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Studies on Acetylenic Compounds. XLIX.[1] Reactions of Linear-Conjugated Diynones[2]

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Linear conjugated diynones, capillin (Ia), and the ethyl analogue, 1-phenyl-2,4-heptadiyn-1-one (Ib), were applied to the synthesis of the corresponding β-triketones, 1-phenyl-1,3,5-hexanetrione (IIIa) and 1-phenyl-1,3,5-heptanetrione (IIIb), respectively. Acid catalyzed hydration of Ia and Ib afforded 2-methyl-6-phenyl-4H-pyran-4-one (IIa), and 2-ethyl-6-phenyl-4H-pyran-4-one (IIb), which were converted to IIIa and IIIb by alkaline hydrolysis, respectively. On the other hand, treatment of Ia and Ib with pyrrolidine gave novel biphenyl derivatives, 3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIa) and 2-methyl-3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIb), in addition to normal enamine products, 1-phenyl-5-N-pyrrolidinyl-4-hexen-2-yn-1-one (Va) and 1-phenyl-5-N-pyrrolidinyl-4-hepten-2-yn-1-one (Vb), respectively. Acid hydrolysis of Va and Vb also afforded the expected 4-pyrone derivatives (IIa, IIb). In order to examine the mechanistic pathway of I to VII, 1-phenyl-5-N-pyrrolidinyl-4-hexen-1,3-dione (IX) derived from IIIa was treated with pyrrolidine to lead to VIIa, which was assumed to form the same intermediate (VI).

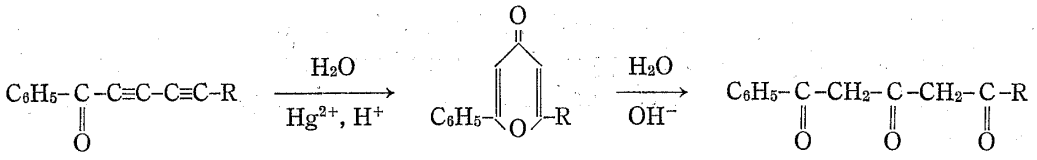
There are many natural products which originate from a linear β-polyketomethylene chain formed by head–to–tail self–condensation of acetate units. For example, tetracyclines, griseofulvines, alternariol, orsellinic acid and acylphloroglucinols are representatives of the natural acetogenines containing the sites of oxygen attachment in a polyacetyl precursor.[4] These compounds have been known to be synthesized under the mild conditions *in vivo* (physiological conditions) from the acetate–malonate pathway.[4,5] On the other hand, in laboratories, it is very difficult to realize the same reactions as those depending on enzymes, which are suggested to condense acetate units stepwise.[5] However, since the first presentation of the acetate hypothesis by Collie,[6] and the brilliant re–examination of the concept by Birch,[7] many studies have been carried out experimentally with fruitful results.[8] Recently Scott and his school investigated the conversion of poly-2-pyrones into phenolic compounds.[9] Besides, Harris and Carney studied a synthesis of 3,5,7-triketo-acids and their cyclization reaction to resorcinol and phloroglucinol derivatives as a model of biosynthesis of natural phenolic compounds.[10] These results brought about a very interesting information about a model for acetogenin biosynthesis.

1) Part XLVIII: Y. Kishida and A. Terada, *Chem. Pharm. Bull.* (Tokyo), **17**, 974 (1969).
2) Synthesis of β-Ketide System I.
3) Location: *2–58, 1–chome, Hiromachi, Shinagawa-ku, Tokyo.*
4) J.H. Richards and J.B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenines," W.A. Benjamine, Inc., New York, 1964, chap. 1—5.
5) F. Lynen, "Biosynthetic Pathways from Acetate to Natural Products," Chemistry of Natural Products, **4**, International Symposium, Stockholm, 1966, Main Lectures, Butterworths, London, 1967 and the references cited therein.
6) J.N. Collie, *J. Chem. Soc.*, **1893**, 63, 122, 329 (1893); *ibid.*, **1907**, 787, 1806.
7) A.J. Birch and F.W. Donovan, *Australian J. Chem.*, **6**, 369 (1953).
8) A.J. Birch, "Fortschr. Chem. Org. Naturstoffe," ed. by L. Zechmeister, **14**, 186 (1957).
9) T. Money, I.H. Quereshi, G.B. Webster ,and A.I. Scott, *J. Am. Chem. Soc.*, **87**, 3004 (1965); *idem, Tetrahedron*, **23**, 3435 (1967); F.W. Comer, T. Money, and A.I. Scott, *Chem. Commun.*, **1967**, 231.
10) T.M. Harris and R.L. Carney, *J. Am. Chem. Soc.*, **88**, 2053 (1966); *idem, ibid.*, **88**, 5686 (1966); *idem, ibid.*, **89**, 6734 (1967).

We intended to apply acetylenic compounds to a synthesis of β-polyketomethylene system. The mechanism of the biosynthesis of triple bonds has not yet been elucidated, although it appears that acetate units are the precursors.[11] Dehydration of ketone functions to triple bonds could be expected to take place in two steps[12] *via* enol phosphates[13] or enol pyrophosphates[14] in nature. In fact the synthesis of acetylenes from enol phosphates by Craig and Moyle supported the proposed biosynthetic pathway.[15] On the other hand, the reverse hydration reaction of a triple bond is very useful in organic chemistry[16] and also occurs biogenetically.[17]

Linear–conjugated diynone, capillin (Ia), which was synthesized by Imai's method,[18] was refluxed in 90% acetic acid containing mercuric acetate and sulfuric acid to afford 2-methyl-6-phenyl-4H-pyran-4-one (IIa) in 70% yield. This γ-pyrone was identical with a sample synthesized from ethyl phenylpropiolate and acetone,[19] in all respects, and converted to the desired 1-phenyl-1,3,5-hexanetrione (IIIa) by alkaline hydrolysis.[19,20] The same treatment of 1-phenyl-2,4-heptadiyn-1-one (Ib)[21] with mercuric acetate in aqueous acetic acid gave the compound assigned to 2-ethyl-6-phenyl-4H-pyran-4-one (IIb), which was also transformed into the corresponding triketone, 1-phenyl-1,3,5-heptanetrione (IIIb) by alkaline hydrolysis. The formation of other possible products containing α-diketone moiety, which had been also expected to be synthesized,[22] was not observed in these two hydration reactions.

