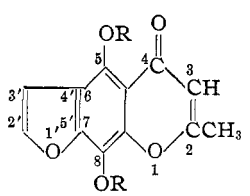
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, FOUAD I UNIVERSITY, ABBASSIA, CAIRO]

On Visnagin and Khellin and Related Compounds. A Simple Synthesis of Chromone

BY ALEXANDER SCHÖNBERG AND ALY SINA

Recently, we have been concerned with the chemistry of khellin[1] (Ib), one of the active crystalline principles of *Ammi visnaga* (L.), the two others being visnagin (Vb) and the khellol-glucoside (II).[2]

Recently, Clarke and Robertson[3] attempted to demethylate khellin by the action of hydriodic acid but did not succeed in obtaining the parent 5,8 - dihydroxy - 2 - methyl - furo - 4′,5′ - 6,7-chromone (Ia). We have obtained this substance by heating khellin with magnesium iodide in the absence of a solvent, followed by hydrolysis with dilute sulfuric acid. Ia forms yellow crystals, soluble in alkali; on methylation with diazomethane in the presence of methyl alcohol or by the methyl iodide–potassium carbonate method, it regenerates khellin. The role of methyl alcohol in the methylation of phenolic compounds with diazomethane has been discussed by Schönberg and Mustafa.[4] We have also prepared other ethers of Ia, namely, the diethyl (Ic), di-*n*-propyl (Id), diallyl (Ie) and the di-(ω-carboethoxymethyl) (Ig) ethers, in the hope of obtaining a compound which is more physiologically active than khellin. The synthesis of these compounds was carried out by allowing Ia to react with ethyl iodide, *n*-propyl iodide, allyl iodide and ethyl bromoacetate, respectively. The 5,8 - di - (ω - carboxymethoxy) derivative (If) was obtained from Ig by acid hydrolysis; If forms a water soluble sodium salt.



(I)

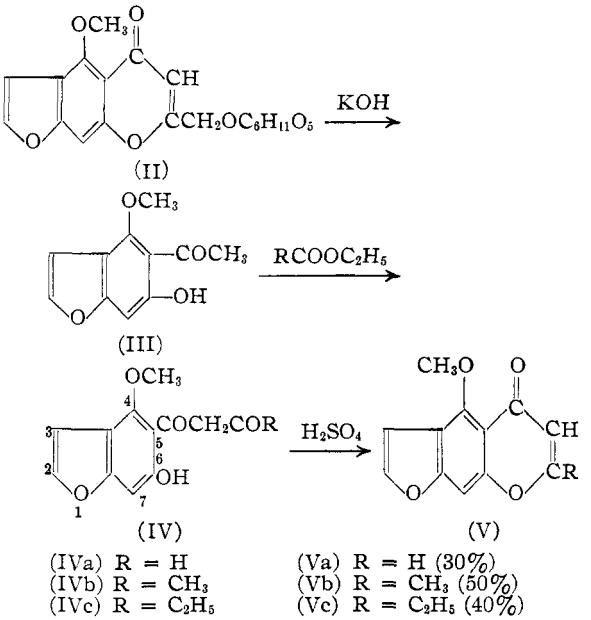
(Ia) R = H(10%)
(Ib) R = CH_3 (100%)
(Ic) R = C_2H_5 (75%)
(Id) R = n-C_3H_7 (20%)
(Ie) R = C_3H_5 (10%)
(If) R = CH_2COOH
(Ig) R = $CH_2COOC_2H_5$

Synthesis of Substances Related to Visnagin (Vb).—The synthesis of norvisnagin (Va) and 2-ethylnorvisnagin (Vc), has been effected by starting with the khellol-glucoside (II) as indicated in the following scheme. For the partial synthesis of (Vb), compare Clarke, Glaser and Robertson.[5]

By similar reactions we have recently[1] synthesized 2-norkhellin and its 2-substituted derivatives.

(1) Schönberg and Sina, THIS JOURNAL, **72**, 1611 (1950).
(2) Späth and Gruber, *Ber.*, **74**, 1492 and 1549 (1941).
(3) Clarke and Robertson, *J. Chem. Soc.*, 302 (1949).
(4) Schönberg and Mustafa, *ibid.*, 746 (1946).
(5) Clarke, *et al.*, *ibid.*, 2260 (1948).

