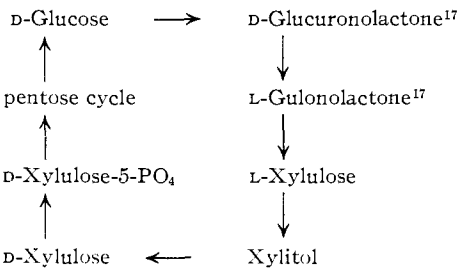
These results indicate that L-gulonolactone is decarboxylated in this system.

Evidence was found for the conversion of at least 15% of the uniformly labeled L-gulonolactone to labeled L-xylulose as follows:[11] 400 mg. of carrier L-xylulose[12] was added to the trichloroacetic acid extract of the incubation mixture and the solution was passed through an Amberlite IR-4B (acetate) column. L-Xylulose, in the effluent, was converted to L-ascorbic acid by the procedure described previously.[13] In brief, this method involved oxidizing L-xylulose to L-xylosone which was converted to imino-L-ascorbic acid by cyanide addition. After hydrolysis, the resulting L-ascorbic acid was purified by ion-exchange chromatography and converted to its 2,4-dinitrophenylosazone derivative which was recrystallized to constant specific activity.[5,14] This procedure does not distinguish between L-xylulose and L-xylose since both isomers are oxidized to L-xylosone. However, identification of the labeled pentose as L-xylulose was established and it was quantitatively determined by the cysteine-carbazole method[15] and a specific enzyme assay.[16]

Finding that L-gulonolactone is converted to L-xylulose suggests the following cyclic pathway for glucose metabolism in animals



The presence of enzyme systems in mammalian tissues for all these steps has been reported by others,[6,18–24] except the conversion of L-gulonolactone to L-xylulose. Evidence for occurrence *in vivo* of such an alternate pathway of glucose metabolism in animals will be presented elsewhere.

(11) A carrier dilution procedure[5] showed less than 0.2% of the added C^{14} present as L-ascorbic acid at the end of incubation.

(12) Carrier L-xylulose was kindly furnished by Dr. Gilbert Ashwell. In some experiments L-xylose was used as carrier instead of L-xylulose.

(13) L. L. Salomon, J. J. Burns and C. G. King, THIS JOURNAL, **74**, 5161 (1952).

(14) Repeated recrystallization of the 2,4-dinitrophenylosazone removes any labeled D-ascorbic acid osazone originating from D-xylulose. This was shown in control experiments with samples of osazone prepared from non-radioactive L-ascorbic acid which contained a trace amount of D-ascorbic acid-1-C^{14}; P. G. Dayton and J. J. Burns, to be published.

(15) Z. Dische and E. Borenfreund, *J. Biol. Chem.*, **192**, 583 (1951).

(16) L-Xylulose was determined by measuring the decrease in absorption of reduced triphosphopyridine nucleotide at 340 mμ in the presence of a purified xylitol dehydrogenase prepared from guinea pig liver. The authors are grateful to Dr. Gilbert Ashwell for carrying out the enzymatic and colorimetric assays for L-xylulose.

(17) It is not known at present whether the lactone or acid form of each compound is the intermediate in this scheme.

(18) J. L. Strominger, H. M. Kalckar, J. Axelrod and E. S. Maxwell, THIS JOURNAL, **76**, 6411 (1954).

(19) O. Touster, V. H. Reynolds and R. M. Hutcheson, *J. Biol. Chem.*, **221**, 697 (1956).

(20) S. Hollmann and O. Touster, THIS JOURNAL, **78**, 3544 (1956).

(21) S. Hollmann and O. Touster, *J. Biol. Chem.*, **225**, 87 (1957).

(22) J. Hickman and G. Ashwell, THIS JOURNAL, **78**, 6209 (1956).

(23) B. L. Horecker, J. Hurwitz and P. Z. Smyrniotis, *ibid.*, **78**, 692 (1956).

(24) P. A. Srere, J. R. Cooper, V. Klybas and E. Racker, *Arch. Biochem. Biophys.*, **59**, 535 (1955).

