Notes

Configuration at the 2-Position of Oxazolidines Derived from *l*-Ephedrine and *p*-Bromobenzaldehyde. An X-ray Structure Redetermination

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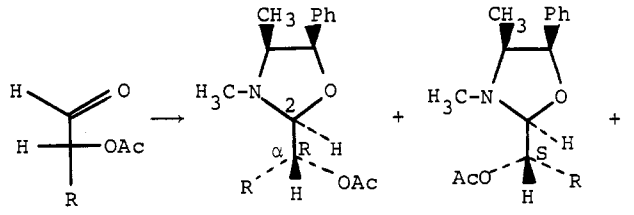
We recently reported that racemic α-acetoxy aldehyde 1 could be resolved by reaction with *l*-ephedrine,[1,2] followed



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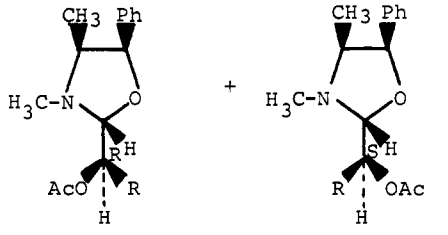

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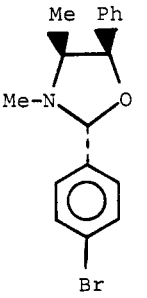
by flash chromatography, which cleanly separated, in order of decreasing R_f values, two major isomers having the α-*R* and α-*S* configurations and two minor isomers having the α-*R* and α-*S* configurations.

The major and minor isomers differed in their stereochemistry at the 2-position of the oxazolidine ring. Originally,[1] we had assigned the trans arrangement **4**/**5** to the major isomers, based on an X-ray crystal structure of the *l*-ephedrine derivative of *p*-bromobenzaldehyde **6** determined by Neelakantan and Molin-Case.[3] We had trouble assigning the ^{1}H NMR data of a variety of oxazolidines prepared.[2,4] on the basis of assumption that the major isomers had structures **4**/**5** and realized that both Beckett and Jones[5] and Baudet and Gelbcke,[6] had presented convincing arguments based on a large volume of spectroscopic data, that the major isomers had structures on type **2**, **3**, or **7**. These authors, however, did not resolve the conflicting assignments.



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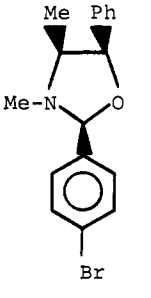

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We therefore decided to redetermine the X-ray crystal structure of **6**/**7**, in particular since Neelakantan and Molin-Case[3] presented no evidence of a spectroscopic or chromatographic nature which might have ascertained the purity of their product or permitted correlation with other 2-substituted oxazolidines.

When Neelakantan's procedure was repeated, a product having the same melting point (85–86 °C) as that reported[3] was obtained; ^{1}H NMR revealed it to consist of a mixture of a major and a minor isomer. A 200-MHz ^{1}H NMR of a crystal having probably the same crystallographic characteristics as those described[3] indicated it to consist mainly of the minor isomer. Crystallizations using a different solvent system gave pure major isomer (mp 90–91 °C) as established by NMR and TLC. Its X-ray structure determination clearly establishes that the major isomer has the all-cis structure **7**.

Neelakantan and Molin-Case therefore had a mixture of isomers even after recrystallization and so probably picked a crystal of a minor isomer for his X-ray work.

This finding resolves the apparent contradiction of X-ray and spectroscopic data and permits assignment of the stereochemistry of the four isomeric *l*-ephedrine derivatives of α-acetoxy aldehydes as **2**–**5** (decreasing R_f value on TLC silica gel, hexane–ethyl acetate mixtures).