It had been a rather difficult problem to synthesize these compounds (IIb, IIIb), because the application of Ruheman's method[19] to methyl ethyl ketone and ethyl phenylpropiolate failed to isolate any amount of IIb. However, Hauser and Work synthesized IIb and IIIb for the first time by the condensation of dilithiobenzoylacetone with propionic ester.[23]



Ia : R=Me
Ib : R=Et

IIa : R=Me
IIb : R=Et

IIIa : R=Me
IIIb : R=Et

Chart 1

The alternate route of I to II under mild conditions *via* enamine system was studied and during this work a novel benzene ring formation was found out. The addition of amines to conjugated acetylenic ketone is enormously facilitated for the carbonyl function and a smooth reaction ensues under moderate conditions in the absence of a catalyst to produce high yield of enamine, *e.g.*,

$$PhC{\equiv}CCO_2Et \xrightarrow{Et_2NH} PhC(NEt_2){=}CHCO_2Et$$

11) J.D. Bu'lock and H. Gregory, *Biochem. J.*, **72**, 322 (1959).
12) J.D. Bu'lock, *Quart. Rev.*, **10**, 371 (1956).
13) F. Bohlmann and Mannhardt, *Progr. Chem. Nat. Prod.*, **14**, 1 (1957).
14) E.R.H. Jones, *Chem. Eng. News.*, **39**, No. 12, 46 (1961).
15) J.C. Craig and M. Moyle, *Proc. Chem. Soc.*, **1962**, 149.
16) R.A. Raphael, "Acetylenic Compounds in Organic Chemistry," Butterworths, London, 1955, p. 40 and the references cited thererin.
17) K. Einjellen, *Acta. Chem. Scand.*, **10**, 1049 (1956).
18) K. Imai, *Yakugaku Zasshi*, **76**, 405 (1956).
19) S. Ruhemann, *J. Chem., Soc.*, **93**, 431 (1908).
20) K. Balenovic and R. Munk, *Arkiv. Kem.*, **18**, 41 (1946); *C.A.*, **42**, 2926a (1948); F. Feist, *Ann.*, **257**, 276 (1890).
21) I. Iwai, Y. Yura, T. Konotsune, and K. Tomita, *Yakugaku Zasshi*, **80**, 156 (1960).
22) K. Bowden, E.A. Brande, and E.R.H. Jones, *J. Chem. Soc.*, **1946**, 945.
23) S.D. Work and C.R. Hauser, *J. Org. Chem.*, **28**, 725 (1963).

Enamines of this type are readily hydrolyzed by mild treatment with acids (*e.g.*, oxalic and hydrochloric acid) to yield the corresponding β-diketones,[24] the process representing a further indirect method of hydration of the triple bond. This reaction has not been applied to a linear–conjugated diynone system as far as we know in literatures and the addition of amines to this system was investigated. Capillin (Ia) was treated with pyrrolidine at room temperature to precipitate the mixture of two kinds of crystals, which was separated into small yellow prisms of mp 133° and pale yellow needles of mp 156.5° by fractional recrystallization. The infrared spectrum of the former showed peaks at 2125 cm^{-1} (C≡C), 1601, 1550, and 1540, characteristic of the α, β-unsaturated carbonyl conjugated with strong electron–releasing group. A ethanol solution of this compound exhibited λ_{max} in mμ (log ε) in the ultraviolet at 262.5 (4.212) and 408 (4.568). The nuclear magnetic resonance (NMR) spectrum and the elemental analysis suggested it as a 1:1 adduct of Ia and pyrrolidine. The possibility of nucleophilic attack of pyrrolidine to Ia is β- and δ-position from the carbonyl group of the conjugated diynone. In order to decide the position, partial hydrogenation of this compound using 5% palladium on charcoal was carried out to absorb just one mole of hydrogen. The NMR spectrum of the reduced compound showed a typical pattern of a linear–conjugated dienone, *i.e.*, δppm in CD_3COCD_3, 8.20, 7.77 (both end peaks of quartet, J_1=13.4 cps, J_2=12.4 cps, β-H from carbonyl of the linear–conjugated dienone), 6.62 (1H, doublet, J_1=13.4 cps, α-H of the dienone), 5.37 (1H, doublet, J_2=12.4 cps, γ-H of the dienone) to propose δ-pyrrolidinyl dienone system. (VIII). Therefore 1:1 adduct of Ia and pyrrolidine was assigned to 1-phenyl-5-N-pyrrolidinyl-4-hexen-2-yn-1-one (Va), the configuration of which was expected to be *cis* referring to the study of Witerfeldt and Preuss.[25] The nuclear Overhauser effects (NOE)[26] of Va was measured using a degassed sample to confirm the *cis* addition product. The irradiation of the methyl peak reduced the integration of the vinyl proton by 5%, and the irradiation of α-methylenes of the pyrrolidine ring increased the integration of the vinyl proton by 36%, which showed the *cis* configuration of the vinyl proton and the pyrrolidine ring (Table I).

