

A Synthesis of 3,7,10-Triazatricyclo[3.3.3.0^{1.5}]undecane, '3,7,10-Triaza[3.3.3]propellane', and some Derivatives

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The previously undescribed 3,7,10-triazatricyclo[3.3.3.0^{1.5}]undecane, '3,7,10-triaza[3.3.3]propellane', and some derivatives have been prepared by an efficient route. The key intermediates, 3a,6a-disubstituted octahydropyrrolo[3,4-c]pyrroles, are formed in a novel, one-step synthesis utilising 1,3,5-trialkylhexahydrotriazines.

The synthesis of 3,7,10-trimethyl-3,7,10-triazatricyclo[3.3.3.0^{1.5}]undecane (1a)^{1a,1b} has been described. The key intermediate in this lengthy procedure was the 3a,6a-disubstituted octahydropyrrolo[3,4-c]pyrrole (2a) which was cyclised in the presence of alkali to the triazatricycloundecane system. All attempts to cyclise the derivative (2b) have failed.² These results indicate that a facile synthesis of a suitably substituted octahydropyrrolo[3,4-c]pyrrole would be a useful starting point.

In a study of the reactions of 1,3,5-trimethylhexahydro-1,3,5-triazine (3a)³ with activated methylene compounds⁴ it was observed that the reaction with tetraethylethane-1,1,2,2-tetracarboxylate (4a) and a catalytic amount of trifluoroacetic acid led to a good yield of a nitrogen-containing, non-basic product of molecular weight 312 (by mass spectroscopy). This compound was assigned the structure (5a) on the basis of the following evidence. The ¹H n.m.r. spectrum was very simple, consisting of the usual resonances for the ethyl ester groups, a singlet for the *N*-methyl groups (δ 2.9), and the two doublets of an AB system (δ 3.79, 4.09, *J* 10.5 Hz), the ring protons. The i.r. spectrum confirmed the presence of the cyclic lactam (ν_{max} 1710 cm⁻¹) as well as the expected ester (ν_{max} 1750 cm⁻¹). Further corroborative evidence from the ¹³C spectrum indicated the bridgehead carbon atoms. A probable mechanism for the production of the ester (5a) may be the reaction of a Mannich-type intermediate formed from compound (3a) with an anion of the tetracarboxylate (4a) followed by cyclisation to the lactam, the whole process being repeated at the other active centre to give the thermodynamically more stable *cis*-fused heterocycle.

Under similar conditions, the formation of the dinitrile (5c) from diethyl 2,3-dicyanosuccinate (4b)⁵ occurred in low yield (5%). When, however, the reaction was carried out without a catalyst, a moderate yield of the nitrile (5c) was obtained. In this case, it appears that compound (4b) is a sufficiently strong acid to act as its own catalyst. The lower yield in these reactions compared with those utilising the ester (4a) can be understood by the fact that, in a step-wise process, there is less chance for the formation of the second lactam ring. It is not at all evident, however, why the addition of a catalytic amount of trifluoroacetic acid should decrease this yield.

The diamides (5d) and (5e) were formed from the ester (5a) using the requisite amine and on heating were converted into the imides (6a) and (6b). Reduction with lithium aluminium hydride gave the triazatricycloundecanes (1a) and (1b). A similar series of reactions using 1,3,5-tribenzylhexahydro-1,3,5-triazine (3b)^{6a,6b} yielded the octahydropyrrolo[3,4-c]pyrrole (5b), the diamide (5f), the imide (6c), and finally the triazatricycloundecane (1c). Inspection of the structures (5a—f) and (6a—c) indicated that they are chiral molecules with a C₂ axis of symmetry, the asymmetric carbon atoms being those at the bridgehead. The method of synthesis resulted

in the production of the racemates of the two possible enantiomers in each case, and, although these were not resolved, evidence of chirality was given from the ¹H n.m.r. spectra of (5b), (5f) and (6c). These spectra show that as well as the AB system for the heterotopic ring protons, a further AB system is observed for the benzylic protons.

