**221.** *Macrocyclic Acetylenic Compounds. Part V.[1] Concentration Effects in the Glaser Coupling Reaction.*

By I. D. CAMPBELL and G. EGLINTON.

The ratio of cyclic dimer to cyclic trimer obtained in the Glaser coupling of octa-1,7-diyne, using cupric acetate in pyridine–methanol, is increased by making the reaction conditions more dilute, although a longer reaction time is necessary.

CUPRIC acetate in pyridine, or pyridine–methanol,[2] is now established as a convenient reagent for the Glaser coupling [3,4] of monoterminal acetylenes (I).

$$2RC{\equiv}CH + 2Cu(OAc)_2 \xrightarrow{\text{pyridine}} R(C{\equiv}C)_2R + 2CuOAc + 2HOAc$$
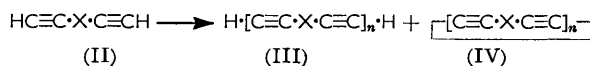
(I)
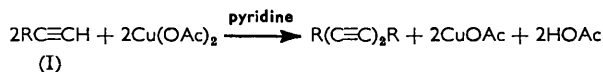
[1] Part IV, Eglinton, Lardy, Raphael, and Sim, preceding paper.
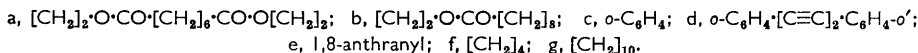[2] Eglinton and Galbraith, *Chem. and Ind.*, 1956, 737; *J.*, 1959, 889.
[3] Glaser, *Ber.*, 1869, **2**, 422; *Annalen*, 1870, **154**, 159.
[4] Eglinton and McCrae, " Recent Advances in Organic Chemistry," 1963, Vol. IV, ed. Raphael, Taylor, and Wynberg, Interscience, New York.

The reagent has also seen extensive use [2,4-7] in the synthesis of macrocyclic acetylenes by the intramolecular coupling of diterminal diynes (II)

$$HC{\equiv}C{\cdot}X{\cdot}C{\equiv}CH \longrightarrow H{\cdot}[C{\equiv}C{\cdot}X{\cdot}C{\equiv}C]_n{\cdot}H + \boxed{[C{\equiv}C{\cdot}X{\cdot}C{\equiv}C]_n}$$

$$(II) \qquad\qquad (III) \qquad\qquad (IV)$$

where X is:

a, $[CH_2]_2{\cdot}O{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO{\cdot}O[CH_2]_2$;   b, $[CH_2]_2{\cdot}O{\cdot}CO{\cdot}[CH_2]_8$;   c, $o\text{-}C_6H_4$;   d, $o\text{-}C_6H_4{\cdot}[C{\equiv}C]_2{\cdot}C_6H_4\text{-}o'$;   e, 1,8-anthranyl;   f, $[CH_2]_4$;   g, $[CH_2]_{10}$.

Low reactant concentrations are generally thought to favour any intramolecular reaction which is in competition with the corresponding intermolecular processes, and it is our experience [2,5,6] that the Glaser coupling when conducted under high-dilution conditions affords good yields of the lowest cyclic oligomer (IV) which is sterically feasible. Small amounts of the higher cyclic and linear polymers (IV and III, respectively) are also formed. Thus, one ester (IIa) gave [2] both cyclic monomer (IVa; $n = 1$) and dimer (IVa; $n = 2$), while a high yield ($\sim$88%) of cyclic monomer was obtained [5] from another (IIb). Only one pure compound, the cyclic dimer, could be isolated from the high-dilution coupling of o-diethynylbenzene [6] (IIc), and this product was obtained in about the same yield (60%) when the " half-closed " dimer (IId) was similarly treated.[8]

By contrast, Sondheimer and his colleagues [9] have successfully coupled numerous $\alpha\omega$-alkadiynes and related compounds at ordinary concentration levels (*e.g.*, *ca.* 0·1 molar in pyridine and saturated in copper acetate), but the products are generally complex mixtures of the lower cyclic oligomers. However, similar conditions [*e.g.*, *ca.* 0·03 molar in pyridine–methanol (1 : 1) and saturated in copper acetate (>0·5 molar)] were used by the Japanese workers [7] in their synthesis of novel cyclic arylacetylenes and quite high yields of single compounds resulted in certain cases (*e.g.*, IIe $\longrightarrow$ IVe, $n = 2$; 95%).

