COMMUNICATION 9. SYNTHESIS OF CAPILLENE, CAPILLIN, AND RELATED COMPOUNDS

B. P. Gusev and V. F. Kucherov

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences, USSR

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Among antibiotics of vegetable origin interesting properties are presented by capillene (agropyrene) and capillin, which are relatively simple derivatives of butadiyne and have exceptionally high fungicidal activity [1-3]. The formula first suggested for capillene as a substituted 1-buten-3-yne [4] was later withdrawn [5], and it was proved by direct synthesis [6] that it is 1-phenyl-2,4-hexadiyne (I). However, the method of synthesizing capillene that is described in the literature is of purely theoretical significance (yield about 1%) and cannot be used for the preparation of its analogs. The second antibiotic of this type, namely capillin, which is 2,4-hexadiynophenone (II), was prepared in satisfactory yield from 1,3-pentadiyne [7]. The structural relationship between these two antibiotics was confirmed by the direct oxidation of capillene to capillin [8].

$$C_6H_5CH_2\cdot C\equiv CMgBr + I\cdot C\equiv C\cdot CH_3 \xrightarrow{CoCl_2} \rightarrow \underset{(I)}{C_6H_5CH_2\cdot C\equiv C\cdot C\equiv C\cdot CH_3} \rightarrow \underset{(II)}{C_6H_5\cdot CO\cdot C\equiv C\cdot C\equiv C\cdot CH_3}$$

$$CH\equiv C\cdot C\equiv C\cdot CH_3 \xrightarrow[2)\ C_6H_5CHO]{1)\ NaNH_2} C_6H_5CH(OH)-C\equiv C-C\equiv C\cdot CH_3 \xrightarrow{CrO_3} C_6H_5CH(OH)-C\equiv C-C\equiv C\cdot CH_3$$

In the literature [3] it is stated also that diacetylenic compounds of the type $C_6H_5CH(OH)-C\equiv C\cdot C\equiv CR$ have bactericidal and fungicidal activity similar to that of capillene and capillin.

We had at our disposal a general method for the preparation of various monosubstituted butadiynes of general formula $R\cdot C\equiv C\cdot C\equiv CH$ where R = -Alk, $-CH_2N(R_1)_2$ and $-C(OH)\begin{matrix}R_2\\R_3\end{matrix}$ [9], and we set ourselves the task of finding accessible ways of synthesizing capillene (I), capillin (II), and related compounds from these butadiynes with the object of making a more detailed study of the physiological activity of the products. The simplest method for the synthesis of capillene and its homologs could be the reaction of metal derivatives of alkylbutadiynes with benzyl chloride or bromide. However, it is stated in the literature that benzyl halides scarcely react with substituted butadiynes, and several attempts to bring about such reactions were not successful [6]. We have shown that in organomagnesium synthesis with alkylbutadiynes benzyl p-toluenesulfonate, used earlier in reactions with acetylene derivatives [10], can be employed successfully in place of a benzyl halide. With the aid of this alkylating agent from alkylbutadiynes we obtained the corresponding alkylbenzylbutadiynes, including capillene itself, in quite satisfactory yields. The yield of the interesting physiologically active compound, capillene, attained 40%, which makes it quite accessible. According to its infrared spectrum the capillene prepared by this method is identical to the natural product [6].

$$Alk\cdot C\equiv C\cdot C\equiv CH \xrightarrow{C_2H_5MgBr} Alk\cdot C\equiv C\cdot C\equiv C\cdot MgBr \rightarrow$$

$$\xrightarrow{C_6H_5CH_2\cdot OSO_2\cdot C_6H_4\cdot CH_3} C_6H_5CH_2\cdot C\equiv C\cdot C\equiv C\cdot Alk$$

It was found that benzyl p-toluenesulfonate readily reacts, not only with alkylbutadiynes, but also with the corresponding diacetylenic alcohols (with acetal protection of the hydroxyl). By this method we readily prepared, for example, 2-methyl-7-phenyl-3,5-heptadiyn-2-ol (III), for whose synthesis by the other possible method the almost inaccessible benzylbutadiyne is required. The yields and constants of the capillene analogs that we prepared are given in the table.

