Rearrangement of *rel*-(4a*R*,7*S*,7a*R*,13*S*)1,2,3,4,4a,5,6,7,7a,12-Decahydro-7-phenylisoindolo[1,2-*d*]quinolizin-13-ium Tosylate to *rel*-(5*S*,6*R*,10*R*,13*S*)-5,6,7,8,9,10,11,12,13,14-Decahydro-13-phenyl-5,6,10-nitrilobenzocyclododecene

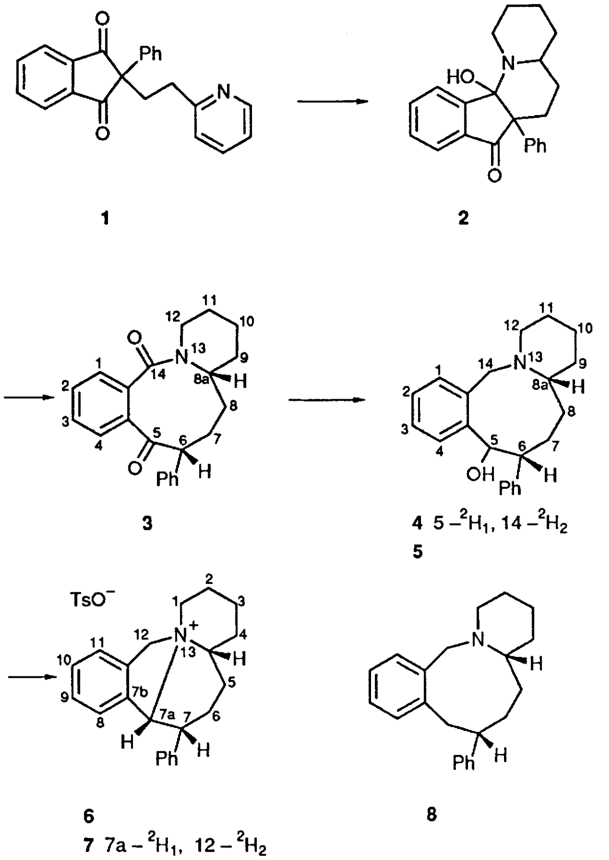
Trevor A. Crabb* and Craig J. Roxburgh
Department of Chemistry, Portsmouth Polytechnic, Portsmouth, Hants, PO1 2DT
Roger F. Newton
Glaxo Group Research Ltd, Greenford, Middlesex, UB6 0HE

Treatment of *rel*-(4a*R*,7*S*,7a*R*,13*S*)1,2,3,4,4a,5,6,7,7a,12-decahydro-7-phenylisoindolo[1,2-*d*]-quinolizin-13-ium tosylate with lithium aluminium hydride gave *rel*-(5*S*,6*R*,10*R*,13*S*)-5,6,7,8,9,10,11,12,13,14-decahydro-13-phenyl-5,6,10-nitrilobenzocyclododecene. An X-ray structural analysis of the product was performed.

The selective catalytic hydrogenation of the pyridine ring of 2-phenyl-2-[2-(2-pyridyl)ethyl]indan-1,3-dione (**1**) has been shown[1] to give *rel*-(6*S*,8a*R*)-6-phenyl-6,7,8,8a,9,10,11,12-octahydropyrido[1,2-*b*][2]benzazonine-5,14-dione (**3**)† *via* the carbinolamine (**2**). Reduction of (**3**) with lithium aluminium hydride gave *rel*-(5*S*,6*S*,8a*R*)-6-phenyl-5,6,7,8,8a,9,10,11,12,14-decahydropyrido[1,2-*b*][2]benzazonin-5-ol (**4**) which upon treatment with toluene-*p*-sulphonyl chloride gave *rel*-(4a*R*,7*R*,7a*R*,13*R*)-1,2,3,4,4a,5,6,7,7a,12-decahydro-7-phenyl isoindolo[1,2-*d*]quinolizin-3-ium tosylate (**6**) (Scheme 1). This paper describes the result of treating (**6**) with lithium aluminium hydride and deuteride undertaken with the aim of producing novel medium-ring heterocyclic compounds.

