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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XVI.[1] SYNTHESES OF ACETYLENIC CARBINOLS AND KETONES OF THIOPHENE

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By taking advantage of the solubility and reactivity of alkali-metal acetylides in liquid ammonia a widely applicable method has been developed for the preparation of acetylenic carbinols as well as glycols (1). The synthetic application of acetylenic carbinols as intermediates has been therefore very broad (1–3).

However, the syntheses of analogous heterocyclic compounds has received little attention. Continuing our studies on the chemistry of heterocyclic compounds the syntheses of acetylenic carbinols, ketones, and their addition as well as condensation products has been carried out.

The thiophene aldehydes used and β-2-thienylacrolein were prepared according to earlier methods (4, 5). The sodium acetylide in liquid ammonia was prepared according to two methods (6a, b). The loss of liquid ammonia by evaporation was diminished and a better control of sub-zero temperatures was obtained by using a Dry Ice-acetone bath. The reaction mixtures were hydrolyzed either with dilute sulfuric acid or ammonium chloride. The yields of the carbinols were slightly greater with the latter.

The yields of the carbinols (IIIa, b) were from 50–60%. Only with lower temperatures ($-50°$) and employing a higher dilution of β-2-thienylacrolein, were the yields of 1-(2-thienyl)-1-pentene-4-yn-3-ol (IIIc) as high as 30%. The yield of the analogous styrylethynylcarbinol was reported as 2% (7). The 2-thienylethynylcarbinol and 3-methyl-2-thienylethynylcarbinol are stable yellowish viscous oils which give rise to the characteristic silver and copper acetylene salts.

The major application of acetylenic carbinols, prepared by condensations with α,β-unsaturated carbonyl compounds, has arisen from the anionotropic rearrangement which has been extensively investigated (1):

$$\text{RCH}{=}\text{CHCH(OH)C}{\equiv}\text{CH} \xrightarrow{\text{H}^+} \text{RCH(OH)CH}{=}\text{CHC}{\equiv}\text{CH},$$
$$\text{where R} = \text{an alkyl group.}$$

In preparing the 1-(2-thienyl)-1-penten-4-yn-3-ol (IIIc) it was intended to study the anionotropic rearrangement in the thiophene series. However, the carbinol (IIIc) polymerizes very easily. Attempts to recrystallize it from ether-petroleum ether gave only a yellowish powder melting at 145°, the analysis of which corresponded to compound (IIIc). This powder, however, did not give the characteristic silver and copper acetylide tests. The infrared absorption

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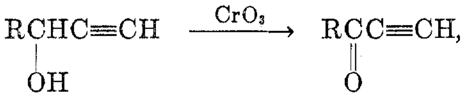
spectrum did not show absorption bands at 3.05 mμ and 13.71 mμ which are characteristic for the acetylenic group linked with a hydrogen atom. The molecular weight (300) determined by the Rast method indicated that the substance was a dimer. The carbinol (IIIc), however, distilled under reduced pressure at 125°/7 mm. and solidified on cooling. Recrystallization from petroleum ether in a nitrogen atmosphere gave crystals, m.p. 38°. This substance gave the silver acetylide test and the infrared absorption spectrum indicated the presence of the acetylenic group linked with a hydrogen atom. (Strong absorption bands at 3.05 mμ and 13.71 mμ). Its elemental analysis corresponded to the compound (IIIc). The anionotropic rearrangement studies on this compound in ethereal solution with dilute sulfuric acid could not be accomplished successfully due to polymerization and the difficulty entailed in the isolation of the monomeric substance. It has been shown (1) that the analogous styrylethynylcarbinol is unaffected by shaking its ethereal solution with 10% sulfuric acid.

