CYCLIZATION OF VICINAL ACETYLENIC DERIVATIVES OF PYRAZOLECARBONAMIDES AND BENZAMIDES

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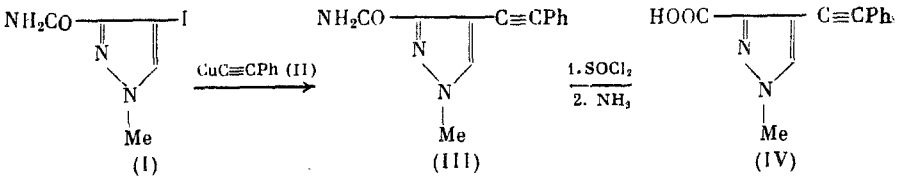
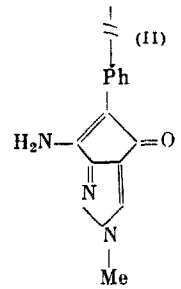
Vicinal acetylenic derivatives of pyrazolecarbonamides and benzamides cyclize in alcoholic solution in the presence of KOH with closure of the six- or five-membered lactam ring. The formation of a γ-lactam (from o-phenylethynylbenzamide) has been noted for the first time. Condensation of vicinal iodopyrazolecarbonamides with copper phenylacetylide gives the pyrazolylacetylenes without concurrent intramolecular cyclization of the product to give the cyclopentadienone ring. We have been unable to repeat the reported similar cyclocondensation of o-iodobenzamide to 3-amino-2-phenylindenone.

The cyclocondensation of o-iodobenzamide with copper phenylacetylide has been reported [1] to afford high yields of 3-amino-2-phenylindenone. The use of pyrazoles in this reaction could provide a route to difficulty accessible bicyclic compounds containing condensed five-membered nonaromatic and pyrazole rings, and furthermore could provide further information on the reasons for the differing courses of the heterocyclization of acetylenylbenzoic and pyrazolecarboxylic acids and their derivatives [2-6].

We have, however, found that on heating with the acetylide (II) in pyridine at 115°C for 9 h, 4-iodo-1-methylpyrazole-3-carboxylic acid (I) affords only the disubstituted acetylene (III) (71%). Its structure is proved conclusively by its analytical and spectral properties (Table 1), and is further confirmed by direct synthesis from the pyrazolecarboxylic acid (IV) [4].

Since the ability of vicinal functionally substituted pyrazolylacetylenes to undergo cyclization is sometimes affected by the positions in the ring of the functional and acetylenic groups [7], attempts were made to carry out the cyclocondensation of (II) with 3-iodo-





1,5-dimethylpyrazole-4-carbonamide (V), in which the amide group and the iodine atom have the opposite positions to those in the pyrazole (I). The reaction was carried out under the

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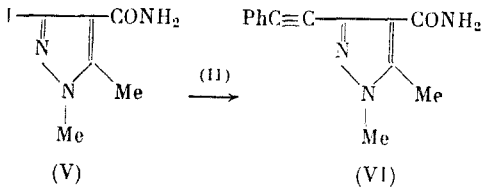
TABLE 1. Synthesis and Cyclization of Acetylenic Carbonamides

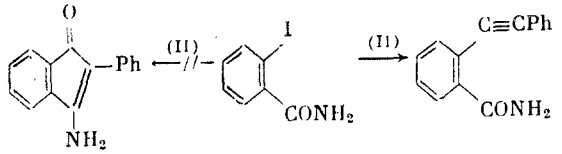
Compound	Reaction time, h	Yield, %	mp, °C (solvent)	Empirical formula	Found/Calculated, %			PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}		
					C	H	N		C=O	C≡C	NH_2 (NH)
(III)	9	70,6	164–165 (CH_2ClCH_2Cl)	$C_{13}H_{11}N_3O$	69,34 / 69,32	5,11 / 4,92	18,66 / 18,65	3,91 (NCH_3), 6,93 and 6,38 br. (NH_2), 7,3–7,5 m (Ph), 7,58 (5-H)	1695	2240	3415, 3520
(VI)	6	62,0	148,5–149,5 (C_6H_6)	$C_{14}H_{13}N_3O$	70,17 / 70,28	5,38 / 5,48	17,51 / 17,56	2.54 (5-CH_3), 3.73 (NCH_3), 6.16 and 7.00 br. (NH_2), 7,1–7,6 m (Ph)	1660	2230	3405, 3520
(XII)	13	75,1	158–159 (AcOEt)	$C_{15}H_{15}N_3O_2$	66,97 / 66,90	5,52 / 5,61	15,48 / 15,60	2,27 (3-CH_3), 4,12 (NCH_3), 5,01 (CH_2), 5,48 and 6,78 br. (NH_2), 7,0–7,4 m (arom. H)	1665	2250	3410, 3520
(VII)	0,5	73,2	155–156 [8]	$C_{15}H_{11}NO$	–	–	–	6,38 br. (NH_2), 7,4–8,0 m (arom. H)	1675	2230	3415, 3520
(XI)	107	75,0	312–313 (EtOH)	$C_{13}H_{11}N_3O$	69,17 / 69,32	5,06 / 4,92	18,61 / 18,65	3.94 (NCH_3), 6,61 (4-H), 7,1–7,6 m (Ph, 3-H), 8,58 br. (NH)	1680		(3410)
(X)	42	70,0	227–228 (EtOH)	$C_{14}H_{13}N_3O$	69,84 / 70,28	5,42 / 5,48	17,57 / 17,56	2,65 (3-CH_3), 3,94 (NCH_3), 6,67 (7-H), 7,4–7,6 m (Ph), 8,58 br. (NH)	1665		(3420)
(XVII)	45	85,0	229–230 (EtOH – AcOEt)	$C_{15}H_{15}N_3O_2$	66,82 / 66,90	5,46 / 5,61	15,48 / 15,60	2.41 (3-CH_3), 4,16 (NCH_3), 4.92 (CH_2O), 6,59 (7-H), 7,0–7,3 m (Ph), 9,3 br. (NH)	1670		(3400)
(IX)	7	80,0	182–183 (EtOH) [5]	$C_{15}H_{11}NO$	–	–	–	6,54 (=CH), 7,3–7,9 m (arom. H), 8,58 (NH)	1710		(3455)