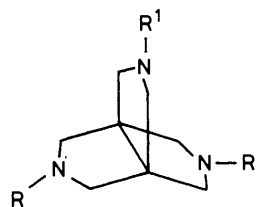
Catalytic reduction of the benzylic compound (1c) gave the title heterocycle 3,7,10-triazatricyclo[3.3.3.0^{1.5}]undecane (1d). This compound is a high melting (250 °C), sublimable solid which, unlike the other members of this series, is only appreciably soluble in highly polar solvents. These properties, for such a low molecular weight molecule, are not wholly explained by its symmetry [the symmetrical trimethyl derivative (1a) is a low melting solid] and suggest that the crystal structure is held together by a lattice of hydrogen bonds.

Experimental

I.r. spectra were determined on a Pye Unicam SP3-200 spectrometer. ¹H N.m.r. spectra on Varian EM 360 and CFT 20 spectrometers. Decoupled and off-resonance decoupled ¹³C n.m.r. spectra were determined on a Varian CFT 20 spectrometer and low-resolution mass spectra on a V.G. Micromass-126 spectrometer.

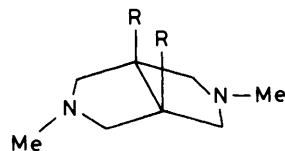
3a,6a-Diethoxycarbonyl-2,5-dimethyl-1,4-dioxo-octahydropyrrolo[3,4-c]pyrrole (5a).—A mixture of tetraethyl ethane-1,1,2,2-tetracarboxylate (4a) (3.18 g), 1,3,5-trimethylhexahydro-1,3,5-triazine (3a) (1.29 g), and trifluoroacetic acid (0.23 g) was heated at 100 °C for 20 h. The reaction mixture was dissolved in toluene (40 ml), extracted with aqueous 2*M*-hydrochloric acid (20 ml), washed with water (2 × 5 ml) and dried (Na₂SO₄). After the solvent had been removed under reduced pressure, the oil obtained was dissolved in diethyl ether (20 ml) and scratched to give the octahydropyrrolo[3,4-c]pyrrole (2.3 g, 74%), m.p. 115–117 °C (Found: C, 54.0; H, 6.5; N, 9.0%; *M*⁺, 312. C₁₄H₂₀N₂O₆ requires C, 53.8; H, 6.50; N, 9.00%; *M*⁺, 312.32); ν_{max} (KBr) 1710s (C=O) and 1750s (C=O) cm⁻¹; δ_{H} (CDCl₃) 1.23 (6 H, t, *J*₁ 8 Hz, Me), 2.9 (6 H, s, NMe), 3.79 and 4.09 (4 H, AB system, *J*_{AB} 10.5 Hz, 3- and 6-CH₂), and 4.2 (4 H, q, *J*₁ 8 Hz, OCH₂); δ_{C} (CDCl₃) 13.94 (Me), 30.31 (NMe), 51.89 (NCH₂), 59.06 (C), 62.03 (OCH₂), 166.54 (C=O), and 168.50 p.p.m. (C=O).

2,5-Dibenzyl-3a,6a-diethoxycarbonyl-1,4-dioxo-octahydropyrrolo[3,4-c]pyrrole (5b) (83.5%), m.p. 105–106 °C (cyclohexane) was prepared similarly from 1,3,5-tribenzylhexahydro-1,3,5-triazine (3b) (Found: C, 67.4; H, 6.1; N, 5.95%; *M*⁺, 464. C₂₆H₂₈N₂O₆ requires C, 67.22; H, 6.08; N, 6.03%; *M*⁺, 464.50); ν_{max} (KBr) 1755s (C=O) and 1700s (C=O) cm⁻¹; δ_{H} (CDCl₃) 1.15 (6 H, t, *J*₁ 7 Hz, Me), 3.75 and 3.95 (4 H, AB system, *J*_(AB) 11 Hz, 3- and 6-CH₂), 4.05 (4 H, q, *J*₁ 7 Hz, OCH₂), 4.2 and 4.8 (4 H, AB system, *J*_(AB) 14 Hz, benzylic



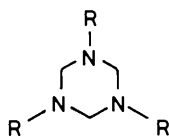
(1)

- a : R = R¹ = Me
 b : R = Me, R¹ = H
 c : R = PhCH₂, R¹ = H
 d : R = R¹ = H



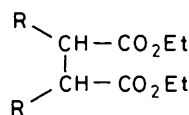
(2)

- a : R = CN
 b : R = CH₂Cl



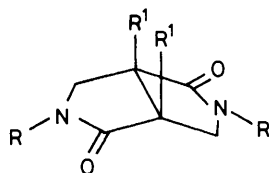
(3)