The secondary acetylenylcarbinols are readily oxidized to the acetylenic ketones with chromic acid in acetone (8):



$$\mathrm{R\underset{\underset{\displaystyle OH}{|}}{C}HC{\equiv}CH} \xrightarrow{\mathrm{CrO_3}} \mathrm{R\underset{\underset{\displaystyle O}{\|}}{C}C{\equiv}CH},$$

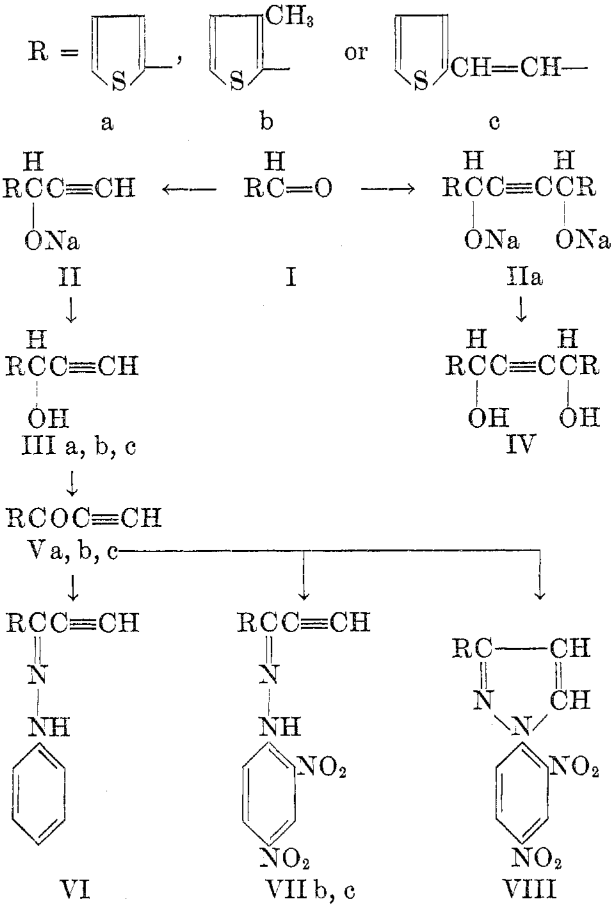
In the present study the acetylenic carbinols (IIIa, b, c) were oxidized to the corresponding acetylenic ketones (Va, b, c) by this method. It has been observed that the concentrations of the reagents and the reaction temperature have a great influence on the reaction. The yields of the 2-thienyl ethynyl ketone (Va) and 3-methyl-2-thienyl ethynyl ketone (Vb) were 70–80% while the ketone (Vc) was formed in 20% yield. The 2-thienyl ethynyl ketone crystallized in long needles and possessed strong lacrymatory properties. The 3-methyl-2-thienyl ethynyl ketone (Vb) is a viscous slightly yellowish oil, which on standing rapidly turns reddish-brown. This ketone and the ketone (Vc) are only slightly lacrymatory. The high reactivity of the hydrogen atom is evidenced by the ready formation of copper and silver acetylides and from the fact that these compounds attack metallic copper. The phenylhydrazone (VI) as well as the 2,4-dinitrophenylhydrazone (VIIb) were obtained in the usual manner. The ketone (Vc) gave the products (VIIc) and (VIII). The compound (VIIc) appears to be the normal 2,4-dinitrophenylhydrazone of 1-(2-thienyl)-1-penten-4-yn-3-one (Vc) which possesses a free acetylenic group. Its melting point is higher than that of the compound (VIII). Attempts to isolate the ketone (Vc) as a pure substance were unsuccessful. Distillation under reduced pressure in a nitrogen atmosphere and repeated recrystallization gave only a polymeric product.

The various reactions are depicted in CHART I.

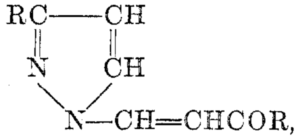
The addition of amines to the acetylenic ketones was studied also. Earlier workers (9) have shown that acetylenic ketones react with amines and that the addition of the amino group occurs in the β-position to the carbonyl group, giving amino ethylenic ketones. With 2-thienyl acetylenic ketones the aniline adduct (IXa) was obtained in good yield at room temperatures. There was no obvious evidence for the existence of an isomeric form as observed with the analogous phenyl ethynyl ketone.

