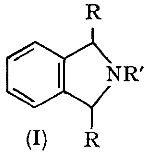
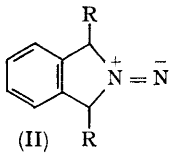
Stereochemistry of the Conversion of *cis*- and *trans*-2-Amino-1,3-dihydro-1,3-diphenylisoindoles into the Corresponding 1,2-Diphenylbenzocyclobutenes

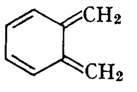
By LOUIS A. CARPINO

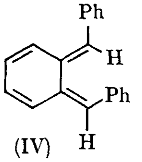
(*Department of Chemistry, University of Massachusetts, Amherst, Mass.*)

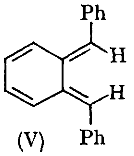
OXIDATION of the isomeric 2-amino-1,3-dihydro-1,3-diphenylisoindoles provides a convenient synthetic route to the *cis*- and *trans*-1,2-diphenylbenzocyclobutenes.[1] Since this method was first described data have become available which serve to establish the nature of the conversion. In the unsubsituted case (I; $R = H$, $R' = NH_2$) the major oxidation pathway appeared to involve fragmentation of the intermediate azamine (II; $R = H$) into nitrogen and the *o*-quinodimethane (III) followed by dimerization and/or cyclization of the latter.[1] Studies by Huisgen[2] and Quinkert[3] demonstrated that the two isomeric diphenyl-*o*-quinodimethanes, (IV) and (V), derived by ring opening of *cis*- and *trans*-1,2-diphenylbenzocyclobutenes (VI), respectively maintain their identity in solution under ordinary conditions. For example each yields a separate Diels–Alder adduct with tetracyanoethylene. These results, coupled with the theoretical studies of Woodward and Hoffmann[4,5] on electrocyclic reactions, have provided for a rational interpretation of the conversion of (I; $R = Ph$, $R' = NH_2$) into (VI) and indeed have suggested that the earlier designations of the relative stereochemistry of the precursor *N*-amino-compounds (I; $R = Ph$, $R' = NH_2$) should be reversed. This has now been verified by examination of the n.m.r. spectra of the *N*-benzyl derivatives (I; $R = Ph, R' = Ph{\cdot}CH_2$) of the precursor secondary amines (I; $R = Ph$, $R' = H$). The *N*-benzyl derivative, m.p. 177—178°, of the amine, m.p. 104—105°, originally described by Boyd and Ladhams[6] shows an AB quartet for the benzylic methylene group centred at 3·5 p.p.m.[7] ($J_{AB} = 14$ c./sec.) and must therefore be the *trans*-isomer.[8] The *N*-benzyl derivative, m.p. 128—129°, of the isomeric amine, m.p. 126—127·5°, shows only a sharp singlet for the benzylic methylene group at 3·78 p.p.m. and can therefore be assigned the *cis*-structure.

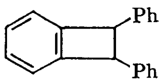

(I)


(II)


(III)


(IV)


(V)


(VI)