- a : R = Me
 b : R = PhCH₂



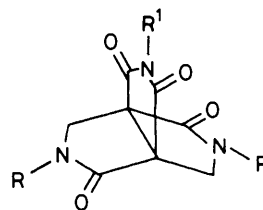
(4)

- a : R = CO₂Et
 b : R = CN



(5)

- a : R = Me, R¹ = CO₂Et
 b : R = PhCH₂, R¹ = CO₂Et
 c : R = Me, R¹ = CN
 d : R = Me, R¹ = CONH₂
 e : R = Me, R¹ = CONHMe
 f : R = PhCH₂, R¹ = CONH₂



(6)

- a : R = Me, R¹ = H
 b : R = R¹ = Me
 c : R = PhCH₂, R¹ = H

CH₂), and 7.2 (10 H, br s, aromatic H); δ_C (CDCl₃) 13.85 (Me), 47.42 (NCH₂), 49.56 (NCH₂), 59.22 (C), 62.29 (OCH₂), 128.10, 128.89, and 135.09 (aromatic C), 166.34 (C=O), and 168.67 p.p.m. (C=O).

3a,6a-Dicyano-2,5-dimethyl-1,4-dioxo-octahydropyrrolo[3,4-c]pyrrole (5c).—A mixture of 1,3,5-trimethylhexahydro-1,3,5-triazine (3a) (4.6 g) and ethyl 2,3-dicyanosuccinate (4b) (4.0 g) was heated at 100 °C for 20 h. Crystals were deposited after 24 h, and were recrystallised from ethanol to give the *pyrrolo[3,4-c]pyrrole* (0.8 g, 21%), m.p. 220–222 °C (Found: C, 54.8; H, 4.6; N, 25.4%; M^+ , 218. C₁₀H₁₀N₄O₂ requires C, 55.0; H, 4.62; N, 25.7%; M^+ , 218.22); $\nu_{\max.}$ (KBr) 1 740b (C=O) and 2 240w (C≡N) cm⁻¹; δ_H (CD₃SOCD₃) 2.8 (6 H, s, NMe) and 3.85 and 4.2 (4 H, AB system, J_{AB} 11 Hz, 3- and 6-H₂); δ_C (CD₃SOCD₃) 30.21 (NMe), 45.54 (C), 52.50 (NCH₂), 114.35 (C≡N), and 163.30 p.p.m. (C=O). When the above experiment was repeated in the presence of trifluoroacetic acid (0.5 g), the yield of product was 5%.

3a,6a-Dicarbamoyl-2,5-dimethyl-1,4-dioxo-octahydro-

pyrrolo[3,4-c]pyrrole (5d).—A solution of the diester (5a) (4.0 g) in ethanol saturated with ammonia (40 ml) was heated in an autoclave at 100 °C for 8 h. The precipitated product was recrystallised from acetic acid to give the *diamide* (3.0 g, 92%), m.p. >340 °C (slow heating) (Found: C, 46.4; H, 5.57; N, 21.6. C₁₀H₁₄N₄O₄·0.25H₂O requires C, 46.42; H, 5.60; N, 21.65%); $\nu_{\max.}$ (KBr) 1 690b (C=O) and 3 320s (NH₂) cm⁻¹; δ_H (CD₃SOCD₃) 2.72 (6 H, s, NMe) and 3.51 and 3.92 (4 H, AB system, J_{AB} 9.5 Hz).

3a,6a-Bis(methylcarbamoyle)-2,5-dimethyl-1,4-dioxo-octahydropyrrolo[3,4-c]pyrrole (5e) (94%), m.p. 305–307 °C (slow heating) (nitromethane) was prepared similarly from (5a) using 33% methylamine in ethanol as reactant (Found: C, 50.6; H, 6.6; N, 19.6. C₁₂H₁₈N₄O₄ requires C, 51.00; H, 6.43; N, 19.85%); $\nu_{\max.}$ (KBr) 1 670bs (C=O), 1710bs (C=O), and 3 340s (NH) cm⁻¹; δ_H (D₂O) 2.72 (6 H, s, NMe), 2.91 (6 H, s, NMe), and 3.81 and 4.11 (4 H, AB system, J_{AB} 10 Hz, 3- and 6-H₂).