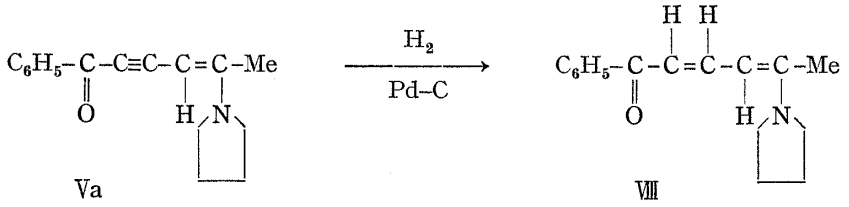


Chart 2

Table I. Nuclear Overhauser Effects of Va

	Irradiation of CH_3	Irradiation of pyrrolidine α–CH_2
Δ Integ. of vinyl-H	−5%	+36%

This is a new type of NOE as far as we know in literatures. Considering the structural environment, the phenomenon has, of course, ample analogy in the work of Woods and others[27] on the NOE of enol–etheric methyl group and the vinyl proton which locates at the *cis* position to –OMe.

The UV spectrum of the latter of mp 156.5°, which showed absorption maxima at 248.5 mμ (log ε=4.626) and 334.0 (3.599), was characteristic of a biphenyl derivative and its NMR

24) R.A. Raphael, "Acetylenic Compounds in Organic Chemistry," p. 39 and references cited therein.
25) E. Winterfeldt and H. Preuss, *Angew. Chem. Intern. Ed. Engl.*, **4**, 689 (1965).
26) F.A.L. Anet and A.J.R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965); M.C. Woods, H.C. Chang, Y. Nakadaira and K. Nakanishi, *J. Am. Chem. Soc.*, **90**, 522 (1968) and the references cited therein.
27) M.C. Woods, I. Miura, A. Ogiso, M. Kurabayashi, and H. Mishima, *Tetrahedron Letters*, **1968**, 2009.

peaks appeared at 5.77 (1H, triplet, J=2.0 cps) and 6.15 (2H, doublet, J=2.0 cps) in addition to the peaks ascribable to the protons on two pyrrolidine rings (16H) and ordinary aromatic protons (5H). Moreover, no triple bond absorption (IR) and elemental analysis ($C_{20}H_{24}N_2$) assigned the structure of this compound to 3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIa).

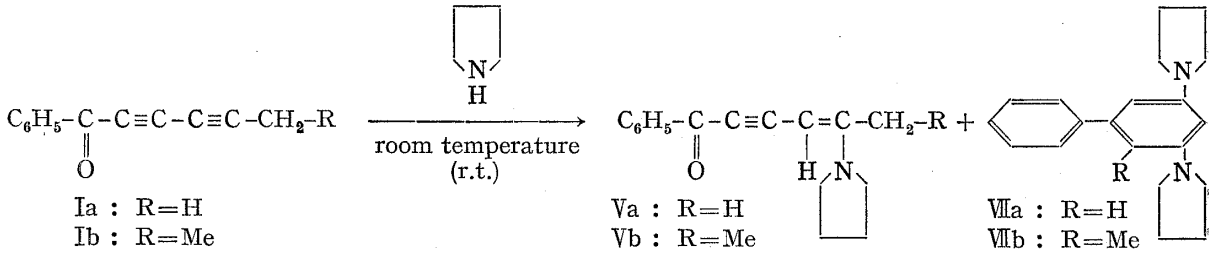


Chart 3

Table II. Yields of Va and VIIa

Molar ratio of pyrrolidine/Ia	Yield of Va (%)	Yield of VIIa (%)
1	36	7.5
2	35	31
4	37	30

Treatment of Ib with pyrrolidine gave 1-phenyl-5-N-pyrrolidinyl-4-hepten-2-yn-1-one (Vb) and 2-methyl-3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIb), analogously. The hydrolysis of Va and Vb with 3% hydrochloric acid gave the anticipated γ-pyrones, IIa and IIb, respectively. This reaction represented another indirect conversion of I to II.

To examine whether Va was an intermediate in the formation of VIIa or not, the enamine (Va) was again treated with pyrrolidine under the same conditions as those in the case of Ia. However any amount of VIIa was not detected and the possibility of the formation of VIIa *via* Va at room temperature was excluded. On the other hand, the reaction at elevated temperature afforded VIIa in a quantitative yield. In addition the change of the molar ratio of pyrrolidine to capillin gave the results summarized in Table II, which suggested that Ia consumed one equivalent pyrrolidine at first to form 1:1 adducts (IV and Va) and more than two equivalence of pyrrolidine was useless to advance the reaction. Although the probable

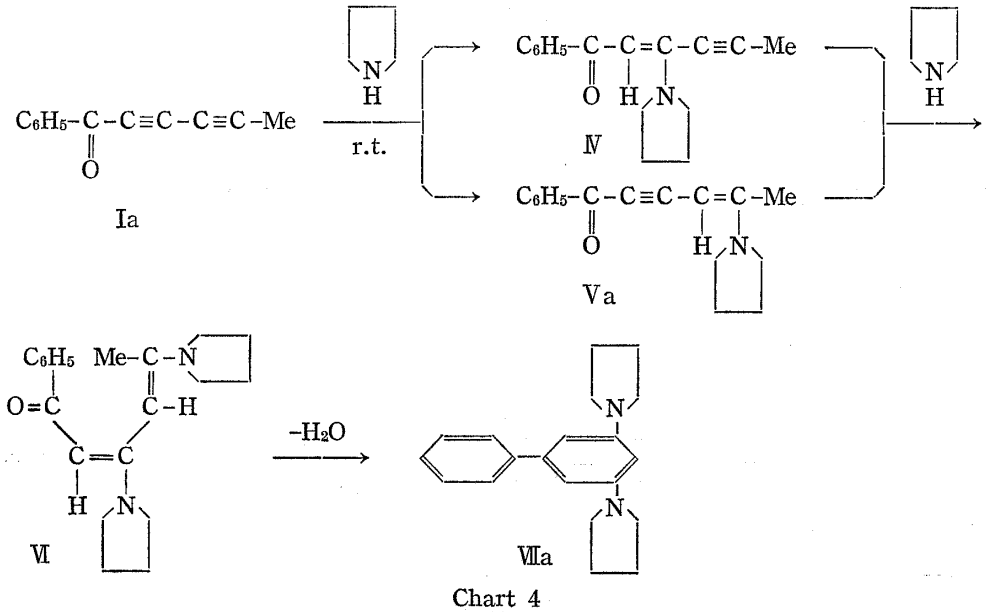


Chart 4

unstable intermediate, IV was not isolated in all efforts, the competitive reaction would be assumed to proceed as to the formation of IV and Va. One way of rationalizing the cyclization to VIIa is an assumption that an intermediate, 1-phenyl-3,5-di-N-pyrrolidinyl-2,3-hexadien-1-one (VI) would be formed from both IV and Va, and then cyclizes by intramolecular aldol condensation. Therefore the reaction paths could be considered as exhibited in Chart 4.