Treatment of (**6**) with lithium aluminium hydride in tetrahydrofuran for 1 h at room temperature effected no reaction but a 48% yield of product was obtained by carrying out the reaction at 40 °C for 30 min. The ^{13}C NMR spectrum of the product showed the presence of four CH nuclei indicating the presence of an extra bridging atom to that present in (**6**) and in a possible structure (**8**). This was confirmed by mass spectrometry which showed the molecular ion to be 303 rather than M^+ 305 for (**8**). COSY 2D and ^1H NMR homonuclear decoupling experiments showed attachment of the protons absorbing at δ_H 4.2 and 2.5 (J_{gem} −14.7 Hz) to the carbon atom at δ_C 38.2 indicating the presence of a benzylic methylene group. Decoupling experiments showed coupling of the proton absorbing at δ 2.5 to a 1H multiplet at δ 3.4 assigned to CHPh and coupling of this to an additional methylene group. These experiments indicate the presence of the $ArCH_2CH(Ph)CH_2$ moiety in the product. The downfield absorption of three of the methine carbon nuclei at δ 59.4, 51.2, and 40.2 suggests the location of these adjacent to the nitrogen atom. The absence from the ^1H NMR spectrum of the product of an AB system for the NCH_2Ar grouping and of absorptions typical of NCH_2 in piperidines [C-1 methylene in (**6**)] is, therefore, only consistent with the structure indicated in (**9**).

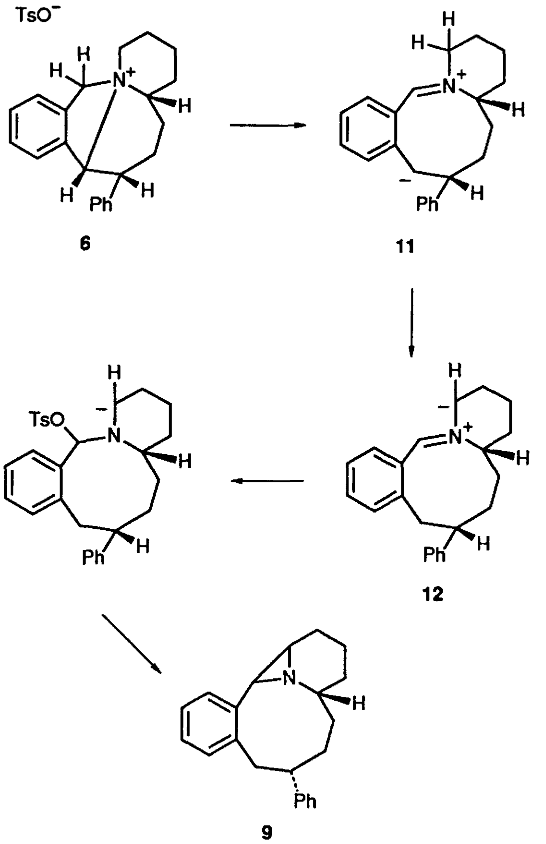
Treatment of the tosylate (**6**) with lithium aluminium deuteride resulted in no incorporation of deuterium (^1H NMR, MS) indicating an intramolecular proton shift during the course of the reaction. In order to investigate this further, deuterium was incorporated into the tosylate (**6**) at the 7a- and 12-positions by the reduction of pyrido[1,2-*b*][2]benzazoninedione (**3**) with lithium aluminium deuteride. The resulting alcohol (**5**) was then converted into the tosylate (**7**). Treatment of (**7**) with either lithium aluminium hydride or lithium aluminium deuteride gave the same product with no additional deuterium incorporation in the latter case. The ^1H NMR spectrum indicated that the 7a-deuterium present in the tosylate (**7**) was still present



Scheme 1. Synthesis of 1,2,3,4,4a,5,6,7,7a,12-decahydro-7-phenyl-isoindolo[1,2-*d*]quinolizin-13-ium tosylate.

---

† Revision of the numbering scheme for this compound in order to bring it into line with IUPAC recommendations for the naming of organic compounds has resulted in a name change: originally it was recorded as *rel*-(12*S*,14a*R*)-12-phenyl-1,2,3,4,12,13,14,14a-octahydropyrido[1,2-*b*][2]benzazonine-6,11-dione.



Scheme 2. Possible mechanism of rearrangement of compound (**6**).

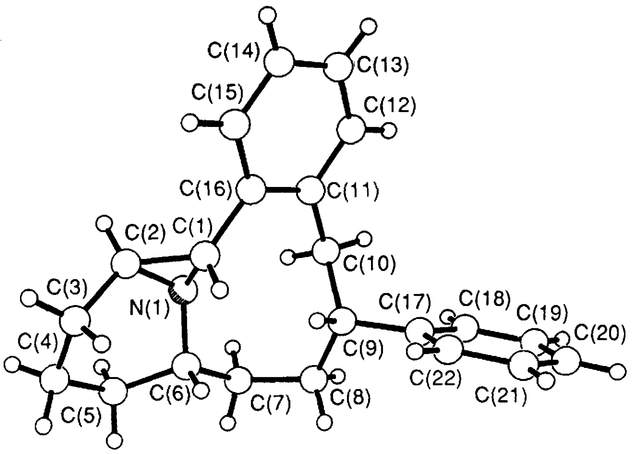
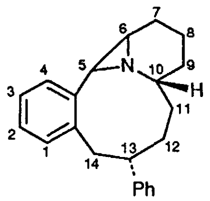
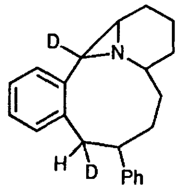


Figure. X-Ray crystal structure of compound (**9**).