For the preparation of capillin (II) and its butyl analog (IV) we condensed the magnesium derivatives of the corresponding alkylbutadiynes with benzaldehyde and oxidized the diacetyl alcohols (V) and (VI) with chromic anhydride

Formula	Yield, %	B.p., °C (p. mm)	n_D^{20}	Found, %		Calc., %	
				C	H	C	H
$C_6H_5CH_2\cdot C\equiv C\ C\equiv C\cdot CH_3$ (I)	40	78 (0,5)	1,5814				
$C_6H_5CH_2\cdot C\equiv C\cdot C\equiv C\cdot C_2H_5$	42,8	88—89 (0,5)	1,5722	92,76	6,90	92,81	7,19
$C_6H_5CH_2\cdot C\equiv C\cdot C\equiv C\cdot C_4H_9$	37	110—111 (0,5)	1,5564	91,84	8,14	91,78	8,22
$C_6H_5CH_2\cdot C\equiv C\cdot C\equiv C-C(OH)(CH_3)(CH_3)$ III	51,5	110—111 (0,1)	1,5674	See Experimental			

In both stages the yields were fairly good, which makes these compounds quite accessible synthetically. Moreover, we synthesized capillin also by the direct condensation of the magnesium derivative of methylbutadiyne [1,3-pentadiyne] with benzoic anhydride.

$$\text{Alk}\ C\equiv C\cdot C\equiv CMgBr \xrightarrow{C_6H_5CHO} \text{Alk}\ C\equiv C\cdot C\equiv C\cdot CH(OH)-C_6H_5$$

(V) Alk = CH_3

(VI) Alk = n-C_4H_9

$$\text{Alk}\cdot C\equiv C\cdot C\equiv C\ CO\cdot C_6H_5 \quad \text{(via } (C_6H_5CO)_2O\text{)}$$

(II) Alk = CH_3

(IV) Alk = n-C_4H_9

$$(R)_2N\cdot CH_2\ C\equiv C\cdot C\equiv C\cdot MgBr \xrightarrow{C_6H_5CHO} (R)_2N\cdot CH_2\cdot C\equiv C\ C\equiv C-CH(OH)-C_6H_5$$

(VII) R = CH_3 (IX) R = CH_3

(VIII) R = C_2H_5. (X) R = C_2H_5

In reactions with benzaldehyde, apart from alkylbutadiynes, we may use the N,N-dialkyl-2,4-pentadiynylamines (VII) and (VIII), the general method of synthesizing such compounds was described by us previously [9]. In this way we obtained, in good yield, the corresponding 6-dialkylamino-1-phenyl-2,4-hexadiyn-1-ols (IX) and (X), the simplest members of a new class of butadiyne derivatives having potential fungicidal activity. We have not yet succeeded in oxidizing these alcohols to the corresponding ketones.

All the above-described compounds are fairly stable, may be crystallized from low-boiling solvents or vacuum-distilled, and may be preserved for a long time in a nitrogen atmosphere at 0°.

EXPERIMENTAL

1-Phenyl-2,4-hexadiyne (Capillene) (I). A solution of 3.2 g of 1,3-pentadiyne in 10 ml of ether was added over a period of 15 minutes at 10° to a solution of ethylmagnesium bromide prepared from 1.2 g of magnesium and 5.5 g of ethyl bromide in 40 ml of ether. The mixture was stirred for two hours at room temperature, then at 20-22° a solution of 26.2 g of benzyl p-toluenesulfonate in 100 ml of ether was added over a period of 30 minutes, and the mixture was stirred for three hours at this temperature. Ice cooling was applied while the mixture was decomposed with ammonium chloride solution. The ethereal solution was separated, washed with sodium carbonate solution and then with water, and dried over potassium carbonate. Ether and benzyl bromide were vacuum-distilled off, and the residue was dissolved in 20 ml of hexane and applied to a column of alumina (h = 10 cm, d = 2.5 cm). The reaction product was eluted with 200 ml of hexane, and after the removal of hexane we obtained 3.1 g (40%) of 1-phenyl-2,4-hexadiyne (I), b.p. 78° (0.05 mm), m.p. 0-1°, n_D^{20} 1.5814. The infrared spectrum corresponded fully to that of natural capillene [6]. λ_{max} 240 and 253 mμ, log ε 2.85 and 2.68 (alcohol).

