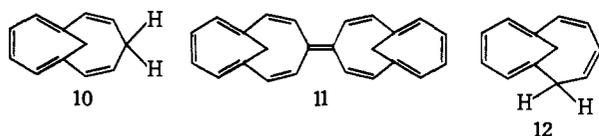


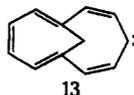
range coupling of 0.5 Hz; H_2-H_{12s} (3.26 and 9.28 τ), long-range coupling of 0.5 Hz; $H_8'H_{11}-H_{12a}$ (3.6 and 6.35 τ), long-range coupling of 0.5 Hz; H_3-H_4 (4.88 and 5.54 τ) with 1-Hz coupling; H_2-H_4 (3.6 and 5.54 τ), long-range coupling <0.5 Hz.

Although more complex, the nmr spectrum of **9** also yielded to extensive decoupling¹⁰ as follows: two sets of two-hydrogen AB resonances, $H_{12a}-H_{12s}$ (4.99 and 8.46 τ) of 10.5-Hz coupling and $H_{12'a}-H_{12's}$ (6.35 and 9.47 τ) of 12-Hz coupling; a complex ABMX system, $H_2-H_3-H_4-H_6$ (3.5, 4.89, 5.10, and 5.39 τ), with 11.5-, 3.0-, and 9.5-Hz coupling, respectively; an AMX system, $H_2-H_3-H_4$ (4.14, 4.57, and 4.01 τ) with 12.5- and 7.5-Hz coupling. Long-range coupling (0.5–1 Hz) was found for H_2-H_{12s} (4.14 and 8.46 τ) and also $H_8'-H_{12's}$ (3.32 and 9.47 τ). Taken with the similarity of the nmr spectra with closely related compounds^{2,11} (such as **8** compared with **10** and **11** or **9** compared with **10** or **11** superimposed on **12**), there is no question



of the gross structures of **8** and **9**, although their stereochemistry remains an open question.

Formation of **8** and **9** from **4** as well as **2** leaves little question but that the arylcarbene **3** undergoes carbene-carbene rearrangement to **5**. Furthermore, the known propensity of both cycloheptatrienylidene¹² and 4,9-methano[11]annulenyliene² (**13**) to dimerize is cer-



tainly sound precedent for the formation of **6** and **7**¹³ which could then undergo electrocyclic ring closures^{13,15} to give **8** and **9**. On the other hand, unless **6** and **7** can actually be detected and shown to undergo the necessary ring closures under the reaction conditions, we do not feel that the possibility of a direct dimerization of **5** to give the final products can be excluded.

Finally, it is worth noting that, if **8** and **9** are formed via **6** and **7**, a gain in homoaromaticity is an attractive rationale for this unique tendency to undergo ring closure (especially when compared with other fulvalenes such as heptafulvalene and the undecafulvalene **11**).

Acknowledgment. The authors gratefully acknowledge financial support of this work by the National

(11) For **10** and **12**, see E. Vogel, F. Feldmann, and H. Duwell, *Tetrahedron Lett.*, 1941 (1970); for other closely related compounds, see H. Prinzbach, *Pure Appl. Chem.*, **28**, 281 (1971).

(12) W. M. Jones and C. L. Ennis, *J. Amer. Chem. Soc.*, **91**, 6391 (1969).

(13) On the basis of steric considerations alone, formation of a predominance of two of the four possible dimers of **5** would be expected if aromatic carbenes dimerize by the same mechanism as has been proposed for the dimerization of methylene.¹⁴ Furthermore, on these same grounds it would be predicted that **6** and **7** would be the syn isomers. Finally, the thermally allowed electrocyclic ring closure of the two syn isomers would lead to structures with the symmetry required by the nmr spectra of **8** and **9**.

(14) R. Hoffmann, R. Gleiter, and F. B. Mallory, *J. Amer. Chem. Soc.*, **92**, 1460 (1970); H. Kellmar, *Tetrahedron Lett.*, 3337 (1970).

(15) For an example of ring closure of a vinylfulvalene, see H. Sauter and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.*, **11**, 296 (1972).

