Additions to Cyclic Nitrones: Synthesis of a Pyrrolo[1,2-b]-1,2-benzisoxazole

By B. G. Murray and A. F. Turner

5,5-Dimethyl-1-pyrroline 1-oxide has been condensed with a number of polarisable olefinic systems forming the expected pyrroloisoxazoles. Two isomeric products are possible depending on the polarisation of the nitrone; using nuclear magnetic resonance we were able to identify the isomers in a number of cases. With 2-cyclo-hexenone the cyclic nitrone formed a pyrrolo[1,2-b]-1,2-benzisoxazol-9-one.

5,5-DIMETHYL-1-PYRROLINE 1-OXIDE will condense with $\alpha\beta$ -unsaturated esters and other olefinic systems to give two isomeric bicyclic addition products.¹ We now report examples of this reaction involving cyclo-additions with $\alpha\beta$ -unsaturated amides and ketones. In some cases the products were characterised directly, but more usually the bases were isolated as their crystalline methiodides.

Addition of methyl methacrylate to the nitrone (I) proceeded normally 1 in the cold to give adduct (IIa) which showed a split carbonyl infrared absorption. Confirmation of this structure came from a study of the nuclear magnetic resonance (n.m.r.) spectrum of the adduct methiodide. The reaction of the nitrone (I) with ethyl crotonate required heat to form the oily adduct. This was not purified but must have been largely the pyrroloisoxazole (IIb) since the carbonyl stretching frequency was a single peak. The product from nitrone (I) and methyl cinnamate, which was isolated pure as an oil, must likewise have been the 3-carboxylate (IIc). Both of these adducts (IIb and c) gave crystalline products with methyl iodide, although the methiodide of the crotonate adduct appeared to decompose slowly on standing. However, the freshly



crystallised material analysed correctly and has been assigned the structure (IIIb) on the basis of its n.m.r. spectrum ($CDCl_3$). The methiodide (IIIc) from the cinnamate adduct also had an n.m.r. (in dimethyl sulphoxide, DMSO) consistent with the expected structure.

Reaction of the nitrone with acrylamide and N-t-butylacrylamide was exothermic and gave the expected products. In the infrared region the amide I band

¹ G. R. Delpierre and M. Lamchen, J. Chem. Soc., 1963, 4693.

of the compounds (IIId and e) was not split, which agrees with previous studies ² with other α -substituted amides. This evidence was reinforced by the nuclear magnetic spectra (IIId, DMSO; IIIe, D₂O). No reaction occurred when the nitrone (I) was mixed with mesityl oxide in the cold, but on warming cyclisation occurred to give the crude pyrroloisoxazole (IIf). This structure followed from spectroscopic results obtained on the methiodide. The nitrone (I) reacts slowly on standing with 2-cyclohexenone. However, in this case we obtained the adduct (IV) by heating, and assigned its structure from the n.m.r. data on its methiodide (D₂O).

The n.m.r. spectra were run on the base methiodides as this gave the necessary variation in the chemical shifts needed for structural determination. A number of the chemical shifts were common to all the spectra at δ 1.5 (non equivalent gem-dimethyl), δ 3.4—3.7 (N⁺·CH₃) and a multiplet at δ 4.8—5.6 (N⁺·CH).

Protons at positions 3 and 3a showed a coupling of 4-6 c./sec. while those at 2 and 3 coupled in the range 8-11 c./sec. This indicated that the former have the trans relationship whilst the latter were cis. The adduct methiodide from the nitrone and methyl methacrylate (IIIa) had significant n.m.r. peaks in DMSO at δ 4.9—5.4, a crude quintet for one proton (N⁺·CH), and a doublet at δ 3.2, (N⁺·CH·CH₂) for two protons with J = 5 c./sec., being consistent with structure (IIIa). The ethyl crotonate adduct methiodide (IIIb) had significant peaks at δ 5.5–5.9, a multiplet (6 peaks) at $\delta 4.6$ —5.2 (O·CH), and a masked quartet (CH·CO₂Et) at δ 4.2-4.5. The direction of addition was assigned on the basis of the chemical shifts since in the alternative structure the complex splitting pattern expected for (CH·CHMe·CH) should have a chemical shift in the range $\delta = 2 - 3$ p.p.m. The multiplet pattern for the protons at positions 2 and 3 analyses well for an AB system with J = 11 c./sec. and a difference in chemical shift of 21 c./sec. Further interaction with the methyl at position 2 with J = 6.5 c./sec. gives the six peaks required with correct relative areas.

