

drying. This final solution was used for the gas chromatographic measurement (flame detector) and, as indicated above, accounted for at least 98% of the basic products. The materials identified were: phenylpyridines, 0.217 g., 0.0014 mole; benzene, 0.343 g., 0.0044 mole; diphenylurea, 0.106 g., 0.0025 mole; and aniline, 0.093 g., 0.001 mole. These accounted for 67% of the phenyl radicals. A residue, 0.266 g., was also formed which would account for the rest.

The results show a definite enhancement of substitution in the 4-position of all the complexes but one, and in the 2-position in most cases. It is not evident whether the amount of substitution at the 3-position is decreased or remains the same. The substituent effects can be explained by considering a back donation of electrons to the pyridine ring by the metal ion. This d-p π -electron conjugation would involve a filled d_{xz} orbital of the metal and its interaction with the π -electron system in the pyridine ring.⁶ The back donation to the ligand would be especially effective toward the 2- and 4-positions and is similar to that shown to occur in other coordination compounds.⁷

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(6) H. C. A. King, E. Koros, and S. M. Nelson, *Nature*, **196**, 572 (1962).

(7) J. Chatt and L. A. Duncanson, *J. Chem. Soc.*, 2939 (1953); see also D. P. Craig and G. Doggett, *ibid.*, 4189 (1963).

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Structure of the Dimer of Tetraphenylcyclobutadiene

Sir:

A three-dimensional X-ray diffraction study of C_8Ph_8 ,^{1,2} where Ph is C_6H_5 , has yielded the octaphenylcyclooctatetraene structure. These results exclude the octaphenylcubane structure,³ as well as the tetrabiphenylcyclooctane formula⁴ which had been rendered improbable earlier on spectroscopic evidence.⁵

We have confirmed the previously reported³ crystal symmetry of $I4_1/a$, the four molecules of C_8Ph_8 per unit cell, and the unit cell dimensions of $a = 19.49$ and $c = 10.65$ Å. The compound $(PhAlNPh)_4$, in which the Al and N atoms are arranged at the corners of a cube,^{6,7} has the same space group and four molecules per unit cell; furthermore, its lattice dimensions of $a = 20.0$ and $c = 10.9$ Å. are increased over those for C_8Ph_8 by an amount which seemed consistent with an initial assumption of a slightly smaller cube for the C_8 unit. Consequently, we chose as a trial molecular structure a cube of eight C atoms to each of which was attached a phenyl group having the C-Ph bond along a body diagonal of the cube, and having the C_6H_5 plane oriented

(1) H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2195 (1961).

(2) E. H. Braye, W. Hübel, and I. Caplier, *ibid.*, **83**, 4406 (1961).

(3) H. H. Freedman and D. R. Petersen, *ibid.*, **84**, 2837 (1962).

(4) R. C. Cookson and D. W. Jones, *Proc. Chem. Soc.*, 115 (1963).

(5) H. H. Freedman and R. S. Gohlke, *ibid.*, 249 (1963).

(6) J. I. Jones and W. S. McDonald, *ibid.*, 366 (1962).

(7) T. R. R. McDonald and W. S. McDonald, *ibid.*, 382 (1963).

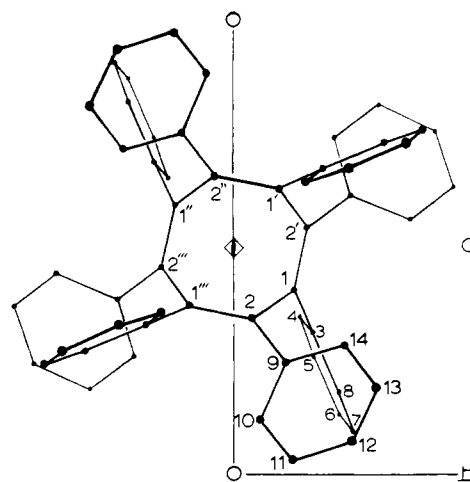


Fig. 1.—The structure and position in the unit cell of one molecule of octaphenylcyclooctatetraene. The origin is at the lower left corner, the $\bar{4}$ axis is at the lower left corner, the $\bar{4}_1$ axis is at $x = 1/4, y = 0$, and the centers of symmetry are shown as circles at $000, 1/8, 1/8, 3/8$, and $0, 1/2, 0$. Bond distances are $1-2 = 1.51, 1-2' = 1.35, 2-2' = 2.48, 1-1' = 2.46, 1-3 = 1.50,$ and $2-9 = 1.50$ Å. The twelve independent C-C distances in the benzene rings have an average distance of 1.39 ± 0.01 Å.

either in the 110 type of plane of the isolated cube or perpendicular to this type of plane. This model, when placed at the four equivalent sites of $\bar{4}$ symmetry in the crystal, has only the one degree of freedom consisting of arbitrary orientation about the $\bar{4}$ axis.

