CYCLIZATION OF ACETYLENYLPYRAZOLECARBOXYLIC ACIDS

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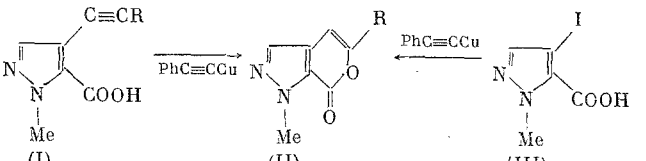
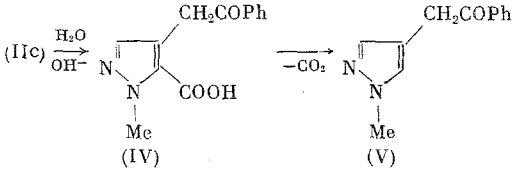
Iodo-N-methylpyrazolecarboxylic acids with the iodine and carboxyl groups on adjacent carbon atoms condense with substituted copper acetylenides in boiling pyridine to give pyranopyrazoles [1, 2]. In contrast, the analogous reaction of o-halobenzoic acids usually results in closure of the five-membered ring to give phthalides [3, 4]. It is assumed that the acetylenide condensation is a two-stage process in which the limiting stage is the formation of acetylenic derivatives of aromatic carboxylic acids [4]. However, the literature contains neither a strict proof of this assumption nor essential information on the behavior under the condensation conditions of the probable intermediates, acetylenyl-substituted acids.

This communication describes a study of the cyclization of acetylenic derivatives of pyrazolecarboxylic acids in pyridine at 110-115° in the presence of catalytic amounts of PhC ≡ CCu. 4-Acetylenyl-1-methylpyrazole-5-carboxylic acids (I), irrespective of the structure of the acetylenic substituent, react completely within 20 min to form the pyranopyrazoles (II) in 62-84% yield. Cyclocondensation of 4-iodo-1-methylpyrazole-5-carboxylic acid (III) with PhC ≡ CCu under analogous conditions is complete only after 1.5 h [yield of (IIc) 75%], and in the case of other iodopyrazolecarboxylic acids ≥ 1-5 h is required [1, 2]. Thus, cyclization of the acid (I), like the cyclocondensation of the acid (III) [1], affords a single product, the pyranopyrazole (II), but it is formed much faster in the first reaction



R = CH_2OMe (a), $CH_2N(CH_2CH_2)_2O$ (b), Ph (c), H (d).

The δ-lactone structure of (IIa and b) is confirmed by the presence in the PMR spectra of singlet signals for the protons of the CH = CR group (6.53 and 6.50 ppm) and the α-CH_2 substituent R (4.42 and 3.36 ppm). Replacement of the aliphatic substituent in the pyranopyrazoles by phenyl results in a shift in the signal of the ethylene proton to lower field by 0.3-1.0 ppm [1, 2]. Hence, the increase in the chemical shift of this proton in (IIc) by 0.5 ppm as compared with (IIa and b) appears to confirm the correctness of the assumed structure or (IIc). Final confirmation of the structure is obtained by hydrolysis of (IIc) to the acid (IV), followed by decarboxylation to the known ketone (V) [1].



The presence in (IId) of the unsubstituted pyran ring is confirmed by the considerable difference in the chemical shifts of the ethylene protons (0.62 ppm) and the value of their coupling constants (6 Hz). In the PMR spectrum of methylenephthalide (VI), a single signal at substantially higher field (δ 5.16 ppm) corresponds to the protons of the exomethylene group. It is noteworthy that the phthalide (VI) cannot be obtained directly by the acetylenide cyclocondensation of o-iodobenzoic acid as a result of the instability of CuC ≡ CH [5]. o-Ethynylbenzoic acid (VII), as we have found, cyclizes readily to (VI) in the presence of PhC ≡ CCu

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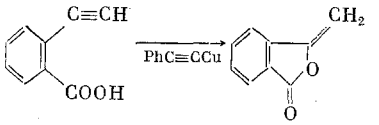
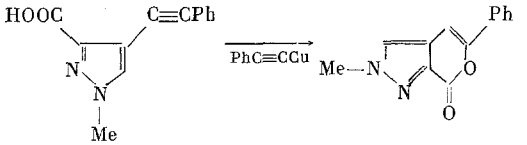
(80% yield). This shows that in the acetylenide cyclocondensation and the cyclization of acetylenic derivatives in the benzoic acid series, closure of the γ-lactone ring is the common course of the reaction