The structure of the adduct methiodide (IIc) from methyl cinnamate was assigned by comparison with the ethylcrotonate adduct. The doublet at δ 5·7—6·0 with J = 10 c./sec. was as expected for (O·CH·Ph) and a quartet at δ 4·6—5·0 with J = 6, 10 c./sec. was assigned to (CH·CHCO₂Me·CH).

Acrylamide gave an adduct methiodide with n.m.r.

² L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1960, p. 210.

peaks (D₂O) at chemical shifts δ 4·8—5·2, a multiplet (N⁺·CH), δ 4·9—5·3, a triplet with J = 9 c./sec. (N⁺·O·CH), and a deformed quartet, J = 4, 9 c./sec., at δ 2·9 (N⁺·CH· CH_2 ·CH), which suggested (IIId) as the structure. Similarly the adduct from N-t-butyl-acrylamide showed significant n.m.r. peaks, a multiplet at δ 5·0 (N⁺·CH), a triplet at δ 4·9—5·3 (N⁺·O·CH), where J = 9 c./sec., and a quartet at δ 2·8—3·1 (N⁺·CH· CH_2 ·CH) with J = 4, 9 c./sec., indicating that the structure was (IIIe).

The mesityl oxide adduct methiodide had the expected structure (IIIf) and exhibited important peaks $(\text{CDCl}_3-\text{CD}_3\text{OD})$ at chemical shifts δ 5·1—5·5, a triplet with J = 3 c./sec. split again (5½ c./sec.) by the proton at position 3 (N⁺·CH), and at δ 4·1 a doublet with a coupling constant of 5½ c./sec. (N⁺·CH·CH·CO). The methiodide of the cyclohexenone adduct has been assigned the structure (IV). This compound had an interesting n.m.r. spectrum. A doublet instead of the expected triplet at δ 3·7 for one proton was assigned to

(CH·CH·CO) and this explained by assuming noncoupling for stereochemical reasons.³ This explanation was reinforced by the complex multiplets at δ 5·3 for two protons which were assigned to (N⁺·CH), as in other spectra, and (N⁺·O·CH).

EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained with a Varian 60 Mc./sec. spectrometer. The solvents are quoted in the discussion, and figures are expressed relative to tetramethylsilane as internal standard.

Methyl Hexahydro-2,2,6,6-trimethylpyrrolo[1,2-b]isoxazole-2-carboxylate (IIa).—The nitrone (I; 6.0 g.) and methyl methylacrylate (30 ml.) were mixed, whereupon the temperature rose to 30°. After standing for 2 days the mixture was distilled to give the base (10.6 g.), b. p. 60—63°/0.4 mm., ν_{max} . 1740, 1750 cm.⁻¹ (Found: C, 61.75; H, 9.0; N, 6.8. C₁₁H₁₉NO₃ requires C, 61.9; H, 9.0; N, 6.6%). The methiodide (IIIa), m. p. 147° (decomp.), ν_{max} . 1760, 1750 cm.⁻¹, was recrystallised from ethanol (Found: C, 40.7; H, 6.0; I, 35.8; N, 4.2. C₁₂H₂₂INO₃ requires C, 40.6; H, 6.2; I, 35.7; N, 3.9%).