The following experiments were carried out for the verification of VI as an intermediate. The β-triketone IIIa reacted with pyrrolidine at room temperature to give an enamine of mp 139—141° in a quantitative yield. This enamine was assigned to 1-phenyl-5-N-pyrrolidinyl-4-hexene-1,3-dione (IX) from the spectroscopic data and elemental analysis. The IR spectrum showed the existence of β-diketone and the NMR spectrum indicated that IX consisted of keto–form, IXa (30%) and enol–form, IXb (70%) in $CDCl_3$ at 35°, *i.e.*, δppm, 5.88 (0.7H, singlet, Hb of IXb), 5.00 (0.3H, singlet, Ha of IXb), 3.62 (0.6H, singlet, $-CH_2-$ of IXa), 2.57 (2.1H, singlet, $-CH_3$ of IXa) in addition to the peaks ascribable to pyrrolidine protons (8H) and ordinary aromatic protons (5H) (Chart 5). The NOE (Table III) using the degassed

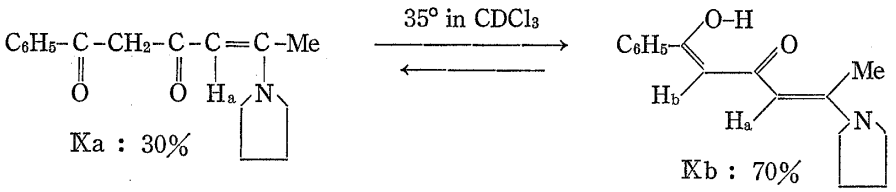


Chart 5

Table III. Nuclear Overhauser Effects of IXa and IXb

	IXa: Keto–Form		IXb: Enol–Form		
	Irradiation of CH_3	Irra. of Pyrrolidine α-CH_2	Irra. of CH_3	Irra. of Pyrrolidine α-CH_2	Irra. of H_b
Δ Integ. of H_a	−1%	+33%	−3%	+22%	+25%

sample decided the configuration of IXa and IXb. Further reaction of IX with pyrrolidine, which was catalyzed by *p*-TsOH at 90—100°, afforded VIIa, although in low yield. Moreover the azeotropic distillation of the mixture of 2-methyl-6-phenyl-4H-pyran-4-one (IIa) in the benzene solution containing a small quantity of *p*-TsOH gave IX and VIIa. These two reactions were considered to complete the cyclization to VIIa passing through the same intermediate VI as in the reaction of Ia with pyrrolidine (Chart 6).

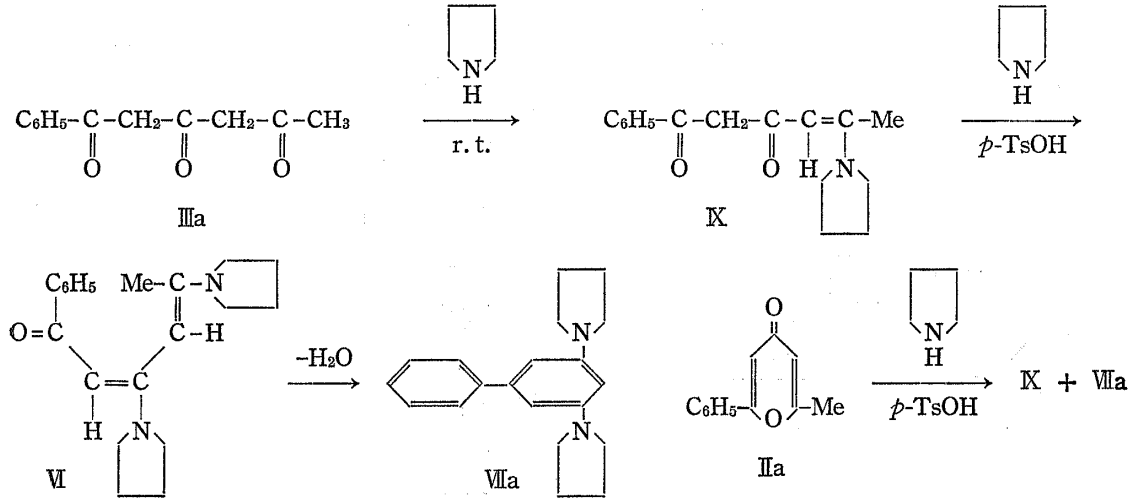


Chart 6

Since the interesting benzene ring formation was observed, it seemed desirable to test the generality of the reaction by using various amines. The reactions of capillin (Ia) with morpholine, piperidine, diethylamine, and cyclohexylamine were carried out, however, only morpholine afforded the expected products, 1-phenyl-5-N-morpholino-4-hexen-2-yn-1-one (X) and 3,5-di-N-morpholino-1,1′-biphenyl (XI).

Considering the mechanistic pathway, this biphenyl formation has ample analogy in the work of Huebner and others[28] on the benzene ring formation of acetylene dicarboxylate and 2-N-pyrrolidinyl-2-penten-4-one.

This common character of the intramolecular aldol type condensation suggested the possibility of various nucleophilic reactions of γ-position carbon in β-cyclicamino-α,β-unsaturated ketone systems. In fact the works on this hypothesis will be published in another report.