With reagents such as ammonium carbonate, guanidine nitrate, hydrazine sulfate, and other amines, the acetylenic ketones react similarly to hydroxymethylene derivatives to give the expected heterocyclic compounds (10). In this paper we report on the condensation products with 2-thienyl ethynyl ketone (Va) and 3-methyl-2-thienyl ethynyl ketone (Vb). With ammonium carbonate the expected pyridines (XIa, b) were obtained in good yields; with guanidine nitrate and sodium carbonate pyrimidines (Xa, b) were formed. The slightly basic conditions must be maintained carefully during the condensation. However, the condensation of the ketones with hydrazine sulfate did not give the expected 3-(2-thienyl)- and 3-(3-methyl-2-thienyl)-pyrazoles. These products

CHART I



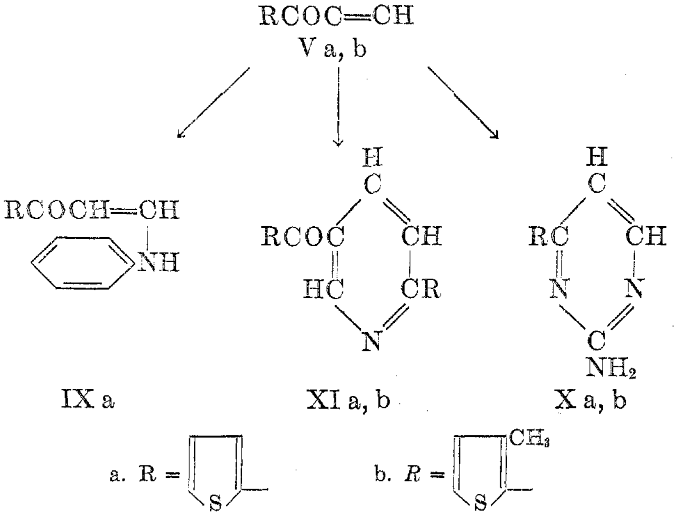
melted higher than the analogous phenyl derivatives and gave analytical values lower than those calculated. The structure of these compounds could not be established with certainty. It is believed, however, that the probable structure, which corresponds to the analytical data would be:



, where R is a 2-thienyl or 3-methyl-2-thienyl radical.

The ketone (Vc) when condensed with ammonium carbonate or guanidine nitrate, and sodium carbonate gave polymeric substances which could not be identified. It seems that the ketone, even under slightly basic conditions, polymerizes before condensing.

CHART II



The addition, as well as condensation reactions are summarized in CHART II.

EXPERIMENTAL[2]

2-Thienylethynylcarbinol (IIIa). To the prepared sodium acetylide (from 0.5 gram-atom of metallic sodium) in 600 ml. of liquid ammonia there was added dropwise freshly distilled (0.5 mole) thiophene-2-aldehyde (4) dissolved in absolute ether with stirring. The time required for the addition of 0.5 mole of the dissolved aldehyde was 1½ hours. The reaction mixture was then stirred for a further 3 hours while dry acetylene gas was bubbled through. The liquid ammonia was allowed to evaporate overnight and the free carbinol was obtained by using either dilute sulfuric acid or ammonium chloride. Both methods gave the same end product, a red brown oil which was extracted with ether, washed twice with ice-cold water, and dried over sodium sulfate. The solvent was allowed to evaporate on the water-bath and the oil distilled under diminished pressure. It boiled at 103–104°/15 mm.; n_D^{20} 1.5700. It is a viscous, slightly yellowish oil. There was obtained 35 g. (0.4 mole) of the primary product, 51%. The yield was slightly higher (56%) when ammonium chloride was

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[2] The analyses were carried out by A. A. Sirotenko of this department.

used for carrying out the hydrolysis. In spite of the fact that dry acetylene gas was bubbled in throughout the reaction, some glycol (IV) was obtained.

