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A NEW SYNTHESIS OF (±)-3-CARONE

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Abstract—A new synthesis of 3-carone based on an intramolecular reaction of diazoketones with olefins has been achieved.

THE bicyclic monoterpene ketone, $C_{10}H_{16}O$ carone (III), has not been found in nature, but in view of the wide distribution of the related hydrocarbons, Δ^3- and Δ^4-carenes, it may be present in essential oils.

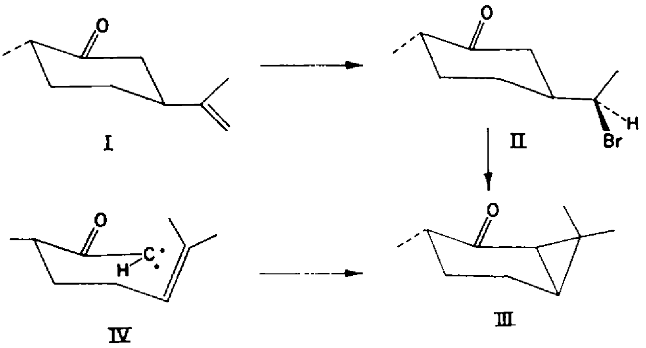
Baeyer[1] prepared this ketone by treatment of dihydrocarvone hydrobromide (II) with an alcoholic solution of potassium hydroxide at 0°; elimination of hydrogen bromide occurs with the formation of the saturated bicyclic ketone. Both the D and L forms of the ketone have been prepared from the corresponding D- and L-dihydrocarvone hydrobromides respectively.

The absorption spectrum of carone indicates some degree of hyperconjugation between the cyclopropane ring and the carbonyl group as shown by the absorption at 207 mμ, $\varepsilon = 4870$ in the UV spectrum[2,3] and by the carbonyl absorption band at 1680 cm^{-1} in the IR spectrum.[3]

Carone can be identified by the preparation of the semicarbazone, both D- and L- have m.p. 167–169°, DL, m.p. 178°, or by oxidation to caronic acid, m.p. 175°.[5]

In a new synthesis, the carbene IV, obtained from the diazoketone XIV, is condensed intramolecularly[6,7] to yield carone.

Scheme I



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* Taken in part from a thesis to be presented to the Escuela Nacional de Ciencias Químicas.

[1] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **27**, 1919 (1894).

[2] I. M. Klotz, *J. Amer. Chem. Soc.* **66**, 90 (1944).

[3] A. E. Gillam and T. F. West, *J. Chem. Soc.* 95 (1945).

[4] G. Ohloff, H. Farnow, W. Phillipp and G. Schade, *Liebigs Ann.* **625**, 212, 217 (1959).

[5] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **28**, 639 (1895).