(VII) (VI)

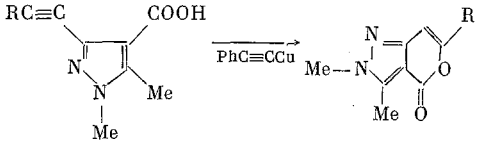
Cyclization of acetylenyl-N-methylpyrazole-3- and acetylenyl-N-methyl-4-carboxylic acids follows the same pattern as pyrazole-5-carboxylic acids.

4-Phenylethynyl-1-methylpyrazole-3-carboxylic acid (VIII), which is isomeric with (Ic), forms the δ-lactone, 7-oxo-2-methyl-5-phenylpyrano[3,4-c]pyrazole (IX), in 71% yield after 20 min. This compound is also obtained by the acetylenide condensation (3 h) of 4-iodo-1-methylpyrazole-3-carboxylic acid [1].



(VIII) (IX)

Similarly, 3-acetylenyl-1,5-dimethylpyrazole-4-carboxylic acids (X) isomerize over 0.5 h to 6-substituted 4-oxo-2,3-dimethylpyrano[4,3-c]pyrazoles (XIa-c) (yield > 80%), one of which (XIc) has been obtained previously by condensation of 3-iodo-1,5-dimethylpyrazole-4-carboxylic acid with PhC ≡ CCu for 3 h [2].



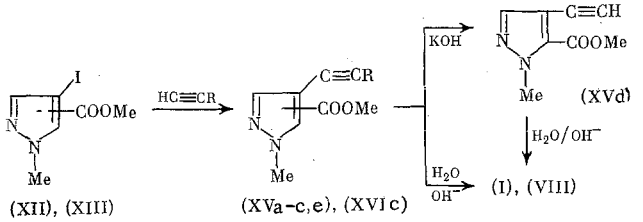
(X) (XI)

R = CH_2OMe (a), $CH_2N(CH_2CH_2)_2O$ (b), Ph (c)

The structures of the new compounds (XIa and b) were confirmed by their PMR spectra.

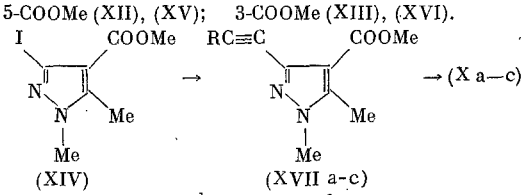
Acetylenyl-N-methylpyrazolecarboxylic acids also cyclize to pyranopyrazoles in aqueous EtOH in the presence of $AgNO_3$ at 20°C.

The acids (I), (VIII), and (X) were synthesized by acetylenide condensation of the methyl esters of the appropriate iodo acids (XII-XIV) by the method described in [6], followed by hydrolysis. To obtain (Id), the acetylenic alcohol (XVe) was cleaved by an inverse Favorski reaction [7] to (XVd), followed by hydrolysis.



(XII), (XIII) (XVa-c,e), (XVIc)

5-COOMe (XII), (XV); 3-COOMe (XIII), (XVI).



(XIV) (XVII a-c)

R = CH_2OMe (a), $CH_2N(CH_2CH_2)_2O$ (b), Ph (c), CPhMe(OH) (e).

EXPERIMENTAL

Methyl Acetylenylpyrazolecarboxylates (XV-XVII). A mixture of (XII) [8], (XIII) [8], or (XIV) [2] (0.01 mole), RC ≡ CH (0.0125 mole), CuI (20 mg), and $Pd(PPh_3)_2Cl_2$ (40 mg) in 50 ml of $NHEt_2$ was stirred at 50°C