"Scheme A"



(II)

(III)

(IV)

(V)

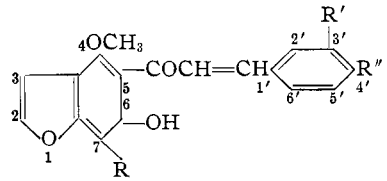
(IVa) R = H
(IVb) R = CH_3
(IVc) R = C_2H_5
(Va) R = H (30%)
(Vb) R = CH_3 (50%)
(Vc) R = C_2H_5 (40%)

IVb occurs in two forms, colorless and yellow which are interconvertible. This may be a case of keto-enol or ring-chain tautomerism. Similar observations were made in the case of ω-acetokhellinone.[1]

Color Reaction of Visnagin with Potassium Hydroxide.—Chromones possessing a 2-methyl group gave a characteristic color reaction, reddish violet, with potassium hydroxide, in contrast to those chromones which are not substituted in the 2-position or have a 2-phenyl group.[1] The importance of the 2-methyl group (or the substituted methyl group, *e. g.*, ethyl) in position 2 has been stressed. In agreement with this observation, we have found that norvisnagin (Va), ω-acetovisnaginone (IVb) and IVc do not give the color reaction in contrast to visnagin (Vb) which gives a strong reddish violet color (for further examples compare the experimental part).

Condensation of Khellinone and Visnaginone (III) with Aromatic Aldehydes.—Visnaginone was condensed with vanillin, veratraldehyde and *p*-dimethylaminobenzaldehyde which led to the formation of the colored chalkones (VIa-c), respectively. Khellinone condenses with veratraldehyde to give (VId). Similar chalkones have been described in our previous communication.[1]

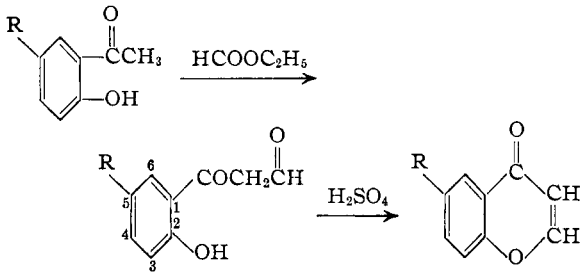
Synthesis of Chromone.—Up to the present time the best method for the preparation of chromone has been by the decarboxylation of



(VI)

(VIa) R = H, R′ = OCH_3, R″ = OH
(VIb) R = H, R′ = R″ = OCH_3
(VIc) R = R′ = H, R″ = $N(CH_3)_2$
(VId) R = R′ = R″ = OCH_3

chromone-2-carboxylic acid.[6] For the preparation of chromone in better yield, we have condensed *o*-hydroxyacetophenone with ethyl formate in the presence of powdered sodium, which resulted in the formation of *o*-hydroxy-ω-formyl acetophenone (VIIa). Ring closure through the elimination of water leading to the production of chromone (VIIIa) was carried out by means of aqueous sulfuric acid (2 g. of chromone was obtained from 3.5 g. *o*-hydroxyacetophenone). This method appears to have a general application for the synthesis of chromones not substituted in the 2-position (compare the synthesis of norkhellin,[1] norvisnagin (Va) and 6-methyl chromone (VIIIb)).



(VII) (VIII)

(VIIa) R = H (VIIIa) R = H
(VIIb) R = CH_3 (VIIIb) R = CH_3

Physiological Effect.—The above derivatives of khellin and visnagin were tested by Prof. G. V. Anrep, Department of Physiology, Fouad I University, using the same method which was previously adopted in testing derivatives of khellin.[1] The percentage activities reported beside the formulas were compared with khellin, the activity of which was taken as 100.

It will be noticed that the effect of alkyl substitution in position 2 in norvisnagin (Va) is similar to that in norkhellin.[1] A peak of activity was obtained with the 2-methyl group, but when the latter was replaced by hydrogen, activity was reduced. When the 2-methyl group was replaced by a 2-ethyl group, activity again dropped, but to a less extent (compare activity of Va-c, and of norkhellin, khellin and 2-ethyl-norkhellin.[1]

Increase in the length of alkoxy chain in the 5,8-positions in khellin led to a decrease in activity (compare Ic-e). The parent 5,8-dihydroxy-furo-chromone (Ia) was only slightly active.

(6) Heywang and Kostanecki, *Ber.*, **35**, 2887 (1902).

