air was passed in 1.2 g of (IX) and 0.3 g of CuCl in 10 ml of DMF at 150-155°C for 1 h, the mixture was diluted with 200 ml of ether, filtered, and the solvent was distilled off in a vacuum. Chromatography of the residue on Al_2O_3 (activity II) in ether separated 0.8 g 71.2%) of (X), mp 182-183°C (EtOH) (compare [5]). PMR spectrum (δ, ppm): 6.54 (CH=C), 7.3-7.9 m (Ph, $H^{4,5,6,7}$), 8.58 (NH). IR spectrum (ν, cm^{-1}): 1710 (C=O), 3455 (NH).

In a similar manner, 0.5 g of (XI) was deaminated; the yield of (XII), recrystallized from dioxane, was 0.25 g (53.2%), mp 245-246°C. Found: C 69.37, H 4.91, N 18.70%. $C_{13}H_{11}N_3O$. Calculated: C 69.32, H 4.92, N 18.65%. PMR spectrum (δ, ppm): 4.36 (Me), 6.73 (H^4), 7.4-7.7 m (Ph), 7.78 (H^3), 10.45 (NH). IR spectrum (ν, cm^{-1}): 1665 (C=O), 3385 (NH).

6,7-Dihydro-4-benzylpyrazolo[3,4-d]pyridazin-7-one (V). Here 1.7 g of (I) and 0.4 g of CuCl in 15 ml of DMF were boiled for 0.5 h (TLC control: Silufol, ether), diluted with 100 ml of ether, filtered, and the residue was washed with dichloroethane. The solution obtained was evaporated dry in a vacuum, and the residue in dichloroethane was filtered through silica gel (20 × 30 mm). The (V) separated (1.6 g) was recrystallized from EtOH; yield of 1.2 g (70.6%), mp 197-198°C. Found: C 65.00, H 5.13, N 23.25%. $C_{13}H_{12}N_4O$. Calculated: C 64.99 H 5.03, N 23.32%. PMR spectrum (δ, ppm): 4.15 (CH_2), 4.35 (Me), 7.27 (Ph), 7.60 (H^3), 11.17 (NH). IR spectrum (ν, cm^{-1}): 1675 (C=O), 3410 (NH).

In a similar manner, 2 g (66.7%), mp 197-198°C (EtOH) (compare [8]), were obtained from 3 g of (IX) in the presence of 1 g of CuCl in 10 ml of DMF (150°C, 6.5 h, Ar). PMR spectrum (δ, ppm): 4.29 (CH_2), 7.26 (Ph), 7.70 ($H^{5,6,7}$), 8.44 br. (H^3), 11.35 (NH). IR spectrum (ν, cm^{-1}): 1680 (C=O), 3415 (NH).

(XI) is not isomerized in similar conditions (150°C, 4 h, Ar); 0.3 g (60%) was recovered unaltered from 0.5 g of (XI). In the presence of CuCl (150°C, 7 h, Ar), (II) is par-

tially transformed into a mixture of (VI), (IX), and an unidentified compound; the reaction is accompanied by resinification.

7-Chloro-2-methyl-4-benzylpyrazolo[3,4-d]pyridazine (XIII). Here 0.55 g of (V) in 4 ml of $POCl_3$ was boiled for 1 h, poured into 100 ml of ice water, extracted with $CHCl_3$, the chloroform solution was dried with $MgSO_4$ and the solvent was distilled off. After recrystallization from EtOH, 0.35 g (59.3%) of (XIII), mp 117.5-118°C, was obtained. Found: C 60.10, H 4.26, Cl 13.66%. $C_{13}H_{11}ClN_4$. Calculated: C 60.35, H 4.29, Cl 13.70%. PMR spectrum (δ, ppm): 4.37 (Me), 4.52 (CH_2), 7.2-7.3 m (Ph), 7.78 (H^3).

Similarly, 0.5 g (46.3%) of (XV), mp 150°C (compare [8]), was obtained from 1 g of (VI). PMR spectrum (δ, ppm): 4.65 (CH_2), 7.1-7.3 m (Ph), 7.8-7.9 m ($H^{6,7}$), 8.0-8.2 m ($H^{5,8}$).

(V) and (VI) are not isomerized when heated in conc. HCl for 5-25 h at 100°C and in toluene and tetralin in the presence of $NH_2NH_2 \cdot H_2O$ for 3-12 h at 110-200°C.

7,8-Dihydro-1-methyl-5-phenyl-4H-pyrazolo[3,4-d]-6,7-diazepin-8-one (III). Here 3 g of (XIV) [10] and 1 ml of $NH_2NH_2 \cdot H_2O$ in 10 ml of PrOH were boiled for 4 h and evaporated dry in a vacuum, and the residue was recrystallized twice from CCl_4. Yield of (III) of 1.9 g (59.6%), bp 173.5-174.5°C. Found: C 64.74, H 5.04, N 23.48%. $C_{13}H_{12}N_4O$. calculated: C 64.99, H 5.03, N 23.32%. PMR spectrum (δ, ppm): 3.87 (CH_2), 4.17 (Me), 7.4-7.8 m (Ph, H^3), 9.07 (NH). IR spectrum (ν, cm^{-1}): 1665 (C=O), 3380 (NH).

Then 0.5 g of (III) was boiled in 10 ml of 20% HCl for 2.5 h, extracted with $CHCl_3$, the chloroform solution was dried with Na_2SO_4 and evaporated dry in a vacuum, and the residue was crystallized from EtOH. Yield of (XI) of 0.3 g (60%), mp 129.5-130.5°C.

CONCLUSIONS

1. The hydrazides of vicinal phenylethynyl derivatives of N-methylpyrazole-5-carboxylic and benzoic acids are respectively cyclized into 6,7-dihydro-6-amino-1-methyl-5-phenylpyrido[3,4-c]pyrazol-7-one and 2-amino-3-benzylideneisoindolin-1-one under the effect of bases.

2. The hydrazide of 4-phenylethynyl-1-methylpyrazole-5-carboxylic acid and the cyclic isomer of tolan-2-carboxylic acid hydrazide, 2-amino-3-benzylideneisoindolin-1-one, are isomerized in the presence of CuCl with closure of the six-membered pyridazine ring.

3. 6,7-Dihydro-6-amino-1-methyl-5-phenylpyrido[3,4-c]pyrazol-7-one and 2-amino-3-benzylideneisoindolin-1-one are deaminated in oxidation with air in the presence of CuCl.

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