69. Propellanes

Part LXXVIII

Preparation of Several Triaza[3.3.3]propellanes and an Oxadiaza[3.3.3]propellane[1])

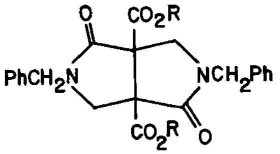
by **Olga Weinberg**[a]), **Philip Knowles**[b]), and **David Ginsburg**[a])*

[a]) Department of Chemistry, Israel Institute of Technology, Haifa
[b]) The Research Laboratories, *May and Baker Ltd.*, Dagenham, Essex RM10 7XS

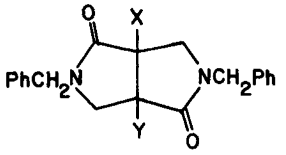
(17.XII.84)

3,7,10-Tribenzyl-3,7,10-triaza[3.3.3]propellane (**4a**), 3,7-dibenzyl-10-phenyl-3,7,10-triaza[3.3.3]propellane (**4c**), 3,7-dibenzyl-10-(*p*-tolyl)-3,7,10-triaza[3.3.3]propellane (**4b**), and 3-oxa-7,10-diaza[3.3.3]propellane (**6**) have been prepared.

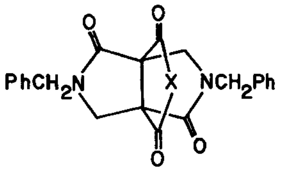
We have long been interested in studying the structures of 3,7,10-triaza-[3.3.3]propellanes and their quarternary salts by NMR spectroscopy, but the lengthy synthetic sequence required to produce them [2] forced us to postpone this. Recently an



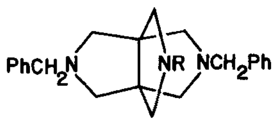
1a R = Me
b R = Et



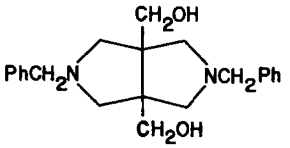
2a X = Y = $CONH_2$
b X = $CONH_2$; Y = CO_2H
c X = $CONH_2$; Y = H
d X = CO_2H; Y = H
e X = Y = CO_2H
f X = CO_2H; Y = $CONHCH_2Ph$
g X = CO_2H; Y = $CONHC_6H_4(p\text{-}CH_3)$
h X = CO_2H; Y = CONHPh



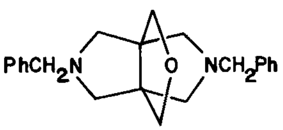
3a X = O
b X = NH
c X = NCH_2Ph
d X = $NC_6H_4(p\text{-}CH_3)$
e X = NPh



4a R = CH_2Ph
b R = $C_6H_4(p\text{-}CH_3)$
c R = Ph



5



6

---

[1]) Part LXXVII: [1].

efficient synthetic route has been discovered which permits rejuvenation of the idea [3]. We also report herein some incidental substances formed *en route* to the triaza[3.3.3]propellanes.

When the diester **1b** was subjected to ammonolysis as described in [3], the monoamide **2c** accompanied the diamide **2a** which has already been reported. Its structure was proved by its spectral properties and by conversion of **2a** with nitrous acid into the mono-acid **2b** and the ready decarboxylation of **2b** to **2c**. The imide **3b** was prepared from **2a** as described in [3], but it should be noted that **2a**, has m.p. 151–154 °C, albeit slow heating in the m.p. tube as described causes slow loss of NH_3 and the m.p. obtained, 234 °C, is in fact that of the imide **3b**.

Although the diacid **2e** could be isolated in low yield from reaction of **2a** with excess nitrous acid at a temperature higher than that leading to **2b**, the method of choice for its formation is by alkaline saponification of the dimethyl ester **1a**. This diacid affords the anhydride **3a** in the usual way. Treatment of **3a** with benzylamine, *p*-toluidine, and aniline, affords **2f**, **2g**, and **2h**, respectively. Subsequent cyclization with Ac_2O gives **3c**, **3d**, and **3e**, respectively. Of course, **3c** may also be obtained by benzylation of **3b**.