(V) (VI)

conditions used for the iodo-compound (I), and also under more severe conditions (DMF, 150°C). In both cases, the only reaction was replacement of the halogen to give the phenylethynylpyrazole (VIb) (62-67%). The structure of (VI) has been proved (Table 1).

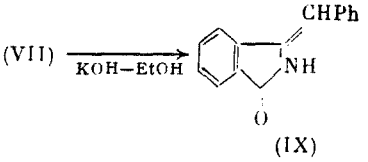
The impossibility of effecting the cyclocondensation of the iodopyrazolecarbonamides (I) and (VI) with the acetylide (II), together with literature reports of the preparation of tolane-2-carbonamide (VII) from o-iodobenzamide (VIII) under conditions similar to those reported in [1] for its cyclocondensation [8], prevented us from reproducing directly the reaction of the iodoamide (VIII) with (II). Despite the earlier report [1], and in agreement with [8], the product of the condensation was the acetylene (VII) (65%), and the formation of 3-amino-2-phenylindenone even in trace amounts was not observed.



(VIII) (VII)

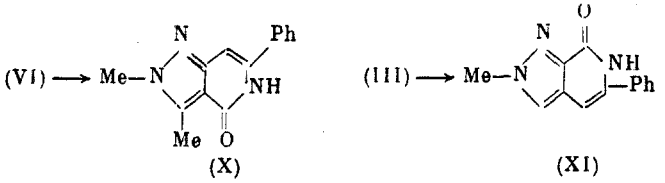
Practical methods for the preparation of bicyclic condensed systems from acetylenic aromatic carbonamides involve the intramolecular heterocyclization of these compounds. The closure of the six-membered lactam ring in similar amides (pyridines, pyrimidines, and isothiazoles) has been reported [9].

We have now found that o-phenylethynylbenzamide (VII) on heating for 7 h in ethanol in the presence of KOH undergoes cycloisomerization to the known isoindolinone (IX) [5] in 80% yield.



(IX)

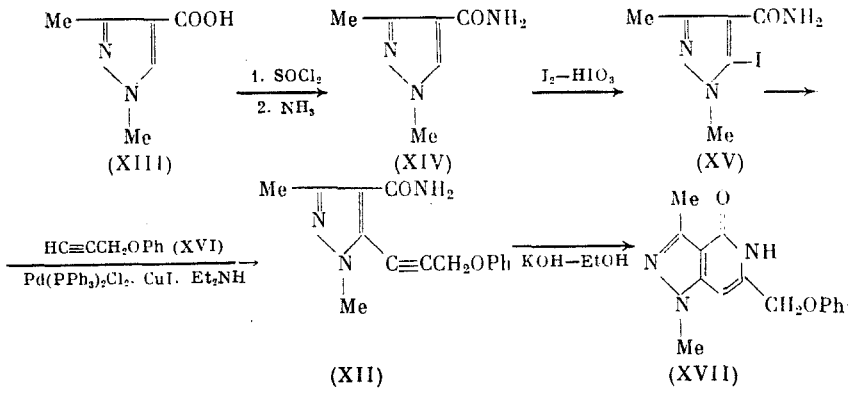
Intramolecular addition of the amide group to the triple bond in pyrazoles is more difficult, and results in closure of the δ-lactam rather than the γ-lactam ring. The reaction



(X) (XI)

time of the amide (VI) under the same conditions as for (VII) is extended to 42 h. The cyclization of (III), in which the acetylenic substituent is located in the least electron-acceptor position 4 of the heterocycle [10], is only complete after 107 h. The yields of the oxopyridopyrazoles (X) and (XI) were 70-75%.

