# ACETYLENE DERIVATIVES OF HETEROCYCLES

## III. Synthesis of N-Alkylpyrazolylacetylenes from Methyl Pyrazolyl Ketones*

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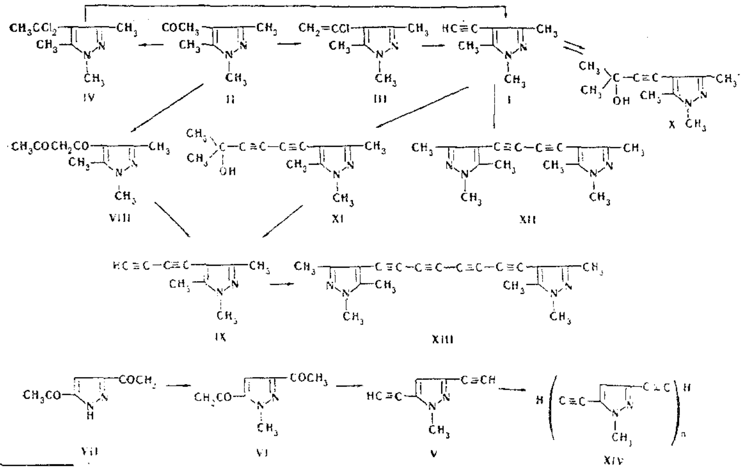
4-Ethynyl-1,3,5-trimethylpyrazole and 3,5-diethynyl-1-methylpyrazole have been synthesized by the reaction of the corresponding methyl N-methyl-pyrazolyl ketones with $PCl_5$ followed by dehydrochlorination. 4-Butadiynyl-1,3,5-trimethylpyrazole has been obtained similarly from 4-acetoacetyl-1,3,5-trimethylpyrazole. The N-substituted pyrazolylacetylenes have been subjected to the Chodkiewicz-Cadiot reaction and to dehydrocondensation. The IR spectra of the acetylene derivatives of pyrazole synthesized are discussed.

The synthesis of 3(5)-ethynylpyrazole by the condensation of diazomethane and diazopropyne with diacetylene and acetylene, respectively, has been described in the literature [2,3]. In the general case, to introduce an acetylenic substituent the principle of the direct formation of a pyrazolylacetylene system is hardly applicable. It would apparently be rational to use for this purpose the possibility of the conversion of other substituents and, in the first place, an acetyl group into an acetylene group. The prospects of the use of this method in the synthesis of heterocyclic acetylenic compounds are not completely clear. The few attempts to obtain such acetylenes from ketones sometimes encountered unexpected difficulties. Thus, the yields of all the possible isomers of ethynylpyridine and ethynylquinoline varied between 0.1 and 33% [4].

We have performed the synthesis of acetylenic derivatives of N-methyl-pyrazoles from the corresponding ketones. The preparation of ethynylpyrazoles unsubstituted on the nitrogen atom is complicated by the presence of a reactive hydrogen atom in them and will be considered separately. 4-Ethynyl-1,3,5-trimethylpyrazole (I) was synthesized from 4-acetyl-1,3,5-trimethylpyrazole (II). The ketone II was obtained by the acetylation of 1,3,5-trimethylpyrazole in the presence of aluminum chloride [5], the yield of II being substantially raised by increasing the amount of reactants and the time of the reaction. The treatment of II with a 15–20% excess of phosphorus pentachloride in boiling benzene gave, exclusively or almost exclusively, 4-(α-chlorovinyl)-1,3,5-trimethylpyrazole (III), which was then smoothly dehydrochlorinated with sodium amide in liquid ammonia to the pyrazolylacetylene I. The yield of I was more than 60% calculated on the ketone II. The use of a two-fold excess of phosphorus pentachloride led to the predominant formation of 4-(α,α-dichloroethyl)-1,3,5-trimethylpyrazole (IV), some of the vinyl chloride III (less than 10%), and, probably, products of chlorination in the methyl groups. On dehydrochlorination, the presence of the latter type of compounds caused resinification, and the ether-insoluble resin absorbed the bulk of the acetylene I, which it was possible to isolate by dissolving the resin in chloroform followed by chromatography on alumina.



