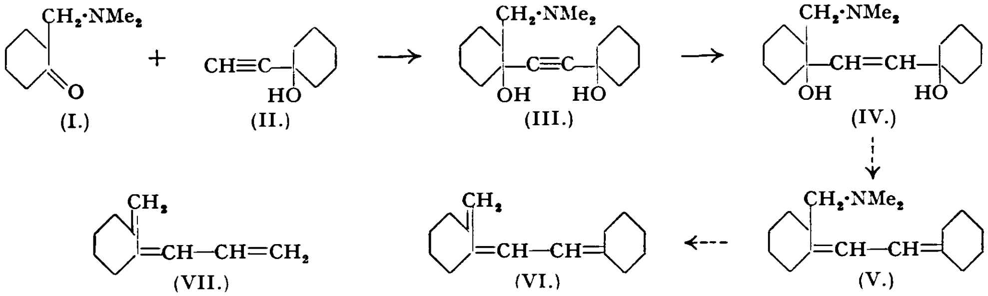
621. *The Condensation of 2-Dimethylaminomethyl*cyclo*hexan-1-one with Acetylenic Compounds.*

By R. A. Raphael and Franz Sondheimer.

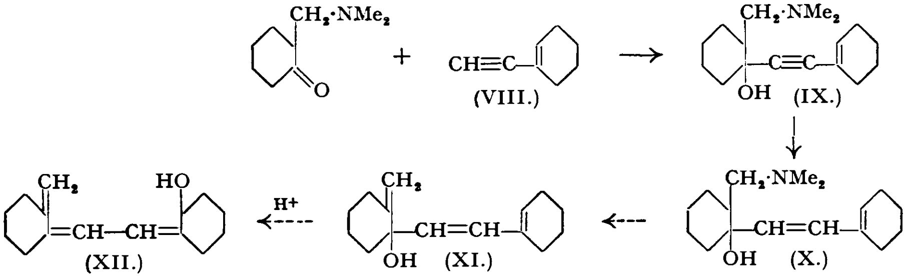
2-Dimethylaminomethyl*cyclo*hexan-1-one and the Grignard compounds of 1-ethynyl*cyclo*hexan-1-ol and 1-ethynyl*cyclo*hex-1-ene react normally to give the expected products. A description is given of the unsuccessful attempts to convert these products into compounds containing a conjugated triene system similar to that occurring in vitamins D.

Although it is fifteen years since the structures of vitamins D were elucidated by Heilbron's and Windaus's schools comparatively few attempts have been made to prepare simple analogues containing their characteristic and unusual conjugated triene system. The only well-authenticated substance of this type is the monocyclic triene (VII) prepared by Milas and Anderson (*J. Amer. Chem. Soc.*, 1939, **61**, 2534). In order to prepare the dicyclic analogue (VI) which would more nearly approximate to the vitamin D structure, the following route was envisaged :


(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

The Grignard complex from 1-ethynyl*cyclo*hexan-1-ol (II) condensed readily with 2-dimethylaminomethyl*cyclo*hexan-1-one (I) to give an easily separable mixture of the expected two racemic glycols (III). Catalytic partial hydrogenation then gave smoothly the corresponding ethylenic glycols (IV). However, (IV) could not be reduced to the diene (V) : phosphorus di-iodide (Kuhn *et al.*, *Helv. Chim. Acta*, 1928, **11**, 87; *Ber.*, 1938, **71**, 1889) yielded only tars, and chromous chloride (Conant and Bigelow, *J. Amer. Chem. Soc.*, 1931, **53**, 676; Kuhn *et al.*, *Ber.*, 1938, **71**, 1510; 1940, **73**, 1410) left the glycols unchanged. Attempted Hofmann reactions with the glycols (III) and (IV) led only to polymers.

Next we considered the following scheme :


(VIII.) (IX.) (X.) (XI.) (XII.)