Experimental

2-Hydroxy-ω-formyl-acetophenone (VIIa).—7 grams of *o*-hydroxyacetophenone was dissolved in 30 cc. of warm ethyl formate in a flask fitted with a reflux condenser; 3 g. of powdered sodium suspended in dry ether was then added gradually and the vigorous reaction was regulated by external cooling when necessary. When the reaction had subsided, another 6 g. of the ester followed by 1 g. of powdered sodium was added, then the mixture was refluxed for ten minutes and left overnight. Ice and water were then carefully added and the resulting solution was extracted twice with ether. The separated aqueous layer was freed from ether in a vacuum, then acidified with acetic acid. An oil separated which quickly solidified into a crystalline precipitate; this was filtered off, washed with water, dried and crystallized from a mixture of benzene and petroleum ether (40/60°) as colorless crystals of (VIIa) m. p. 105° with decomposition. An alcoholic solution of the substance gave with ferric chloride, a red color. With sulfuric acid (VIIa) gave a yellow color. *Anal.* Calcd. for $C_9H_8O_3$: C, 65.8; H, 4.9. Found: C, 65.9; H, 4.9.

Chromone[7] **(VIIIa).**—One gram of (VIIa) was heated on a water-bath under a reflux condenser with 30 cc. of aqueous sulfuric acid (16 cc. of 98% sulfuric acid mixed with 70 cc. of water) for thirty minutes. After cooling, the solution was neutralized with sodium bicarbonate and allowed to stand. A colorless crystalline precipitate was obtained and was recrystallized from petroleum ether (40/60°), as colorless crystals m. p. 59° not depressed by an authentic sample of chromone.[6] With sulfuric acid it gave a colorless solution with bluish-violet fluorescence. *Anal.* Calcd. for $C_9H_6O_2$: C, 74.0; H, 4.0. Found: C, 74.0; H, 4.0. From 7 g. of *o*-hydroxyacetophenone and 30 g. of ethyl formate 4 g. of chromone was obtained.

2-Hydroxy-5-methyl-ω-formyl-acetophenone (VIIb).—Three grams of 2-hydroxy-5-methyl-acetophenone was condensed with 6 g. of ethyl formate in presence of 2 g. of powdered sodium as described in (VIIa). *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.6. Found: C, 67.7; H, 5.7.

6-Methylchromone (VIIIb).—One gram of (VIIb) was refluxed with 30 cc. of alcoholic sulfuric acid (16 cc. of 98% sulfuric acid mixed with 96% alcohol and made up to 100 cc.) for thirty minutes. On neutralization with sodium bicarbonate and dilution with water, the colorless crystalline precipitate of (VIIIb)[8] was obtained, washed with water and recrystallized. *Anal.* Calcd. for $C_{10}H_8O_2$: C, 75.0; H, 5.0. Found: C, 74.7; H, 5.0.

6-Hydroxy-4-methoxy-5-ω-formylacetylcoumarone (IVa).—4.1 grams of visnaginone was condensed with 20 g. of ethyl formate by the addition of 2 g. of powdered sodium as in the case of (VIIa). *Anal.* Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3. Found: C, 61.1; H, 4.6.

Norvisnagin (Va).—ω-Formylvisnaginone (IVa) was cyclized as in (VIIIa). *Anal.* Calcd. for $C_{12}H_8O_4$: C, 66.7; H, 3.7. Found: C, 66.4; H, 4.0.

6-Hydroxy-4-methoxy-5-acetoacetylcoumarone (IVb).—The colorless crystals of (IVb)[5] were transformed into the yellow form by boiling the solution in xylene for five minutes and then concentrating, on which yellow crystals were obtained m. p. about 105–106° giving a yellow melt. The yellow form gave a brownish red color with ferric chloride and with sulfuric acid a yellow color as is the case with the colorless form. The yellow form is reconverted into the colorless by crystallizing from dilute alcohol. The following is the analysis of the yellow form. *Anal.* Calcd. for $C_{13}H_{12}O_5$: C, 62.9; H, 4.8. Found: C, 62.8; H, 5.0.

6-Hydroxy-4-methoxy-5-propioacetylcoumarone (IVc).—4.0 grams of visnaginone was condensed with 8 g. of ethyl propionate in presence of 2 g. of powdered sodium as described in VIIa. *Anal.* Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.3. Found: C, 64.7; H, 5.3.

(7) Mentzer and Meunier, *Bull. soc. chim.*, [5] **11**, 302 (1944).
(8) Ruhemann and Bausor, *J. Chem. Soc.*, **79**, 474 (1901).