There would therefore appear to be some doubt as to the value of high-dilution techniques in the synthesis of macrocyclic acetylenes by the Glaser coupling reaction. The object of the present short study has been to adduce some quantitative evidence which would reveal any relation there might be between the initial concentration of diyne and the composition of the coupled product. The diyne chosen was octa-1,7-diyne (IIf) which has been reported [9] as giving a complex mixture of cyclic dimer, trimer . . . hexamer,* and long-chain polymer when coupled at ordinary concentrations (cyclic monomer, IVf, $n = 1$, is not feasibly sterically). The reaction products were analysed for insoluble long-chain polymer by collecting the precipitate, and for the cyclic and acyclic dimers and trimers by total hydrogenation of the mixture and gas–liquid chromatography (g.l.c.) of the resulting cyclo- and n-hexadecane and tetracosane. This procedure avoids difficulties due to preferential loss incurred either by more conventional analytical procedures such as crystallisation or column chromatography, or by rearrangement and decomposition of the parent acetylenes during g.l.c. Further, it permits quantitative comparison with standard hydrocarbons. Cyclic tetramers, pentamers, etc., which may have been present, were not detected.

The results of runs at four different concentrations are summarised in the Table. In each case the molar concentration of the cupric acetate is four times the initial diyne concentration. A decrease in this concentration is seen to be accompanied by, (*a*) a decrease in the quantity of insoluble long-chain polymer precipitated from the reaction

---

* For convenience the terms dimer, trimer . . . oligomer, polymer, *etc.*, are used in the sense of the starting unit, *less* the hydrogen atoms removed in the coupling.

[5] Behr, Eglinton, Galbraith, and Raphael, *J.*, 1960, 3614.
[6] Carnduff, Eglinton, McCrae, and Raphael, *Chem. and Ind.*, 1960, 559.
[7] Akiyama, Misumi, and Nakagawa, *Bull. Chem. Soc. Japan*, 1962, **35**, 1826, 1829.
[8] Behr, Eglinton, Lardy, and Raphael, *J.*, 1964, 1147.
[9] Sondheimer, Amiel, and Wolovsky, *J. Amer. Chem. Soc.*, 1959, **81**, 4600, and subsequent papers in the same series.

mixture, (b) an increase in the proportion of acyclic to cyclic dimer and trimer, and (c) an increase in the proportion of the cyclic dimer relative to cyclic trimer.

TABLE.

The coupling of octa-1,7-diyne (IIf) by cupric acetate in pyridine–methanol
(1 : 1 by vol.) at 55°.

Run	Initial diyne concn. (mmoles/l.)	Initial Cu(OAc)$_2$ concn. (mmoles/l.)	Polymer * (%)	Cyclic dimer † Cyclic trimer	Acyclic † Cyclic
1	100	400	55	1·1	‡
2	50	200	43	1·6	0·15
3	25	100	26	2·4	6·7
4	12·5	50	0	3·9	20

* Insoluble precipitate expressed as a percentage of starting diyne; although solution volumes changed no further ether-insoluble material was obtained after removal of the pyridine. † Ratio of molar proportions as determined for the corresponding alkanes formed on hydrogenation. The acyclic alkanes in runs 3 and 4 were in the ratio 6 : 1 : : dimer : trimer. ‡ No acyclic alkanes detected.

The reaction time of 24 hours is too short for completion of the oxidative coupling of this relatively inactive[4] diyne and no attempt has been made to isolate the individual coupled products. However, the results do seem to show that high-dilution conditions favour the formation of lower as against higher cyclic oligomers. This adds support to the isolated finding[2] that the relative amounts of cyclic monomer and dimer changed with the degree of dilution of the starting diyne (IIg). Further investigations are desirable, particularly into any effect related to the proportion of [Cu^{2+}] present, and into the stereo-chemical requirements of the ethynyl compounds and of any intermediate copper complex.