Experimental Section

l-Ephedrine (2.05 g, 12.4 mmol) and *p*-bromobenzaldehyde (2.30 g, 12.4 mmol) were dissolved in 10 mL of chloroform and heated at 55–60 °C. After about 24 h, disappearance of the aldehyde peak corresponding to the *p*-bromobenzaldehyde indicated that the reaction was complete. Removal of the solvent by rotary evaporation afforded 3.95 g (96%) of product as a white precipitate. The crude product, which consisted of a 6:1 mixture of major and minor isomers, was then recrystallized twice from methanol and once from absolute ethanol. This yielded colorless, well-defined crystals of what proved to be (by NMR) the pure major isomer: mp 90–91 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.77 (d, 3 H, CCH_3), 2.16 s, 3 H, NCH_3), 2.98 (m, 1 H, H_4), 4.66 (s, 1 H, H_2), 5.13 (d, 1 H, H_5), 7.22–7.63 (m, 9 H, arom).

By differential comparison of the NMR spectra of the mixture and the pure major product the signals corresponding to the minor isomer are: 0.70 (d, 3 H, CCH_3), 2.20 (s, 3 H), NCH_3), 3.63 (m,

(1) Just, G.; Oh, H. *Tetrahedron Lett.* **1980**, *21*, 3667.
(2) Just, G.; Luthe, C.; Potvin, P. *Tetrahedron Lett.* **1982**, *23*, 2285.
(3) Neelakantan, L.; Molin-Case, J. A. *J. Org. Chem.* **1971**, *36*, 2261.
(4) Potvin, P. Ph.D. Thesis, McGill University, 1982.
(5) (a) Beckett, A. H.; Jones, G. R. *Tetrahedron* **1977**, *33*, 3313. (b) Beckett, A. H.; Jones, G. R.; Hollingsbee, D. *J. Pharm. Pharmacol.* **1978**, *30*, 15.
(6) Baudet, M.; Gelbcke, M. *Anal. Lett.* **1979**, *12*, 325, 641.

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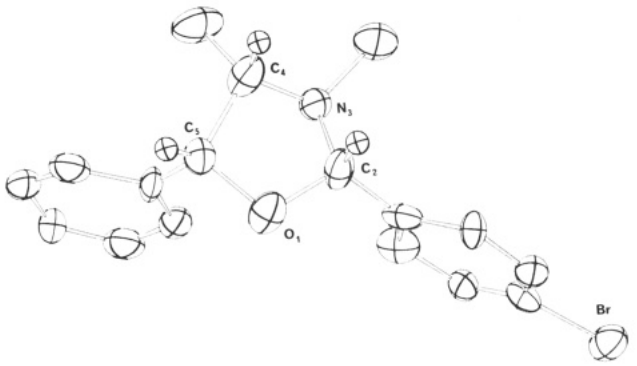

Figure 1. Molecular structure of (2*S*,4*S*,5*R*)-2-(*p*-bromophenyl)-3,4-dimethyl-5-phenyloxazolidine (hydrogen atoms have been placed in calculated positions for clarity; labels in parentheses are conventional).

1 H, H_4), 5.28 (s, 1 H, H_2), 5.50 (d, 1 H, H_5), 7.20–7.60 (m, 9 H, arom).

Structure Determination

Crystal data are as follows: $C_{17}H_{18}BrNO$, fw = 332.239; monoclinic; space group $P2_1$; a = 16.473 (3), b = 8.303 (2), c = 5.668 (3) Å; β = 99.30 (3)°; V = 764.92 Å^3; Z = 2; ρ_{calcd} = 1.443, ρ_{obsd} = 1.45 (2) g cm^{-3} (Mo Kα, λ = 0.710 69 Å, 20°, μ = 26.54 cm^{-1}).