TABLE I

Number	Color	M. p., °C.	Medium of crystallization	$FeCl_3$ reaction[a]	Sulfuric acid reaction
VIIb	Colorless	About 150[b]	Alcohol	Reddish-brown developed gradually	Deep yellow
IVa	Colorless	166[b]	Methyl alcohol	Red developed gradually	Crystals orange giving yellow solution
IVc	Colorless	107[c]	Dilute alcohol	Red	Yellow
VIIIb	Colorless	88–89	Petrol (60/90°)	...	Colorless solution with blue fluorescence
Va	Colorless	152	Methyl alcohol	...	Yellow
Vc	Colorless	139	Dilute methyl alcohol	...	Yellow
VIa[d]	Orange	198 red melt	Alcohol	Deep brown	Reddish-brown
VIb	Orange	146	Alcohol	Brown	Reddish-brown
VId	Orange	153	Alcohol	Brown	Reddish-brown
VIc[e]	Orange	162	From acetone then benzene	Blood-red	Orange-brown

[a] Aqueous ferric chloride added to alcoholic solution of substance. [b] With decomposition and evolution of gas. [c] Deep yellow melt. [d] Soluble in dilute potassium hydroxide giving orange solution. [e] Soluble in dilute hydrochloric acid giving yellow solution.

2-Ethylnorvisnagin (Vc).—IVc was cyclized as in the case of chromone. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 4.9. Found: C, 69.4; H, 5.0.

6-Hydroxy-4-methoxy-4′-hydroxy-3′-methoxybenzalcoumarone (VIa).—One gram of visnaginone together with 0.8 g. of vanillin was dissolved in 10 cc. of alcohol. To the hot solution potassium hydroxide solution (4 g. in 4 cc. of water) was added and the mixture refluxed on a steam-bath for thirty minutes and left overnight. It was then acidified with hydrochloric acid and the precipitate filtered off, washed with hot water several times and then crystallized from alcohol. The crystals (VIa) were then treated with cold benzene for five minutes, filtered and then crystallized twice. *Anal.* Calcd. for $C_{19}H_{16}O_6$: C, 67.1; H, 4.7. Found: C, 67.4; H, 4.9.

6-Hydroxy-4-methoxy-3′,4′-dimethoxybenzalcoumarone (VIb).—0.83 gram of visnaginone and 0.66 g. of veratraldehyde were condensed as described in VIa. After acidification, the oil that separated solidified gradually on standing, was filtered off, washed with water and then crystallized. VIb was soluble in hot alcohol and benzene and very difficultly soluble in petroleum ether (60/90°). *Anal.* Calcd. for $C_{20}H_{18}O_6$: C, 67.8; H, 5.1. Found: C, 68.1; H, 5.3.

6-Hydroxy-4,7-dimethoxy-3′,4′-dimethoxybenzalcoumarone (VId).—0.93 gram of khellinone and 0.66 g. of veratraldehyde were condensed as in case of VIb. *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.2. Found: C, 65.5; H, 5.2.

6-Hydroxy-4-methoxy-4′-dimethylaminobenzalcoumarone (VIc).—One gram of visnaginone was condensed with 0.7 g. of *p*-dimethylaminobenzaldehyde as in case of VIa. The reaction mixture was then acidified with hydrochloric acid on which an orange solution was obtained; any precipitate was filtered off and the filtrate rendered alkaline with ammonia and the precipitate formed was crystallized. It is easily soluble in hot acetone and more difficultly in hot alcohol. *Anal.* Calcd. for $C_{20}H_{19}O_4N$: C, 71.2; H, 5.6; N, 4.2. Found: C, 71.7; H, 5.6; N, 4.3.

Demethylation of Khellin.—A solution of 6.7 g. of khellin (1 mole) in dry benzene was added to an ether–benzene mixture of magnesium iodide[9] (2 moles). The solvent in the mixture was removed *in vacuo*, the residue was dried in a vacuum at 130°, and was kept at 160–165° (bath temperature) for one and one-half hours. After cooling the solid was pulverized and decomposed with dilute sulfuric acid; the resulting product was filtered off, washed with water, treated with dilute aqueous solution of sodium hydrogen sulfite to remove iodine, washed again with water and finally crystallized from alcohol or from absolute acetic acid as yellow crystals of 5,8-dihydroxy-2-methylfuro-(4′-5′,6,7)-chromone (Ia) m. p. 277°. An alcoholic solution gave a green color with an aqueous solution of ferric chloride. With sulfuric acid, Ia gave an orange color which on gentle heating changed into olive green and on further heating to reddish brown. It dissolved in aqueous alkali with a reddish brown color. *Anal.* Calcd. for $C_{12}H_8O_5$: C, 62.1; H, 3.4. Found: C, 62.1; H, 3.5.

