by least-squares also performed quite well with about equal performance on the "positive" and "negative" drugs. The least-squares results are even more encouraging in light of the fact that the procedure used 1 order of magnitude less computer time. This may be more significant in the much larger studies currently in progress. The feedback learning results were also encouraging even though the two classes are not linearly separable.

In conclusion, the results of this first study show that the activity of a chemical compound can be predicted by computer analysis, using pattern recognition methodology, of structural features obtained from the molecule. It is not suggested that computer screening can or will eliminate the need for biological testing. Instead, computer screening can be used to provide priorities for drugs yet to be tested in over-taxed testing programs and can aid significantly in prospective studies by analyzing previously tested molecules and providing a more rational approach to "drug design." Pattern recognition "learns" about biological activity by processing data from retrospective studies and making connections to the structural features of the drugs. This advance can save the scientist much time and money.

Although several other screening applications are either in progress or planned for the near future, emphasis is currently on screening studies for anticancer activity. Computer screening applications in five other systems are in progress. These include the L1210 (leukemia) and Walker 256 (solid tumor) systems which have received most of the emphasis in the cancer chemotherapy program.

The Sarcoma 180, Lewis Lung, and KB tissue culture tests are also being studied. Results are equally encouraging and are forthcoming. Better structure coding methods are being considered to replace the more naive structural features used in this study. Computer extraction of molecular substructures from connection tables[8] and the Wiswesser line notation[9] are probably the most fruitful approaches being contemplated at this time. Also, the inclusion of chemical properties and pharmacological information will also be important. New data on several other classes of biologically active compounds are currently being amassed.

Classification performance will also improve when powerful preprocessing methods (*e.g.*, orthogonalization) within pattern recognition are applied to the input features. Also, unsupervised learning methods have yet to be applied. These and other improvements promise to aid significantly in screening applications and rational "drug design" for cancer chemotherapy as well as for any system where better and more active chemical compounds are needed.

Acknowledgments. The authors would like to express their gratitude to George Hess, M.D., University of California, Davis Medical School, for his help and encouragement and to Paul Murphy, Colgate University, for coding the structural features of the molecules used in this study. B. R. K. gratefully acknowledges the financial support of the National Science Foundation (GP-36578X) and the Office of Naval Research.

(10) This work was performed under the auspices of the U. S. Atomic Energy Commission.

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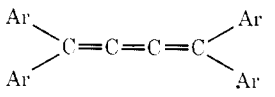
Received August 25, 1973

Photochemistry of Crystalline Cumulenes. Reassignment of the Structure of the Solid-State Photodimer of Tetraphenylbutatriene

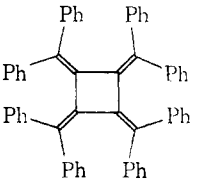
Sir:

The role of the crystal structures of substituted ethylenes in determining the stereochemistry of the cyclobutane photodimers obtained therefrom has been demonstrated.[1] A separation of 4.0 ± 0.2 Å between potentially reactive C=C double bonds is necessary for photodimerization. However, it has been observed[1,2] that neighboring C=C bonds, which fulfill the above requirement but which are far offset implying insufficient overlap of their π-electrons, do not dimerize. A system which allows systematic analysis of the importance of the alignment of the π-electrons is provided by the cumulenes in which the π-lobes of alternate C=C bonds lie in mutually perpendicular planes. We undertook photochemical and crystallographic studies of several substituted butatrienes.

The tetraarylbutatrienes (I and II) dimerize in the solid state.[3] The dimer of I was reported to be the radialene III.[4] On the assumption that the reaction



I, Ar = C_6H_5
II, Ar = p-$CH_3OC_6H_4$



III

I–III must involve pronounced overlap between the π-electrons in the ground state of the neighboring C=C bonds,[1,2] the monomer butatriene molecules must approach each other edge-on. Furthermore, steric factors permit the potentially reactive 4 Å approach between the central C=C bonds only if the molecules would be crossed in the unusual structure of Figure 1. However, in the course of our studies, we found that