The capillene obtained was a fairly stable compound and could be kept for a long time at 0° in a nitrogen atmosphere. By an analogous procedure, starting from 1,3-hexadiyne and from 1,3-octadiyne we obtained 1-phenyl-2,4-heptadiyne and 1-phenyl-2,4-nonadiyne, respectively (see table).

2-Methyl-7-phenyl-3,5-heptadiyn-2-ol (III). A solution of 9 g of the acetal derivative of 2-methyl-3,5-hexadiyn-2-ol [9] in 10 ml of ether was added for 20 minutes at 5-8° to a solution of ethylmagnesium bromide prepared from 1.2 g of magnesium and 5.5 g of ethyl bromide in 40 ml of ether, and the mixture was stirred for two hours at room temperature. A solution of 26.2 g of benzyl p-toluenesulfonate in 100 ml of ether was then added at 5-8° over a period of 30 minutes. The reaction mixture was stirred further for two hours at this temperature and then for five hours at room temperature, it was left overnight. The mixture was cooled with ice water while 30 ml of dilute (1:5) hydrochloric acid was added slowly, it was then stirred for 90 minutes at room temperature. The ethereal solution was separated, washed with sodium carbonate solution and then with water, and dried over potassium carbonate. Ether and benzyl bromide were vacuum-distilled off, and the residue was dissolved in 20 ml of a 1:1 mixture of hexane and ether and applied to a column of alumina (h = 10 cm, d = 2.5 cm). The reaction product was eluted with 200 ml of a 1:1 mixture of hexane and ether, and after removing this we obtained 5.1 g (51.5%) of -methyl-7-phenyl-3,5-heptadiyn-2-ol (III), b.p.110-111° (0.1 mm), n_D^{20} 1.5674. Found C 84.55%; H 7.31%. $C_{14}H_{14}O$. Calculated C 84.81%, H 7.12%.

1-Phenyl-2,4-hexadiyn-1-ol (V). A solution of 2.56 g of 1,3-pentadiyne in 10 ml of ether was added at 5-7° to a solution of ethylmagnesium bromide prepared from 1 g of magnesium and 4.5 g of ethyl bromide in 30 ml of ether, and the mixture was stirred for two hours at room temperature. A solution of 4.24 g of benzaldehyde in 10 ml of ether was then added at 3-5°. The reaction mixture was stirred for three hours at room temperature and left overnight. The reaction mixture was cooled with ice water while being decomposed with saturated ammonium chloride solution. The reaction product was extracted with ether, and the extract was dried with potassium carbonate. Ether was distilled off, and we obtained 3.1 g (45.5%) of 1-phenyl-2,4-hexadiyn-2-ol (V), m.p. 82-84°, which, after crystallization from 50% alcohol, melted at 86°, this corresponds to data in the literature [7].

1-Phenyl-2,4-nonadiyn-1-ol (VI). Under the above-described conditions from 3.18 g of 1,3-octadiyne and 3.18 g of benzaldehyde we obtained 3.7 g (58%) of 1-phenyl-2,4-nonadiyn-1-ol (VI), b.p. 124-125° (0.08 mm). n_D^{20} 1.5724. Found: C 84.80%, 84.62%, H 7.79%, 7.66%. $C_{15}H_{16}O$. Calculated C 84.87%, H 7.60%.

2,4-Hexadiynophenone (Capillin) (II). A mixture of 0.5 g of chromic anhydride, 0.4 ml of concentrated sulfuric acid, and 1.2 ml of water was added with cooling to a solution of 1.2 g of 1-phenyl-2,4-hexadiyn-1-ol in 1.2 ml of acetone; the mixture was shaken in a nitrogen atmosphere for 90 minutes at room temperature. The reaction mixture was poured into ice water and extracted with ether. Ether was driven off, and the crystals that separated were recrystallized from hexane. We obtained 0.8 g (66.6%) of 2,4-hexadiynophenone (II), m.p. 80-81°, which agrees with data in the literature [7]. The 2,4-dinitrophenylhydrazone had m.p. 214° (chloroform-alcohol).