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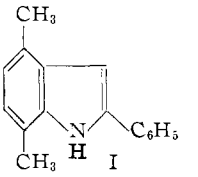
RECEIVED APRIL 27, 1957

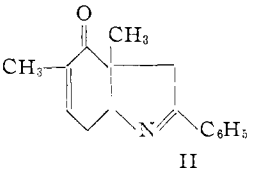
EVIDENCE FOR A HIGH ENERGY INTERMEDIATE IN THE FISCHER INDOLE SYNTHESIS. A NEW CLASS OF HYDROINDOLES

Sir:

When acetophenone 2,6-dimethylphenylhydrazone was heated at 130° in nitrobenzene solution with anhydrous zinc chloride for one hour, five products were isolated, among which 2-phenyl-4,7-dimethylindole (I), 4% yield, and 3a,4,7,7a-tetrahydro-2-phenyl-3a,5-dimethyl(3H)pseudoindolone-4 (II), 33% yield, were the most significant.



I



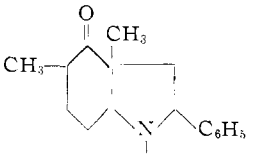
II

The structure of I, m.p. 65.5–66.5°, (calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.38; N, 6.33. Found: C, 86.69; H, 7.17; N, 6.24) was established by its independent synthesis from acetophenone 2,5-dimethylphenylhydrazone. The structure of II was proven by degrading it to 2-(β-phenylethyl)-2,6-dimethylcyclohexanone (VI), b.p. 143° (1–2 mm.), $n^{20}D$ 1.5205, (Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.20; H, 9.66. Oxime, m.p. 115–116°, calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.51; H, 9.28; N, 5.64) which was synthesized by treating 2,6-dimethylcyclohexanone with sodamide and then with β-phenylethyl bromide. The infrared spectra of the two samples of VI were identical, and their oximes had the same m.p. and gave no mixed m.p. depression.

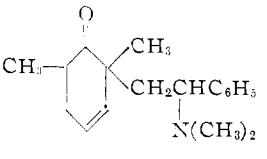
Crystalline II, m.p. 92–101°, was obtained as a hemihydrate (Calcd. for $C_{16}H_{17}NO \cdot {}^1/_2H_2O$: C, 77.39; H, 7.31; N, 5.64. Found: C, 77.46; H, 7.31; N, 5.68.), but the oxime, m.p. 230° (dec.), (Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.42; H, 7.25; N, 11.20), picrate, m.p. 224° (dec.), (Calcd. for $C_{22}H_{20}N_4O_8$: C, 56.41; H, 4.30: N, 11.96. Found: C, 56.19; H, 4.02; N, 12.20.), and hydrochloride, m.p. 214° (dec.) (Calcd. for $C_{16}H_{17}NO \cdot HCl$: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.74; H, 6.49; N, 5.16) all crystallized without bound water. The infrared spectrum ($CHCl_3$) of II featured bands at 2.72 μ (water), 6.02 μ (conj. C=O); 6.22 μ (conj. C=N, conj. phenyl) which split into two bands at

6.12 μ and 6.24 μ in acid solution. The ultraviolet absorption spectrum in ethanol showed a major band at 242 mμ (ϵ, 21,500) which split into two bands in acid solution (λ_1 242 mμ; ϵ_1 10,500; λ_2 273 mμ; ϵ_2, 16,500). Both the infrared and the ultraviolet spectra are characteristic of the conjugated carbonyl and conjugated imine chromophores.[1]

Hydrogenation of II over Adams catalyst in acetic acid afforded stereoisomeric forms of III (R = H), m.p. 56.5–58° and 92.5–93.5° (Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.01 and 78.94, resp.; H, 8.80 and 8.86, resp.; N, 5.67 and 5.60, resp.). Oximes, m.p. 162–164° and 177–179°, resp. (Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.44 and 74.32, resp.; H, 8.40 and 8.39, resp.; N, 10.74 and 10.83, resp.)

