able axial and equatorial resonances of monosubstituted cyclohexanes can be obtained by assuming that the variations with temperature of the chemical shifts of the individual types of resonances in the cyclohexyl and 4-*t*-butylcyclohexyl derivatives are the same. Thus the chemical shift of the individual resonances of the cyclohexyl derivative at room temperature can be approximated by correcting the observed individual low-temperature resonances in the monosubstituted cyclohexanes by the change observed between low temperature and room temperature for the corresponding resonances of the 4-*t*-butylcyclohexyl compounds. *A* values calculated from these corrected chemical shifts are tabulated in Table II. The *A* values were also measured by the peak area measurement method[4] at about −80°. For comparison, the values determined by the method of Eliel and coworkers are also included. They differ considerably from those obtained by the method outlined herein.

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Frederick R. Jensen, Barbara Hardin Beck
Department of Chemistry, University of California
Berkeley, California 94720
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The Crystal Structure of *o*-Di-*t*-butylquinoxaline

Sir:

Continued interest in the synthesis and the chemical and physical properties of *o*-di-*t*-butyl aromatic systems has made it important to know the detailed molecular structure of at least some representative compounds. Recently Arnett and coworkers[1] reported that C. H. Stam (Amsterdam) had carried out an X-ray analysis of 1,2,4,5-tetra-*t*-butylbenzene, but no details were given.[1a]

We wish to report the results of a refined X-ray analysis of 2,3-di-*t*-butylquinoxaline (Figure 1)[2] taken at room temperature. Suitable crystals of 2,3-di-*t*-butylquinoxaline (mp 53–54°)[3] were obtained from a solution in petroleum ether (bp 60–80°). The unit cell of 2,3-di-*t*-butylquinoxaline was found to be monoclinic with $a = 10.048 \pm 0.010$ Å, $b = 9.923 \pm 0.004$ Å, $c = 29.002 \pm 0.010$ Å; $\beta = 91.76 \pm 0.01°$. The space group is $P2_1/c$ with eight molecules per unit cell, and consequently there are two independent molecules.

The 3296 reliable *hkl* intensities (out of 6500 reflections measured) were measured by an automatic Nonius diffractometer. No absorption corrections needed to be applied. The structure was solved by means of the symbolic addition method[4] and refined by anisotropic least-squares methods on a TR4 computer.[5] The hydrogen atoms were located from a difference map and included in the refinement with fixed parameters, and this resulted in a final *R* value of 0.075.

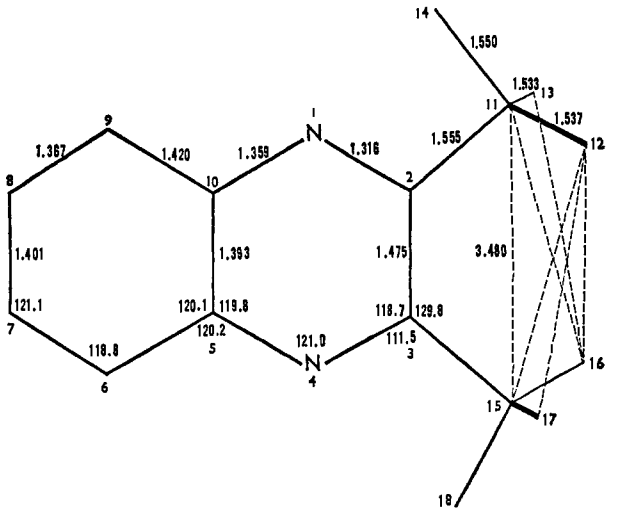

Figure 1. The bond lengths and angles of the average 2,3-di-*t*-butylquinoxaline molecule as projected onto the average plane of atoms 1–10.

The values of chemically equivalent bonds and angles in the two molecules are not significantly different; average values are given in Figure 1. The six distances, indicated in Figure 1, between the *t*-butyl groups fixed at one ring range from 3.33 to 3.50 Å.