It had been assumed earlier that the differences between the chemical shifts of the α-methinyl protons of the *cis*- and *trans*-1,3-dihydro-1,3-diphenylisoindoles, although smaller, would parallel those of the 1,2-diphenylbenzocyclobutenes. However, examination of a more extensive series of *N*-substituted-1,3-dihydro-1,3-diphenylisoindoles (I; $R = Ph, R' = H, NH_2, Ph{\cdot}CH_2, CO{\cdot}Me, Ph{\cdot}CH_2{\cdot}SO_2$, Ts, TsNH, Ph·CO) than previously available shows no consistency between the stereochemistry of the substituted amine and the relative positions of the α-methinyl protons. Thus the first four compounds show the α-methinyl protons at higher fields in the *cis*-isomer whereas for the last four compounds the situation is reversed. The stereochemistry of the conversion of (I; $R = Ph$, $R' = NH_2$) into (VI) is also beclouded by the differing results reported by two groups of workers. Baker, McOmie, and Preston[9] reported that alkaline degradation of the toluene-*p*-sulphonyl derivative (not isolated) of the hydrazine (hydrochloride, m.p. 225—228° dec., free base not isolated) derived from the Boyd and Ladham's amine, m.p. 104—105°, now definitely established as the *trans*-isomer, gave the *trans*-benzocyclobutene (VI) in 36% yield. On the other hand we found that manganese dioxide oxidation of the same hydrazine (m.p. 140—142·5°; hydrochloride, m.p. 225·5—227°) in dichloromethane at room temperature gave the *cis*-hydrocarbon (VI) in 27% yield whereas under similar conditions the *cis*-hydrazine (m.p. 104—106°) was converted by mercuric oxide oxidation into the *trans*-hydrocarbon in 81% yield. Since only the *trans*- into *cis*-[*trans*-(I) into *cis*-(VI) through the intermediacy of (IV)] and *cis*- into *trans*-[*cis*-(I) into *trans*-(VI) through the intermediacy of (V)] conversions are consistent with the theoretical predictions based on the results of Woodward and Hoffmann[4,10] we suspected that the reaction conditions chosen by Baker, McOmie, and Preston might have caused isomerization of the initially-formed labile *cis*-hydrocarbon to the *trans*-isomer or alternatively isomerization of the labile intermediate (IV) to (V) prior to closure to (VI). This postulation is now supported by repetition of the alkaline degradation of *cis*- and *trans*-(I; R = Ph, R′ = NHTs) by the method of Baker, McOmie, and Preston except that the intermediate toluene-*p*-sulphonylhydrazides were first isolated and then treated with ethanolic potassium hydroxide at room temperature for 1—3 days. Under these conditions, in agreement with our earlier results on the direct oxidation of the hydrazines, the *cis*-toluene-*p*-sulphonyl derivative (I; R = Ph,R′ = NHTs, m.p. 138—140° dec.) gave the *trans*-hydrocarbon, m.p. 78—79·5°, lit.[1] m.p. 77—79°, in 80% yield. None of the *cis*-isomer could be detected in the initial crude product (m.p. 70—74°, 100%) by n.m.r. analysis. Under the same conditions the *trans*-toluene-*p*-sulphonyl derivative (I; R = Ph, R′ = NHTs, m.p. 137—139° dec.) gave in 79% yield a mixture, m.p. 59—70°, which was shown by n.m.r. analysis to consist of approximately 75% *cis*- and 25% *trans*-(VI). Repeated recrystallization gave pure *cis*-(VI), m.p. 84·8—86·8° (lit.[1] m.p. 85·5—87·5°).

(*Received, May 6th,* 1966; *Com.* 300.)

---

[1] L. A. Carpino, *J. Amer. Chem. Soc.*, 1962, **84**, 2196.

[2] R. Huisgen and H. Seidl, *Tetrahedron Letters*, 1964, 3381.

[3] G. Quinkert, K. Opitz, W. W. Wiersdorff, and M. Finke, *Tetrahedron Letters*, 1965, 3009.

[4] R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, 1965, **87**, 395, 2046, 2511.

[5] More recently D. M. Lemal and S. D. McGregor (*J. Amer. Chem. Soc.*, 1966, **88**, 1335, have applied the Woodward–Hoffmann approach to a reaction related to the fragmentation of (II).

[6] D. R. Boyd and D. E. Ladhams, *J. Chem. Soc.*, 1928, 2091.

[7] N.m.r. shifts are given in p.p.m. downfield from tetramethylsilane and were determined in deuterochloroform on a Varian A-60 instrument.

[8] Compare: W. F. Reynolds and T. Schaefer, *Canad. J. Chem.*, 1964, **42**, 2119, and R. K. Hill and T.-K. Chan, *Tetrahderon*, 1965, **21**, 2015.

[9] W. Baker, J. F. McOmie, and D. R. Preston, *J. Chem. Soc.*, 1961, 2971.

[10] Correlation diagrams set up according to the method of Woodward and Hoffmann by Profs. C. P. Lillya and R. M. Williams of this Department show that direct coupling of the 1- and 3-carbon atoms, as in a one-step conversion of (II) into (VI), is not allowed on the basis of orbital symmetry arguments. Although diradical intermediates are not excluded there is no evidence to suggest their involvement in these reactions.