SYNTHESIS OF N,N'-DIBENZYL PYRROLIDINE-2,5-DICARBOXIMIDE
(3,8-DIAZABICYCLO[3,2,1]OCTANE-2,4-DIONE)

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3,8-Diazabicyclo[3,2,1]octanes (1; X = H₂) have been prepared on numerous occasions usually using lithium aluminium hydride reduction of dicarboximides (1; X = O).1 The dicarboximides (1; X = O) can be prepared from esters of pyrrolidine-2,5-dicarboxylic acid (2; R¹ = R³ = OR)² and by cyclization of derivatives of 5-carbamoylp油画olidine-2-carboxylic acid (2; R¹ = NHR, R³ = OR or OH).³⁻⁵ We wish to record an example of an alternative milder cyclization that could be used in other cases.

We attempted to prepare the title dicarboximide (1; X = O, R¹ = R² = PhCH₂) from diethyl 1-benzylpyrrolidine-cis-2,5-dicarboxylate (2; R¹ = R³ = OEt, R² = PhCH₂) using the method described by Blackman and Baltzly.² However, the infrared spectrum of the product, after it had been distilled twice, contained absorptions characteristic of a mono-amide (2; R¹ = NHCH₂Ph, R² = CH₂Ph, R³ = OEt) and the dicarboximide (1; X = O, R¹ = R² = CH₂Ph).⁴ The mixture was hydrolysed with aqueous sodium hydroxide and yielded 1-benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylic acid (2; R¹ = NHCH₂Ph, R² = CH₂Ph, R³ = OH) in quantitative yield. This carboxylic acid had the expected spectral properties and was characterized as the methyl ester (2; R¹ = NHCH₂Ph, R² = CH₂Ph, R³ = OMe), which, contrary to previous observations, was stable to vacuum distillation.⁶ The carboxylic acid (2; R¹ = NHCH₂Ph, R² = CH₂Ph, R³ = OH) was smoothly converted into the hydrochloride of N,N'-dibenzylpyrrolidin-2,5-dicarboximide.

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(1; X = O, R₁ = R₂ = CH₂Ph) in excess thionyl chloride at room temperature. The crude product from the reaction was contaminated with some acyl chloride (2; R₁ = NHCH₂Ph, R₂ = CH₂Ph, R₃ = Cl) from the trans-carboxylic acid but this was readily removed by fractional crystallization. Although this is a simple modification of previous work it is interesting to note that 1-benzyl-5-benzylamino-2-chloromethylpyrrolidine could not be induced to undergo a cyclization reaction.

Experimental

All melting points are uncorrected. The infrared spectra were measured with a Unicam SP-200 spectrophotometer. The p.m.r. spectra were recorded on a Varian A60 spectrometer with chemical shifts (δ) quoted in p.p.m. from TMS as internal standard. The p.m.r. spectra were measured by Dr A. V. Robertson and Mr C. Dehlsen at the University of Sydney. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

1-Benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylic Acid

Diethyl 1-benzylpyrrolidine-cis-2,5-dicarboxylate was converted into N,N'-dibenzylpyrrolidine-2,5-dicarboximide (53%) using the method described by Blackman and Baltzly, b.p. 175/0.3 mm (lit. 195-210 mm); ν₅₅₅ (neat): 3450m, 1725s, and 1680s cm⁻¹. The above liquid was hydrolysed with 2% sodium hydroxide solution (room temperature, 24 hr) giving, after acidification and crystallization from water, fine white needles of 1-benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylic acid (100%), m.p. 187-188° (Found: C, 70.8; H, 6.4; N, 8.0. C₂₀H₂₂N₂O₂ requires C, 71.0; H, 6.6; N, 8.3%). ν₅₅₅ (Nujol): 3250w, 1675s, and 1640s cm⁻¹. The hydrochloride crystallized as a hydrate, m.p. 187° (Found: C, 59.7; H, 6.7; Cl, 8.7; N, 6.8. C₂₀H₂₃ClN₂O₃·1.5H₂O requires C, 59.8; H, 6.5; Cl, 8.8; N, 7.0%). ν₅₅₅ (Nujol): 3300s, 3190s, 1700s, and 1670s cm⁻¹. The water of crystallization was removed by heating under vacuum (168°/1-1 mm), m.p. 182-184°; ν₅₅₅ (Nujol): 3230w, 1675s, and 1645s cm⁻¹. Methylation with ethereal diazomethane yielded methyl 1-benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylate, b.p. 198/0.1 mm, which crystallized from pentane as white needles, m.p. 63-64° (Found: C, 71.4; H, 6.7; N, 7.5. C₂₇H₃₁N₃O₂ requires C, 71.6; H, 6.9; N, 7.9%). ν₅₅₅ (Nujol): 3400m, 1735s, and 1650s cm⁻¹. P.m.r. (CDCl₃): signals centred at δ 3.43 (s, 3, CO₂CH₃), 3.78 (s, 2, NCH₂), 4.37 (d, J 6.0Hz, 2, CONHCH₂), 7.18 and 7.27 (s, 10, aromatic), and 8.57 (broadened s, 1, CONH). The picrate of the methyl ester crystallized from ethanol as yellow needles, m.p. 101-102° (Found: C, 55.5; H, 4.7; N, 11.9. C₂₇H₂₇N₅O₁₀ requires C, 55.7; H, 4.7; N, 12.0%).

N,N'-Dibenzylpyrrolidine-2,5-dicarboximide

1-Benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylic acid was stirred with excess thionyl chloride (room temperature, 1 hr) and the mixture evaporated to dryness at room temperature leaving a sticky yellow solid, ν₅₅₅ (Nujol): 1820m, 1690s, and 1670s cm⁻¹. Recrystallization of the solid from methanol-acetone gave white needles of the hydrochloride of N,N'-dibenzylpyrrolidine-2,5-dicarboximide (75%), m.p. 187° (lit. 189-190°) (Found: C, 67.7; H, 6.1; Cl, 9.8. Calc. for C₂₀H₂₂Cl₂N₂O₄: C, 67.3; H, 5.9; Cl, 9.9%). ν₅₅₅ (Nujol): 2250s, 1740m, and 1695s cm⁻¹. P.m.r. (CD₃N): signals centred at δ 3.58 (s, 2, NCH₂), 5.03 (s, 2, (CO)₂NCH₂), and 7.30 (s, 10, aromatic). N,N'-Dibenzylpyrrolidine-2,5-dicarboximide was obtained from the hydrochloride as a white solid, m.p. 40-42°; ν₅₅₅ (neat): 1730s and 1675s cm⁻¹.

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