A very good approximation to the molecular orientation finally found was obtained by comparison of values of $R = \sum |F_o| - |F_c| / \sum |F_o|$ computed for various orientations from about 10% of the observed diffraction maxima. The minimum value of R yielded a structure which later comparison showed was very similar to the $(PhAlNPh)_4$ structure, kindly communicated to us by W. S. McDonald. However, the C atoms of the previously assumed C_8 cube moved considerably, during the course of least-squares refinement, to the final positions shown in Fig. 1. Clearly, this refinement has yielded the octaphenylcyclooctatetraene structure. The present value of R is 0.12 for the 1627 observed reflections, $1.4 \leq F_{hkl} \leq 336$, and the thermal motion is highly anisotropic. Hence we considered the possibility that octaphenylcubane might be transformed *within the single crystal* to octaphenylcyclooctatetraene upon exposure to X-rays. Therefore, a sample previously unexposed to X-rays was examined first by infrared and then by Raman techniques, exposed to X-rays for a day, and then re-examined by infrared and Raman methods. No evidence of transformation of the molecule by X-ray irradiation could be detected. Hence, we conclude that the original sample as prepared is indeed octaphenylcyclooctatetraene. The intermolecular contacts are, however, primarily determined by the phenyl groups, which are oriented within the molecule in such a way that an α -H atom of one phenyl group points toward the center of the closest neighboring benzene ring. This suggestion of a "dimple" toward the center of a benzene ring was first noted in the intermolecular packing of the biphenylene crystal.⁸

The internal angles of the tub-shaped cyclooctatetraene (COT) ring are 120° , in agreement with pre-

(8) J. Waser and C. S. Lu, *J. Am. Chem. Soc.*, **66**, 2035 (1944).

sumed sp^2 -hybridization within nearly planar ethylene-like residues. The angle between the π -system about atom C_1 and its adjoining ring is 50.3° , and that between C_2 and its adjoining ring is 46.2° . These angles would permit some conjugation, but the double bond distance of 1.35 Å. and the single bond distance of 1.51 Å. within the COT ring as well as the normal sp^2 to sp^2 bond length of 1.50 Å. for both C_1C_3 and C_2C_9 give no indication of abnormal bond shortenings. Indeed, the 1.334- and 1.462-Å. distances of the electron diffraction study⁹ and the 1.31- and 1.46-Å. distances of the X-ray diffraction study¹⁰ of COT itself suggest that perhaps intramolecular strain is more important than conjugation in C_8Ph_8 . Certainly the ring has not assumed one of the highly distorted forms found¹¹ in the iron tricarbonyl complexes.

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(9) O. Bastiensen, L. Hedberg, and K. Hedberg, *J. Chem. Phys.*, **27**, 1311 (1957).

(10) J. Bregman, private communication, 1958.

(11) B. Dickens and W. N. Lipscomb, *J. Chem. Phys.*, **37**, 2084 (1962).

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Reticuline as the Benzyltetrahydroisoquinoline Precursor of Thebaine in Biosynthesis with Carbon-14 Dioxide¹

Sir:

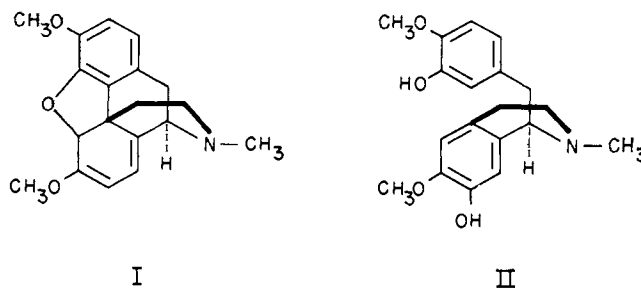
Earlier work² established the rapid *de novo* synthesis of thebaine (I) from $^{14}CO_2$ and its primacy in the hydrophenanthrene alkaloid series. Recent evidence, based on feeding experiments, showed that reticuline (II) can serve as a precursor of thebaine.³ We now present evidence, derived from short exposures to $^{14}CO_2$ of both seedlings and budding plants of *P. somniferum* L., which confirms these findings and establishes beyond question the role of reticuline as the true biosynthetic benzyltetrahydroisoquinoline precursor of the hydrophenanthrene alkaloids.