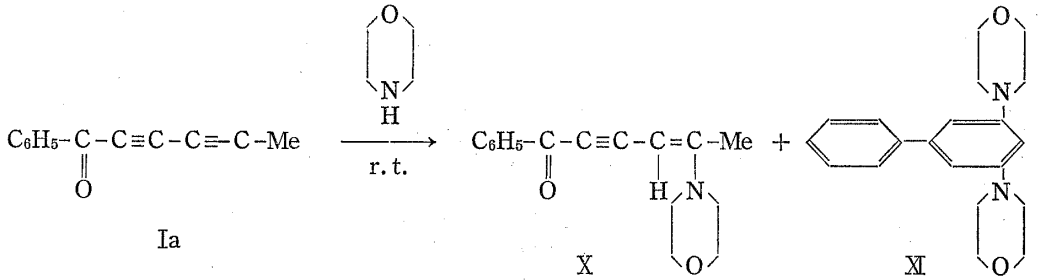


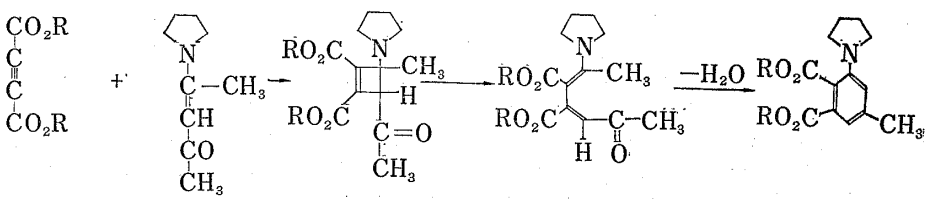
Chart 7

Experimental[29]

2-Methyl-6-phenyl-4H-pyran-4-one (IIa) from Capillin (Ia)——To a solution of capillin (Ia) (500 mg) in 90% AcOH (140 ml) was added Hg $(OAc)_2$ (750 mg) and conc. H_2SO_4 (0.5 ml). The resulting mixture was heated under reflux for 4 hr. After allowing to stand at room temperature overnight, the mixture was condensed to *ca.* 20 ml. and poured into 100 ml of H_2O. The aqueous solution was extracted with ether. The ethereal solution was dried over Na_2SO_4 and the solvent was evaporated to give an oily residue, 585 mg, while the aqueous layer was green with strong fluorescence. The oily residue was purified by chromatography on silica gel (9.0 g). Elution with benzene–acetone (9:1) followed by recrystallization from *n*-heptane gave 2-methyl-6-phenyl-4H-pyran-4-one (IIa) as prisms of mp 86.0°—86.5°, which was identified by mixed melting point test and IR spectrum comparison with an authentic sample prepared from ethyl phenylpropiolate and acetone according to Ruheman's method.[15] Yield, 390 mg (70%). UV λ_{max}^{EtOH} mμ (log ε): 271.5 (4.313). IR ν_{max}^{Nujol} cm^{-1}: 3070 (vinyl protons), 1662 (C=O), 1616. NMR δ ppm in $CDCl_3$: 7.90—7.40 (5H, multiplet, $C_6\underline{H}_5$), 6.71 (1H, doublet, J_1=2.3 cps, C_5–$\underline{H}$), 6.21 (1H, quartet of doublet, J_1=2.3 cps, J_2=0.7 cps, C_3–$\underline{H}$), 2.37 (1H, doublet, J_2=0.7 cps, –$C\underline{H}_3$).

2-Ethyl-6-phenyl-4H-pyran-4-one (IIb) from 1-Phenyl-2,4-heptadiyn-1-one (Ib)——1-Phenyl-2,4-heptadiyn-1-one (Ib)[21] was prepared by the analogous method of the synthesis of capillin (Ia). The same treatment of Ib (2.0 g) as that of Ia afforded 2-ethyl-6-phenyl-4H-pyran-4-one (IIb) as prisms of mp 61°, whose physical properties were almost identical with those of a reference.[23] Yield, 1.1 g (50%). UV λ_{max}^{EtOH} mμ (log ε): 271.5 (4.355). IR ν_{max}^{Nujol} cm^{-1}: 3070 (vinyl protons), 1660 (C=O), 1614. NMR δ ppm in $CDCl_3$: 7.90—7.40 (5H, multiplet, $C_6\underline{H}_5$), 6.71 (1H, doublet, J_1=2.3 cps, C_5–$\underline{H}$), 6.20 (1H, triplet of doublet, J_1=2.3 cps, J_2=0.8 cps, C_3–$\underline{H}$), 2.68 (2H, doublet of quartet, J_2=0.8 cps, J_3=7.5 cps, –$C\underline{H}_2$–), 1.31 (3H, triplet, J_3=7.5 cps, –$C\underline{H}_3$).

28) C.S. Huebner, L. Dorfman, M.M. Robison, E. Donoghue, W.G. Pierson, and P. Strachan, *J. Org. Chem.*, **28**, 3134 (1963).



The dienone intermediate is assumed to cyclize by intramolecular aldol condensation.

29) All melting points were uncorrected. NMR spectra were obtained in the specified solvents on a Varian A-60 and a Varian HA-100 spectrometer with tetramethylsilane as an internal standard.

1-Phenyl-1,3,5-hexanetrione (IIIa)——2-Methyl-6-phenyl-4H-pyran-4-one (IIa) (220 mg) was dissolved in 90% aq. EtOH solution (10 ml) containing 500 mg of KOH. The resulting solution was stirred at room temperature for 5 hr. After cooling, to the mixture was added 50 ml of ether. The ethereal solution was washed successively with H_2O, satd. $NaHCO_3$ solution and H_2O, and then dried over Na_2SO_4. Evaporation of the solvent gave crude solid, which was recyrstallized from 95% EtOH affording colorless needles, mp 101—102°, whose physical properties were almost identical with those of a reference.[19] Yield, 200 mg (83%). UV λ_{max}^{EtOH} mμ (log ε): 247.0 (3.750), 345.0 (4.161). IR ν_{max}^{Nujol} cm^{-1}: 1636, 1604, 1575.