It is easy to effect the conversion of acetyl groups in positions 3 and 5 of the pyrazole ring into acetylene groups by the method under consideration. This was demonstrated by the synthesis under similar conditions of 3,5-diethynyl-1-methylpyrazole (V) (yield 62%) from 3,5-diacetyl-1-methylpyrazole (VI). The ketone VI was obtained by the methylation of 3,5-diacetylpyrazole VII [6] with dimethyl sulfate at room temperature.

The successful synthesis of ethynyl- and diethynylpyrazoles from ketones gave grounds for assuming that the method of preparing arylbutadiynes from 1,3-diketones [7] could also be extended to butadiynylpyrazoles.

The methyl ketone II was condensed with ethyl acetate by Claisen's method in the presence of sodium

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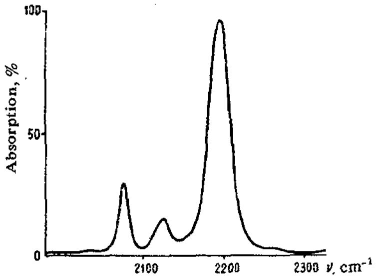
*For part II, see [1].

methoxide to form 4-acetoacetyl-1, 3, 5-trimethylpyrazole (VIII) which, by the general method, gave 4-butadiynyl-1, 3, 5-trimethyl-pyrazole (IX) with a yield of 36%. The diacetylene IX was also synthesized by extending the acetylenic chain of the pyrazole I [8]. It was previously shown that the acetylene I takes part in the Favorskii reaction with acetone, and the 3-methyl-1-(1', 3', 5'-trimethylpyrazol-4'-yl)but-1-yn-3-ol (X) formed, in contrast to analogous alcohols of the pyrazole series unsubstituted on the nitrogen atom [1], decomposes almost quantitatively into the starting materials when heated with a catalytic amount of caustic potash. The pyrazolylacetylene I was coupled with 1-bromo-3-methylbut-1-yn-3-ol by the Chodkiewicz-Cardiot reaction, giving 5-methyl-1-(1', 3', 5'-trimethylpyrazol-4'-yl)hexa-1, 3-diyn-5-ol (XI). On being carefully heated with caustic potash in an apparatus for vacuum sublimation, the alcohol XI decomposed into the diacetylene IX and acetone. The yield of IX was small and, because of its instability, varied considerably according to the conditions of performing the reaction.



IR spectrum of 1, 8-di(1', 3', 5'-trimethylpyrazol-4'-yl)octatetrayne (XIII).

All the N-methylpyrazolylacetylenes take part in the dehydrocondensation reaction in pyridine in the presence of cuprous chloride. The acetylenes I and IX dimerized in high yield to form 1, 4-di(1', 3', 5'-trimethylpyrazol-4'-yl)-butadiyne (XII) and 1, 8-di(1', 3', 5'-trimethylpyrazol-4'-yl)octatetrayne (XIII), respectively. Under these conditions the diethynylpyrazole V formed a polymeric product XIV, which is the heterocyclic analog of the poly(diethynylarene)s—polymers with a system of conjugated bonds [9].

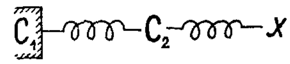
The individuality of the compounds synthesized was confirmed by gas-liquid and thin-layer chromatography. It was found that the various alkyl, alkenyl, alkynyl, acetyl, methoxycarbonyl, and other derivatives of the N-alkyl-pyrazoles can be analyzed by the GLC method using 2% of poly(ethylene glycol) adipate on Celite 545 as the stationary phase at a temperature of 50–175° C ("Pye" chromatograph).