9



10

in the reduction product together with a geminal proton resonating at δ4.2 indicating the presence of the Ar-CHD-CH(PH)CH$_2$ moiety and ruling out nucleophilic attack by the deuteride at C-7a. The fact that the molecular ion, obtained by treatment of the deuteriated tosylate (**7**) with lithium aluminium hydride, is only two mass units higher than that for the product obtained by lithium aluminium hydride reduction of the non-deuteriated tosylate (**6**) confirm that one of the new bonds formed on reduction of the tosylate is to the NCD$_2$Ar carbon atom.

The total evidence is, therefore, only in accord with the product from (**6**) being the nitrilobenzocyclododecene (**9**). This structure was confirmed by X-ray crystallography (see Figure and Table). The structure of the corresponding product from the deuteriated compound (**7**) may accordingly be assigned structure (**10**).

One possible mechanism for the formation of (**9**), shown in Scheme 2, involves abstraction of a proton from the benzylic methylene with breakage of the N–C(7a) bond to give (**11**). Intramolecular proton shift then results in (**12**) which may cyclise directly to (**9**) or *via* the intermediate tosylate.

Experimental

Experimental analyses were carried out at Glaxo Group Research Limited. UV spectra were recorded on a Shimadzu UV-240 spectrometer. ^{1}H and ^{13}C NMR spectra were determined at 270 and 68 MHz respectively on a JEOL GSX spectrometer. Mass spectra were recorded on a JEOL JMS-DX303 GC/Mass Spectrometer. Column chromatography was carried out over silica. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected.

Crystal Data.—$C_{22}H_{25}N$, $M = 303.4$, monoclinic, $a = 10.313(3)$, $b = 13.990(4)$, $c = 12.046(3)$ Å, $\beta = 97.98(2)$; $U = 1\,721$ Å^3, space group $P2_1/a$, $Z = 4$, $D_c = 1.17$ g cm^{-3}, μ-Cu-K_α) = 5 cm^{-1}, $F(000) = 656$. 2 310 Independent reflections $<\theta\langle 58°\rangle$ were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. Of these 1 957 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. No absorption correction was applied. The protons on C(1) and C(2) were located from a ΔF map and refined isotropically. The positions of the remaining hydrogen atoms were idealised, C–H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}$ (C), and allowed to ride on their parent carbon atoms. Refinement converged to give $R = 0.041$, $R_w = 0.046$ [$w^{-1} = \sigma^2(F) + 0.000\,38F^2$]. The maximum residual electron density in the final F map was 0.14 e Å^{-3} and mean and maximum shift/error in final refinement was 0.033 and 0.169 respectively.

rel-(5S,6S,8aR)-6-*Phenyl*-5,6,7,8,8a,9,10,11,12,14-*decahydro*-[5-^{2}H,14-^{2}H$_2$]*pyrido*[1,2-*b*][2]*benzazonin*-5-*ol* (**5**).—rel-(6*S*,8a*R*)-6-phenyl-6,7,8,8a,9,10,11,12-octahydropyrido[1,2-*b*][2]benzazonine-5,14-dione (**3**) (1 g, 3 mmol) in tetrahydrofuran (25 ml) was added to a stirred slurry of lithium aluminium deuteride (0.4 g) in tetrahydrofuran (25 ml). The mixture was stirred and heated at *ca.* 40 °C for 20 h after which water was carefully added until the excess of lithium aluminium deuteride

Table. Atom co-ordinates (× 10^4) with estimated standard deviations in parentheses for (**9**).