The estimated standard deviations following from the least-squares refinement are 0.006–0.010 Å in the bond lengths and 0.4–0.6° for the bond angles. Meanwhile a refinement of data collected at −150° has been undertaken.[6]

This appears to be the first experimental evidence about bond lengths and angles in an *o*-di-*t*-butyl compound.

The distances between all of the methyl groups of the two *t*-butyl groups are such that we can speak of a fit between these groups as in a gear. The angles at the bonds C_{11}–C_{12} and C_{15}–C_{16} deviate from the normal value of 109.5° such as to increase the $C_{12}\cdots C_{16}$ distance; observed values are 113–116° for angles of type C_{12}–C_{11}–C_2, 112–114° for C_{12}–C_{11}–C_{13}, and 104–106° for C_{12}–C_{11}–C_{14}.

In both types of molecules carbons 11, 2, 3, and 15 are in one plane. Significant is the 129.8° external C_2–C_3–C_{15} angle. This is a 10° deviation from the similar angle in 2,3,5,6-tetramethylpyrazine (see Figure 2).

A slight but perhaps significant amount of bond stretching is noticeable between ring carbon atoms 2 and 3. This bond length is 1.475 Å compared to 1.434 Å in the pyrazine ring.[7] The C_2–C_{11} bond appears to be stretched also, 1.555 Å in the quinoxaline as compared to 1.505 Å in the pyrazine (see Figure 2). Although one molecule is completely planar, the other one is nearly, but not completely, so. The latter molecule shows a

(1) E. M. Arnett, J. C. Sanda, J. M. Bollinger, and M. Barber, *J. Am. Chem. Soc.*, **89**, 5389 (1967). Arnett's paper contains an up-to-date bibliography of papers pertaining to *o*-di-*t*-butylbenzenes but excludes heteroaromatic analogs.

(1a) NOTE ADDED IN PROOF. See, however, A. van Bruijnsvoort, L. Eilermann, H. van der Meer, and C. H. Stam, *Tetrahedron Letters*, 2527 (1968).

(2) The numbering of the atoms in Figure 1 is completely arbitrary and has no relation to the normal numbering in quinoxalines.

(3) Ae. de Groot and H. Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).

(4) Performed in the Naval Research Laboratory, Washington, D. C., with computer programs written by Dr. S. Brenner; see J. Karle and I. L. Karle, *Acta Cryst.*, **21**, 849 (1966).

(5) D. W. J. Cruickshank, "Computing Methods and the Phase Problem in X-Ray Crystal Analysis," Pergamon Press, Ltd., London, 1961.

(6) The results and the comparison with this room-temperature refinement will be published in *Acta Crystallographica*.

(7) D. T. Cromer, *J. Phys. Chem.*, **61**, 254 (1957).

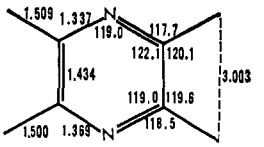

Figure 2. The bond lengths and angles of 2,3,5,6-tetramethylpyrazine.[7] Standard deviations in bond lengths and angles are about 0.01 Å and 0.6°, respectively.

nitrogen-containing ring that deviates significantly from true planarity. The distances of atoms 1, 2, 3, 4, 5, 10, 11, and 15 to the average plane of the ring are +0.009, +0.080, −0.080, −0.009, +0.067, −0.068, +0.446, and −0.380 Å, respectively (accurate to 0.005 Å).

This "twisted" ring may best be compared to a highly flattened boat with angles of about 3° deviation from planarity. The benzene ring and the conformation of atoms 11, 2, 3, and 15 of this molecule are practically planar. The slight twist in this molecule is probably a function of the best crystal fit. It is not due to steric repulsion between the *t*-butyl groups since inspection clearly shows that this twist does not significantly increase the distance between the *t*-butyl groups.

The C–N–C angle of 121° in Figure 1 is larger than the values found in pyrazine (115.1°),[8] 2,3,5,6-tetramethylpyrazine (119.0),[7] α-phenazine (116.3°),[9] and α-pyrazinamide (115.7°).[10]

It is clear that a combination of bond stretching and angle deformation in the plane of the ring is involved in relieving the strain in *o*-di-*t*-butyl aromatics. We have found no literature pertaining to the crystal structure of quinoxaline itself, and further detailed discussion of bond lengths appears premature at this stage.

