

The Reaction of β -Aminoalcohols with *o*-Phthalaldehyde

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The reaction of *o*-phthalaldehyde with β -aminomonoalcohol compounds leads to *ortho*-substituted phenyloxazolines. β -Aminodiols or -triols give tetracyclic bisoxazolines when reacted with *o*-phthalaldehyde. These two type of ring systems are generated in one step under extremely mild conditions.

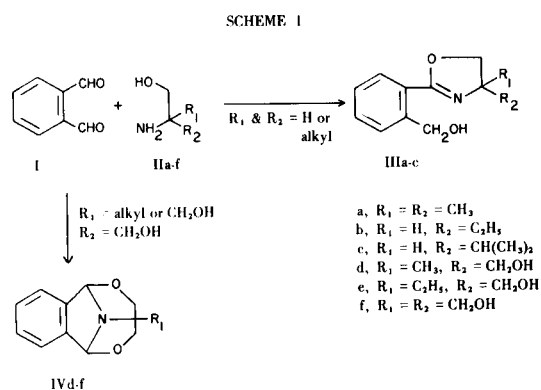
J. Heterocyclic Chem., 14, 305 (1977).

The reaction of alkyl substituted β -aminoalcohols with aldehydes leads, in general, to the corresponding oxazolines (1). For example, the reaction of 2-amino-2-methyl-1-propanol (IIa) with benzaldehyde gave crystalline 2-phenyl-4,4-dimethyloxazolidine (2). It has now been found that such an oxazolidine (V, $R_1 = R_2 = \text{CH}_3$) can not be isolated when a formyl group is present in the *ortho*-position. Thus, mixing *o*-phthalaldehyde (I) with an equimolar quantity of IIa in benzene led to a rise in temperature to 42° from 26°. Evaporation gave a nearly quantitative yield of a product with the spectral data indicative of 4,4-dimethyl-2-[2-(hydroxymethyl)phenyl]-

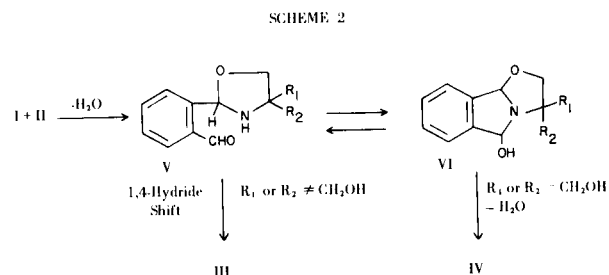
via lithiation to give *ortho*-substituted phenyloxazolines (4-6). The present method permits one to obtain this class of compounds in one-step involving a simple mixing of the two reactants under extremely mild conditions. Oxazolines IIIb and IIIc were, similarly, obtained when I was reacted with 2-amino-1-butanol (IIb) and 2-amino-3-methyl-1-butanol (IIc), respectively.

Such oxazoline ring formation was prevented when the amino alcohol had more than one vicinal hydroxyl group as recently reported by Broadbent, *et al.*, (7) and confirmed in the present study. Thus, mixing I with equimolar quantities of 2-amino-2-methyl-1,3-propanediol (IIe), 2-amino-2-ethyl-1,3-propanediol (IIe), and 2-amino-2-hydroxymethyl-1,3-propanediol (IIe) in an appropriate solvent gave good yields of tetracyclic bisoxazolines IVd, IVe, and IVf, respectively.

It is proposed that the reaction of I with amino alcohols II leads initially to oxazolidine V which is in equilibrium with VI (Scheme 2). Intermediate VI leads to



2-oxazoline (IIIa) (Scheme 1). In the proton magnetic resonance spectrum, the two methylene groups and the aromatic proton deshielded by the *ortho*-imino group were quite distinct. Absorptions in the infrared (OH and C=N stretchings at 3305 and 1635 cm^{-1} , respectively) and the ultraviolet regions supported the assignment. No molecular ion peak appeared in the 70 eV mass spectrum. This peak was visible in the 10 eV spectrum at 205 m/e followed by the base peak at 174 m/e. The generation of 2-oxazolines is generally carried out in two steps requiring high temperatures (140-200°) (3) followed by substitution



tetracyclic compound IV *via* dehydration when a hydroxymethyl group is present. In the absence of this function, a 1,4-hydride shift followed by a protomeric shift occurs in V leading to oxazoline III. Yamamoto *et al.*, (8) reported a similar hydride shift when I was heated to 170° with isocyanates.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. A Perkin-Elmer 21 spectrophotometer was used to obtain ir spectra in potassium bromide discs for solids and neat for oils. A Varian A60-A instrument was used to record pmr spectra in deuteriochloroform with TMS as an internal standard. A Spectronic 505 instrument was used for uv spectra in methanol. A Hewlett-Packard 5710-A instrument (with 36' column packed with 17% SE-30 on Gas Chrom Q) was used for gas chromatographic analyses. All evaporations were carried out on a rotary evaporator. Microanalyses were performed by Microanalysis, Inc., Wilmington, Delaware. Mass spectra were obtained through the courtesy of Mass Spectrometer Center, University of Illinois.