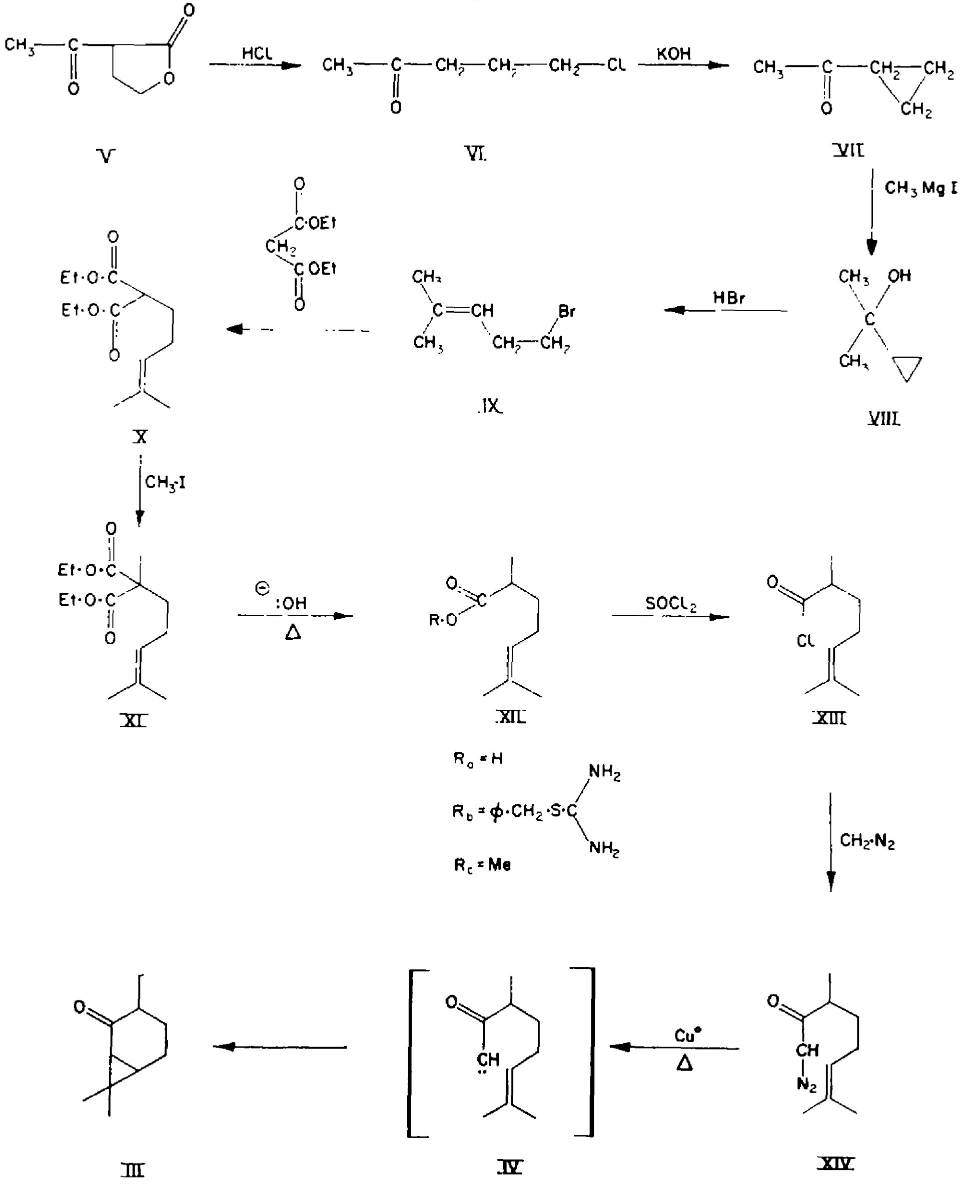
[6] G. Stork and J. Ficini, *J. Amer. Chem. Soc.* **83**, 4678 (1961).

[7] H. Zollinger, *Azo and Diazo Chemistry Aliphatic and Aromatic Compounds* Vol. I; p. 116. Interscience, New York (1961).

Conformational considerations indicate that IV should cyclize to a carone in which the methyl group at C-1 is *trans* to the cyclopropane ring. The fact that Baeyer's carone was obtained is in accord with Klyne's findings concerning the configuration of dihydrocarvone (I).[8]

The carbene IV was prepared in accordance with the following scheme:

Scheme II



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[8] W. Klyne, *Experientia* 12, 119 (1956).

The known reaction of α-acetylbutyrolactone with hydrochloric acid affords methyl cyclopropyl ketone (VII),[9] from which the dimethylcyclopropyl carbinol (VIII) is formed on treatment with methyl magnesium iodide. The three membered ring, opened with hydrobromic acid, according to Julia *et al.*[10] condenses with diethyl malonate to yield ethyl 2-carbethoxy-6-methyl-Δ^5-heptenoate (X), which produces ethyl 2-carbethoxy-2,6-dimethyl-Δ^5-heptenoate (XI) on treatment with methyl iodide. Hydrolysis and decarboxylation affords 2,6-dimethyl-Δ^5-heptenoic acid (XIIa), characterized as its benzylthiouronium salt (XIIb). The methyl ester (XIIc) shows peaks in the NMR spectrum at 1·08, 1·20 (doublet), 1·6, 1·69 (doublet), 1·82–2·65, 3·69 and 5·1 ppm which are assigned to CH_3, $\begin{matrix}CH_3\\CH_3\end{matrix}\!>$, CH_2, OCH_3 and vinyl protons. The corresponding acid chloride (XIII) and the diazoketone (XIV) were not isolated and their identification was made by means of their IR spectra.

The product from the cyclization yields two ketonic compounds. One, obtained in minor quantity with UV maxima at 235 mμ; ε, 5200 and semicarbazone melting at 202–203°, was identified as carvenone. This is in accordance with Gillam and West,[3] who pointed out the possibility that from the fission of the cyclopropane ring of carone, carvenone may be produced.