EXPERIMENTAL

Infrared measurements were made with a Unicam S.P. 100 spectrophotometer, equipped with a S.P. 130 prism-grating double monochromator operated under vacuum conditions. The ethynyl estimations were obtained by scanning carbon tetrachloride extracts over the region 3200—3400 cm.$^{-1}$ at a rate of 75 cm.$^{-1}$ per min. (spectral slit width, 5 cm.$^{-1}$). The cali-bration curve was based on the peak intensity near 3313 cm.$^{-1}$ for octa-1,7-diyne as standard. G.l.c. measurements were made with a Pye " Argon " gas chromatograph [46 in. × $\frac{1}{8}$ in. column, 0·5% Apiezon " L " on Celite (80—100 mesh)]. Octa-1,7-diyne[10] was distilled and then rigorously purified (1-ml. batches) by preparative g.l.c. [Perkin-Elmer model 451, poly-propylene glycol column (36 in. × 1 in., 20%)] at 90°. The purity of this material was further checked (R_T = 8 min.) by analytical g.l.c. on a similar column (46 in. × $\frac{1}{8}$ in., 25%, 84°, flow rate 60 ml./min.).

Oxidative Coupling of Octa-1,7-diyne.—A standard solution of cupric acetate was used in all the runs; it consisted of cupric acetate monohydrate (7·52 g.) in pyridine–methanol (1 : 1 by volume, 100 ml.) and was approximately 0·4 molar.

(a) *Preliminary study.* Octa-1,7-diyne (105 mg.) was dissolved in the standard copper acetate solution (10·5 ml.) contained in a stoppered flask immersed in a water-bath held at 55°. Portions (0·5 ml.) were removed at frequent intervals, poured into ice-cold sulphuric acid (18N), and then extracted with carbon tetrachloride. The washed and dried extracts were made up to 6 ml. with fresh carbon tetrachloride and the optical densities of the solutions at 3313 cm.$^{-1}$, ν(≡C–H), determined (5 mm. cell.). The ethynyl content fell rapidly and was virtually zero after 12 hr.

(b) *Dilution study.* Each run listed in the Table was carried out with a solution as des-cribed under (a), after an appropriate volume of the pyridine–methanol 1 : 1 mixture had been added as diluent. After incubation at 55° for 24 hr. in a stoppered flask the precipitated poly-mer was collected by filtration and then washed, dried, and weighed. It was an off-white powder, insoluble in the common organic solvents, showing weak absorption at 3294 cm.$^{-1}$ ν(≡C–H) and was therefore a linear polymer (IIIf). The filtrate was poured into cold sulphuric acid (25 ml.; 18N) and extracted with ether, and the ether extract washed, dried, and evaporated.

[10] Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619.

The solution of the residue in ethyl acetate (25 ml.) was then hydrogenated over 10% palladium–charcoal catalyst (50 mg.), the uptake of hydrogen approximating to theory in each case. After filtration the solution of cyclo- and n-alkanes was concentrated to smaller bulk (*ca.* 5 ml.) and analysed by g.l.c.

(c) *Gas–liquid chromatography.* A preliminary examination on the 0·5% Apiezon " L " column showed two main peaks which were so widely different in retention times that iso-thermal analysis was unsatisfactory and that some form of temperature programming was desirable. The first peak was proved to be cyclohexadecane by comparison of its retention time with those of cyclododecane and cyclotetradecane. Suitable standards were not available for the second peak, ascribed to cyclotetracosane, but it bore the expected relation to the peaks for the n-C_{24} and n-C_{25} alkanes.

The internal standard method was adopted for the analysis of the hydrogenated product. A known mixture of the n-C_{18} and n-C_{26} alkanes was added to each sample, and the solution carefully homogenised and then gas chromatographed, first at 125° for the cyclo-C_{16} : n-C_{18} ratio, and secondly at 210° for the cyclo-C_{24} : n-C_{26} ratio. The known molar ratio of the n-C_{18} : n-C_{26} mixture then enabled the ratio of cyclo-C_{16} to cyclo-C_{24} to be calculated. The same procedure was used for the n-C_{16} and n-C_{24} alkanes. Peak heights were used for the calculations, all peaks being symmetrical. Retention times were as follows: at 125°; 5, 8, and 14 min. for n-C_{16}, cyclo-C_{16}, and n-C_{18} alkanes, respectively; at 210°; 5, 7, and 10 min, for n-C_{24}, cyclo-C_{24}, and n-C_{16} alkanes, respectively.

DEPARTMENT OF CHEMISTRY, THE UNIVERSITY, GLASGOW W.2.   [*Received, August* 31*st,* 1963.]