The IR spectra of all the acetylenic pyrazole derivatives obtained showed the stretching vibrations of the C≡C bond in the 2100–2200 $cm^{-1}$ region. The corresponding frequencies (recorded on a UR-10 spectrophotometer) are given below:

| Compound | I | X | IX | XI |
|---|---|---|---|---|
| Frequency, $cm^{-1}$ | 2112 (s) | 2228 (m) | 2212 (v. s) | 2150 (w)<br>2232 (s) |

| Compound | XII | XIII | V |
|---|---|---|---|
| Frequency, $cm^{-1}$ | 2147 (s)<br>2215 (w) | 2078 (m)<br>2125 (w)<br>2195 (v. s) | 2122 (m) |

Recently, Popov and Lubuzh [10], on the basis of a mechanical model and a set of force constants determined by them, have carried out a calculation of the frequencies of polyacetylene groupings. Unfortunately, the calculation is fairly complex and in the literature the characteristics of the IR spectra of acetylenic compounds are, as a rule, given on the purely descriptive level without attempts at their interpretation. Furthermore, a simple qualitative method permitting the structure of such a compound to be connected to a first approximation with the number and position of the bands in its spectrum would apparently be useful. With this aim, we have attempted to interpret the main features of the spectra (in the region of the stretching vibrations of the ternary bonds) of the acetylenes synthesized in this work, basing ourselves on a consideration of a mechanical model and using the results of an analysis of the calculation, but not having recourse to the calculation itself.



A consideration of a diatomic model of an oscillator shows that an increase in the mass of x increases the rigidity of the fixing of the atom $C_{(2)}$ and, consequently, leads to a rise in the frequency of its characteristic vibrations. In actual fact, while in the spectrum of the ethynylpyrazole I the triple bond appears at 2112 $cm^{-1}$, in the spectrum of the carbinol X, as in other disubstituted acetylenes, its frequency is raised by approximately 100 $cm^{-1}$. We may note that the high intensity of the 2112 $cm^{-1}$ band in compound I is probably a consequence of an increased electron density in position 4 of the pyrazole ring [11] and of the consequent increase in the dipole moment of the triple bond conjugated with the nucleus.

The vibrations of the diacetylene grouping in the pyrazole IX are split into symmetrical and antisymmetrical vibrations and, in accordance with the linear model of two oscillators with a resilient link, the former must have a higher frequency because of the influence of the rigidity of the $C_{(2)}$—$C_{(3)}$ bond. It can be shown that the intensity of the line of the symmetrical vibrations in a series of monotypical acetylenic compounds is determined by the sum of the dipole moments of the acetylene groups that have the same direction and that of the line of the antisymmetrical vibrations by their difference. Consequently, in the spectrum of the diyne IX essentially only the symmetrical vibrations appear in the form of a very strong line at 2212 cm$^{-1}$. The appearance of both bands in the spectrum of the diacetylenic alcohol **XI** is explained by a change in the ratio of the sum and a difference of the dipole moments of the C≡C bonds. In compound XII, the dipoles of the C≡C bonds are equal and in opposite directions, which leads to a marked increase in the intensity of the antisymmetrical band (2147 cm$^{-1}$) in parallel with a decrease in the intensity of the symmetrical band (2215 cm$^{-1}$). The polyyne system in the tetraacetylene XIII can be represented by four linked oscillators the solution of the vibrational equations of which, as is well known, gives the following system of eigenvectors:

$$\begin{array}{cccc} + & + & + & + \\ + & - & + & - \\ + & + & - & - \\ + & - & - & + \\ \omega_1 & \omega_2 & \omega_3 & \omega_4 \end{array}$$

The values of the generalized force in these normal coordinates determine the order of arrangement of the vibrations with respect to frequencies, $\omega_2 < \omega_4 < \omega_3 < \omega_1$, which also obviously follows from the simplest mechanical model. The relative intensities of the absorption bands can be evaluated if a symmetrical distribution of the dipole moments over the bonds $-\overrightarrow{C{\equiv}C}-\overrightarrow{C{\equiv}C}-\overleftarrow{C{\equiv}C}-\overleftarrow{C{\equiv}C}-$ is assumed. Vibrations 1 and 4 should not appear in the spectrum, or only weakly, vibrations 3 should give the strongest line, and vibrations 2 a line of medium intensity (see figure).