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(9) F. L. Hirshfeld and G. M. J. Schmidt, *J. Chem. Phys.*, **26**, 923 (1957).
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G. J. Visser, Aafje Vos
Laboratory of Structural Chemistry
The University, Groningen, The Netherlands

Ae. de Groot, Hans Wynberg
Department of Organic Chemistry
The University, Groningen, The Netherlands

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Synthesis of Peptides in Aqueous Medium. V. Preparation and Use of 2,5-Thiazolidinediones (NTA's). Use of the ^{13}C–H Nuclear Magnetic Resonance Signal as Internal Standard for Quantitative Studies

Sir:

The use of α-amino acid N-carboxyanhydrides (NCA's) in the synthesis of heteropeptides has been described.[1-3] The sulfur analogs[4] of the NCA's, the 2,5-thiazolidinediones (N-thiocarboxyanhydrides, NTA's), appeared worthy of study, especially since we found thiocarbamate salts to be more stable than the corresponding carbamate salts. We therefore[2] expected NTA's to give higher yields in peptide synthesis than NCA's. Furthermore, we found the optimal pH for NTA reactions to be lower (9.0–9.5) than for NCA reactions (10.2–10.5). The lower pH favors the desired aminolysis of an anhydride over hydrolysis[2] and this, too, should improve the yield of the desired product. That this proved indeed to be the case is illustrated by the preparation of alanylleucylphenylalanine. After acidification of the crude reaction mixtures, the crystalline tripeptide precipitated in 70.3% yield from the alanine NCA reaction but in 92% yield after use of the NTA.

A further distinction was seen between the NCA and the NTA of glycine. The α-amino acid N-carboxyanhydride of glycine is a unique NCA because of its marked propensity to form the isocyanate I (R = H) which competes with NCA's for nucleophiles to yield hydantoic acids rather than the desired peptides. We found that 2,5-thiazolidinedione[5-7] (II, R = H) (glycine NTA) has little tendency to undergo this side reaction. For example, the condensation of the NCA of glycine with phenylalanine at 0° and pH 10.2 gave the hydantoic acid in >20% yield,[2] but the reaction of II (1.5% excess) at 0° and pH 9.5 gave glycylphenylalanine in about 93% yield by direct analysis of the total reaction mixture on a Beckman-Spinco amino acid analyzer. The yield of the hydantoic acid was calculated to be <3%. Similarly, phenylalanylleucine afforded crystalline glycylphenylalanylleucine in 95 and 37% yields with the NTA (20% excess) and the NCA (10% excess), respectively.

NTA's of L-amino acids,[8] in contrast to L-NCA's, do not yield optically pure peptides. That this lack of optical purity may result from partial racemization in the preparation and in the use of these NTA's was suggested by comparison of the total amount of racemization (tlc[2] and leucine aminopeptidase studies) with the extent of racemization during peptide bond formation in aqueous medium (tritium incorporation[1] studies).

The reaction of L-alanine with methyl methylxanthate in aqueous alkali at 40–50° afforded the analytically pure[9] thionourethan: mp 113–115°; $\lambda_{max}^{CH_2Cl_2}$ 2.83, 3.30, 5.61, 5.80, and 6.63 μ; $[\alpha]^{25}_{589}$ −19.3°[9] (*c* 0.97, CH_2Cl_2). Treatment with PBr_3 in the presence of 1 equiv of imidazole gave the analytically pure NTA II (R = CH_3): mp 91–93°; $\lambda_{max}^{CH_2Cl_2}$ 2.81 and 5.82 μ,

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(8) The preparation of NTA's of L-amino acids has not been previously reported.
(9) We believe the thionourethans to be optically pure, because tritium was not incorporated when the thionourethan of proline was prepared in tritiated water[1] (R. G. Strachan, unpublished observation).