If reticuline is a true precursor of thebaine, it should be present with specific activity equal to or greater than that of thebaine after short-term exposure of plants to $^{14}CO_2$. The maximum ratio of the specific activities should exceed the inverse mole ratios of the two alkaloids in the plant, this difference becoming greater with shorter exposure times. To obtain such

(1) Sponsored in part by the United States Atomic Energy Commission and Grant B-570 from the National Institutes of Health, United States Public Health Service.

(2) F. R. Stermitz and H. Rapoport, *J. Am. Chem. Soc.*, **83**, 4045 (1961).

(3) A. R. Battersby, R. Birks, D. M. Foulkes, R. J. Francis, D. J. McCaldin, and H. Ramuz, *Proc. Chem. Soc.*, 203 (1963); D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *ibid.*, 203 (1963).



data, we used gas-liquid chromatography combined with continuous combustion and flow counting,⁴ carrying out multiple analysis on single mature plants or a few grams of seedlings. The column temperature was programmed from 180–260°, and the total effluent was passed through a triode-argon detector followed by combustion and counting with a flow-through proportional counter. A dual pen recorder simultaneously plotted the output of a counting ratemeter and the ion current from the triode-argon mass detector, giving mass and radioactivity in differential-type curves. The useful mass range was 0.1 to 20 $\mu g.$, and activities of about 100 c.p.m. were detectable in any one peak.

A mixture of codeine, thebaine, laudanosine, pavarine, cryptopine, and narcotine was completely resolved ($3/16$ in. \times 6 ft. column, nonpolar silicone gum on silanized Celite), as were the four phenolic alkaloids morphine, laudanosine, reticuline,⁵ and laudanine, as their trimethylsilyl ethers⁶ (cyano-silicone polymer as liquid phase). As confirmatory analytical adjuncts two-dimensional chromatography on alumina impregnated paper, paper chromatography using two different systems,⁷ and thin layer chromatography⁸ were employed.

After the natural occurrence of reticuline⁹ in very low concentrations in 120-day poppies and 5-day seedlings was shown by g.l.c. (Table I), several hundred 5-day seedlings were exposed to $^{14}CO_2$ for 2.5 hr., and the alkaloids were extracted immediately (after addition of 1 mg. of reticuline carrier). Gas, paper, and thin layer chromatography showed reticuline to account for more than 80% of the activity in the phenolic alkaloids, while thebaine accounted for more than 50% of the nonphenolic alkaloid activity. Similar results were obtained using a 120-day plant (1 day prior to blossom). Comparison of the specific activities of reticuline and thebaine shows reticuline to have a much higher specific activity than thebaine; the reticuline:

(4) F. Caece, A. Guarise, and Inam-ul-Haq, *Ann. Chim. (Rome)*, **50**, 915 (1960).

(5) K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Ber.*, **92**, 1657 (1959).

(6) Prepared according to C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).

(7) M. Tomita and I. Kikkawa, *Chem. Pharm. Bull. (Tokyo)*, **4**, 230 (1956); T. Swain, *Biochem. J.*, **53**, 200 (1953).

(8) D. Walki, K. Schnackerz, and F. Munter, *J. Chromatog.*, **6**, 61 (1961).

(9) The isolation from opium of a compound characterized as *dl*-reticuline was reported by R. Brockmann-Hanssen and T. Furuya at the Third International Symposium on Chemistry of Natural Products, Kyoto, Japan, April 13, 1964. This finding, if correct, raises the question as to the fate of (*S*)-(+)-reticuline, since only the (*R*)-(-) isomer should lead to thebaine (assuming no inversion during the conversion), and since there is no accumulation of reticuline. (*S*)-(-)-Reticuline may prove to be the precursor of narcotine, the major nonphenanthrene alkaloid in this species of poppy, which has been shown¹⁰ to have the same steric configuration as (*S*)-(-)-reticuline. In this connection, it is noteworthy that narcotine appears in the seedlings a few days after the maximum thebaine concentration is found.

(10) M. Ohta, H. Tani, S. Morozumi, S. Kodaira, and K. Duritama, *Tetrahedron Letters*, 1857 (1963); A. R. Battersby and H. Spencer, *ibid.*, 11 (1964).