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4,9-Methano[11]annulenyliene. An Example of a Ten- π -Electron Carbocyclic Aromatic Carbene

Sir:

The chemistry of singlet carbenes in which the vacant orbital is integrated into a conjugated carbocyclic ring system with two or six π electrons has been found to be significantly different from that of their less highly perturbed relatives.^{1,2} For example, neither diphenylcyclopropenyliene nor cycloheptatrienylidene shows any tendency to insert into single bonds or add to electron-rich double bonds.³ On the other hand, both intermediates add readily to electron-deficient double bonds and, in addition to a strong tendency to dimerize, cycloheptatrienylidene has recently been found to add to substituted styrenes as a nucleophilic species⁴ ($\rho = +1.0$; $\rho_{\text{CCl}_2} = -0.619$ at 80°,⁵ -0.378 at 0°⁶).

At this time we present a preliminary report of the apparently successful generation of 4,9-methano[11]annulenyliene, an example of a ten- π -electron carbocyclic aromatic carbene.⁷



The ten- π -electron carbene was generated by the Bamford-Stevens⁸ reaction. The requisite 4,9-methano[11]annulenone⁹ (**1**) was synthesized by the method developed by Vogel.¹⁰ The ketone was converted to its tosylhydrazone¹¹ **2** by refluxing with *p*-toluenesulfonhydrazide for 3 hr in acidic absolute ethanol.

The sodium salt was generated by treating a solution of **2** in dry THF with 10% excess sodium hydride (dry-

(1) For a theoretical treatment, see R. Gleiter and R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 5457 (1968).

(2) (a) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1971, Chapter 8; (b) J. Hine, "Divalent Carbon," Roland Press, New York, N. Y., 1964, p 43.

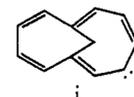
(3) W. M. Jones and C. L. Ennis, *J. Amer. Chem. Soc.*, **91**, 6391 (1969), and references cited therein.

(4) L. W. Christensen, E. E. Waali, and W. M. Jones, *ibid.*, **94**, 2118 (1972).

(5) D. Seyferth, J. Y.-P. Mui, and R. Damrauer, *ibid.*, **90**, 6182 (1968).

(6) J. H. Sadler, *J. Chem. Soc. B*, 1024 (1969).

(7) For a report of the generation of 3,8-methano[11]annulenyliene (i), see P. H. Gebert, R. W. King, R. A. LaBar, and W. M. Jones, *J.*



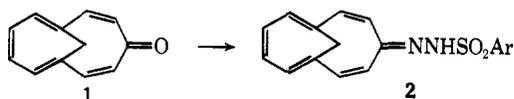
Amer. Chem. Soc., **95**, 9357 (1973).

(8) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); W. Kirmse, B. G. von Bulow, and H. Schepp, *Justus Liebigs Ann. Chem.*, **691**, 41 (1966).

(9) W. Grimme, J. Reisdorff, W. Junemann, and E. Vogel, *J. Amer. Chem. Soc.*, **92**, 6335 (1970).

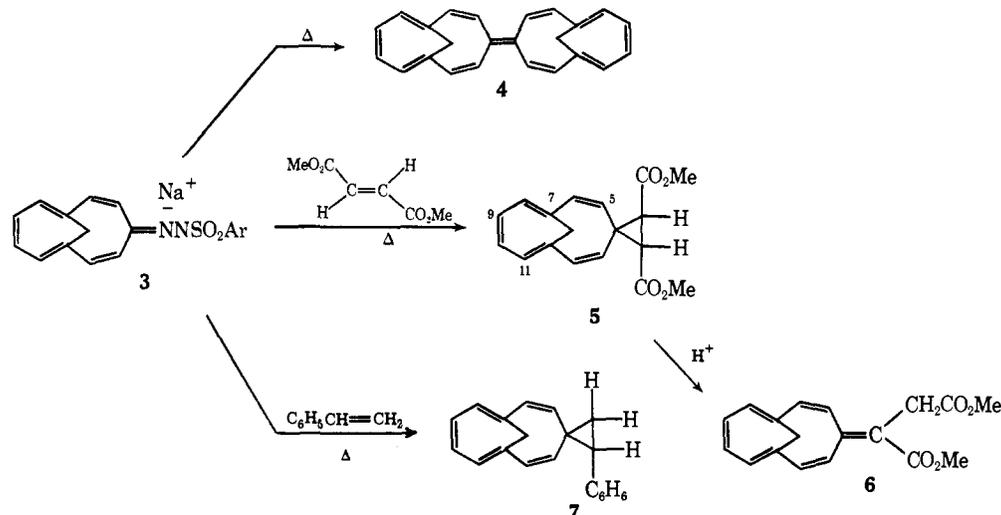
(10) We are indebted to Professor Vogel for his encouragement and helpful suggestions in all of our work on the methanoannulenylienes.