Ethyl Hexahydro-2,6,6-trimethylpyrrolo[1,2-b]isoxazole-

3-carboxylate (IIb).—The nitrone (6.0 g.) and ethyl crotonate (30 ml.) were heated for 6 hr. at 100°. Distillation gave the base (9.4 g.), b. p. 98°/0.8 mm., ν_{max} . 1735 cm.⁻¹. The methiodide (IIIc), m. p. 121—123°, ν_{max} . 1740 cm.⁻¹ was recrystallised from methyl cyanide–ether (Found: C, 42·2;

Methyl Hexahydro-6,6-dimethyl-2-phenylpyrrolo[1,2-b]isoxazole-3-carboxylate (IIc).—Methyl cinnamate (8.6 g.) was heated with the nitrone (6.0 g.) for 3 hr. at 100°. The mixture was distilled to yield the crude base (12.0 g.) which was redistilled to give pure base, b. p. 100—103°/0·2 mm., ν_{max} . 1740 cm.⁻¹ (Found: C, 69.6; H, 8.0; N, 5.2. C₁₆H₂₁NO₃ requires C, 69.8; H, 7.7; N, 5.1%). The methiodide, recrystallised from ethanol, had m. p. 145° (decomp.), ν_{max} . 1744 cm.⁻¹ (Found: C, 48.7; H, 5.8; I, 30.0; N, 3.45. C₁₇H₂₄INO₃ requires C, 48.9; H, 5.8; I, 30.4; N, 3.35%).

Hexahydro-6,6-dimethylpyrrolo[1,2-b]isoxazole-2-carboxyamide (IId).—Nitrone (8·1 g.) and acrylamide (5·1 g.) were allowed to react, the temperature reaching 35°. After standing for 2 days the mixture was distilled to give the crude base (11·8 g.), b. p. 126—135°/0·2 mm. The methiodide, recrystallised from methanol-ether, had m. p. 156° (decomp.), $\nu_{\rm max}$ 1670, 1600 cm.⁻¹ (Found: C, 36·35; H, 5·7; I, 39·4; N, 8·7. C₁₀H₁₉IN₂O₂ requires C, 36·8; H, 5·9; I, 38·9; N, 8·6%).

Hexahydro-6,6-dimethyl-N-t-butylpyrrolo[1,2-b]isoxazole-2carboxyamide (IIe).—5,5-Dimethyl-1-pyrroline-1-oxide (5.6 g.) and N-t-butylacrylamide (6.3 g.) were mixed, the temperature rising to 30°, then allowed to stand for 2 days. This material was distilled to give the base (10.3 g.), b. p. 94—104°/0·1—0·2 mm. The methiodide, recrystallised from methanol-ether, had m. p. 129.5° (decomp.), v_{max} . 1694, 1540 cm.⁻¹ (Found: C, 44.3; H, 7.3; I, 32.6; N, 7.2. C₁₄H₂₇IN₂O₂ requires C, 44.0; H, 7.1; I, 33.2; N, 7.3%). Hexahydro-3-acetyl-2,2,6,6-tetramethylpyrrolo[1,2-b]isox-

azole (IIf).—The nitrone (9.0 g.) and mesityl oxide (7.8 g.) were heated at 100° for 12 hr. and then distilled to give the base (10.6 g.), b. p. 70—73°/0.4 mm., v_{max} 1710 cm.⁻¹. The *methiodide*, recrystallised from methanol–ether, had m. p. 209—210° (decomp.), v_{max} 1715 cm.⁻¹ (Found: C, 44.2; H, 6.8; I, 36.3; N, 4.2. C₁₃H₂₄INO₂ requires C, 44.2; H, 6.85; I, 35.9; N, 4.0%).

Decahydro-3,3-dimethylpyrrolo[1,2-b]-1,2-benzisoxazol-9one (IV).—Nitrone (2.0 g.) and 2-cyclohexenone (1.7 g.) were heated for 6 hr. at 100° to give crude base. It was characterised as the methiodide, m. p. 143—145°, ν_{max} , 1715 cm.⁻¹, from methanol-ether (Found: C, 44.25; H, 6.2; I, 36.25; N, 4.3. C₁₃H₂₂INO₂ requires C, 44.45; H, 6.3; I, 36.1; N, 4.0%).

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RIKER LABORATORIES, WELWYN GARDEN CITY, HERTS. [5/1295 Received, December 6th, 1965]

⁸ H. Conroy, "Advances in Organic Chemistry," Interscience, London, 1960, vol. II, p. 311.

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