Anal. Calc'd for C_7H_6OS: C, 60.85; H, 4.38.

Found: C, 61.20; H, 4.13.

3-Methyl-2-thienylethynylcarbinol (IIIb). This preparation is analogous to that given for 2-thienylethynylcarbinol. From 0.312 mole of 3-methylthiophene-2-aldehyde there was obtained 30 g. (0.2 mole) of a viscous, slightly yellowish oil, b.p. 114°/3 mm.; n_D^{20} 1.5650, yield 59%.

Anal. Calc'd for C_8H_8OS: C, 63.12; H, 5.28.

Found: C, 63.17; H, 5.18.

1,4-Di-(2-thienyl)but-2-yn-1,4-diol (IV). During the decomposition of the carbinol mixture with ammonium chloride as well as from the distillation residues of IIIa, above, there was obtained *ca.* 5 g. of a crystalline substance which after recrystallization from dilute ethanol gave colorless needles melting at 116°.

Anal. Calc'd for $C_{12}H_{10}O_2S_2$: C, 57.5; H, 4.02.

Found: C, 57.16; H, 3.56.

1-(Thienyl)-1-penten-4-yn-3-ol (IIIc). Metallic sodium (0.14 gram-atom) was dissolved in 500 ml. of liquid ammonia and the sodium acetylide prepared without adding hydrated iron nitrate as catalyst. The bath temperature was cooled to *minus* 45–50° and β-2-thienylacrolein (0.138 mole), dissolved in 1 mole of absolute ether, was added dropwise. The addition required 1 hour. The reaction mixture was stirred for 3 additional hours and 0.19 mole of ammonium chloride was added. The liquid ammonia was allowed to evaporate overnight. There was obtained 4.5 g. of a brown, amorphous powder which was insoluble in ether. The residue was soluble in ether. The ethereal extract was washed with ice-cold water and dried over sodium sulfate. There was obtained 7 g. (0.042 mole) of a yellowish oil, b.p. 125°/7 mm.; m.p. 38° which solidified on cooling. Yield 31%. Upon redistillation it analyzed as follows:

Anal. Calc'd for C_9H_8OS: C, 65.90; H, 4.92.

Found: C, 65.70; H, 5.02.

This substance gave a positive acetylene test with ammoniacal silver nitrate and the infrared absorption spectrum showed a free acetylenic group. (Strong absorption bands at 3.05 mμ and 13.71 mμ). In trying to isolate directly the carbinol by recrystallization from ethereal solution there was obtained a yellowish-grey substance which, after recrystallization, melted at 142–145°.

Anal. Calc'd for C_9H_8OS: C, 65.90; H, 4.92.

Found: C, 65.36; H, 5.06.

However, the substance did not give the positive acetylene test and the infrared spectrum did not show any free acetylenic group. The molecular weight (300) determined by the method of Rast identified it as a dimer.

2-Thienyl ethynyl ketone (Va). A solution of chromic acid (0.0572 mole) in 20 ml. of water and 5 ml. of conc'd sulfuric acid was added slowly to a stirred solution of 2-thienylethynylcarbinol (0.087 mole) in 80 ml. of acetone. The oxidation was carried out at 5° under nitrogen. The addition required 3 hours. The solution then was stirred for one-half hour more and the reaction mixture was diluted with ice-cold water, washed until neutral, and extracted with ether. The ethereal extract was dried over sodium sulfate and the solvent allowed to evaporate giving 9 g. (77%) of a brownish oil. This oil solidified on standing at 0° resulting in long needles melting at 34°. The product is a strong lachrymator, attacks metallic copper, and gives the silver and copper acetylides. The copper salt has a red-brown color, turning to pink while the silver salt is white.

Anal. Calc'd for C_8H_6OS: C, 61.74; H, 2.98.

Found: C, 61.5; H, 3.14.

Phenylhydrazone of 2-thienyl ethynyl ketone (VI). 2-Thienyl ethynyl ketone in ethanol with phenylhydrazine gave the phenylhydrazone. Recrystallization from dilute methanol gave brown plates, m.p. 141°.