The crystal selected for the structure determination was a thin plate (approximately 0.4 × 0.3 × 0.05 mm). The thinness of the crystals caused rather low intensity diffraction and severely limited the precision of the final structure analysis. Photographic data were used to determine the space group, and intensity data were collected on a Picker FACS-1 diffractometer. A unique quadrant of 783 reflections (3.5° > 20° > 40.0°) yielded 668 with $I > 30(I)$ which were used in the solution by the heavy-atom method and refinement by the block-diaganol least-squares method.[7] All nonhydrogen atoms were included with anisotropic thermal parameters. A final difference Fourier synthesis was devoid of significant features with electron density greater than 0.7 electrons/Å^3. Both enantiomorphs were tested in refinement, yielding final discrepancy indices R_f = 0.0663, R_{wf} = 0.0862 and R_f = 0.0696, R_{wf} = 0.0898 for the expected and opposite enantiomers, respectively. The final coordinates and anisotropic thermal parameters are collected in Table I.[8] A listing of bond lengths and angles may be found in Table II.[8] Figure 1 shows the molecular structure: the key finding is that the bromophenyl group is found on the *same* side of the five-membered ring as the phenyl group and the *C*-methyl group.

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Registry No. **6**, 29863-93-2; **7**, 86392-56-5; *l*-ephedrine, 299-42-3; *p*-bromobenzaldehyde, 1122-91-4.

Supplementary Material Available: A listing of final position and thermal parameters and distances and angles (2 pages). Ordering information is given on any current masthead page.

(7) Data collection operations and all structure solution and refinement were handled by using programs written for the Digital PDP-8a minicomputer by Dr. E. Gabe et al. at the National Research Council, Ottawa, Canada.

(8) See the note on supplementary material at the end of this paper.

New Heterocyclic Syntheses from Benzil Dianils

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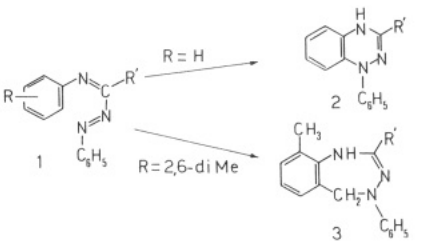
Arylazo imines **1** undergo acid-catalyzed or thermal cyclization to form dihydrobenzo-1,2,4-triazines **2**.[1] If two methyl groups are present in the ortho positions of the aromatic ring bound to the imine nitrogen, dihydrobenzo-1,3,4-triazepines **3**[2] are formed.

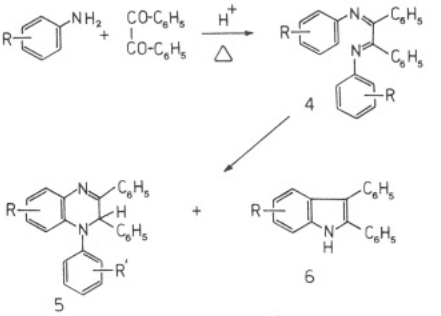


This paper reports the preliminary results of an effort to determine whether similar reactions occur in the case of dianils of α-diketones, in particular of benzil **4**.

Results

The parent compound **4a**, which has been known in the literature for nearly a century, has been prepared under a great variety of experimental conditions from benzil and aniline in the presence of acid catalysts and at high temperatures. Reported yields are generally modest due to concomitant formation of unidentified byproducts characterized by strong green fluorescence in solution.[3]

We have determined that benzil reacts with an excess of aniline, 4-toluidine, or 3,5-dimethylaniline at 200 °C for 3–4 h in the presence of 4-toluenesulfonic acid as catalyst, to give in all cases the corresponding 1,2-dihydroquinoxaline **5** in yields of 30–50%.



4a, R = H
b, R = 4-Me
c, R = 3,5-Me$_2$
d, R = 2,6-Me$_2$

5a, R = R′ = H
b, R = 7-Me; R′ = 4-Me
c, R = 6,8-Me$_2$; R′ = 3,5-Me$_2$

6a, R = 5-Me
b, R = 4,6-Me$_2$

Solutions of **5** in most organic solvents showed a typical blue-green fluorescence.

Concomitant formation of the indole derivatives **6** was observed in two cases, due to partial reduction of benzil to benzoin, possibly involving **5**, which is readily oxidized

(1) Blatter, H. M. *Chem. Abstr.* **1969**, *70*, 68435w. Blatter, H. M.; Lukaszewski, H. *Tetrahedron Lett.* **1968**, 2701. Neugebauer, F. A.; Umminger, I. *Chem. Ber.* **1980**, *113*, 1205.

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