The carbinol (IX) was obtained as a liquid mixture of the two racemates from which a proportion of one component crystallised. Partial hydrogenation of (IX) over palladium–calcium carbonate produced the required compound (X) possessing the *cis*-configuration, and reduction with lithium aluminium hydride furnished the *trans*-isomer (cf. Chanley and Sobotka, *J. Amer. Chem. Soc.*, 1949, **71**, 4140). A model of *cis*-(X) indicates considerable steric interference between the *cyclo*hexenyl ring and the substituted *cyclo*hexane nucleus, so that the uniplanarity of the light-absorbing diene system is hindered. This inhibition of resonance is indicated by the low intensity of the maximal light absorption ($\lambda_{max.}$ 2280 A., ε = 6500) (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). No such steric hindrance occurs in the case of the more extended molecule of *trans*-(X), and this is mirrored in its normal light absorption properties ($\lambda_{max.}$ 2365 A., ε = 20,500; $\lambda_{infl.}$ 2290 A., ε = 18,500).

Attempts to carry out the Hofmann elimination reaction with *cis*- or *trans*-(X), in order to obtain (XI), led only to polymers. It is realised that subjecting such sensitive compounds to the relatively drastic conditions of the Hofmann reaction could be avoided if 2-methylene*cyclo*hexan-1-one were employed in the first condensation. In practice, however, this ketone readily dimerises irreversibly (Mannich, *Ber.*, 1941, **74**, 554) so that it is difficult to use it for synthetic purposes. In spite of this, investigations along these lines are in hand.

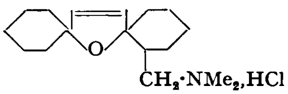
EXPERIMENTAL.

2-Dimethylaminomethyl*cyclo*hexan-1-one was prepared essentially by the method of Mannich and Braun (*Ber.*, 1920, **53**, 1875; cf. Howton, *J. Org. Chem.*, 1947, **12**, 379).

Acetylenic Glycols (III).—The Grignard complex of 1-ethynyl*cyclo*hexan-1-ol (31 g.) was prepared in the usual manner from the carbinol, ethylmagnesium bromide (from magnesium, 12 g.), and ether (750 c.c.). 2-Dimethylaminomethyl*cyclo*hexan-1-one (39 g.) in an equal volume of benzene was then added dropwise with cooling and stirring. The homogeneous reaction mixture was kept at room temperature for 16 hours and then decomposed with excess of ice-cold 2N-sulphuric acid. The aqueous layer was extracted twice with fresh ether and then basified with ammonia (*d* 0·880); the resulting oil was isolated by means of ether. The crude product was dissolved in an equal volume of warm dry ether, and the solution set aside at 0° overnight. The white 1-(*2-dimethylaminomethyl-1-hydroxy*cyclo*hexyl*)-2-(*1-hydroxy*cyclo*hexyl*)*acetylene* which separated was filtered off, washed with a little cold ether, and crystallised from light petroleum (b. p. 80—100°), from which it formed rosettes, m. p. 136—137° (22·3 g.) [Found: C, 73·2; H, 10·5; N, 4·8%; active H (Zerewitinoff), 2·02. $C_{17}H_{29}O_2N$ requires C, 73·1; H, 10·5; N, 5·0%; active H, 2]. The *hydrochloride* crystallised from alcohol–ether in small prisms, m. p. 182—183° (Found: N, 4·0. $C_{17}H_{30}O_2NCl$ requires N, 4·4%); the *methiodide*, m. p. 148—149°, crystallised in platelets from alcohol–ethyl acetate (Found: N, 3·1. $C_{18}H_{32}O_2NI$ requires N, 3·3%).

Evaporation of the ethereal mother-liquor furnished a viscous liquid which solidified on being triturated with light petroleum (b. p. 40—60°). Crystallisation from light petroleum (b. p. 60—80°) gave the isomeric *glycol* (17·2 g.) as needles, m. p. 102—103° [Found: C, 72·95; H, 10·35; N, 5·3%; active H (Zerewitinoff), 2·05]. The *hydrochloride* crystallised from alcohol–ether as a microcrystalline powder, m. p. 193—194° (Found: N, 4·5%); the *methiodide*, m. p. 244°, crystallised in platelets from alcohol–ether (Found: N, 3·05%).