Anal. Calc'd for $C_{13}H_{10}N_2S$: N, 12.30. Found: N, 12.07.

5-(2-Thienoyl)-2-(2-thienyl)pyridine (XIa). To 1 g. (0.0074 mole) of 2-thienyl ethynyl ketone dissolved in 15 ml. of ethanol a solution of 0.8 g. (0.008 mole) sodium carbonate, dissolved in a minimum quantity of water, was gradually added and the mixture was refluxed for 2½ hours. The solvent was removed under reduced pressure and the product isolated with ether. When recrystallized from benzene-petroleum ether it gave yellow plates, m.p. 112–114°.

Anal. Calc'd for $C_{14}H_9NOS_2$: N, 5.16. Found: N, 5.31.

1-Anilino-3-(2-thienyl)propen-3-one (IX). To 1.1 g. (0.008 mole) of 2-thienyl ethynyl ketone dissolved in 15 ml. of ethanol a solution of aniline (0.8 g., 0.0088 mole) dissolved in 15 ml. of ethanol was gradually added. The temperature was kept below 40°. After 30 minutes a yellow precipitate was obtained. Yield 1.27 g. (75%). From diluted methanol it formed yellow needles, m.p. 99°.

Anal. Calc'd for $C_{13}H_{10}NOS$: N, 6.12. Found: N, 5.96.

2-Amino-4-(2-thienyl)pyrimidine (Xa). To a solution of 2.4 g. (0.0176 mole) 2-thienyl ethynyl ketone and 2.1 g. (0.0176 mole) of guanidine nitrate in 60 ml. of ethanol there was added 1.2 g. (0.011 mole) of sodium carbonate dissolved in the minimum quantity of water. The addition required 45 minutes; the reaction mixture then was refluxed for further ten hours. The product was extracted with benzene and dried. When recrystallized from benzene it gave yellow needles, m.p. 174°.

Anal. Calc'd for $C_8H_7N_3S$: N, 23.70. Found: N, 23.00.

3-Methyl-2-thienyl ethynyl ketone (Vb). To the solution of 3-methyl-2-thienylethynylcarbinol (0.066 mole) in 80 ml. of acetone, a solution of chromic acid (0.058 mole) dissolved in 20 ml. of water and 5.2 ml. of conc'd sulfuric acid was gradually added under nitrogen with stirring. The temperature was kept under 5°. After all of the oxidation mixture had been added the mixture was stirred for 15 minutes, diluted with water, and the reaction product extracted with ether. The ethereal extract was dried over sodium sulfate. There was obtained 9.5 g. (96%) of a brown oil. When redistilled it boiled at 103–105°/1 mm.; n_D^{20} 1.5930. On standing under sub-zero temperatures some crystalline substance precipitated. The identification of the crystalline substance which melted at 67° was unsuccessful.

Anal. Calc'd for C_8H_6OS: C, 63.97; H, 4.03.
Found: C, 63.90; H, 4.26.

2,4-Dinitrophenylhydrazone of 3-methyl-2-thienyl ethynyl ketone (VIIa). 3-Methyl-2-thienyl ethynyl ketone (0.005 mole) and 2,4-dinitrophenylhydrazine (0.004 mole) were brought together in 50 ml. of ethanol. The hydrazone precipitated readily after cooling and when recrystallized from benzene gave red-brown needles melting at 172°. It was found to be the normal derivative of the above ketone.

Anal. Calc'd for $C_{14}H_{10}N_4O_4S$: N, 16.97. Found: N, 16.86.

2-Amino-4-(3-methyl-2-thienyl)pyrimidine (Xb). The preparation is analogous to that given for 2-amino-4-(2-thienyl)pyrimidine. From 0.0067 mole of the ketone there was obtained 0.75 g. of product, yield 61%. Recrystallized from benzene-petroleum ether it gave yellow needles, m.p. 127°.