Reduction of the dilactam-imides **3c–e** gives the required triamines **4a–c**, respectively. Reduction of the dilactam-anhydride **3a** gave the diol **5** which when heated with dicyclohexyldiimide afforded the ether-diamine **6**.

Experimental Part

IR spectra were recorded on a *Perkin-Elmer 237* spectrometer, ^{1}H-NMR spectra on a *Varian T-60* spectrometer and mass spectra on a *Varian MAT-711* spectrometer. M.p.'s are uncorrected.

*Amidation of Diethyl 2,5-Dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxylate* (**1b**). The diester **1b** [3] (18.9 g) in EtOH (180 ml) sat. with ammonia was heated in an autoclave at 100° for 75 h. After cooling, the whole was filtered. *2,5-Dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxamide* (**2c**) crystallized (1.2 g; 8%), m.p. 168–169.5° (AcOEt). IR ($CHCl_3$): 3480, 3365, 1695. ^{1}H-NMR ($CDCl_3$): 7.10 (*m*, 10 arom. H); 4.40 (*s*, 4 benzylic H); 3.55 (*m*, 5H, CH_2, CH). MS: 363 (58, M^+), 319 (21), 90 (100). M.W.: calc. 363.1343, found 363.1480.

The mother liquor was evaporated to dryness and the residue triturated twice with $CHCl_3$. Filtration afforded *2,5-dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxamide* (**2a**; 4.2 g; 25.4%), m.p. 151–154° (dec.). The m.p. reported for this substance, 234° [2], is actually that of **3b**. **2a** was identical in all respects with substance previously described [3]. MS: 389 (19, $M^+ - NH_3$), 363 (21), 319 (124), 90 (100).

The $CHCl_3$ mother liquor was evaporated to dryness, and the residue (8.9 g) was heated under reflux with MeOH (charcoal) for 10 min. After removal of charcoal and evaporation of solvent, $CHCl_3$ was added to the residue. Addition of hexane precipitated a solid (4.92 g). Treatment of this with aq. bicarbonate soln. (5 ml), washing with $CHCl_3$, and acidification of the aq. phase gave *2,5-dibenzyl-6a-carbamoyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxylic acid* (**2b**; 2.1 g; 12.8%), m.p. 185–187° (dec.). IR (KBr): 3370, 3300, 3220, 2970, 1770, 1720, 1695, 1675. ^{1}H-NMR ($CDCl_3$): 6.93 (br. *s*, 12H, arom. H and NH_2); 4.21 (*s*, 4 benzylic H); 3.50 (*m*, 4 CH_2). MS: 389 (3), 363 (26), 91 (100). More of **2c** (1.5 g; 10.2%) was obtained from the $CHCl_3$/hexane mother liquor.

*2,5-Dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxylic Acid* (**2d**). The amide **2c** (100 mg), AcOH (glacial; 15 ml), and conc. H_2SO_4 (3 drops) were mixed and aq. sodium nitrite (10%; 0.2 ml) was added. After heating for 3 h at 72° and standing overnight, the whole was poured into ice water. The precipitate was removed by filtration and washed with H_2O and Et_2O: **2d** (88.5 mg; 88%) had m.p. 193–194° (AcOEt). IR ($CHCl_3$): 1745, 1710. ^{1}H-NMR ($CDCl_3$): 7.15 (*m*, 10 arom. H); 630 (*s*, 1H, CO_2H); 4.40 (*s*, 4 benzylic H); 3.80–3.25 (*m*, 5H, CH_2, CH). MS: 364 (33, M^+); 320 (21); 91 (100). M.W.: calc. 364.1423, found, 364.1478.

The diamide **2a** (80 mg) in AcOH (glacial, 1.5 ml) was treated with conc. H_2SO_4 (3 drops) and aq. sodium nitrite soln. (10%; 0.4 ml). After workup as above for **2c**, **2b** (45 mg; 56%) was obtained, m.p. 185–187° (dec.), identical with that described above. After evaporation of the mother liquor to dryness, the residue was taken in

Et_2O. Removal of Et_2O gave *2,5-dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxylic acid* (**2e**; 25 mg; 31%), m.p. 188–190° (dec.) identical with that described above.