Since the intensity of the line of the stretching vibrations of the bond is determined, according to the considerations given above, by the distribution of charges in the pyrazole ring, and the electron density in positions 3 and 5 is lower than in 4, the corresponding bands in 3'- and 5'-ethynylpyrazoles must be weaker than in 4-ethynylpyrazole. This is in fact confirmed by the spectra of 3, 5-diethynyl-1-methylpyrazole (V) and 3-ethynylpyrazole [1], though the reservation must be made that in the pyrazole I the electron density in the ring has an additional general increase because of the positive induction effect of the methyl groups.

## EXPERIMENTAL

**4-Acetyl-1,3,5-trimethylpyrazole (II)** [5] was obtained from 88.8 g (0.807 mole) of 1,3,5-trimethylpyrazole, 120 g (1.515 mole) of acetyl chloride, and 390 g (2.92 mole) of $AlCl_3$ in 600 ml of $CCl_4$ at −5 to 20° C with a reaction time of 24 hr; after distillation and recrystallization from petroleum ether (bp 70–100° C), yield 73.7 g (60%), mp 69–69.5° C, Bp 134–137° C (11 mm); IR spectrum: C=O 1655 cm$^{-1}$.

**Reaction of the ketone II with $PCl_5$.** A mixture of 19.5 g (0.128 mole) of the ketone II and 31.8 g (0.152 mole) of $PCl_5$ in 150 ml of absolute benzene was boiled for 6 hr and, after cooling, was poured into a mixture of conc aqueous KOH and ice and was then extracted with ether. Distillation yielded 17.7 g (81%) of the chloride III, bp 112–115° C (14 mm); $n_D^{20}$ 1.5240, which crystallized on prolonged standing in the cold. Found, %: Cl 20.86. Calculated for $C_8H_{11}ClN_2$, %: Cl 20.78. An increase in the amount of $PCl_5$ (0.31 mole) in the reaction yielded mainly the dichloride IV, bp 108–109° C (1.5 mm); $n_D^{20}$ 1.5380. Found, %: Cl 34.33. Calculated for $C_8H_{12}Cl_2N_2$, %: Cl 34.24. The vinyl chloride III and products with a higher chlorine content were formed simultaneously.

**4-Ethynyl-1,3,5-trimethylpyrazole (I).** To the sodium amide prepared from 23 g (1 g-at) of sodium in 1.7 *l* of liquid ammonia was gradually added 19.7 g (0.116 mole) of the vinyl chloride III in 250 ml of ether (an ethereal benzene solution of the distilled chlorides obtained in the preceding stage was usually used), and the mixture was stirred for 3 hr and treated with 300 ml of ether, after which the ammonia was driven off. The excess of sodium amide was decomposed with water, the ethereal solution was dried with calcium chloride, and the solvent was distilled off in vacuum. The pyrazolylacetylene I (13 g, mp 74–76° C) was sublimed at 55° C (2 mm), yield 11.6 g (74.7%), mp 78° C (from petroleum ether). IR spectrum, cm$^{-1}$: C≡C 2112, C≡C–H 3315. PMR spectrum ($CCl_4$; JNM-4H-100 spectrometer; ppm, $\delta_{TMS} = 0$): 3.58 (1-$CH_3$), 3.04 (4-HC≡C), 2.20 and 2.15 (3- and 5-$CH_3$). Found, %: N 20.83. Calculated for $C_8H_{10}N_2$, %: N 20.88.