Anal. Calc'd for $C_9H_9N_3S$: N, 22.00. Found: N, 22.06.

5-(3-Methyl-2-thienoyl)-2-(3-methyl-2-thienyl)pyridine (XIb). 3-Methyl-2-thienyl ethynyl ketone (0.047 mole) was treated as described under 5-(2-thienoyl)-2-(2-thienyl)pyridine. There was obtained 6 g. of a pale yellow substance, yield 89%. When recrystallized from benzene-petroleum ether it melted at 103–105°.

Anal. Calc'd for $C_{16}H_{13}NOS_2$: N, 4.69. Found: N, 4.31.

1-(2-Thienyl)-1 penten-4-yn-3-one (Vc). To the solution of (IIIc) (0.085 mole) in 50 ml. of acetone a solution of chromic acid (0.055 mole) in 20 ml. of water and 2.8 ml. of conc'd sulfuric acid was gradually added. The oxidation temperature was kept below 3°. Despite the nitrogen atmosphere, the solution at once turned dark brown. The reaction mixture after continuous stirring for 3 hours was diluted with water, extracted with ether, washed with ice-cold water, and dried. There was obtained 7 g. of a dark-brown oil, which on standing at −9° partly solidified. The purification of the substance yielded mostly polymeric material, so the yield was never greater than 20%. When recrystallized from benzene-petroleum ether it gave a grey powder melting at 90°. However, the analysis was not satisfactory. Attempts to distill it in nitrogen atmosphere caused polymerization before the boiling temperature was reached. A very hard resinous material remained in the distilling flask. The raw product, however, gave a 2,4-dinitrophenylhydrazone which could be isolated and identified.

2,4-Dinitrophenylhydrazone of the ketone Vc (VIIc). The preparation of the derivative was carried out as before. There were obtained red-brown crystals which when recrystallized from benzene melted at 214°. The freshly prepared compound gave a positive acetylene test; however, not so readily as derivatives of 2-thienyl ethynyl ketone and 3-methyl-2-thienyl ethynyl ketone.

Anal. Calc'd for $C_{15}H_{10}N_4O_4S$: N, 16.40. Found: N, 16.63.

It should be noted here that after filtering the compound (VIIc) a secondary product crystallized out on standing. This product did not give the characteristic acetylene test and when recrystallized melted at 175°.

Anal. Calc'd for $C_{15}H_{10}N_4O_4S$: N, 16.40. Found: N, 16.80.

It is probable that the free acetylenic group cyclizes with the ketone (Vc) more readily to give the compound (VIII).

The attempted preparation of 3-(2-thienyl)pyrazole and 3-(3-methyl-2-thienyl)pyrazole. 2-Thienyl ethynyl ketone (Va) (0.04 mole) and hydrazine sulfate (0.04 mole) were refluxed with ethanol (40 ml.) and sufficient water to render the mixture homogenous. Sodium carbonate (0.038 mole) dissolved in the minimum quantity of water was added dropwise to the boiling solution during one hour. The refluxing was continued for 3 hours. After dilution with water and isolation with ether there was obtained a brown resinous mass which, when recrystallized from benzene-ligroin, gave a brown powder (1.5 g.) melting at 115°. This substance analyzed as follows:

Anal. Calc'd for $C_{14}H_{10}N_2OS_2$: N, 10.99. Found: N, 10.15, 10.45.

The condensation with 3-methyl-2-thienyl ethynyl ketone and hydrazine sulfate gave an analogous substance melting at 145°.

Anal. Calc'd for $C_{16}H_{14}N_2OS_2$: N, 9.81. Found: N, 9.66, 9.45.

SUMMARY

1. Three new acetylenic carbinols were synthesized from the corresponding thiophene aldehydes using sodium acetylide in liquid ammonia.

2. The carbinols obtained were oxidized to the corresponding ketones with chromic acid in acetone.

3. The acetylenic ketones were condensed with ammonia and amines to give the expected thiophene pyridines and pyrimidines.

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