1-Phenyl-1,3,5-heptanetrione (IIIb)——The same treatment of 2-ethyl-6-phenyl-4H-pyran-4-one (IIb) (350 mg) as that of 2-methyl-6-phenyl-4H-pyran-4-one (IIa) afforded 1-phenyl-1,3,5-heptanetrione (IIIb) as needles of mp 33.5—34.5°, whose physical properties were almost identical with a reference.[23] Yield, 250 mg (65%). UV λ_{max}^{EtOH} mμ (log ε): 247.0 (3.800), 345.0 (4.212). IR ν_{max}^{Liquid} cm^{-1}: 1720, 1595, 1575.

Reaction of Capillin (Ia) with Pyrrolidine——(a) Molar ratio of Ia/pyrrolidine=1/2. To a solution of capillin (Ia) in 10 ml of dehyd. THF was added pyrrolidine (710 mg, 10.0 mmole) with 5 ml of dehyd. THF at room temperature. At the initiation of addition the mixture was darkened to opacity. The mixture was stirred for 5 hr and then condensed to dryness under diminished pressure. The resin-like substance was dissolved in ether and to the solution was added hexane to give a crystalline substance, which was recrystallized from EtOH to afford pure 1-phenyl-5-N-pyrrolidinyl-4-hexen-2-yn-1-one (Va) as small prisms of mp 133°. Yield, 420 mg (35%). *Anal.* Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.20; H, 7.33; N, 5.79. UV λ_{max}^{EtOH} mμ (log ε): 262.5 (4.212), 408 (4.568). IR ν_{max}^{Nujol} cm^{-1}: 2125 (C≡C), 1601, 1550, 1530. NMR δ ppm in $CDCl_3$: 8.22—8.02, 7.60—7.33 (5H, multiplet, $C_6\underline{H}_5$), 4.28 (1H, singlet, vinyl proton), 3.50—3.13 (4H, multiplet, α-methylenes on the pyrrolidine ring), 2.30 (3H, singlet, $C\underline{H}_3$), 2.08—1.80 (4H, multiplet, β-methylenes on the pyrrolidine ring). The oily residue was condensed and crystallized from EtOH. Recrystallization from hexane gave 300 mg of 3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIa) as needles of mp 156.5°. The mother liquor was condensed (800 mg) and chromatographed on Al_2O_3 (80 g, Woelm, grade III, neutral). Elution with benzene afforded another crop of VIIa (150 mg). Combined yield, 450 mg (31%). *Anal.* Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 81.91; H, 8.30; N, 9.52, UV λ_{sh}^{EtOH} mμ (log ε): 237.0 (4.606). λ_{max}^{EtOH} mμ (log ε): 248.5 (4.626), 334.0 (3.599). IR ν_{max}^{Nujol} cm^{-1}: 1598, 1575. NMR δ ppm in $CDCl_3$: 7.75—7.25 (5H, multiplet, $C_6\underline{H}_5$), 6.15 (2H, doublet, J=2.0 cps, 2-H and 6-H on the pyrrolidine substituted benzene ring), 5.77 (1H, triplet, J=2.0 cps, 4-H), 3.50—3.17 (8H, multiplet, α-methylenes on the pyrrolidine rings), 2.12—1.83 (8H, multiplet, β-methylenes on the pyrrolidine rings).

(b) Molar ratio of Ia/pyrrolidine=1/1. The same treatment of Ia (840 mg, 5.0 mmole) with pyrrolidine (355 mg, 5.0 mmole) as (a) gave Va (440 mg, 36%) as small prisms and the oily residue (750 mg) was chromatographed on Al_2O_3 (100 g, Woelm, grade III, neutral). Elution with benzene afforded VIIa (110 mg, 7.5%) as needles.

(c) Molar ratio of Ia/pyrrolidine=1/4. The same treatment of Ia (840 mg, 5.0 mmole) with pyrrolidine (1.42 g, 20 mmole) as (a) and (b) gave Va (450 mg, 37%) and VIIa (340 mg) as specified crystals. The mother liquor was condensed (900 mg) and chromatographed on Al_2O_3 (50 g, Woelm, grade III, neutral). Elution with benzene gave VIIa (100 mg). The combined yield of VIIa was 440 mg (30%).

Reaction of 1-Phenyl-2,4-heptadiyn-1-one(Ib) with Pyrrolidine——To a solution of Ib (1.82 g, 10 mmole) in 15 ml of dehyd. dioxane was dropwise added pyrrolidine (1.56 g, 22 mmole) with 10 ml of dehyd. dioxane in an ice-water bath under vigorous stirring. After complete addition the mixture was stirred at room temperature for 2 days. The solvent was removed under reduced pressure at 45° and chromatographed on Al_2O_3 (140 g, Woelm, grade III, nextral). Elution with benzene and recrystallization from benzene-hexane gave 1-phenyl-5-N-pyrrolidinyl-4-hepten-2-yn-1-one (Vb) as pale yellow needles of mp 127°. Yield 330 mg (13%). *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.47; H, 7.64; N, 5.66. UV λ_{max}^{EtOH} mμ (log ε): 262.5 (4.236), 408 (4.601). IR ν_{max}^{Nujol} cm^{-1}: 2170 (C≡C), 1605, 1598. 1578, 1550, 1527. NMR δ ppm in $CDCl_3$: 8.27—8.07, 7.60—7.33 (5H, multiplet, $C_6\underline{H}_5$), 4.27 (1H, singlet, vinyl proton), 3.50—3.15 (4H, multiplet, α-methylenes on the pyrrolidine ring), 2.77 (2H, quartet, J=7.7 cps, $C\underline{H}_2$), 2.10—1.80 (4H, multiplet, β-methylenes on the pyrrolidine ring), 1.25 (3H, triplet, J=7.7 cps, $C\underline{H}_3$). The mother liquor of Va (700 mg) was chromatographed on Al_2O_3 (30 g, Woelm, grade III, neutral). Elution with benzene and recrystallization from hexane gave 2-methyl-3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIb) as small prisms of mp 118°, Yield, 305 mg (10%). *Anal.* Calcd. for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.14; H, 8.61; N, 9.16. UV λ_{max}^{EtOH} mμ (log ε): 238.6 (4.531), 320.2 (3.586). IR ν_{max}^{Nujol} cm^{-1}: 1609, 1563. NMR δ ppm in $CDCl_3$: 7.32 (5H, singlet, $C_6\underline{H}_5$), 6.23, 6.13 (2H, a pair of doublet, J=2.6 cps, 4-H and 6-H on the pyrrolidine-substituted benzene ring), 3.30—3.05 (8H, multiplet, α-methylenes on the pyrrolidine rings), 2.10—1.75 (8H, multiplet, β-methylenes on the pyrrolidine rings), 2.03 (3H, singlet, $C\underline{H}_3$).