Compounds (X) and (XI) are assigned the δ-lactam structure from the frequencies of the CO group absorption in their IR spectra. The increased strain in the five-membered ring as compared with the six-membered is known to increase the νCO values by 30-35 cm^{-1} [11, 12]. Accordingly, in authentic δ-lactams of this type νCO is normally in the range 1660-1680 cm^{-1}, whereas in γ-lactams it is at least 1695-1700 cm^{-1} [5, 6]. The νCO values in the IR spectra of the lactams (IX)-(XI) (Table 1) are in full agreement with the assigned structures. In addition, 1,3-dimethyl-5-(3-phenoxyprop-1-ynyl)pyrazole-4-carbonamide (XII) was prepared and subjected to heterocyclization. In this compound, a methylene group is present in the α-position to the triple bond, which enables the PMR spectrum to be used to establish unambiguously the size of the lactam ring formed on cyclization.



As expected, the product of the cyclization of (XII) is the oxopyridopyrazole (XVII) (85%). The presence in its PMR spectrum of single signals for the CH_2O- and endocyclic methine groups with δ 4.92 and 6.99 ppm (the spectrum of the alternative γ-lactam contains a doublet and a triplet respectively), in conjunction with the other spectral and analytical data (Table 1), provides conclusive proof of its structure.

EXPERIMENTAL

PMR spectra were obtained on a Varian XL-200 spectrometer in $CDCl_3$, and IR spectra on a UR-20 in $CHCl_3$.

1-Methyl-4-phenylethynylpyrazole-3-carbonamide (III). a) A mixture of 1.9 g of (I) and 1.1 g of (II) in 50 ml of pyridine was stirred at the boil under argon for 9 h (followed by TLC: Silufol–ether), diluted with 0.5 liter of ether, and the copper salts removed. The solution was filtered through a thin layer of anhydrous alumina, the solvent removed, and the residue recrystallized from dichloroethane to give 1.2 g of (III) (Table 1). The same method was used to obtain (VI) and (VII) (Table 1).

b) A mixture of 2.7 g of (IV) and 12 ml of $SOCl_2$ was boiled for 2 h, unreacted $SOCl_2$ distilled off, and the residue dissolved in a mixture of chloroform and dioxane. A small excess of liquid ammonia was added with care, and the mixture was kept for 12 h, filtered through anhydrous alumina, and (III) eluted with chloroform and ether to give 2.2 g of product which was recrystallized from dichloroethane to give 1.7 g (61.5%) of (III).

Similarly, from (XIII) [3] there was obtained 1,3-dimethylpyrazole-4-carbonamide (XIV), which on recrystallization from butanol was obtained in 10.1 g (72.1%) yield, mp 172-173°C (from acetone). Found: C 51.52; H 6.72; N 30.49%. $C_6H_9N_3O$. Calculated: C 51.79; H 6.52; N 30.20%. IR spectrum (ν, cm^{-1}): 1665 (C=O), 3428 and 3545 (NH_2). PMR spectrum (δ, ppm): 2.46 (3-CH_3), 3.83 (1-CH_3), 5.77 br (NH_2), 7.73 (5-H).

5-Iodo-1,3-dimethylpyrazole-4-carbonamide (XV). A mixture of 6.95 g of (XIV), 4.7 g of iodine, 1.5 g of HIO_3, 3 ml of CCl_4 and 6 ml of 30% sulfuric acid in 50 ml of acetic acid was heated for 6 h at 80°C, neutralized with sodium acetate, and the solvent removed to dryness under reduced pressure. The residue was treated with saturated potassium carbonate solution, decolorized by adding sodium sulfite, and the solid filtered off, washed with water, and dried. Recrystallization from ethanol gave 10.8 g (81.5%) of (XV), mp 204-205°C. Found: C 27.29; H 3.21; I 48.07%. $C_6H_8IN_3O$. Calculated: C 27.19; H 3.04; I 47.88%. IR spectrum (ν, cm^{-1}): 1670 (C=O), 3420 and 3530 (NH_2). PMR spectrum (δ, ppm): 2.47 (3-CH_3), 3.91 (1-CH_3), 5.70 br (NH_2).

1,3-Dimethyl-5-(3-phenoxyprop-1-ynyl)pyrazole-4-carbonamide (XII). A mixture of 3.8 g of (XV), 3.4 g of (XVI), 70 mg of $Pd(PPh_3)_2Cl_2$, and 35 mg of CuI in 40 ml of diethylamine was stirred under argon for 13 h at 50-55°C, diluted with 350 ml of ether, the salts which separated filtered off, and the solvent removed. The residue was dissolved in benzene, filtered through anhyd. alumina, and recrystallized from ethyl acetate to give 2.9 g of (XII) (Table 1).

2-Methyl-5-phenyl-2H-pyrazolo[3,4-c]pyridin-7(6H)-one (XI). A mixture of 0.6 g of (III) and 0.2 g of KOH in 20 ml of ethanol was boiled for 107 h, the solvent removed, and the residue dissolved in chloroform and filtered through a thin layer of anhyd. alumina. The product (XI) was eluted with chloroform and ether to give crude material (0.55 g), which was recrystallized from ethanol to give 0.45 g of product (Table 1).

Obtained similarly were (X), (XVII), and (IX) (Table 1).

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