**3,5-Diacetyl-1-methylpyrazole (VI).** To 14.8 g (0.097 mole) of 3,5-diacetylpyrazole (VIII) obtained with a yield of 44.9% by the condensation of β-chlorovinyl methyl ketone and diazoacetone [6] in 30 ml of 40% NaOH solution was added 14 ml (0.148 mole) of dimethyl sulfate at such a rate that the temperature did not exceed 25–30° C, and the mixture was stirred for 3 hr, decomposed with water, and extracted with chloroform. After recrystallization from petroleum ether (bp 70–100° C) 9.8 g (60.6%) of the diketone VI was obtained with mp 100–100.2° C. IR spectrum, cm$^{-1}$: C=O 1690. Found, %: N 16.94. Calculated for $C_9H_{10}N_2O_2$, %: N 16.87.

**3,5-Diethynyl-2-methylpyrazole (V).** To a suspension of 10 g of $PCl_5$ in 80 ml of absolute benzene was added 8.4 g (0.05 mole) of the diketone VI, the mixture was heated to 30° C, and, as the reactants dissolved, another 50 g of $PCl_5$ (making a total of 0.121 mole) was added in two portions. The reaction mixture was stirred at 30° C for 3 hr and was then poured into a mixture of ether, saturated sodium bicarbonate solution, and ice. The ethereal benzene solution of the chlorides was dried with calcium chloride and added over 30 min to sodium amide (from 14.5 g of sodium) in 1 *l* of liquid ammonia; the mixture was stirred for 2.5–3 hr, the ammonia was driven off, a small amount of water was added, and the diacetylene V was extracted with chloroform. Compound V was purified by vacuum distillation at 40° C (1 mm). Yield 4 g (62%), mp 41–41.5° C (from petroleum ether). IR spectrum, cm$^{-1}$: C≡C 2122, C≡C–H 3313. PMR spectrum ($CCl_4$), ppm: 3.92 (1-$CH_3$), 2.95 (3-HC≡C), (5-HC≡C), 6.53 (4-H). Found, %: N 21.44. Calculated for $C_8H_6N_2$, %: N 21.53.

**4-Acetoacetyl-1,3,5-trimethylpyrazole (VIII).** To 10 g (0.453 mole) of sodium wire in 200 ml of benzene was added 17 ml of absolute methanol and, after 2 hours' stirring, 38 g (0.15 mole) of the ketone II in 64.5 ml (0.66 mole) of ethyl acetate. The reaction mixture was heated at 40° C for 2 hr and at 50–60° C for 12 hr and was then acidified with acetic acid, filtered, and distilled in vacuum. The yield of the diketone VIII was 22.5 g (46.5%), mp 45.5–46.5° C (from petroleum ether) bp 110–114° C (2 mm). IR spectrum, cm$^{-1}$: C=O group in enolized β-diketones at 1600. Found, %: N 14.73. Calculated for $C_{10}H_{14}N_2O_2$, %: N 14.43. At the same time, 10–13 g of the ketone II was recovered.

**4-Butadiynyl-1,3,5-trimethylpyrazole (IX).** Over 30 min at 5–10° C, a solution of 9.7 g (0.05 mole) of the pyrazole VIII in 150 ml of benzene was added to 23 g (0.11 mole) of $PCl_5$ in 50 ml of benzene, and the mixture was stirred at 20° C for 2 hr, after which the temperature was raised to 60° C over 2 hr and it was stirred at this temperature for 4 hr. The subsequent procedure, including dehydrochlorination, was the same as in the synthesis of the diethynyl-pyrazole V. The diacetylene IX was extracted with ether, and the solution was concentrated and filtered through a layer of $Al_2O_3$ of activity V. Yield 2.9 g (36.8%), mp 109–110° C (the analytical sample was sublimed in vacuum). IR spectrum, cm$^{-1}$: C≡C 2212, C≡C–H 3310. PMR spectrum ($CCl_4$), ppm: 3.51 (1-$CH_3$), 2.06 and 2.16 (3- and 5-$CH_3$), 2.26 (C≡C–C≡CH). Found, %: N 18.2. Calculated for $C_{10}H_{10}N_2$, %: N 17.72.