Reaction of Capillin (Ia) with Morpholine——To a solution of Ia (1.68 g, 0.01 mmole) in 20 ml of dehyd. THF was dropwise added morpholine (1.74 g, 0.01 mole) in 15 ml of dehyd. THF at room temperature. After completion of addition the mixture was stirred for 4 hr and condensed to dryness to be resin-like substance, to which was added EtOH and benzene. The precipitated crystalline substance was collected on glass filter and recrystallized from EtOH to afford 1-phenyl-5-N-morpholino-4-hexen-2-yn-1-one (X) as pale yellow prisms of mp 132°. Yield, 825 mg (32.5%). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49.

Found: C, 75.01; H, 6.65; N, 5.35. UV λ_{max}^{EtOH} mμ (log ε): 262.0 (4.251), 395.0 (4.477). IR ν_{max}^{Nujol} cm^{-1}: 3060 (olefinic proton), 2135 (C≡C), 1610, 1577, 1540. NMR δ ppm in $CDCl_3$: 8.25—7.35 (5H, multiplet, $C_6\underline{H}_5$), 4.63 (1H, singlet, olefinic proton), 3.85—3.60 (4H, multiplet, $-C\underline{H}_2-O-C\underline{H}_2-$), 3.40—3.10 (4H, multiplet, $-C\underline{H}_2-N-C\underline{H}_2-$), 2.28 (3H, singlet, $C\underline{H}_3$). The mother liquor (2.5 g) was chromatographed on Al_2O_3 (100 g, Woelm, grade I, neutral). Elution with benzene–ether (95:5) and recrystallization from EtOH gave 3,5-di-N-morpholino-1,1′-biphenyl as small prisms of mp 189°. Yield, 550 mg (17%). *Anal.* Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.18; H, 7.45; N, 8.58. UV λ_{max}^{EtOH} mμ (log ε): 245.5 (4.604), 314 (3.384). IR ν_{max}^{Nujol} cm^{-1}: 3060 (C=C–H), 1594, 1578. NMR δ ppm $CDCl_3$: 7.70—7.30 (5H, multiplet, $C_6\underline{H}_5$), 6.68 (2H, doublet, J=2.3 cps, 2-H and 6-H on the morpholine-substituted benzene ring), 6.47 (1H, triplet, J=2.3 cps, 4–H on the morpholine-substituted benzene ring), 4.00—3.75 (8H, multiplet, $-C\underline{H}_2-O-C\underline{H}_2-$), 3.34—3.08 (8H. multiplet, $-C\underline{H}_2-N-C\underline{H}_2-$).

Reaction of 1-Phenyl-5-N-pyrrolidinyl-4-hexen-2-yn-1-one (Va) with Prryolidine——To a solution of Va (120 mg, 0.5 mmole) in 5 ml of dehyd. dioxane was added 355 mg (5 mmole) of pyrrolidine in 5 ml of dehyd. dioxane. The mixture was allowed to stand at room temperature for 70 hr, but no change was observed by TLC, then warmed on water bath at 70° for 35 hr. After removing the solvent in reduced pressure, the crystallized substance was purified by recrystallization from EtOH to afford needles of mp 156°, which was identified by mixed melting point test, TLC and IR spectrum comparison with an atuthentic sample (VIIa). Yield, 140 mg (96%).

Reduction of 1-Phenyl-5-N-pyrrolidinyl-4-hexen-2-yn-1-one (Va)——The enaminoketone (Va) (239 mg, 1.0 mmole) was hydrogenated in dehyd. dioxane (15 ml) over 5% Pd-C (70 mg) at atmospheric pressure and room temperature. The hydrogenation was stopped after 90 min, when just one mole of H_2 had been absorbed. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue solidified forming orange crystals. Recrystallization from EtOH gave orange neeldes of mp 118—120° (decomp.). Yield, 200 mg (80%). *Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.33; H, 7.98; N, 5.74. UV λ_{max}^{EtOH} mμ (log ε): 263.5 (3.954), 447 (4.736). IR ν_{max}^{Nujol} cm^{-1}: 1620, 1600, 1577, 1513. NMR δ ppm in CD_3COCD_3; 8.20, 7.77 (both end peaks of quartet, J_1=13.4 cps, J_2=12.4 cps, β-H from carbonyl of linear conjugated dienone moiety), 8.08—7.30 (5H, multiplet, $C_6\underline{H}_5$), 6.62 (1H, doublet, J_1=13.4 cps, α-H of dienone), 5.37 (1H, doublet, J_2=12.4 cps, γ-H of dienone), 3.60—3.20 (4H, multiplet, α-methylenes of the pyrrodiline ring), 2.17 (3H, singlet, $C\underline{H}_3$), 2.10—1.75 (4H, multiplet, β-methylenes of the pyrrolidine ring).