Ethylenic Glycols (IV).—The higher-melting acetylenic glycol (3·4 g.) in methanol (25 c.c.) was shaken with hydrogen in the presence of palladium–calcium carbonate (500 mg.; 5%) until one mole of hydrogen had been absorbed; a distinct check in the rate of uptake was then observed. Removal of catalyst and solvent yielded a thick oil which was taken up in light petroleum (b. p. 40—60°) and set aside at room temperature overnight. The small amount of unchanged acetylenic glycol that had separated was filtered off, the light petroleum evaporated from the filtrate, and the residue distilled in a high vacuum. 1-(*2-Dimethylaminomethyl-1-hydroxy*cyclo*hexyl*)-2-(*1-hydroxy*cyclo*hexyl*)*ethylene* (IV) (2·9 g.) distilled as a viscous liquid, b. p. 105—110° (bath-temp.)/10^{-5} mm., n_D^{19} 1·5100 [Found: C, 72·9; H, 10·9%; active hydrogen (Zerewitinoff), 2·05. $C_{17}H_{31}O_2N$ requires C, 72·5; H, 11·1%; active hydrogen, 2]. An attempt to prepare the dibenzoate by the benzoyl chloride–pyridine method gave a compound crystallising from nitroethane in large prisms, m. p. 175—176°; analysis indicated it to be *2-dimethylaminomethyl-2′*: *5′-dihydro*dispiro-(cyclo*hexane-1*: *2′-furan-5′-1″*-cyclo*hexane*) *hydrochloride* [*5*: *5-(1-dimethylaminomethylpentamethylene)-2*: *5-dihydro-2*: *2-pentamethylenefuran hydrochloride* (XIII), formed by dehydration of the glycol (Found: C, 68·6; H, 9·8; N, 4·4. $C_{17}H_{30}ONCl$ requires C, 68·05; H, 10·1; N, 4·65%).



(XIII.)

Under exactly similar conditions the lower-melting acetylenic glycol (1·76 g.) furnished the corresponding ethylenic *glycol* (1·4 g.) as a viscous liquid, b. p. 110° (bath-temp.)/10^{-5} mm., n_D^{18} 1·5060 [Found: C, 72·7; H, 10·9%; active hydrogen (Zerewitinoff), 2·1].

Attempted Reduction of the Ethylenic Glycols (IV).—(*a*) To a solution of phosphorus di-iodide [from phosphorus (0·25 g.) and iodine (2·05 g.); Germann and Traxler, *J. Amer. Chem. Soc.*, 1927, **49**, 307] in carbon disulphide (50 c.c.) was added a solution of either of the ethylenic glycols (2 g.) in carbon disulphide (10 c.c.). An immediate tarry black precipitate was formed. After 30 minutes the solvent was removed under reduced pressure and the residue basified with ammonia; extraction with ether followed by evaporation of the solvent furnished a dark gum from which no pure entity could be isolated.

(*b*) A solution of chromous chloride was made by treating chromic chloride hexahydrate (9 g.) in water (10 c.c.) with zinc (15 g.) and concentrated hydrochloric acid (21 c.c.) (cf. *Inorg. Synth.*, Vol. I, 124); the resulting blue solution was filtered under nitrogen into a solution of either of the ethylenic glycols (4 g.) in 6N-hydrochloric acid (25 c.c.). After one hour at room temperature the solution was cooled, basified with strong ammonia, and extracted continuously with ether; drying ($MgSO_4$) and evaporation of the extract furnished the unchanged ethylenic glycol.