The major product is carone, identified by comparison of its UV, IR and NMR spectra and semicarbazone (mixed m.p. with Baeyer's carone showed no depression).

EXPERIMENTAL*

5-Chloro-2-pentanone (VI). In a 500 ml flask provided with a condenser, 87·5 ml conc. HCl, 102 ml water and 75 g α-acetyl-γ-butyrolactone (V) were mixed. As soon as evolution of CO_2 was complete, the mixture was distilled and the organic layer separated. The aqueous layer was extracted 3 times with ether and the ethereal extract combined with the oily layer and dried (Na_2SO_4). After removal of the solvent 54·5 g of a clear liquid was obtained.

Methyl cyclopropyl ketone (VII). To a 40% NaOH solution (60 ml) in a 250 ml 3-necked flask provided with a condenser and mechanical stirrer, 5-chloro-2-pentanone (VI; 54·5 g) was added. Reflux was maintained during 1 hr and then water (60 ml) added dropwise; reflux was prolonged 1 hr, the mixture then distilled and the organic layer separated. The aqueous layer was extracted twice with ether and combined with the organic layer already separated, dried (Na_2SO_4) and evaporated yielding 31·8 g of a liquid which was distilled affording a fraction (31·2 g) b.p. 103/582 mm; n_D^{25} 1·4250; ν_{max} 2999, 1697, 1384, 1254, 1190 and 895 cm^{-1}.

Dimethylcyclopropyl carbinol (VIII). Anhydrous diethyl ether (150 ml) and Mg turnings (9·6 g) were placed in a 3-necked flask, fitted with a mechanical stirrer, a dropping funnel and a condenser, and a stream of N_2 was passed through. The flask was cooled on an ice bath and an ethereal solution of methyl iodide (60 g) added dropwise. Stirring was prolonged until the Mg was dissolved and the methyl cyclopropyl ketone (VII; 31 g) added. After stirring 3 hr at room temp, a solution of H_2SO_4 (11·8 g) in water (150 ml) was added dropwise, the organic layer separated washed with water and dried (Na_2SO_4). Removal of the solvent yielded a clear liquid (33·2 g); n_D^{25} 1·4646; ν_{max} 3400, 3955, 1465, 1380, 1155, 1648 and 910 cm^{-1}.

1-Bromo-4-methyl-Δ^3-pentene (IX). To 600 ml HBr solution (48%), 30 g of a solution of carbinol (VIII) in 50 ml pentane was added with stirring which was continued 20 min and the organic layer,

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* M.ps were determined in a Kofler block. IR spectra were determined in film on a Perkin-Elmer model 21 spectrophotometer, and the UV spectra with a Beckman D-K2 spectrophotometer. The NMR spectrum was determined in CCl_4 solution containing T.M.S. as internal standard using a Varian A-60 machine. Chemical shifts are given in ppm (δ). Distillations were carried out through a 20 cm Wiedmer column. Microanalysis by Dr. F. Pascher, Bonn, Germany.

[9] G. W. Cannon, R. C. Ellis and J. R. Leal, *Organic Synthesis* **31**, 74 (1951).

[10] M. Julia, S. Julia and R. Guégan, *C. R. Acad. Sci., Paris* **248**, 820 (1959).

separated, washed with $NaHCO_3$ aq, dried (Na_2SO_4) and evaporated, yielding a dark liquid. Distillation yielded 36 g of a fraction b.p. 90–92/100 mm; n_D^{20} 1·4881; ν_{max} 2960, 1443, 1376, 1268 and 829 cm^{-1}.

Ethyl 2-carbethoxy-6-methyl-Δ^5-heptenoate (X). To a suspension of 8 g NaH in Nujol (50%) in 180 ml benzene–dimethylformamide mixture (3:1), 39·6 g diethyl malonate was slowly added with stirring. After the addition was complete, gentle reflux was started and 36 g of the bromo compound (IX) added. Reflux was maintained during 2 hr and the mixture then poured into water. The organic layer was worked up as usual to afford an oil, 41 g of which distilled at 99–101°/0·75 mm; ν_{max} 2965, 1735, 1640, 1470, 1390, 1170, 1105 and 1030 cm^{-1}.