TABLE 1. Synthesis of Methyl Acetylenylpyrazolecarboxylates

Ester	Time, h	Yield, %	mp, °C (hexane)	Molecular formula	Found / Calculated, %			IR spectrum ($CHCl_3$), ν, cm^{-1}		PMR spectrum*
					C	H	N	C≡C	C=O	
(XV a)	20	74,5	55–56	$C_{10}H_{12}N_2O_3$	57,70 / 57,68	5,88 / 5,81	13,59 / 13,45	2248 (CCl_4)	1722	3,33 (OCH_3), 4,20 (CH_2), 3,86, 4,10 (1-CH_3, $COOCH_3$), 7,34 (3-H)
(XV b)	26	55,2	83–85	$C_{13}H_{17}N_3O_3$	59,18 / 59,30	6,42 / 6,51	15,81 / 15,96	2242 (CCl_4)	1722	3,41 ($CH_2C\equiv$), 2,50 t (CH_2NCH_2), 3,59 t (CH_2OCH_2), 3,86, 4,08 (1-CH_3, $COOCH_3$), 7,40 (3-H)
(XV c)	5,5	75.0	116–117 (EtOH)	$C_{14}H_{12}N_2O_2$	69,78 / 69,99	5,00 / 5,03	11,71 / 11,66	2238	1722	3,91, 4,11 (1-CH_3, $COOCH_3$), 7,61 (3-H), 7,2–2,7, 4 m (Ph)
(XV e)	25	99,7	109,5–110,5 (C_6H_6 – petr. ether)	$C_{16}H_{16}N_2O_3$	67,53 / 67,59	5,68 / 5,67	9,70 / 9,85	2255	1740	3,83, 4,00 (1-CH_3, $COOCH_3$), 1,83 (CH_3CO), 7,45 (3-H), 7,3–7,6 m (Ph)
(XVI c)	5,5	80,8	154–155 (EtOH)	$C_{14}H_{12}N_2O_2$	69,82 / 69,99	5,05 / 5,03	11,81 / 11,66	2235	1725	–
(XVII a)	5	67,6	55–56	$C_{11}H_{14}N_2O_3$	59,20 / 59,45	6,34 / 6,35	12,54 / 12,60	2250	1710	2,48 (5-CH_3), 3,60 (OCH_3), 3,78, 3,83 (1-CH_3, $COOCH_3$), 4,34 (CH_2)
(XVII b)	13	54,2	88–89	$C_{14}H_{19}N_3O_3$	60,56 / 60,63	6,91 / 6,91	15,18 / 15,15	2250	1710	2,41 (5-CH_3), 2,55 t (CH_2NCH_2), 3,64 t (CH_2OCH_2), 3,46 ($CH_2C\equiv$), 3,67, 3,73 (1-CH_3, $COOCH_3$)
(XVII c)	6	65,0	93–94	$C_{15}H_{14}N_2O_2$	70,81 / 70,85	5,56 / 5,55	11,07 / 11,02	2235	1705	2,50 (5-CH_3), 3,78, 3,88 (1-CH_3, $COOCH_3$), 7,4–7,8 m (Ph)

* Solvents CCl_4 for (XVa and b) and $CDCl_3$ for the remaining compounds. All signals for which the multiplicity is not given are singlets.