**Reaction of the pyrazolylacetylene I with acetone.** A solution of 8 g (0.06 mole) of the acetylene I in 80 ml of ether, and then 8 ml (0.103 mole) of acetone in 12 ml of ether were added to 14.8 g (0.264

mole) of KOH in 100 ml of absolute ether at 0° C, and the mixture was stirred at 0–2° C for 3.5 hr and at 20° C for 10 hr. Decomposition with water and neutralization with $CO_2$ yielded about 2 g of the pyrazole I and 8 g (69.8%) of the alcohol **X**, mp 93.5° C (from petroleum ether), bp 118–119° C (3 mm). IR spectrum, $cm^{-1}$: C≡C 2228, OH 3600. Found, %: N 14.78. Calculated for $C_{11}H_{16}N_2O$, %: N 14.58.

When 4.1 g of the alcohol **X** was distilled with 0.09 g of KOH in vacuum (3.5 mm), 2.6 g (90.8%) of the acetylene **I** was obtained.

**Reaction of the acetylene I with 1-bromo-3-methylbut-1-yn-3-ol.** Over 2 hr, 19.8 g (0.135 mole) of 1-bromo-3-methylbut-1-yn-3-ol was added to a mixture of 14 g (0.105 mole) of the pyrazolyacetylene **I**, 20 ml of ethylamine, 1.2 g of hydroxylamine hydrochloride and 0.3 g of cuprous chloride in 80 ml of methanol at 40° C in an atmosphere of nitrogen, and the mixture was stirred for 3 hr at the same temperature, diluted with water, and extracted with ether. In a vacuum sublimation apparatus (50° C, 3 mm), the reaction product yielded 2.5 g of the acetylene I. The residue consisted of the diacetylenic alcohol XI, yield 17 g (75%), mp 134.5° C (from petroleum ether). IR spectrum, $cm^{-1}$: C≡C 2150 and 2232, OH 3595. Found, %: N 13.16. Calculated for $C_{13}H_{16}N_2O$, %: N 12.95.

**Decomposition of the diacetylenic alcohol XI.** A finely-ground mixture of 0.3 g (0.0014 mole) of the alcohol **XI** and ~0.05 g of KOH was heated in a vacuum sublimation apparatus at 80–90° C (2.5 mm); this gave about 0.1 g (45.5%) of the pyrazolyldiacetylene IX.

**Oxidative condensation.** A mixture of 1.34 g (0.01 mole) of the acetylene **I**, 0.25 g of cuprous chloride, 55 ml of pyridine, and 8 ml of methanol was shaken in an atmosphere of oxygen until the absorption of the latter ceased and was then poured into ~0.5 *l* of water and the precipitate was filtered off and washed with aqueous ammonia and water until it was free from $Cu^{2+}$ and $Cl^-$ ions. The dimer **XII** was purified by chromatography on $Al_2O_3$ (activity V) in chloroform; yield 1.2 g (90.8%), mp 107.5–108° C (from petroleum ether–benzene). IR spectrum, $cm^{-1}$: C≡C 2147 and 2215. Found, %: N 21.03. Calculated for $C_{16}H_{18}N_4$, %: N 21.05.

The pyrazolyldiacetylene **IX** was oxidized similarly, giving an 84% yield of the tetrayne **XIII**, mp 179–179.5° C (from petroleum ether). IR spectrum, $cm^{-1}$: C≡C 2078, 2125, and 2195. Found, %: N 17.58. Calculated for $C_{20}H_{18}N_4$, %: N 17.82.

In the same way, the diethynylpyrazole V gave 88% of the oligomer **XIV**, a yellowish brown substance not melting below 330° C, insoluble in organic solvents, and exploding on contact with a heated wire. IR spectrum, $cm^{-1}$: C≡C 2162 and 2223, C≡C—H 3315. Found, %: N 20.44.

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