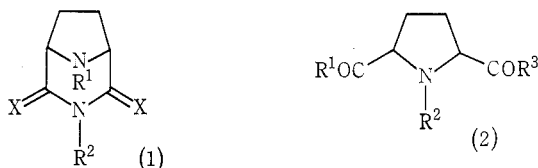


SYNTHESIS OF *N,N'*-DIBENZYLPIRROLIDINE-2,5-DICARBOXIMIDE (3,8-DIAZABICYCLO[3,2,1]OCTANE-2,4-DIONE)

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3,8-Diazabicyclo[3,2,1]octanes (1; $X = H_2$) 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; $R^1 = R^3 = OR$)² and by cyclization of derivatives of 5-carbamoylpyrrolidine-2-carboxylic acid (2; $R^1 = NHR$, $R^3 = OR$ 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; $X = O$, $R^1 = R^2 = \text{PhCH}_2$) from diethyl 1-benzylpyrrolidine-*cis*-2,5-dicarboxylate (2; $R^1 = R^3 = \text{OEt}$, $R^2 = \text{PhCH}_2$) 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; $R^1 = \text{NHCH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{Ph}$, $R^3 = \text{OEt}$) and the dicarboximide (1; $X = O$, $R^1 = R^2 = \text{CH}_2\text{Ph}$).⁴ The mixture was hydrolysed with aqueous sodium hydroxide and yielded 1-benzyl-5-benzylcarbamoylpyrrolidine-2-carboxylic acid (2; $R^1 = \text{NHCH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{Ph}$, $R^3 = \text{OH}$) in quantitative yield. This carboxylic acid had the expected spectral properties and was characterized as the methyl ester (2; $R^1 = \text{NHCH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{Ph}$, $R^3 = \text{OMe}$), which, contrary to previous observations, was stable to vacuum distillation.⁶ The carboxylic acid (2; $R^1 = \text{NHCH}_2\text{Ph}$, $R^2 = \text{CH}_2\text{Ph}$, $R^3 = \text{OH}$) was smoothly converted into the hydrochloride of *N,N'*-dibenzylpyrrolidine-2,5-dicarboximide

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¹ Mauger, A. B., and Witkop, B., *Chem. Rev.*, 1966, **66**, 47.

² Blackman, S. W., and Baltzly, R., *J. org. Chem.*, 1961, **26**, 2750.

³ Cignarella, G., and Testa, E., *Gazz. chim. ital.*, 1962, **92**, 1093.

⁴ Cignarella, G., Nathansohn, G., and Ocelli, E., *J. org. Chem.*, 1961, **26**, 2747.

⁵ Cignarella, G., and Nathansohn, G., *J. org. Chem.*, 1961, **26**, 1500.

⁶ Schipper, E., and Boehme, W. R., *J. org. Chem.*, 1961, **26**, 3599.

(1; $X = O$, $R^1 = R^2 = CH_2Ph$) in excess thionyl chloride at room temperature. The crude product from the reaction was contaminated with some acyl chloride (2; $R^1 = NHCH_2Ph$, $R^2 = CH_2Ph$, $R^3 = Cl$) 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-methyl-2-chloromethylpyrrolidine could not be induced to undergo a cyclization reaction.^{6,7}

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-dicarboxylate⁵ was converted into *N,N'*-dibenzylpyrrolidine-2,5-dicarboximide (53%) using the method described by Blackman and Baltzly,² b.p. 178°/0.3 mm (lit.² 205–211°/1 mm); ν_{max} (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. $C_{26}H_{22}N_2O_3$ requires C, 71.0; H, 6.6; N, 8.3%). ν_{max} (Nujol): 3250w, 1670s, and 1640s cm^{-1} . The hydrochloride crystallized as a hydrate, m.p. 181–182° (Found: C, 59.7; H, 6.7; Cl, 8.7; N, 6.8. $C_{26}H_{23}ClN_2O_3 \cdot 1.5H_2O$ requires C, 59.8; H, 6.5; Cl, 8.8; N, 7.0%). ν_{max} (Nujol): 3300s, 3190s, 1700s, and 1670s cm^{-1} . The water of crystallization was removed by heating under vacuum (168°/0.1 mm), m.p. 182–184°; ν_{max} (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. $C_{21}H_{24}N_2O_3$ requires C, 71.6; H, 6.9; N, 7.9%). ν_{max} (Nujol): 3400m, 1735s, and 1650s cm^{-1} . P.m.r. ($CDCl_3$): signals centred at δ 3.43 (s, 3, CO_2CH_3), 3.78 (s, 2, NCH_2), 4.37 (d, J 6.0 Hz, 2, $CONHCH_2$), 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. $C_{27}H_{27}N_5O_{10}$ 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, ν_{max} (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.² 189.5°) (Found: C, 67.7; H, 6.1; Cl, 9.8. Calc. for $C_{20}H_{21}ClN_2O_2$: C, 67.3; H, 5.9; Cl, 9.9%). ν_{max} (Nujol): 2250s, 1740m, and 1695s cm^{-1} . P.m.r. (C_5D_5N): signals centred at δ 3.58 (s, 2, NCH_2), 5.03 (s, 2, $(CO)_2NCH_2$), 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°; ν_{max} (neat): 1730s and 1675s cm^{-1} .

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⁷ Cignarella, G., and Nathansohn, G., *Gazz. chim. ital.*, 1960, 90, 1495.