(1) G. M. J. Schmidt, *Pure Appl. Chem.*, 27, 647 (1971).
(2) (a) L. Leiserowitz and G. M. J. Schmidt, *Acta Crystallogr.*, **18**, 1058 (1965); (b) M. Lahav and G. M. J. Schmidt, *J. Chem. Soc. B*, 312 (1967); (c) N. J. Leonard, R. S. McCredie, M. W. Logue, and R. L. Cundall; *J. Amer. Chem. Soc.*, **95**, 2320 (1973); (d) J. K. Frank and I. C. Paul, *ibid.*, **95**, 2324 (1973).
(3) (a) K. Brand, *Ber.*, **54**, 1987 (1921); (b) K. Brand and F. Kercher, *ibid.*, **54**, 2007 (1921).
(4) (a) R. O. Uhler, H. Shechter, and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **84**, 3397 (1962); (b) R. O. Uhler, *Diss. Abstr.*, **21**, 765 (1960). This work has been reviewed [M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967, Chapter 5; A. Schönberg, "Preparative Organic Photochemistry," Springer Verlag, New York, N. Y., 1968, p 89]. In terms of the correct structure IV the mechanism of its reactions with alkali metals should be revised: R. Nahon and A. R. Day, *J. Org. Chem.*, 30, 1973 (1965).

(8) M. F. Lynch, J. M. Harrison, W. G. Town, and J. E. Ash, "Computer Handling of Chemical Structure Information," American Elsevier, New York, N. Y., 1971.
(9) E. J. Smith, "W. J. Wiswesser's Line Formula Chemical Notation," McGraw-Hill, New York, N. Y., 1968.

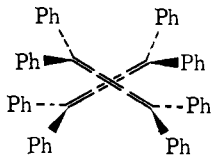
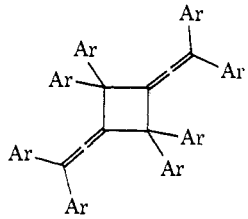


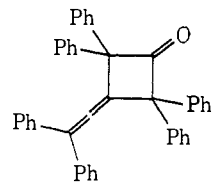
Figure 1.

the photodimer obtained from crystals of I is not III[4] but rather the 1,3-bis(diphenylvinylidene)-2,2,4,4-tetraphenylcyclobutane (IV).[5] II behaves similarly, yielding the photodimer V.

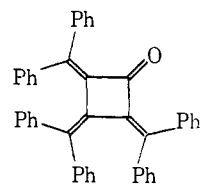


IV, Ar = C_6H_5
V, Ar = p-$CH_3OC_6H_4$

Photodimer IV was obtained from monomorphic crystals of I[6] as described[4] and was identified by the physical and spectroscopic data previously reported:[4] mp 280–281°; nmr τ ~3.0, a broad singlet for the aromatic hydrogens; $\lambda_{max}^{CHCl_3}$ 274 nm (ϵ 18,000) and 307–308 (ϵ 39,500).[7] We found the following additional information proving the structure (IV). The allene band at 1930 cm^{-1}, inactive in the ir, is active in the Raman.[8] Partial ozonolysis of IV,[9] performed under conditions identical with those in ref 4, gives benzophenone and 3-diphenylvinylidene-2,2,4,4-tetraphenylcyclobutanone (VI), mp 184–185°,[10] and not the ketone (VII) as reported.[4] Structure VI follows from its molecular weight M^+ = 550 [VII would have M^+ = 562], ν_{max} ir 1960 cm^{-1} (w) and Raman 1946 cm^{-1} (*s*) due to an alenic group, and ir 1780 (*s*) and Raman 1760 (*s*)



VI



VII

(5) We have been informed by H. Shechter (private communication Oct 1973) that in 1972 C. F. Sheley and H. Shechter had independently reassigned correctly the structure of the photodimer IV, its ozonolysis monoketone (VI), and its principal diozonolysis diketone (VIII).

(6) To exclude the possibility that III is formed in a different crystalline modification, we searched for polymorphism of I. Crystals were obtained from ethyl methyl ketone, chloroform, chloroform–ethanol, benzene, and sublimation. Triclinic, a = 10.07, b = 10.52, c = 10.08 Å; α = 105.04, β = 104.65, γ = 92.15°; Z = 2; ρ_{calcd} 1.2.

(7) The uv band, λ_{max} 274 (ϵ 18,300), is in accordance with IV; see H. Fischer, "The Chemistry of Alkenes," S. Patai, Ed., Wiley-Interscience, London, 1964, and references cited therein.