TABLE 2. Acetylenylpyrazolecarboxylic Acids

Acid	Yield, %	mp, °C (solvent)	Molecular formula	Found / Calculated, %			PMR spectrum,* δ, ppm
				C	H	N	
(Ia)	83,3	149,5–150,5 (C_6H_6)	$C_9H_{10}N_2O_3$	55,54 / 55,67	5,18 / 5,19	14,56 / 14,49	3,59 (1-CH_3), 4,13 (OCH_3), 4,49 (CH_2), 7,89 (3-H)
(Ib)	89,4	142–143 (EtOH)	$C_{12}H_{15}N_3O_3$	57,94 / 57,82	6,04 / 6,07	18,89 / 18,86	4,16 (1-CH_3), 3,66 ($CH_2C\equiv$), 2,85 t (CH_2NCH_2), 3,95 t (CH_2OCH_2), 7,76 (3-H)
(Ic)	96,9	224–225 (EtOH)	$C_{13}H_{10}N_2O_2$	68,85 / 69,02	4,26 / 4,46	12,30 / 12,38	–
(Id)	29,0†	179–180 (decomp., EtOH)	$C_7H_6N_2O_2$	55,72 / 56,04	4,21 / 4,03	18,48 / 18,67	–
(VIII)	89,5	133,5–134,5 (C_6H_6)	$C_{13}H_{10}N_2O_2$	69,08 / 69,02	4,50 / 4,46	12,47 / 12,38	3,98 (1-CH_3), 7,60 (5-H), 7,2–7,5 m (Ph)
(Xa)	69,4	152–153 (C_6H_6)	$C_{10}H_{12}N_2O_3$	57,65 / 57,68	5,83 / 5,81	13,46 / 13,45	3,75 (1-CH_3), 3,42 (OCH_3), 4,33 (CH_2), 11,23 (COOH), 2,48 (5-CH_3)
(Xb)	97,0	165–166 (dioxane)	$C_{13}H_{17}N_3O_3$	59,08 / 59,30	6,75 / 6,51	15,78 / 15,96	3,75 (1-CH_3), 3,58 ($CH_2C\equiv$), 2,74 t (CH_2NCH_2), 3,74 t (CH_2OCH_2), 2,48 (5-CH_3)
(Xc)	98,8	196,5–197,5 (MeOH)	$C_{14}H_{12}N_2O_2$	69,74 / 69,99	5,09 / 5,03	11,70 / 11,66	3,60 (1-CH_3), 7,1–7,9 m (Ph), 2,46 (5-CH_3)

* Solvent $D_2O-K_2CO_3$ for (Ia and b), C_5D_5N for (Xc), and $CDCl_3$ for the remaining compounds. All signals for which the multiplicity is not given are singlets.

† Calculated on (XVe).

TABLE 3. Cyclization of Acetylenic Acids

Product	Yield, %	mp, °C (solvent)	Molecular formula	Found / Calculated, %			νC=O ($CHCl_3$), cm^{-1}	PMR spectrum* ($CDCl_3$), δ, ppm
				C	H	N		
(IIa)	70,8	110–111 (C_6H_6 – (petr. ether)	$C_9H_{10}N_2O_3$	55,46 / 55,67	5,14 / 5,19	14,40 / 14,43	1750 (CCl_4)	4,25 (1-CH_3), 7,63 (3-H), 6,53 (4-H), 3,40 (OCH_3), 4,42 (CH_2)
(IIb)	79,2	136,5–137,5 (C_6H_6 – (petr. ether)	$C_{12}H_{15}N_3O_3$	57,63 / 57,82	5,91 / 6,07	16,80 / 16,86	1750 (CCl_4)	4,26 (1-CH_3), 7,66 (3-H), 6,50 (4-H), 3,36 (5-α-CH_2), 2,50 (CH_2NCH_2), 3,70 t (CH_2OCH_2)
(IIc)	84,1	150,5–151,5 (EtOH)	$C_{13}H_{10}N_2O_2$	69,01 / 69,02	4,52 / 4,46	12,42 / 12,38	1740	4,35 (1-CH_3), 7,83 (3-H), 7,03 (4-H), 7,3–7,7 m(Ph)
(IId)	62,5	126–127 (C_6H_6 – (petr. ether)	$C_7H_6N_2O_2$	56,01 / 56,04	4,13 / 4,03	18,69 / 18,68	1745	4,23 (1-CH_3), 7,66 (3-H), 6,53 d (4-H), 7,15 d (5-H)
(IX)	70,8	174–175 (EtOH) [1]	$C_{13}H_{10}N_2O_2$	–	–	–	–	–
(XIa)	96,2	119–120 (hexane)	$C_{10}H_{12}N_2O_3$	57,65 / 57,68	5,83 / 5,81	13,46 / 13,45	1735	3,87 (2-CH_3), 2,58 (3-CH_3), 3,42 (OCH_3), 4,20 (CH_2), 6,52 (7-H)
(XIb)	80,0	153–154 (dioxane)	$C_{13}H_{17}N_3O_3$	59,35 / 59,30	6,65 / 6,51	15,36 / 15,96	1735	3,82 (2-CH_3), 2,56 (3-CH_3), 3,26 (6-α-CH_2), 2,50 t (CH_2NCH_2), 3,65 t (CH_2OCH_2), 6,40 (7-H)
(XIc)	~100	210–211 (EtOH) [2]	$C_{14}H_{12}N_2O_2$	–	–	–	–	–
(VI)	80,0	57–58 (petr. ether) [10]	$C_9H_6O_2$	–	–	–	–	5,16 (CH_2), 7,4–7,9 m (C_6H_4)

* All signals for which the multiplicity is not given are singlets.

in a stream of inert gas until all the iodo compound had disappeared from the reaction mixture, then diluted with 0.5 liter of ether, filtered, and the solvent removed. The product was purified by chromatography on silica gel, and recrystallized. The reaction times, yields, and constants of the compounds obtained are shown in Table 1.