(11) Except where noted, all new compounds gave satisfactory elemental analyses and spectra consistent with the assigned structures.



box) followed by the addition of pentane to complete precipitation. The carbene was generated by slow addition of a suspension of the sodium salt in dry diglyme (~ 20 ml) to diglyme (~ 50 ml under N_2), which was maintained at 127° (external temperature).¹²

In the absence of substrate, a hydrocarbon was formed (67%), which showed all of the properties expected for the fulvalene 4. The infrared showed a



weak carbon-carbon double bond absorption at 1600 cm^{-1} , the ultraviolet showed maxima (*n*-hexane) at 413 nm (ϵ 17,600), 320 (41,200), and 222 (26,700), and the nmr¹³ ($CDCl_3$) showed a symmetrical spectrum with an AA'BB' triene system centered at τ 3.1 and 3.5, two superimposed AB doublets with the low-field protons at τ 3.35 and the upfield protons at τ 4.37 ($J = 11.4$ Hz), and an AB doublet (methylene bridge) at τ 6.25 and 9.31 ($J = 11.0$ Hz). A satisfactory elemental analysis of the red-brown solid, mp $254\text{--}256^\circ$ dec, could not be obtained, but a quantitative mass spectrum¹⁴ gave a parent and base peak at m/e 308.1563 (calcd for $C_{24}H_{18}$, $P = 308.1564$).

In the presence of dimethyl fumarate (0.72 g in 70 ml; 10:1 molar ratio), the yield of dimer 4 dropped to 1.7% with concomitant formation of 52.5% of the adduct 5. Adduct 5 is a white solid, mp $100\text{--}101^\circ$ (recrystallized from pentane). The ir showed a strong broad carbonyl absorption at 1720 cm^{-1} , and the ultraviolet showed maxima at 317 nm (ϵ 2700), 258 (25,100), and 240 (21,900). The 100-MHz nmr ($CDCl_3$) showed a pattern typical of the four carbon bridge of a 2,5,7,9,11-bicyclo[5.4.1]dodecapentaene centered at τ 2.96 and 3.40 with the lower part of two AX systems overlapping at τ 3.4 and the upfield portions as doublets at τ 5.02 and 5.19 ($J = 11.8$ Hz), two sharp singlets

(12) Attempts to generate the carbene by photolysis were unsuccessful. This may have been due to the insolubility of 3 in the solvent (THF), although the reaction has not been fully examined.

(13) For an analysis of the nmr spectra of bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene and 4,9-methano[11]annulene, see E. Vogel, F. Feldmann, and H. Duwell, *Tetrahedron Lett.*, 1941 (1970); E. Vogel, "XXXIIIrd International Congress of Pure and Applied Chemistry," Vol. I, Boston, 1971.

(14) Mass spectral analysis was performed by the Florida State University High Resolution Mass Spectrometry Laboratory, Tallahassee, Fla.

(OCH₃) at τ 6.12 and 6.28, doublets (cyclopropyl H) at τ 6.98 and 7.28 ($J = 6.0$ Hz), and one methylene proton at τ 9.84 ($J = 12.0$ Hz). Double irradiation experiments¹⁵ showed the other methylene proton to be located at τ 6.28. Mass spectral results gave a parent peak at m/e 298 and a base peak at m/e 180.

As in the case of the dimethyl fumarate adducts of both diphenylcyclopropenyldiene and cycloheptatrienyldiene,³ adduct 5 underwent acid-catalyzed ring opening to give fulvene 6. Interestingly, the ring opening of 5 required heating at reflux (methanol) for 3 hr in 1% HCl and could not be accomplished by

passage over an acid alumina column as in the case of both diphenylcyclopropenyldiene and cycloheptatrienyldiene adducts. The fulvene 6 showed strong broad absorption at 1733 and 1702 cm^{-1} in the ir and maxima at 237 nm (ϵ 23,100) and 305 (19,100) and a shoulder at 370 nm (ϵ 4200) in the ultraviolet region. The nmr (CCl_4) gave a multiplet at τ 2.92 (2 H), a multiplet at τ 3.40 (5 H), a doublet at τ 4.43 (1 H, $J = 12.1$ Hz), two sharp singlets at τ 6.21 and 6.32 (3 H each), a broad singlet at τ 6.50 (2 H), and doublets at τ 7.0 and 10.02 ($J = 11.8$ Hz). Mass spectral results gave a parent and base peak at m/e 298.