4,4-Dimethyl-2-[2-(hydroxymethyl)phenyl]-2-oxazoline (IIIa).

o-Phthalaldehyde (I) (6.4 g., 50 mmoles) in benzene (50 ml.) was mixed with IIa (4.5 g., 50 mmoles) in benzene (10 ml.). After 2 hours of stirring at ambient temperature, the solvent was evaporated and the water was removed by coevaporation with 2 x 20 ml. of benzene. A yellow oil weighing ca. 10 g. resulted. This oil could not be induced to crystallize even though it was pure as indicated by its pmr spectrum. Distillation (b.p. 165°/0.5 mm) provided an oil (6 g.) which gave crystals, m.p. 78-79° (from benzene-cyclohexane); ir, 745, 1060, 1205, 1235, 1400, 1465, 1635, 3305 cm⁻¹; pmr: δ 1.43 (s, 6H), 3.88 (d, 2H), 4.50 (s, 2H), 5.25 (t, 1H, exchangeable with deuterium oxide), 7.30-7.70 (m, 3H), 7.70-7.95 ppm (m, 1H); uv λ max: 278 (log ε, 3.26), sh 269 (3.48), sh 239 (3.84), 229 (3.89), sh 221 nm (3.86); mass spectrum: (10 ev), 205 (weak, M⁺), 174 m/e (base, M⁺ - CH₂OH).

Anal. Calcd. for C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.17; H, 7.34; N, 6.80.

4-Ethyl-2-[2-(hydroxymethyl)phenyl]-2-oxazoline (IIIb).

Equimolar quantities of I and IIb were reacted as in the case of IIIa and the resulting oil of 94.1% purity was purified to 98.3% purity (gc) by preparative tlc (silica gel plates with ethyl acetate as the eluant). The product was characterized by its spectral data; ir: 735, 1060, 1210, 1410, 1450, 1465, 1655, 2900, 3330 cm⁻¹; pmr: δ 0.85 (t, 3H), 1.60 (q, 2H), 3.50-4.60 (m, 6H), 7.20-7.55 (m, 3H), 7.55-7.90 ppm (m, 1H); uv λ max: 280 (log ε, 3.29), sh 270 (3.43), sh 238 (3.85), 228 (3.89), sh 221 nm (3.38); mass spectrum: (10 ev), 205 (weak, M⁺), 174 m/e (base); high resolution mass spectrum, Calcd. for C₁₂H₁₅NO₂: 205.1103, Found: 205.1104 m/e.

4-(1-Methylethyl)-2-[2-(hydroxymethyl)phenyl]-2-oxazoline (IIIc).

This compound was prepared in an analogous fashion and purified through distillation and crystallization, m.p. 62-72° (benzene-cyclohexane); ir: 735, 1070, 1210, 1410, 1465, 1640, 2900, 3335 cm⁻¹; pmr: δ 0.8 (d, 3H), 1.0 (d, 3H), 2.06 (m, 1H), 3.60-4.35 (m, 4H), 4.48 (pseudo d, 2H), 7.15-7.55 (m, 3H), 7.75-7.85 ppm (m, 1H); uv λ max: 278 (log ε, 3.26), sh 270 (3.52), sh 240 (3.89), 229 (3.95), sh 222 nm (3.93).

Anal. Calcd. for C₁₃H₁₇NO₂: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.05; H, 7.94; N, 6.11.

11-Methyl-9,13-dioxo-14-azatetracyclo[6.5.1.0^{2,7}.0^{11,14}]tetradeca-2,4,6-triene (IVd).

o-Phthalaldehyde (I) (6.7 g., 50 mmoles) and IIc (5.2 g., 50 mmoles) were stirred in methanol (50 ml.) for 0.5 hour at ambient temperature and allowed to stand overnight. Evaporation gave a yellow oil (8 g., 92.8% pure by gc) which was purified by distillation to give 7.5 g. of a colorless oil, b.p. 85°/0.1 mm; ir: 750, 950, 960, 1015, 1080, 1365, 2850 cm⁻¹; pmr: δ 1.28 (s, 3H), 3.61 (d, 2H), 3.78 (d, 2H), 5.83 (s, 2H), 7.32 ppm (apparent s, 4H); uv λ max: 268 (log ε, 2.45), 260 (2.53), 253 (2.53), 210 (3.67).

Anal. Calcd. for C₁₂H₁₃NO₂: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.97; H, 6.38; N, 6.61.

11-Ethyl-9,13-dioxo-14-azatetracyclo[6.5.1.0^{2,7}.0^{11,14}]tetradeca-2,4,6-triene (IVe).

The above experiment was repeated with IIc (6.0 g., 50 mmoles) in benzene (50 ml.). The resulting oil (10 g., 71.3% pure by gc) was purified by distillation to yield 4 g. of a colorless oil, b.p. 105°/0.35 mm; ir: 750, 945, 960, 1040, 1075, 1110, 1360, 1460, 2820, 2900 cm⁻¹; pmr: δ 1.00 (t, 3H), 1.72 (q, 2H), 3.68 (d, 2H), 3.93 (d, 2H), 5.83 (s, 2H), 7.38 ppm (apparent s, 4H).

Anal. Calcd. for C₁₃H₁₅NO₂: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.94; H, 6.98; N, 6.62.

11-Hydroxymethyl-9,13-dioxo-14-azatetracyclo[6.5.1.0^{2,7}.0^{11,14}]tetradeca-2,4,6-triene (IVf).

o-Phthalaldehyde (I) (6.7 g., 50 mmoles) and IIc (6.0 g., 50 mmoles) were stirred together in methanol (50 ml.) for 2 hours at ambient temperature. Cooling in an ice bath produced crystals which were separated by filtration and air dried to yield 6.9 g., m.p. 123-125°. The mother liquor upon concentration gave 2.5 g. of additional crystals, m.p. 123-125° (lit. (7) m.p. 125.5-126.5°) (total yield 93%).

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