Acetylenic Carbinols (IX).—The Grignard complex of 1-ethynyl*cyclo*hex-1-ene was prepared in the usual manner from the hydrocarbon (27 g.), ethylmagnesium bromide (from magnesium, 6 g.), and ether (500 c.c.). 2-Dimethylaminomethyl*cyclo*hexan-1-one (39 g.) in an equal volume of benzene was added dropwise with stirring; the homogeneous reaction mixture was set aside at room temperature for 16 hours and then decomposed with excess of ice-cold 2N-sulphuric acid. The aqueous layer was extracted twice with fresh ether and then basified with concentrated aqueous ammonia. The resulting oil was isolated by means of ether; distillation furnished a mixture of the two acetylenic carbinols (IX) (37 g.) as a colourless liquid, b. p. 132°/10^{-4} mm., n_{D}^{18} 1·5215 (Found : C, 78·2; H, 10·5; N, 5·4. Calc. for $C_{17}H_{27}ON$: C, 78·1; H, 10·4; N, 5·35%). Light absorption (in ethanol) : $\lambda_{\mathrm{max.}}$ 2280 A., $\varepsilon = 16{,}000$. After some time the product deposited a small quantity (3 g.) of one form of 1-(2-*dimethylaminomethyl*-1-*hydroxy*cyclo*hexyl*)-2-(cyclo*hex*-1-*enyl*)*acetylene* in a crystalline form; crystallisation from light petroleum (b. p. 40—60°) furnished silky needles, m. p. 99—100° (Found : C, 78·4; H, 10·4; N, 5·6%). Light absorption (in ethanol) : $\lambda_{\mathrm{max.}}$ 2270 A., $\varepsilon = 15{,}000$.

Ethylenic Carbinols (X).—(*a*) A solution of the acetylenic carbinol (IX) (7·53 g.) in methyl acetate (50 c.c.) was shaken under hydrogen in the presence of palladium–calcium carbonate (750 mg.; 0·3%) until one mole of hydrogen had been absorbed. Removal of catalyst and solvent followed by distillation furnished cis-1-(2-*dimethylaminomethyl*-1-*hydroxy*cyclo*hexyl*)-2-(cyclo*hex*-1-*enyl*)*ethylene* (X) (6·6 g.), b. p. 112—114°/10^{-4} mm., n_{D}^{20} 1·5106 (Found : C, 77·5; H, 11·35. $C_{17}H_{29}ON$ requires C, 77·5; H, 11·1%). Contrary to the experience of Chanley and Sobotka (*loc. cit.*) with a similar compound no difficulty was encountered in obtaining a good yield of homogeneous product.

(*b*) A suspension of lithium aluminium hydride (15 g.) in dry ether (500 c.c.) was heated under reflux for 30 minutes; a solution of the acetylenic carbinol (IX) (28 g.) in ether (100 c.c.) was then rapidly added and the heating continued for four hours. The reaction mixture was then cautiously decomposed with ice and dilute sulphuric acid, the aqueous layer basified with sodium hydroxide solution, and the precipitated oil isolated by means of ether. Distillation furnished the trans-*carbinol* (X) (23 g.) as a pale yellow liquid, b. p. 116—118°/10^{-3} mm., n_{D}^{18} 1·5352 (Found : C, 77·1; H, 11·2%).

Attempted Hofmann Reaction on (X).—To a solution of the *trans*-carbinol (X) (27 g.) in light petroleum (b. p. 60—80°; 100 c.c.) was added methyl iodide (30 g.), and the reaction mixture kept at room temperature for 2 days. The solid mass formed was filtered off, washed with light petroleum, and air-dried; it was dissolved in water (150 c.c.), and the solution shaken for 1 hour with silver oxide (from silver nitrate, 30 g.). Filtration and evaporation under reduced pressure gave a crystalline mass of the corresponding quaternary hydroxide, which, on being heated to 130°/10^{-4} mm., rapidly evolved gas with the formation of a thick undistillable oil setting to a glassy resin on being cooled. The few drops of distillate obtained were completely soluble in acid and probably consisted of a small quantity of regenerated parent base. When subjected to this reaction the *cis*-carbinol behaved in an exactly similar fashion.

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