Ethers of 5,8-Dihydroxy-2-methylfuro-(4′,5′,6,7)-chromone (Ia). 5,8-Dimethyl Ether (Ib).—(a) 0.5 gram of Ia was suspended in a mixture of dry ether and absolute methyl alcohol; to the suspension an excess of an ethereal solution of diazomethane was added and the mixture left in ice for three days. The solution was then concentrated in a vacuum to a small volume, on which a crystalline deposit was obtained; this was filtered off and the solid was triturated with methyl alcohol at room temperature and allowed to stand for fifteen minutes. The solution was then filtered from a small amount of unchanged phenolic substance and the filtrate evaporated to dryness. The crystalline residue was freed from oily impurities by pressing over a porous plate and washing with a mixture of equal volumes of ether and petroleum ether (40/60°). It was finally crystallized from dilute methyl alcohol as colorless crystals of Ib m. p. 153° undepressed by admixture with an authentic sample of khellin. With sulfuric acid it gave an orange yellow color. *Anal.* Calcd. for $C_{14}H_{12}O_5$: C, 64.6; H, 4.6. Found: C, 64.7; H, 4.4.

(b) 0.5 gram of Ia was mixed with 3 g. of potassium carbonate, 50 cc. of acetone and 3 cc. of methyl iodide and refluxed for thirty hours. The solution was filtered hot and the residue washed twice with hot acetone. The mixed filtrate and washings were evaporated to dryness in a vacuum, triturated with water and the solid filtered, washed with water and crystallized from methyl alcohol as colorless crystals of Ib m. p. 153° not depressed by admixture with an authentic sample of khellin. The following ethers were prepared by adopting the same procedure:

5,8-Diethyl Ether (Ic).—From Ia and ethyl iodide, as colorless crystals of Ic, after being once crystallized from methyl alcohol and twice from petroleum ether (60/90°) m. p. 94°. It gave an orange yellow color with sulfuric acid. It was easily soluble in cold alcohol and benzene, but difficultly soluble in petroleum ether. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.5. Found: C, 66.7; H, 5.5.

5,8-Di-*n*-propyl Ether (Id).—From Ia and *n*-propyl iodide, Id separated from petroleum ether (40/60°) as almost colorless crystals m. p. 81°. With sulfuric acid it gave an orange yellow color. It dissolved easily in cold methyl and ethyl alcohol and in hot petroleum ether (40/60°) but was very difficultly soluble in water. *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.4; H, 6.3. Found: C, 68.3; H, 6.5.

5,8-Diallyl Ether (Ie).—From Ia and allyl iodide, Ie was obtained from petroleum ether (60/90°) as almost colorless crystals m. p. 124°. Its solubilities are similar to Id. With sulfuric acid Ie gave an orange brown color. *Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.2; H, 5.1. Found: C, 69.1; H, 5.0.

(9) Schönberg and Moubasher, *J. Chem. Soc.*, 462 (1944).

5,8-Di-(ω-carboethoxymethoxy)-2-methylfuro-4′,5′,-6,7-chromone (Ig).—Obtained from Ia and ethyl bromoacetate as described in Ib. End of reaction is known when a small portion of the filtered acetone solution gives no color with aqueous ferric chloride (about 48 hours reflux). Ig separated from dilute alcohol as colorless crystals m. p. 125° and gave with sulfuric acid an orange yellow color. It was very difficultly soluble in water and petroleum ether (60/90°) and soluble in alcohol. *Anal.* Calcd. for $C_{20}H_{20}O_9$: C, 59.4; H, 4.9. Found: C, 59.0; H, 4.8.