Finally, the carbene was generated in the presence of styrene (0.52 g in 70 ml; 10:1 molar ratio) to give 19.8% of dimer and 31.2% of adduct. The product was a mixture of geometrical isomers which we have not succeeded in separating. The mixture gave a satisfactory elemental analysis, strong absorption at 2999, 2960, 2920, 1600, 1268, and 788 cm^{-1} in the ir, and maxima in the ultraviolet at 318 and 262 nm (ϵ 4500 and 29,800, respectively). Mass spectral results gave a parent and base peak at m/e 258. The nmr showed a multiplet at τ 2.80 (5 H), multiplets at τ 3.16 (2 H) and 3.62 (4 H), a complex multiplet between τ 4.90 and 6.22 (3 H), a distorted triplet at τ 7.30 and one at τ 7.76 (total of 1 H), a multiplet between τ 8.21 and 8.82 (2 H), and a 1 H "triplet" from two superimposed doublets at τ 9.90. By comparison of the benzylcyclopropyl protons at τ 7.30 and 7.76 and the bridge methylene protons at τ 5.77 and 6.20, the ratio of the isomers was estimated to be 1.7:1.

We are looking forward to determining the ρ value

(15) We are indebted to Dr. R. W. King for recording the 100-MHz spectra and performing double resonance experiments.

for this reaction which should yield an interesting comparison of relative nucleophilicities of cycloheptatrienylidene and 4,9-methano[11]annulenyliidene.

Acknowledgment. The authors are indebted for support of this work received from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation.

(16) University of Florida postdoctoral fellow, 1971–1972.

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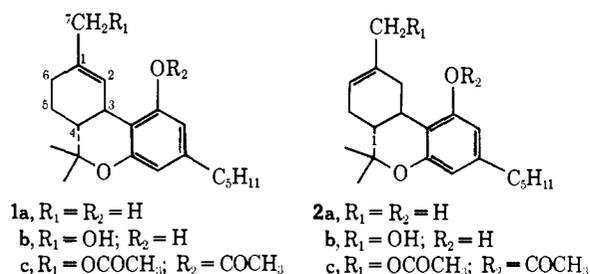
Hashish.¹ Synthesis of

7-Hydroxy- Δ^1 -tetrahydrocannabinol (THC).

An Important Active Metabolite of Δ^1 -THC in Man²

Sir:

Knowledge of the metabolic pathways of Δ^1 -THC (**1a**) is of great importance in understanding its physio-



logical activity. Recent studies in humans³ and animals^{4,5} have established that 7-OH- Δ^1 -THC (**1b**) is an important active metabolite of Δ^1 -THC. Similarly, Δ^1 -THC (**2a**) is metabolized to the biologically active **2b**.^{6,7} Thus, an urgent need exists for the ready availability of **1b** for further biological and toxicological investigations.

The main problem in the synthesis of *trans*-THC derivatives containing the Δ^1 double bond is that they are thermodynamically less stable than the corresponding compounds with the $\Delta^{1(6)}$ unsaturation.⁸ Hence, during

chemical reactions derivatives containing the $\Delta^{1(6)}$ double bond generally predominate. Whereas, numerous syntheses of **2b** have appeared,^{6,7,9} including one from this laboratory,¹⁰ thus far only one practical although low yield synthesis of **1b** has been published.^{11,12}

We wish to report in this communication the practical synthesis of 7-OH- Δ^1 -THC (**1b**) from (–)- Δ^1 -THC (**3a**, Scheme I) utilizing high-pressure liquid chromatography. This is the first successful application of high-pressure liquid chromatographic (lc) techniques in the cannabinoid field.