3,7,10-Tribenzyl-3,7,10-triaza[3.3.3]propellane (**4a**). *a*) A mixture of tetramethyl ethane-1,1,2,2-tetracarboxylate [4] (13.1 g), 1,3,5-tribenzylhexahydro[1.3.5]triazine [5] (17.85 g), and CF_3COOH (0.8 ml) was heated under reflux in benzene (200 ml) for 38 h. After cooling, washing with 2M HCl (100 ml) and with H_2O (2 × 25 ml), removal of solvent at the water pump, the crystalline product was triturated with hexane, dissolved in AcOEt (300 ml), and filtered through a column of silica (50 g). Addition of hexane (150 ml) afforded the *dimethyl 2,5-dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxylate* (**1a**; 18.8 g; 86.1%), m.p. 130–132°. ([4]: 136°). IR ($CHCl_3$): 1760. ^1H-NMR ($CDCl_3$): 7.05 (br., *s*, 10 arom. H); 4.58, 4.18 (*AB*, $J = 14$, 4H, benzylic CH_2); 3.88, 3.62 (*AB*, $J = 11$, 4H, CH_2); 3.53 (*s*, 6H, CH_3). MS: 436 (98, M^+), 405 (12), 377 (20), 349 (51), 91 (100). M.W.: calc. 436.1634, found 436.1619.

b) The dimethyl ester **1a** (18.8 g) was treated with a methanolic (90 ml) soln. of KOH (6.3 g). After standing overnight at r.t. the precipitated K salt was removed by filtration, washed with cold MeOH (20 ml) and with Et_2O (20 ml). It was dissolved in H_2O (50 ml) and acidified with HCl (16%). The precipitate was removed by filtration, washed with cold H_2O (10 ml) and with Et_2O (20 ml), affording **2e** (16.3 g; 92.6%), m.p. 204–205° (aq. MeOH). IR (KBr): 1760, 1675. ^1H-NMR (DMSO): 7.02 (br. *s*, 10 arom. H); 4.28 (*s*, 4 benzylic H); 3.65, 3.37 (*AB*, 4H, CH_2). MS: 364 (23, $M^+ - CO_2$), 320 (11), 273 (9), 229 (13), 91 (100).

c) The diacid **2e** (12.7 g) and Ac_2O (35 ml) were heated under reflux for 4 h. After evaporation at the water pump, toluene was added and removed at the water pump (thrice) to give *2,5-dibenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboxylic anhydride* (**3a**). A purified sample (Ac_2O/Et_2O) had m.p. 210–213°. IR (KBr): 1860, 1795, 1705. ^1H-NMR ($CDCl_3$): 7.05–7.4 (*m*, 10 arom. H); 4.68, 4.3 (*AB*, $J = 14$, 4 benzylic H); 3.88, 3.7 (*AB*, $J = 11$, 4 CH_2). MS: 390 (small, M^+); 367 (16); 318 (26); 317 (50); 227 (20); 91 (100). The residual anhydride was dissolved in CH_2Cl_2 (50 ml). Benzylamine (1.4 ml) and CH_2Cl_2 (10 ml) were added. The precipitate obtained was removed by filtration, washed with CH_2Cl_2 (20 ml), affording the *2,5-dibenzyl-6a-(*N*-benzylcarbamoyl)-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxylic acid* (**2f**; 6.0 g; 91%), m.p. 178° (dec.). IR (KBr): 1765, 1705, 1675. MS: 479 (5, $M^+ - H_2O$); 453 (3, $M^+ - CO_2$); 320 (53); 229 (41); 90 (100).

d) A mixture of **2f** (5.8 g), Ac_2O (17 ml), NaOAc (0.5 g) was stirred on a steam bath for 3 h. The cold mixture was poured into ice water (50 ml). The precipitate was collected, washed with cold H_2O (30 ml) and Et_2O (30 ml). The obtained *N,2,5-tribenzyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboximide* (**3c**; 5.2 g; 93%) had m.p. 215–216° (AcOEt). IR ($CHCl_3$): 1810, 1755, 1710. ^1H-NMR: 7.00 (*m*, 15 arom. H); 4.55 (*s*, 2H, benzylimide); 4.32 (*s*, 4H, benzyl-lactam; 3.63 (*s*, 4H, CH_2). MS: 479 (100, M^+); 388 (37), 319 (11), 132 (15). M.W.: calc. 479.1845, found 479.1837.