(8) J. H. Wotiz and D. E. Maucuso, *J. Org. Chem.*, **22**, 207 (1957).

(9) Ozonolysis of hindered ethylenes, such as phenylmesitylethylene, gives an epoxide rather than a ketone: P. S. Bailey and A. G. Laue, *J. Amer. Chem. Soc.*, **89**, 4473 (1967); P. S. Bailey, J. W. Ward, and R. E. Hornish, *ibid.*, **93**, 3552 (1971). Diphenylmethylenecyclobutane has been reported to form 2,2-diphenylcyclopentanone: S. H. Graham and A. J. S. Williams, *J. Chem. Soc.*, 4066 (1959). Hindered alenes, however, have recently been reported to give the corresponding ketones: P. Kolsoker and B. Tiege, *Acta Chem. Scand.*, **24**, 2102 (1970); J. K. Crandall and W. W. Conover, *J. Chem. Soc., Chem. Commun.*, 340 (1973).

(10) This ozonolysis product has been reported to be dimorphic:[4] white plates mp 171.5–172.0° and white needles mp 184–185°. We obtained only the white needles.

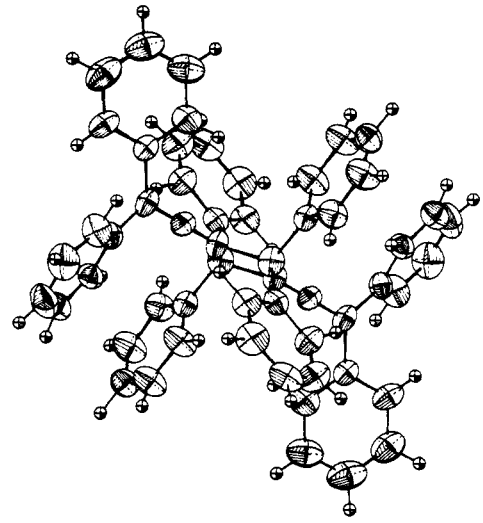
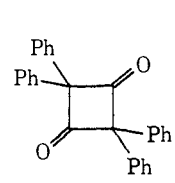
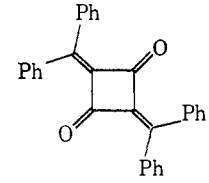


Figure 2. 1,3-Bis(diphenylvinylidene)-2,2,4,4-tetraphenylcyclobutane (IV).

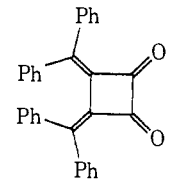
designating the >C=O bond. Diozonolysis of IV in $CHCl_3$ for 10 min gives 2,2,4,4-tetraphenyl-1,3-cyclobutanedione (VIII), mp 252–253°. The structure of VIII was confirmed[11] by M^+ = 388 and by comparison



VIII



IX



X

(X-ray powder photograph, melting point, mixture melting point, ir) with an authentic sample obtained by thermal dimerization of diphenyl ketene.[12]

The structure of IV has been independently confirmed by an X-ray analysis: $C_{56}H_{40}$, M = 712; a = 10.227 (13), b = 21.297 (7), c = 9.318 (3) Å, β = 93.80 (06)°; V = 2025 Å^3; Z = 2; ρ_{calcd} = 1.16, F(000) = 752; space group $P2_1/n$.

A total of 4010 reflections (including 1219 unobserved) were measured in the range $0 < \theta < 26°$ on an automatic diffractometer using Mo Kα radiation. The structure was solved by MULTAN.[13] Block-diagonal least-squares refinement, with the carbon atoms treated anisotropically and the hydrogens isotropically, yielded a residual R = 0.13. The molecule[14] (Figure 2) consists of a cyclobutane ring with diphenyl and diphenylvinylidene substituents. A comparison of chemically equivalent bond lengths yielded a σ of 0.02 Å. The alene residue is linear (C=C=C = 178°) with C=C bond lengths of 1.29 and 1.34 Å, and a dihedral angle of 87° between the planes of its terminal C=C< groups. The two phenyl rings substituted at the cyclobutane carbon are almost at right angles to each other (95°)

(11) After the initial report of the structure of the photodimer of I, 2,4-bis(diphenylmethylene)-1,3-cyclobutanedione (IX) and 3,4-bis(diphenylmethylene)-1,2-cyclobutanedione (X) were synthesized, and it was clear that they are not the products presumed to be formed by diozonolysis of IV [G. A. Taylor, *J. Chem. Soc. C*, 1755 (1969); F. Toda and K. Akagi, *Tetrahedron*, **27**, 2801 (1971)].