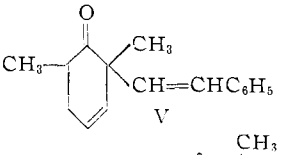


III R

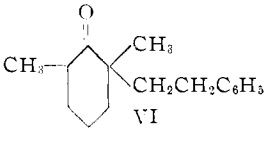


IV

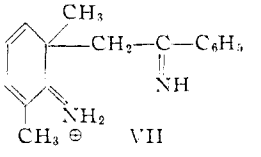
Formaldehyde and formic acid converted either stereoisomeric form of III (R = H) to the same III (R = CH_3) which infrared data indicated to be a mixture of two stereoisomers of which only one was obtained in crystalline form, m.p. 42–44° (Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.12; H, 9.16; N, 5.48). Oxime, m.p. 138–140° (Calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.26; H, 8.89; N, 10.18). The methiodide of III (R = CH_3) (Calcd. for $C_{18}H_{26}NOI$: C, 54.14; H, 6.56; N, 3.51. Found: C, 54.27; H, 6.65; N, 3.61) was converted to the methohydroxide by passage of its water solution through a column of the hydroxide form of Amberlite IRA-400. Heating the methohydroxide at 120° (1μ) afforded IV (methiodide, m.p. 158–213° (dec.), Calcd. for $C_{19}H_{28}NOI$: C, 55.21; H, 6.83; N, 3.39. Found: C, 55.33; H, 7.18; N, 3.26). Action of 30% hydrogen peroxide on IV gave the amine oxide (picrate, m.p. 133–134.5°, Calcd. for $C_{24}H_{28}N_4O_9$: C, 55.81; H, 5.46; N, 10.85. Found: C, 56.13; H, 5.56; N, 10.95) which decomposed[2] at 100° (15–20 mm.) to V, not obtained analytically pure, (Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 83.60; H, 7.71). Hydrogenation of V in absolute methanol over Adams catalyst yielded VI.



V



VI



VII

(1) B. Witkop, *Experientia*, **10**, 420 (1954).

(2) A. C. Cope, T. T. Foster and P. H. Towle, THIS JOURNAL, **71**, 3929 (1949).

The formation of both I and II can be rationalized in terms of a single intermediate VII, an analog of the kind of intermediate shown to take part in the *para* Claisen rearrangement[3] and also an analog of intermediates postulated in the Fischer reactions of acetophenone 2,6-dihalogenphenylhydrazones.[4] A more complete account of the degradation of II to VI, with the properties of this new group of hydroindole derivatives, and a mechanism to account for the formation of I and II through VII will be forthcoming.

(3) H. Conroy and R. A. Firestone, *ibid.*, **78**, 2290 (1956); D. Y. Curtin and H. W. Johnson, *ibid.*, **78**, 2611 (1956).

(4) R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).

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BENZOCYCLOBUTADIENOQUINONE

Sir:

Although no stable cyclobutadiene has yet been found, the monophenyl derivative of cyclobutadienoquinone has been prepared and appears to have considerable stability despite the great ring strain which it possesses.[1] It has been suggested[1] that the quinones of other unstable cyclic polyolefin systems might have a corresponding stability. We now wish to report some confirmation of this principle in the synthesis of a stable quinone of the unstable benzocyclobutadiene.[2]

A solution of 1,2-diiodobenzocyclobutene[2a] (I) and two equivalents of silver nitrate in acetonitrile gave, after stirring eight days at room temperature, a mixture of the isomeric *cis*-benzocyclobutene-1,2-diol dinitrate (II) and *trans*-benzocyclobutene-1,2-diol dinitrate (III), separable by crystallization from methanol. Isomer A:[3] m.p. 110°. *Anal.* Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67; N, 12.39. Found: C, 42.50; H, 2.59; N, 12.42. Isomer B:[3] m.p. 55.5–56.5°. *Anal.* Found: C, 42.24; H, 2.88; N, 12.29. Either isomer, when refluxed one hour with 1:1 methylene chloride–triethylamine gave, in 75% yield, the pale yellow 1,2-diketobenzocyclobutene, or benzocyclobutadienoquinone (IV), m.p. 132.5°. *Anal.* Calcd. for $C_8H_4O_2$: C, 72.73; H, 3.05. Found: C, 72.77; H, 3.08; λ_{max}^{EtOH} 271 mμ (log E = 3.45), 277 mμ (log E = 3.83). In the infrared (CS_2 solution), the strained carbonyls absorbed as a doublet at 5.51 and 5.61 μ.

The quinone IV was quite stable thermally and sublimed unchanged at 100° (0.2 mm. pressure). It reacted rapidly with *o*-phenylenediamine (V) to give the first known heterocyclic biphenylene analog, 1,4-diaza-benzo[b]biphenylene (VI), m.p. 238–239°. *Anal.* Calcd. for $C_{14}H_8N_2$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.21; H, 3.84; N, 13.83.

(1) E. J. Smutney and J. D. Roberts, THIS JOURNAL, **77**, 3420 (1955).

(2) (a) M. P. Cava and D. R. Napier, *ibid.*, **79**, 1701 (1957); (b) M. P. Cava and J. F. Stucker, *ibid.*, **79**, 1706 (1957).

(3) The configurations of isomers A and B remain unassigned as yet.