2,5-Dibenzyl-3a,6a-dicarbamoyle-1,4-dioxo-octahydropyrrolo[3,4-c]pyrrole (5f) (58.5%), m.p. 234–236 °C (slow heating) (the product crystallised slowly from the reaction

mixture) was prepared similarly from (5b) and ethanol saturated with ammonia (reaction period 72 h) (Found: C, 65.0; H, 5.5; N, 13.4. $C_{22}H_{22}N_4O_4$ requires C, 65.01; H, 5.46; N, 13.79%; ν_{\max} (KBr) 1 670bs (C=O) cm^{-1} ; δ_H (CD_3SOCD_3) 3.6 and 3.9 (4 H, AB system, $J_{(AB)_1}$ 10 Hz, 3- and 6- H_2), 4.33 and 4.67 (4 H, AB system, $J_{(AB)_2}$ 14 Hz, benzylic CH_2), and 7.3 (10 H, br s, aromatic H).

7,10-Dimethyl-2,4,6,9-tetraoxo-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (6a).—The diamide (5d) (22 g) was heated at 290–300 °C in a slow stream of nitrogen for ca. 2 h or until ammonia evolution had ceased. An aqueous solution of the product (500 ml) was treated with activated charcoal and the water was removed under reduced pressure. Recrystallisation from dimethylformamide-ether gave the *imide* (14 g, 69%), m.p. 340–360 °C (slow decomp.) (Found: C, 50.4; H, 4.95; N, 18.0%; M^+ , 237. $C_{10}H_{11}N_3O_4$ requires C, 50.63; H, 4.67; N, 17.72%; M^+ , 237.22); ν_{\max} (KBr) 1 690s (C=O), 1 750bs (C=O), 1 800m (C=O), and 3 300m (NH) cm^{-1} ; δ_H (CD_3SOCD_3) 2.7 (6 H, s, NMe) and 3.6 and 3.8 (4 H, AB system, J_{AB} 10 Hz, 8- and 11- CH_2); δ_C (CD_3SOCD_3) 29.41 (NMe), 51.33 (CH₂), 55.86 (C), 165.98 (C=O), and 173.00 p.p.m. (C=O).

3,7,10-Trimethyl-2,4,6,9-tetraoxo-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (6b) (69%), m.p. 305–307 °C (decomp.) (nitromethane-ether) was prepared similarly from (5e) (reaction period 1.25 h) (Found: C, 52.3; H, 5.35; N, 16.5%; M^+ , 251. $C_{11}H_{13}N_3O_4$ requires C, 52.58; H, 5.21; N, 16.73%; M^+ , 251.24); ν_{\max} (KBr) 1 685s (C=O), 1 720bs (C=O), and 1 788m (C=O) cm^{-1} ; δ_H (CD_3SOCD_3) 2.7 (6 H, s, 7- and 10-NMe), 2.82 (3 H, s, 3-NMe), and 3.7 (4 H, s, 8- and 11- CH_2); δ_C (CD_3SOCD_3) 26.03 (NMe), 30.16 (NMe), 52.19 (CH₂), 55.32 (C), 165.94 (C=O), and 171.51 p.p.m. (C=O).

7,10-Dibenzyl-2,4,6,9-tetraoxo-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (6c) (78%), m.p. 234–236 °C (acetonitrile) was prepared similarly from (5f) (reaction period 1.25 h, reaction temperature 235–240 °C, clarification with activated charcoal unnecessary) (Found: C, 67.4; H, 4.85; N, 10.7%; M^+ , 389. $C_{22}H_{19}N_3O_4$ requires C, 67.85; H, 4.91; N, 10.79%; M^+ , 389.40); ν_{\max} (KBr) 1 730bs (C=O), 1 800m (C=O), and 3 280m (NH) cm^{-1} ; δ_H (CD_3SOCD_3) 3.4 and 3.65 (4 H, AB system, $J_{(AB)_1}$ 11 Hz, 8- and 11- H_2), 4.05 and 4.5 (4 H, AB system, $J_{(AB)_2}$ 14 Hz, benzylic CH_2), and 7.2 (10 H, m, aromatic H); δ_C (CD_3SOCD_3) 45.95 (NCH₂), 49.51 (NCH₂), 55.99 (C), 127.51, 128.67, and 135.56 (aromatic C), 166.16 (C=O), and 172.60 p.p.m. (C=O).