(12) H. Das and E. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **84**, 965 (1965).

(13) P. Main, M. M. Woolfson, and G. Germain, "MULTAN: A computer programme for the automatic solution of crystal structures," York/Louvain, 1971.

(14) See paragraph at end of paper regarding supplementary material.

whereas the phenyl rings of the diphenylvinylidene group make an angle of 53°.

Tetra-*p*-anisylbutatriene (II) is dimorphic (A,B).[15] Both modifications yield the same photoproduct, form *B* reacting faster. V has mp 293°: M^+ 952, strong peak at M/2 476; nmr a multiplet centered at τ 3.1 (aromatic protons) and two singlets at 6.23 and 6.18 (OCH_3), which do not coalesce on heating above 150° in DMSO; ν_{max} Raman 1960 cm^{-1}(*s*) (alenic group). These physical data together with the match in cell constants of the dimers IV and V,[16] strongly indicate that V is 1,3-bis(di-*p*-anisylvinylidene)-2,2,4,4-tetra-*p*-anisylcyclobutane.

These results suggest that the solid-state photodimerizations of cumulenes may differ from thermal cycloaddition reactions which take place *via* the central C=C bond to form radialenes.[17]

The X-ray analysis of I as well as the photochemical studies of other tetraarylbutatrienes, presently in progress, will be reported in a full paper.

Acknowledgments. We thank Dr. V. Zaretzky and Dr. F. Nader for the mass spectra, Dr. E. Huler for the Raman spectra, and Professor M. D. Cohen for helpful discussions. Partial support from a Minerva Grant is also acknowledged.

Supplementary Material Available. A listing of atomic coordinates, thermal parameters, bond distances and angles, and structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-918.

(15) Form A, *ex* ethyl methyl ketone, chloroform, chloroform–ethanol: triclinic; $a = 9.8, b = 11.7, c = 10.9$ Å; $\alpha = 96.5, \beta = 103.0, \gamma = 87.1°$; $Z = 2$; $\rho_{calcd} = 1.31$. Form B, *ex* benzene, single crystal suitable for cell constant determination not obtained.

(16) Cell constants of V: triclinic; $a = 10.5, b = 21.6, c = 11.8$ Å; $\alpha = 100.2, \beta = 101.3, \gamma = 88.0°$; $Z = 2$; $\rho_{calcd} = 1.2$.

(17) H. D. Hartzler, *J. Amer. Chem. Soc.*, **88**, 3155 (1966); B. Heinrich and A. Roeding, *Angew. Chem., Int. Ed. Engl.*, 7, 375 (1968).

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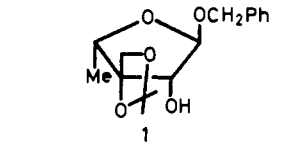
Total Synthesis of Dihydrostreptomycin

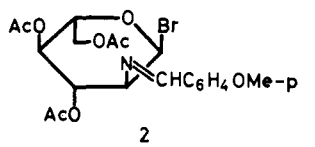
Sir:

Streptomycin is the first useful *Streptomyces* antibiotic discovered by Waksman and coworkers[1] in 1943. Dihydrostreptomycin[2,3] is obtained by hydrogenation of streptomycin or by direct fermentation.[4] The structure of streptomycin was established by 1948 except for the glycosidic linkage between streptose and streptidine which was again revised[5,6] to be α-L. We wish here to report the total synthesis of dihydrostreptomycin. This represents the first synthesis of an antibiotic of the streptomycin series.