The conversion of (–)- Δ^1 -THC (**3a**)^{9,13} to its acetate (**3b**) was carried out in nearly quantitative yield.¹⁰ Treatment of the acetate (**3b**) with *m*-chloroperbenzoic acid in chloroform gave the epoxide **4**: δ (CCl₄) 0.90, 1.08, 1.35 (CH₃ groups) 2.12 (acetate CH₃), 2.53 (s, 2 H, C-7 methylene), 6.20, 6.40 (2 H, aromatic). Without further purification the epoxide was hydrolyzed with a 0.3 *N* solution of potassium hydroxide in 85% aqueous DMSO¹⁴ at 100° for 8 hr. Basic conditions were chosen for the epoxide opening to avoid formation of $\Delta^{1(6)}$ dehydration products. The crude triol **6a** was acetylated in pyridine to form the diacetate alcohol **6b**: δ (CDCl₃) 0.87, 1.07, 1.35 (CH₃ groups), 2.26 (phenolic acetate CH₃), 2.06 (C-7 acetoxy CH₃), 3.94 (AB, *J* = 11 Hz, 2 H, C-7 protons), 6.36, 6.53 (2 H, aromatic). Treatment of **6b** with thionyl chloride in pyridine at 0° for 16 hr furnished a mixture of the two metabolites as their diacetates **1c** and **2c** (ratio of 1:2).¹⁵ The metabolite diacetate **1c** was separated from the mixture¹⁶ by liquid chromatography as described below. It was then hydrolyzed with a 2:1 mixture of methanol/1 *N* sodium hydroxide solution at room temperature to give **1b**: nmr (100 MHz) δ (CCl₄) 0.86, 1.04, 1.36 (CH₃ groups), 3.86 (s, C-7, hydroxymethyl), 5.89, 6.02 (2 H, aromatic), 6.51 (br, 1 H, vinylic); mass spectrum (70 eV) *m/e* 330 (M⁺), 315, 312, 299 (base peak), 297, 271, 231, 193 (consistent with published data).⁴ The identity was further established by comparison with an authentic sample¹⁷ on glc and lc. The overall yield of isolated **1b** from **3a** is 13%.

Alternatively, **6b** was obtained from **3b** by hydroxylation of the exocyclic double bond with osmium tetroxide in ether followed by acetylation.⁹ This material

(1) Part IX. For part VIII see B. A. Zitko, J. F. Howes, R. K. Razdan, B. C. Dalzell, H. C. Dalzell, J. C. Sheehan, H. G. Pars, W. L. Dewey, and L. S. Harris, *Science*, **177**, 442 (1972).

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(9) J. L. G. Nilsson, I. M. Nilsson, S. Agurell, B. Akermarck, and I. Lagerlund, *Acta Chem. Scand.*, **25**, 768 (1971).

(10) K. K. Weinhardt, R. K. Razdan, and H. C. Dalzell, *Tetrahedron Lett.*, **4827** (1971).

(11) C. G. Pitt, F. Hauser, R. L. Hawks, S. Sathe, and M. E. Wall, *J. Amer. Chem. Soc.*, **94**, 8578 (1972).

(12) The formation of minute quantities of **1b** is mentioned during selenium dioxide oxidation of Δ^1 -THC acetate.⁶ The problem of obtaining the material completely free of toxic selenium combined with the miniscule yield renders this method unsuitable for practical purposes.

(13) J. W. Wildes, N. H. Martin, C. G. Pitt, and M. E. Wall, *J. Org. Chem.*, **36**, 72 (1971); R. K. Razdan, A. J. Puttick, B. A. Zitko, and G. R. Handrick, *Experientia*, **28**, 121 (1972). (–)- Δ^1 -THC (**3a**) has become available in large quantities as an impurity during the large scale conversion of $\Delta^{1(6)}$ -THC to Δ^1 -THC. We have been supplied with 200 g of **3a** (85% pure by glc) by the National Institutes of Mental Health and as far as we are aware more material is available.

(14) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Lett.*, **3421** (1965).

(15) The relative amounts of **1c** and **2c** were determined by hydrolysis to **1b** and **2b** and glc analysis of a silylated sample using a Varian Aerograph Model 1400 equipped with a 6 ft \times 1/8 in. s.s. column packed with 2% OV-17 on 100–200 mesh Gas Chrom Q and a flame ionization detector. Retention time (248°) **1b**, 4 min 36 sec; **2b**, 4 min 54 sec.

(16) The mixture showed a single spot on tlc in various solvent systems even after multiple developments.

(17) Kindly supplied by Dr. C. G. Pitt, Research Triangle Institute, N. C.