Reaction of 1-Phenyl-1,3,5-hexanetrione (IIIa) with Pyrrolidine——To a solution of IIIa (1.02 g, 5 mmole) in a mixture of 7 ml of AcOEt and 7 ml of THF was added 710 mg (10 mmole) of pyrrolidine at room temperature. The mixture was allowed to stand at room temperature for 28 hr and the solvent was removed under reduced pressure. The crystalline residue was washed with *n*-hexane on glass filter and recrystallized from acetone to give 1-phenyl-5-N-pyrrolidinyl-4-hexen-1,3-dione(IX) as pale yellow needles with fluorescence of mp 139—141°. Yield, 1.24 g (96%). *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.59; H, 7.51; N, 5.57. UV λ_{max}^{EtOH} mμ (log ε): 243.3 (3.849), 301 (3.898), 390 (4.504). IR ν_{max}^{Nujol} cm^{-1}: 1540 (broad). NMR δ ppm in $CDCl_3$: 8.20—7.25 (5H, multiplet, $C_6\underline{H}_5$), 5.88 (0.7H, singlet, $C_6H_5-C(OH)=C\underline{H}-$ of IXb,) 5.00 (0.3H, singlet, $-C\underline{H}=C(CH_3)-$ of IXa), 4.78 (0.7H, singlet, $-C\underline{H}=C(CH_3)-$ of IXb), 3.62 (0.6H, singlet, $-C\underline{H}_2-$ of IXa), 3.55—3.10 (4H, multiplet, α-methylenes of the pyrrolidine ring), 2.57 (2.1H, singlet, $-C\underline{H}_3$ of IXb), 2.47 (0.9H, singlet, $-C\underline{H}_3$ of IXa), 2.10—1.75 (4H, multiplet, β-methylenes of the pyrrolidine ring).

3,5-Di-N-pyrrolidinyl-1,1′-biphenyl (VIIa) from 1-Phenyl-5-N-pyrrolidinyl-4-hexen-1,3-dione (IX)——The enaminoketone (IX) (514 mg, 2 mmole) and pyrrolidine (156 mg, 2.2 mmole) were dissolved in 12 ml of dioxane. The resulting miuture was heated at 90—100° for 11 hr, but no change was detected by TLC, and after addition of a catalytic amount of *p*-TsOH the mixture was heated at *ca.* 100° for 11 hr. A small amount of 3,5-di-N-pyrrolidinyl-1,1′-biphenyl was observed by TLC and the solvent was removed under reduced pressure. The residue (660 mg) was chromatographed on Al_2O_3 (50 g, Woelm, Grade I, neutral), Elution with benzene and recrystallization from EtOH afforded VIIa as needles of mp 156°, which was identified by mixed melting point test, TLC and IR spectrum comparison with an authentic saample. Yield, 44 mg (8.0%).

Reaction of 2-Methyl-6-phenyl-4H-pyran-4-one (IIa) with Pyrrolidine——The γ-pyrone (IIa) (1.86 g, 0.01 mole) and pyrrolidine (1.42 g, 0.02 mole) were dissolved in 50 ml of dehyd. benzene containing a catalytic amount of *p*-TsOH. The resulting mixture was distilled azeotropically for 2 hr. After removal of the solvent the residue solidified and was washed with EtOH to give yellow solid, which was recrystallized from EtOH to afford IX as yellow neeldes of mp 138—140°, which was identified by mixed melting point test, TLC and IR spectrum comparison with an authentic sample. Yield, 650 mg (25%). The mother liquor and washings were combined and condensed to dryness (1.19 g) and chromatographed on Al_2O_3 (50 g, Woelm, Grade I, neutral). Elution with benzene and recrystallization from EtOH gave VIIa as needles of mp 157°, which was identical with an authentic sample in all respects. Yield, 50 mg (20%). Elution with benzene–ether (100:1) and recrystallization from hexane gave recovered IIa (780 mg).

2-Methyl-6-phenyl-4H-pyran-4-one (IIa) from 1-Phenyl-5-pyrrolidinyl-4-hexen-2-yn-1-one (Va)——The enaminoketone (Va) (60 mg, 0.25 mmole) was suspended in 6 ml of 2% HCl and stirred for 1 hr to be homo-

geneous. After allowing to stand at room temperature overnight, the resulting red-colored mixture was extracted with ether. The organic layer was shown to contain the pyrone (IIa) and 1-phenyl-1,3,5-hexanetrione (IIIa) by TLC. To the extract was added one drop of conc. HCl, and the mixture was washed with water to be neutral and dried over Na_2SO_4. After removing the solvent the solidified residue was recrystallized from *n*-heptane to afford IIa as prisms of mp 86.0—86.5°, which was identical with an authentic sample in all respects. Yield, 35 mg (75%).

2-Ethyl-6-phenyl-4H-pyran-4-one (IIb) from 1-Phenyl-5-N-pyrrolidinyl-4-hepten-2-yn-1-one (Vb)——The enaminoketone (Vb) (126 mg, 0.5 mmole) was dissolved in 3.5 ml of 3% HCl, and the resulting mixture was stirred for 3 hr and extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue (80 mg) was chromatographed on Al_2O_3 (20 g, Woelm, grade III, neutral). Elution with benzene–ether (10:1) and recrystallization from ether–hexane gave IIb as prisms of mp 61°, which was identical with an authentic sample in all respects. Yield, 60 mg (30%).

2-Methyl-3,5-di-N-pyrrolidinyl-1,1′-biphenyl (VIIb) from 1-Phenyl-5-N-pyrrolidinyl-4-hepten-2-yn-1-one (Vb)——The enamine (Vb) (51 mg, 0.2 mmole) and pyrrolidine (71 mg, 1 mmole) were dissolved in 10 ml of dehyd. dioxane. The resulting mixture was heated at 80° for 40 hr. After removal of the solvent the residue (66 mg) was chromatographed on Al_2O_3 (10 g, Woelm, grade III, neutral). Elution with benzene and recrystallization from EtOH afforded VIIb as prisms of mp 118°, which was identical with an authentic sample in all respects. Yield, 23 mg (35%).

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