e) A suspension of **3c** (5.0 g) and LAH (3.4 g) in anh. Et_2O (50 ml) was heated under reflux for 30 h. Decomposition with aq. NaOH and the usual workup gave **4a** (4.3 g; 97.9%), m.p. 98–101°. The product was dissolved in Et_2O and passed through a column of alumina (*Merck*, activity III). Evaporation of Et_2O gave the product, m.p. 112–114°. IR ($CHCl_3$): 2960, 2920, 2820, 1600, 1450, 1370, 1270, 1125. ^1H-NMR: 7.20 (*s*, 15 arom. H); 3.60 (*s*, 6 benzylic H); 2.50 (*s*, 12H, CH_2). MS: 423 (25, M^+), 332 (85), 303 (7), 184 (18), 134 (10), 91 (100). M.W.: calc. 423.2674, found 423.2692.

*7,10-Dibenzyl-3-(*p*-tolyl)-3,7,10-triaza[3.3.3]propellane* (**4b**). *a*) The diacid **2e** and *p*-toluidine gave, as for the analogous reaction using benzylamine to prepare **2f**, the *2,5-dibenzyl-6a-[*N*-(*p*-tolyl)carbamoyl]-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxylic acid* (**2g**) in 87% yield, m.p. 212–213° (dec.). IR (KBr): 1770, 1700, 1680. MS: 479 (8, $M^+ - H_2O$), 453 (38), 90 (100).

b) *2,5-Dibenzyl-*N*-(*p*-tolyl)-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboximide* (**3d**) was prepared from **2g** in analogy to the preparation of **3c**, in 90% yield, m.p. 200–201° (AcOEt). IR ($CHCl_3$): 1815, 1760, 1710. ^1H-NMR ($CDCl_3$): 7.10 (*m*, 14 arom. H); 4.60, 4.20 (*AB*, $J = 14$, 4H, benzylic CH_2); 3.86, 3.65 (*AB*, $J = 10$, 4H, CH_2); 2.37 (*s*, 3H, CH_3). MS: 479 (88, M^+), 388 (26), 214 (12), 132 (7), 91 (100). M.W.: calc. 479.1845, found 479.1841.

c) Reduction of **3d** (2.3 g) as above with $LiAlH_4$ gave after analogous workup the *3,7-dibenzyl-10-(*p*-tolyl)-3,7,10-triaza[3.3.3]propellane* (**4b**) in 60.3% yield after filtration through a column of silica using hexane/AcOEt 6:1, m.p. 138–140° (EtOH). IR ($CHCl_3$): 2940, 2900, 2790, 1620, 1465, 1335, 1150, 1125. ^1H-NMR ($CDCl_3$): 7.10 (*s*, 10 arom. H); 6.74 (*m*, 4 arom. H); 3.53 (*s*, 4 benzylic H); 3.15 (*s*, 4 CH_2); 2.37 (*AB*, $J = 10$, 8H, CH_2). MS: 423 (100, M^+), 332 (100), 303 (31), 211 (19), 184 (86). M.W.: calc. 423.2674, found 423.2650.

3,7-Dibenzyl-10-phenyl-3,7,10-triaza[3.3.3]propellane (**4c**). *a*) The diacid **2e** and aniline gave as for the analogous reaction using benzylamine to prepare **2f**, *2,5-dibenzyl-6a-(*N*-phenylcarbamoyl)-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a-carboxylic acid* (**2h**) in 80% yield. M.p. 220–222° (dec., EtOH). IR (KBr): 1755, 1685, 1660. ^1H-NMR (DMSO): 13.3 (br. *s*, 1H, OH); 9.72 (*s*, 1H, NH); 7.6–7.0 (*m*, 15H, arom. H); 4.64, 4.42 (*AB*,

J = 14, 2H, benzylic H), 4.56; 4.42 (*AB*, J = 14, 2H, benzylic H); 4.00, 3.60 (*AB*, J = 10, 2H, CH_2); 3.94, 3.84 (*AB*, J = 10, 2H, CH_2). MS: 465 (5, $M^+ - H_2O$), 439 (6).