3,7,10-Trimethyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (1a).—A suspension of (6b) (1.6 g) and lithium aluminium hydride (2.18 g) in tetrahydrofuran (50 ml) was stirred and heated under reflux under nitrogen for 48 h. The resulting complex was decomposed by addition of water (2.2 ml), 15% aqueous sodium hydroxide (2.2 ml), and finally water (6.6 ml). The aluminium salts were removed using a filtration aid and the filtrate was dried (NaOH). Evaporation of the solvent under reduced pressure gave the triazatricycloundecane (0.8 g, 61%), b.p. 120–125 °C (bath temp.)/15 mmHg, which solidified on standing m.p. 35–38 °C (lit.^{1a} m.p. 37–74 °C) (Found: C, 67.3; H, 11.0; N, 21.1%; M^+ 195. Calc. for

$C_{11}H_{21}N_3$: C, 67.64; H, 10.84; N, 21.50%; M^+ , 195.31); ν_{\max} (liq. film) 2 800s (NMe) cm^{-1} ; δ_H ($CDCl_3$) 2.3 (9 H, s, NMe) and 2.5 (12 H, s, CH_2); δ_C ($CDCl_3$) 41.33 (NMe), 62.78 (C), and 66.44 (CH₂).

3,7-Dimethyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (1b) (75%), b.p. 130–135 °C (bath temp.)/15 mmHg was prepared similarly from (6a) (Found: C, 66.3; H, 10.8; N, 23.1%; M^+ , 181. $C_{10}H_{19}N_3$ requires C, 66.25; H, 10.57; N, 23.1%; M^+ , 181.28); ν_{\max} (liq. film) 2 800s (NMe), 3 300bw cm^{-1} (NH); δ_H ($CDCl_3$) 2.25 (6 H, s, NMe), 2.35 and 2.55 (8 H, AB system, J_{AB} 9 Hz, 2-, 4-, 6-, and 8- CH_2), and 2.8 (4 H, s, 9- and 11- CH_2); δ_C ($CDCl_3$) 41.42 (NMe), 57.82 (NCH₂), 64.37 (C), and 66.51 p.p.m. (NCH₂).

3,7-Dibenzyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (1c) (91%), b.p. 250 °C (bath temp.)/0.01 mmHg was prepared similarly from (6c) (Found: C, 78.7; H, 8.3; N, 12.5%; M^+ , 333. $C_{22}H_{27}N_3$ requires C, 79.23; H, 8.16; N, 12.6%; M^+ , 333.47); ν_{\max} (liq. film) 3 280b cm^{-1} ; δ_H ($CDCl_3$) 2.3 and 2.5 (8 H, AB system, J_{AB} 10 Hz, 2-, 4-, 6-, and 8- CH_2), 2.75 (4 H, s, 9- and 11- CH_2), 3.5 (4 H, s, benzylic CH_2), and 7.15 (10 H, br s, aromatic H); δ_C 58.08 (NCH₂), 58.98 (NCH₂), 63.04 (C), 63.91 (NCH₂), 126.69, 128.12, 128.32, and 139.56 p.p.m. (aromatic C).

3,7,10-Triazatricyclo[3.3.3.0^{1,5}]undecane (1d).—A solution of (1c) (3.6 g) in acetic acid (50 ml) was hydrogenated [45 lb in^{-2} , 5% Pd-C (0.5 g)]. After uptake had ceased (3 h), the catalyst was removed and diethyl ether saturated with hydrogen chloride (30 ml) was added. The precipitated *hydrochloride* was dissolved in water (20 ml) and potassium hydroxide was added until precipitation of the free base occurred. Recrystallisation from a large volume of toluene gave the *triazatricycloundecane* (0.96 g, 58%), m.p. 246–250 °C (with sublimation) (Found: C, 62.3; H, 9.9; N, 27.5%; M^+ , 153. $C_8H_{15}N_3$ requires C, 62.7; H, 9.87; N, 27.5%; M^+ , 153.23); ν_{\max} (KBr) 3 200b cm^{-1} (NH); δ_H (D_2O) 2.7 (12 H, s); δ_C (D_2O) 53.76 (NCH₂) and 64.91 p.p.m. (C).

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