Acetylenylpyrazolecarboxylic Acids (I), (VIII), and (X). Hydrolysis of (XVa-c), (XVIc), (XVIIa-c) were carried out with aqueous-methanolic NaOH at 20°, as described for iodopyrazolecarboxylate esters [2]. The yields and constants of the compounds obtained are shown in Table 2.

4-Ethynyl-1-methylpyrazole-5-carboxylic Acid (Id). A mixture of 8.5 g of (XVe) and 4.6 g of powdered KOH in 5 g of m-pentaphenyl ether was heated at 110-130° (1 mm). Distillation of the reaction product afforded a mixture of (XVd) and acetophenone, which was mixed without separation with 20 ml of 25% KOH, kept for 48 h at 20°, extracted with ether, and acidified with conc. HCl. The (Id) was filtered off, washed with ice water, and recrystallized from alcohol (cf. Table 2). Preparative TLC on silica gel separated the mixture of (XVd) and acetophenone (eluent $CHCl_3$) to give pure (XVd), mp 77-78° (from CCl_4). Found: C 58.44; H 5.06; N 16.87%. $C_8H_8N_2O_2$. Calculated: C 58.53; H 4.91; N 17.06%. PMR spectrum ($CDCl_3$, δ, ppm): 3.83, 4.02 (1-CH_3, $COOCH_3$), 3.13 (HC ≡ C), 7.50 (3-H). IR spectrum (CCl_4, ν, cm^{-1}): 3328, 2130 (HC ≡ C), 1730 (C=O).

Cyclization of Acetylenylpyrazolecarboxylic Acids (I), (VIII), and (X). A mixture of 0.01 mole of (Ia-d), (VIII), or (Xa-c) and 0.2 g of PhC ≡ CCu in 50 ml of pyridine was boiled in a nitrogen atmosphere until reaction was complete (followed by TLC), diluted with 0.5 liter of ether, the precipitate filtered off, the filtrate washed with aqueous NH_3 and dried over K_2CO_3. After removal of the solvent, the product was recrystallized. Yields and constants are given in Table 3.

The phthalide (VI) was obtained similarly from (VII) [9] (cf. Table 3).

Acetylenic Condensation of 4-Iodo-1-methylpyrazole-5-carboxylic Acid (III). Compound (III) was condensed with PhC ≡ CCu according to [2]. Reaction time 1.5 h. Yield of (IIc) 75.2%.

Hydrolysis of 7-Oxo-1-methyl-5-phenylpyrano[3,4-c]pyrazole (IIc). Compound (IIc) (1.1 g) was heated with 80 ml of 0.1 N KOH on a boiling water bath for 30 min, cooled, and acidified with conc. HCl. The keto-acid (IV) separated, and was filtered off, washed with water, and recrystallized from alcohol. Yield of (IIc) 1 g (82%), mp 189-190°. Found: C 63.96; H 4.97; N 11.58%. $C_{13}H_{12}N_2O_3$. Calculated: C 63.93; H 4.95; N 11.47%.

Decarboxylation of the Ketoacid (IV). Compound (IV) (0.20 g) was heated in a sublimation apparatus at 190-200° (14-15 mm), when the ketone (V) sublimed. Yield of (V) 0.15 g (91.5%), mp 92-93° (from benzene–petroleum ether) [1].

CONCLUSIONS

Acetylenyl-N-methylpyrazolecarboxylic acids containing an acetylenic substituent and a carboxyl group on adjacent carbon atoms cyclize in pyridine in the presence of copper phenylacetylenide to pyranopyrazoles. The same compounds are obtained by the acetylenide cyclocondensation of the appropriate iodopyrazolecarboxylic acids, but at a much lower rate.

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