5,8-Di-(ω-carboxymethoxy)-2-methylfuro-4′,5′,6,7-chromone (If).—0.8 gram of Ig was dissolved in 20 cc. of glacial acetic acid and to the solution 20 cc. of water and 1 cc. of sulfuric acid (sp. gr. 1.84) were added and the mixture refluxed for twenty minutes, cooled and the crystalline precipitate filtered off, washed with water and then with alcohol; finally it was crystallized from alcohol as colorless crystals of If m. p. 276° with decomposition giving a brown melt. With sulfuric acid it gave an orange yellow color. It was very difficultly soluble in water and petroleum ether (60/90°) and benzene, soluble in hot alcohol. It dissolved in an aqueous solution of sodium bicarbonate and was precipitated by acidification with hydrochloric acid. *Anal.* Calcd. for $C_{16}H_{12}O_9$: C, 55.2; H, 3.4. Found: C, 55.5; H, 3.6.

Color Reactions with Potassium Hydroxide.—These were carried out as in the case of khellin[1] with the following results:

Visnagin (Vb)	Red violet
5,8-Diethoxyfuro-2-methylchromone (Ic)	Red violet
5,8-Di-(ω-carboxymethoxy)-furo-2-methyl-chromone (If)	Red violet
Norvisnagin (Va)	No color reaction
6-Hydroxy-4-methoxy-5-acetoacetyl-coumarone (IVb)	No color reaction
6-Hydroxy-4-methoxy-5-propioacetyl-coumarone (IVc)	No color reaction
2-Ethylnorvisnagin (Vc)	Weak brownish-red

Summary

1. Demethylation of khellin (Ib) by the action of magnesium iodide led to the production of Ia from which the derivatives Ic–Ig were obtained.

2. Norvisnagin (Va) and 2-ethylnorvisnagin (Vc) were synthesized (compare scheme "A").

3. By a similar route, using *o*-hydroxyacetophenone and ethyl formate, chromone was synthesized in good yield.

4. Khellin and visnagin analogs were submitted to the potassium hydroxide test and the results obtained emphasized the previous findings,[1] pointing to the importance of the methyl group in position 2 in chromones and in γ-pyrones for this test.

5. The chalkones (VIa–d) obtained from khellinone and visnaginone were synthesized.

6. The physiological activities of analogs of khellin and visnagin are stated in percentage beside the formulas, taking the activity of khellin as 100.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Cyclic Polyolefins. IX. Synthesis from Carbonyl-bridged Intermediates. 2,4-Diphenylcycloöcta-1,4-diene

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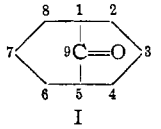
The synthesis of unsaturated eight-membered ring compounds by cleavage of the bridge of bicyclic structures is advantageous because only sterically favored cyclizations are required in some instances for preparation of the bicyclic intermediates. Moreover, cleavage of the bridge may provide groups which can be degraded with introduction of unsaturation into the ring. An example is the Willstätter synthesis[3] of cyclooctatetraene, in which cleavage of a methylamino bridge by successive Hofmann exhaustive methylations permits the introduction of two double bonds. Removal of the carbonyl bridge in compounds containing the bicyclo[3.3.1]nonan-9-one ring system (I) appeared to offer a promising method for the synthesis of substituted cyclooctapolyenes. This paper reports the synthesis of 2,4-diphenylcycloöcta-1,4-diene (XI) by a route involving cleavage of the carbonyl bridge of the easily synthesized bicyclic ketone, 2,4-diphenylbicyclo[3.3.1]non-2-en-9-one (III).



I

The bicyclic ketone III was prepared in 88% yield by cyclization of 2-(α-phenyl-β-benzoylethyl)-cyclohexanone (II),[4] which was obtained in 80% yield by the Michael addition of cyclohexanone to benzalacetophenone. Cyclization in the presence of acetic acid and hydrochloric acid gave an improved yield (88%) compared to concentrated sulfuric acid in absolute ethanol (55%).[4] The double bond in III was considered by Allen to be at the bridgehead (α,β) position, although this location would violate Bredt's rule,[5] on the basis of indirect evidence.[4,6] Direct evidence concerning the location of the double bond was obtained by comparing the ultraviolet absorption spectra of the 2,4-dinitrophenylhydrazones of III and the corresponding saturated ketone, IV, prepared from III by hydrogena-

(1) du Pont Fellow, 1947–1948.

(2) du Pont Postdoctorate Fellow, 1948–1949.

(3) Willstätter and Waser, *Ber.*, **44**, 3423 (1911); Willstätter and Heidelberger, *ibid.*, **46**, 517 (1913).

(4) Allen and Sallans, *Can. J. Research*, **9**, 574 (1933).

(5) Bredt, *Ann.*, **437**, 1 (1924).

(6) Allen, *Chem. Rev.*, **37**, 212, 215 (1945).