A solution of 2.56 g of 1,3-pentadiyne in 20 ml of benzene was added to a solution of ethylmagnesium bromide prepared from 1 g of magnesium and 4.5 g of ethyl bromide in 20 ml of ether, and the mixture was stirred for two hours at room temperature. The complex prepared in this way was added to a solution of 18.08 g of benzoic anhydride in 100 ml of ether at from -35° to -40° in the course of 20 minutes, and the mixture was stirred for two hours at this temperature and then allowed to warm up to room temperature in the course of one hour. 50 ml of water was added with cooling, the organic layer was separated, and the aqueous layer was extracted with ether. The ethereal solution was washed several times with sodium carbonate solution and dried over potassium carbonate. Ether was distilled off, and we obtained 1.1 g (10%) of 2,4-hexadiynophenone (II), m.p. 75-78°, after crystallization from hexane it had m.p. 81-81.5°, undepressed by admixture of the above-described sample.

2,4-Nonadiynophenone (IV). A mixture of 0.9 g of chromic anhydride, 0.8 ml of concentrated sulfuric acid, and 3 ml of water was added to a solution of 2.9 g of 1-phenyl-2,4-nonadiyn-1-ol in 3 ml of acetone, and the mixture was shaken for 90 minutes at room temperature. The reaction mixture was poured into ice water, extracted with ether, and dried with potassium carbonate. Ether was distilled off, and vacuum distillation gave 1.5 g (52%) of 2,4-nonadiynophenone (IV), b.p. 135° (0.15 mm), n_D^{20} 1.5792. Found C 85.20%, H 7.11%. $C_{15}H_{14}O$. Calculated: C 85.68%, H 6.71%. The 2,4-dinitrophenylhydrazone had m.p. 131-132° (chloroform-alcohol).

6-Dimethylamino-1-phenyl-2,4-hexadiyn-1-ol (IX). A solution of 5.35 g of N,N-dimethyl-2,4-pentadiynylamine (VII) in 10 ml of ether was added to a solution of ethylmagnesium bromide prepared from 1.2 g of magnesium and 5.5 g of ethyl bromide in 40 ml of ether. To dissolve the complex we added 30 ml of benzene. The mixture was stirred for two hours, and a solution of 5.3 g of benzaldehyde in 10 ml of ether was added at 5-7°. Stirring was continued further for four hours at room temperature. The mixture was left overnight and then cooled with ice water while being decomposed with saturated ammonium chloride solution. The reaction product was extracted with ether, 15 ml of 5 N HCl was added to the ethereal solution, and the mixture was shaken vigorously. The aqueous solution

was separated and neutralized with concentrated ammonia solution. The crystals that separated were recrystallized from acetone, and we obtained 5.7 g (53.5%) of 6-dimethylamino-1-phenyl-2,4-hexadiyn-1-ol (IX), m.p. 71.5-72°. Found: C 78.42%, 78.66%; H 7.06%, 7.08%. $C_{14}H_{15}ON$. Calculated: C 78.84%, H 7.09%.

6-Diethylamino-1-phenyl-2,4-hexadiyn-1-ol (X). By the procedure described above, from 5.4 g of N,N-diethyl-2,4-pentadiynylamine (VIII) and 4.24 g of benzaldehyde we obtained, after recrystallization from acetone, 8.4g (87%) of (X), m.p. 79.5-80°. Found C 80.36%, 79.88%; H 8.01%, 7.88%, N 5.67%, 5.88%. $C_{16}H_{19}ON$. Calculated: C 79.63%; H 7.94%, N 5.80%.

SUMMARY

Simple and preparatively convenient methods of synthesizing the natural fungicidal antibiotics capillene, capillin, and related compounds were developed.

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