Ethyl 2-carbethoxy-2,6-dimethyl-Δ^5-heptenoate (XI). To a suspension of 8·8 g NaH in Nujol (50%), benzene (180 ml) and dimethylformamide (60 ml), were added dropwise and with stirring 40·5 g of the ester (X). After refluxing the mixture 30 min, methyl iodide (26·2 g) was added; reflux was prolonged 2 hr and the mixture poured into water and worked up in the usual manner, yielding an oil. Distillation afforded a fraction (33·2 g) b.p. 86–88°/0·5 mm.

2,6-*Dimethyl-Δ^5-heptenoic acid* (XIIa). A solution of XI (33 g) in ethylene glycol (100 ml), water (2 ml) and KOH (11 g) was heated (100°) during 2 hr. The acidic fraction was isolated in the usual manner giving an oil which was distilled; the fraction (16·3 g) b.p. 100–102°/1·5 mm showed ν_{max} 2850, 1705, 1653, 1440, 1415 and 1225 cm^{-1}.

S-*Benzylthiouronium salt* (XIIb) *of* 2,6-*dimethyl-Δ^5-heptenoic acid.* A suspension of acid XIa (300 mg) in water (5 ml) and one drop of an alcoholic phenolphthalein solution was neutralized with a 5% KOH aq. To the solution formed, a hot solution of 1 g S-benzylthiouronium chloride in alcohol (10 ml) was added; a crystalline precipitate formed immediately. It was collected and the analytical sample obtained by crystallization from methanol–water, m.p. 149–150 (Found: N, 8·69. $C_{17}H_{26}O_2N_2S$ requires: N, 8·71%).

Methyl 2,6-*dimethyl-Δ^5-heptenoate* (XIIc). A solution of acid (XIIa; 1 g) in ether was mixed with an ethereal solution of diazomethane (prepared from 1 g N-nitrosomethylurea). After 30 min at room temp, the excess diazomethane was destroyed with acetic acid and the ethereal solution washed with a 10% NaOH aq, water and evaporated to dryness. The oily residue was purified by VPC (using a 4 m silicone 200 D.C. 30% on chromosorb W. column). The NMR spectrum showed doublets at 1·08, 1·20 and 1·6, 1·69, peaks at 1·82–2·65, 3·69 and 5·1 ppm, ν_{max} 3010, 1755, 1480, 1450, 1390, 1200, 1170, 1000, 900 and 850 cm^{-1}.

2,6-*Dimethyl-Δ^5-heptenoic acid chloride* (XIII). To a solution of acid (XIIa; 15 g) in ether (60 ml), 26·6 g thionyl chloride and 0·5 ml pyridine were added. The mixture was left at room temp for 1 hr and evaporated to dryness. The oily residue was distilled yielding a fraction (8·3 g) b.p. 40–42°/0·75 mm; ν_{max} 2910, 1790, 1634, 1462 and 1375 cm^{-1}.

Diazoketone (XIV). A solution of the acid chloride (8·3 g) in ether (20 ml) was added to an ethereal solution of diazomethane prepared from 22 g N-nitrosomethylurea. The solution was left 2 hr at room temp and the solvent and excess of diazomethane removed (water pump), yielding 9·2 g of yellow oily product. ν_{max} 2880, 2100, 1640, 1445, 1376 and 1142 cm^{-1}.

Carone (III). A suspension of diazoketone (XIV; 9·5 g) in cyclohexane (150 ml) and Cu dust (1 g) was boiled with stirring until the bands of diazoketone disappeared from the IR spectrum (24 hr). The mixture was cooled, filtered through celite and evaporated to dryness yielding 9·2 g of an oil which showed two spots when a chromatoplate was developed with 2,4-dinitrophenylhydrazine reagent. This product was dissolved in hexane–benzene (1:1) and chromatographed in 500 g of alumina (Brockman 1). From the benzene eluate a clear oil (4·65 g) was obtained, λ_{max}^{EtOH} 209·5 mμ; ε, 3860; $n_D^{20} = 1{\cdot}4671$; b.p. 47–48/0·5 mm. The semicarbazone, m.p. 176–177°, in a mixed m.p. with Baeyer's carone semicarbazone showed no depression.

From the benzene–ether (4:1) eluate, 215 mg carvenone was obtained. λ_{max}^{EtOH} 235 mμ; ε, 5200; semicarbazone m.p. 202–203°. Baeyer's carone was prepared from carvone according to Wallach[11] and Baeyer[1].

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[11] O. Wallach, *Liebigs Ann.* **279**, 377 (1894).