b) *2,5-Dibenzyl-*N*-phenyl-1,4-dioxo-octahydropyrrolo[3,4-*c*]pyrrole-3a,6a-dicarboximide* (**3e**) was prepared from **2h** in analogy to the preparation of **3c** in 88% yield, m.p. 244–246°. IR (KBr): 1800, 1730, 1690. ^{1}H-NMR ($CDCl_3$): 7.6–7.1 (*m*, 15 arom. H); 4.62, 4.28 (*AB*, J = 14, 4H, benzylic CH_2); 3.88, 3.74 (*AB*, J = 11, 4H, CH_2). MS: 465 (82, M^+); 374 (40), 200 (27), *118* (27), *91* (100).

c) Reduction of **3e** as above with $LiAlH_4$ gave the **4c** in 64% yield, m.p. 140–142° (MeCN). IR (KBr): 2940, 2900, 2790, 1600, 1465, 1340, 1155. ^{1}H-NMR ($CDCl_3$): 7.5 (*m*, 12 arom. H); 6.75 (*m*, 3 arom. H); 3.60 (*s*, 4 benzylic H); 3.25 (*s*, 4H, CH_2); 2.65, 2.50 (*AB*, J = 10, 8H, CH_2). MS: 409 (5, M^+), 318 (85), 170 (32), 91 (100).

3-Oxa-7,10-diaza[3.3.3]propellane (**6**). *a*) The anhydride **3a** was obtained as above, without isolation from the diacid **2e** (3.42 g). Reduction with $LiAlH_4$ (3.17 g) and workup as above gave *2,5-dibenzyloctahydropyrrolo[3,4-*c*]-pyrrole-3a,6a-dimethanol* (**5**) (2.57 g; 92%), m.p. 101–102° (benzene/hexane), 104–105° (cyclohexane). IR ($CHCl_3$): 3610, 3400. ^{1}H-NMR ($CDCl_3$): 7.13 (*s*, 10 arom. H); 3.95 (br. *s*, 2H, OH); 3.56 (*s*, 4 benzylic H); 3.53 (*s*, 4 CH_2O); 2.55 (*s*, 8 CH_2). MS: 352 (7, M^+), 261 (74), 243 (5), 214 (7), 90 (100). M.W.: calc. 352.2150, found 352,2125. This compound may also be obtained (80%) by reduction of **1b** with $LiAlH_4$.

b) A mixture of **5** (2.42 g) and DCC (1.79 g) was heated at 165–175° for 3 h under N_2. After cooling, CH_2Cl_2 was added and the soln. was washed with 1N HCl (4 × 20 ml). The combined acid extracts were basified (NaOH) and extracted with Et_2O (4 × 25 ml). The combined Et_2O extracts were dried (Na_2SO_4). Removal of solvent gave **6** (1.99 g; 87.3%). An Et_2O soln. was passed through a column of alumina (*Merck*, III), affording the pure product as an oil (1.88 g; 81.9%). It solidified on standing, m.p. 71.5–73.5°, 75–76° (pentane, –70°). IR ($CHCl_3$): 2940, 2900, 2860, 2800, 1600, 1450, 1270, 1127, 1020, 917. ^{1}H-NMR ($CDCl_3$): 7.15 (*m*, 10 arom. H); 3.56 (*s*, 4 benzylic H); 3.52 (*s*, 4 CH_2O); 2.57, 2.39 (*AB*, J = 9, 8H, CH_2). MS: 334 (16, M^+), 243 (90), 215 (12), 184 (7), 134 (8), 90 (100). M.W.: calc. 334.2045, found 334.2035.

REFERENCES

[1] E. Cohen, D. Ginsburg, *Tetrahedron*, in press.
[2] J. Altman, E. Babad, J. Itzchaki, D. Ginsburg, *Tetrahedron* **1966**. Suppl. 8, Part 1, 279.
[3] P. Knowles, N. V. Harris, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1475.
[4] C. A. Bischoff, *Chem. Ber.* **1896**, *29*, 1283.
[5] A. F. McDonagh, H. E. Smith, *J. Org. Chem.* **1968**, *33*, 8.