Condensation of the blocked derivative[7] (**1**) of dihydrostreptose[8] with the L-glucosamine[9] derivative[10] (**2**) in benzene in the presence of mercuric cyanide at room temperature, followed by hydrolysis of the Schiff base with 50% acetic acid and reaction with methyl chloroformate (Na_2CO_3, aq acetone), gave the disaccharide **3** in 42% overall yield from **1**: $[\alpha]^{24}D$ −133° (*c* 0.8, $CHCl_3$). N-Methylation (MeI, Ag_2O, DMF) gave **4** (72%). Deacetylation (MeONa–MeOH) followed



1



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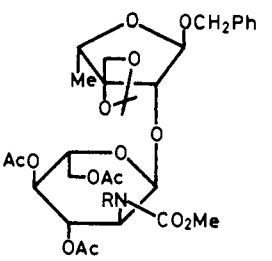
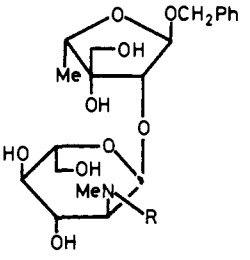


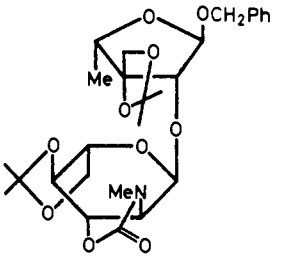
3, R = H
4, R = Me

by deisopropylidenation (1 *N* HCl, aqueous MeOH) gave **5** (70% yield from **4**; mp 184.5–185°; $[\alpha]^{18}D$ −153° (*c* 2, MeOH)), which was identical with the natural specimen derived from benzyl α-L-dihydrostreptobiosaminide[11] similarly with methyl chloroformate. Hydrolysis of **5** (10% $Ba(OH)_2$, 70°, 72%) afforded benzyl α-L-dihydrostreptobiosaminide (**6**).

Treatment of **6** with 2,2-dimethoxypropane (*p*-toluenesulfonic acid, molecular sieve type 5A, acetone, reflux, 69%) gave a diisopropylidene derivative, and further blocking by use[12] of *p*-nitrophenoxycarbonyl chloride (NaOH, aqueous acetone, −10°, 75%) gave **7**: $[\alpha]^{23}D$ −152° (*c* 1, MeOH); ir 1770 cm^{-1}



5, R = CO2Me
6, R = H



7

(1) A. Schatz, E. Bugie, and S. A. Waksman, *Proc. Soc. Exp. Biol. Med.*, **55**, 66 (1944); review: R. U. Lemieux and M. L. Wolfrom, *Advan. Carbohyd. Chem.*, **3**, 337 (1948).

(2) Q. R. Bartz, J. Controulis, H. M. Crooks, Jr., and M. C. Rebstock, *J. Amer. Chem. Soc.*, **68**, 2163 (1946).

(3) R. L. Peck, C. E. Hoffhine, Jr., and K. Folkers, *J. Amer. Chem. Soc.*, **68**, 1390 (1946).

(4) S. Tatsuoka, T. Kusaka, A. Miyake, M. Inoue, H. Hitomi, Y. Shiraishi, H. Iwasaki, and M. Imanishi, *Chem. Pharm. Bull.*, **5**, 343 (1957).

(5) I. J. McGilveray and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **87**, 4003 (1965).

(6) S. Neidle, D. Rogers, and M. B. Hursthouse, *Tetrahedron Lett.*, 4725 (1968).

(7) Compound **1**, benzyl α-L-dihydrostreptoside ($[\alpha]^{25}D$ −100° (*c* 1, $CHCl_3$)), prepared from dihydrostreptose,[8] was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in DMF to give **1** $[\alpha]^{18}D$ −85° (*c* 1, $CHCl_3$).

(8) J. R. Dyer, W. E. McGonigal, and K. C. Rice, *J. Amer. Chem. Soc.*, **87**, 654 (1965).

(9) R. Kuhn and W. Kirschenlohr, *Justus Liebigs Ann. Chem.*, **600**, 115 (1956).

(10) Compound 2, L-glucosamine,[9] was treated with *p*-anisaldehyde. The resulting Schiff base was acetylated and followed by treatment with hydrogen bromide–acetic acid in methylene chloride to give **2** in 30% overall yield: mp 110–111°; $[\alpha]^{26}D$ −194° (*c* 1, $CHCl_3$).

(11) G. K. J. Ferguson, I. J. McGilveray, and J. B. Stenlake, *J. Pharm. Pharmacol.*, **17**, Suppl. 68S–70S (1965).

(12) S. Umezawa, Y. Takagi, and T. Tsuchiya, *Bull. Chem. Soc. Jap.*, **44**, 1411 (1971).