Atom	*x*	*y*	*z*
N(1)	1 788(1)	2 522(1)	1 741(1)
C(1)	1 164(2)	3 459(1)	1 728(1)
C(2)	1 114(2)	2 906(2)	672(2)
C(3)	– 125(2)	2 405(2)	176(2)
C(4)	– 10(2)	1 323(2)	238(2)
C(5)	902(2)	906(2)	1 259(2)
C(6)	1 141(2)	1 697(1)	2 187(2)
C(7)	2 012(2)	1 333(1)	3 230(2)
C(8)	1 925(2)	1 881(1)	4 325(2)
C(9)	1 918(2)	2 980(1)	4 269(1)
C(10)	3 122(2)	3 391(1)	3 803(2)
C(11)	2 869(2)	4 283(1)	3 085(1)
C(12)	3 604(2)	5 109(1)	3 387(2)
C(13)	3 468(2)	5 927(2)	2 738(2)
C(14)	2 619(2)	5 935(2)	1 755(2)
C(15)	1 904(2)	5 122(1)	1 431(2)
C(16)	2 017(2)	4 299(1)	2 079(1)
C(17)	1 731(2)	3 382(1)	5 400(1)
C(18)	2 675(2)	3 286(2)	6 334(2)
C(19)	2 450(3)	3 607(2)	7 379(2)
C(20)	1 279(3)	4 028(2)	7 514(2)
C(21)	344(2)	4 137(2)	6 601(2)
C(22)	576(2)	3 820(2)	5 557(2)

[a] X-Ray data have been deposited at the Cambridge Crystallographic Data Centre.* [b] The numbering of the atoms in the X-ray structural formula corresponds to that in the table. This is however, different from the conventional numbering system used in the text.

* For details of the deposition scheme see 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

had been decomposed. The resulting mixture was filtered and the solvent removed under reduced pressure to give an oil. The oil was dissolved in light petroleum and left in an ice box overnight to give a white crystalline solid. Recrystallisation of this from light petroleum (b.p. 40–60 °C) gave the title compound as colourless prisms (0.72 g, 71%), m.p. 98–99 °C; ν_{max}(liquid film) 3 500, 2 100, and 1 600 cm^{-1}; λ_{max}(EtOH) 210 (ε 20 500) and 260 (900); δ(CDCl$_3$) 8.85 (1 H, br d, OH), 7.1–7.3 (9 H, m, ArH), 3.3 (1 H, dd, C*H*Ph), 3.3 (1 H, br d, NCH$_{eq}$), 2.2 (1 H, m, NCH$_{ax}$), 2.4 [1 H, m, NCH(CH$_2$)$_2$], and 1.3–2.9 (10 H, m, aliphatic H) (Found: C, 81.4; H, 9.3; N, 4.3. $C_{22}H_{24}D_3NO$ requires C, 81.5; H, 9.2; N, 4.3%)

rel-[(4aR,7S,7aR,13S)-1,2,3,4,4a,5,6,7,7a,12-*Decahydro*-7-*phenyl*[7a-^{2}H$_1$,12-^{2}H$_2$]*isoindolo*[1,2-*d*]*quinolizin*-13-*ium Tosylate* (**7**).—Compound (**5**) (4 g, 12 mmol) was dissolved in dry pyridine (8 ml) and cooled to ice temperature. Freshly crystallized toluene-*p*-sulphonyl chloride (3.5 g, 18 mmol) was then added portionwise with cooling during which time the solution turned a pink/red colour. The mixture was left for 48 h at 0 °C after which time it was poured onto crushed ice–saturated aqueous sodium hydrogen carbonate (200 ml) with stirring. The colourless crystalline solid which formed was filtered off and dried *in vacuo* at room temperature to yield the title compound (3.8 g, 64%), m.p. 120–125 °C; ν_{max}(liquid film) 1 600, 1 410, 1 160, and 750 cm^{-1}; λ_{max}(EtOH) 210 (ε 21 000) and 260 (650); δ(CDCl$_3$) 7.2, 8.0 (4 H, dd, TsAr*H*), 5.6 (1 H, d, ArH), 7.0–7.4 (8 H, m, ArH), 5.0 [1 H, m, NC*H*(CH$_2$)$_2$], 5.1 (1 H, dt, NC*H*$_{ax}$), 5.15 [1 H, dd, C*H*(Ph)], 3.25 (1 H, bd, NC*H*$_{eq}$), 2.35 (3 H, s, TsMe), and 1.5–2.2 (10 H, m, aliphatic H) (Found: C, 72.6; H, 7.5; N, 3.0. $C_{29}H_{30}D_3NO_3S$ requires C, 72.8; H, 7.5; N, 2.9%).

rel-(5S,6R,10R,13S)-5,6,7,8,9,10,11,12,13,14-*Decahydro*-13-*phenyl*-5,6,10-*nitrilobenzocyclododecene* (**9**) *and the Corresponding*[5-^{2}H,14-^{2}H$_1$]*Compound* (**10**).—To a stirred slurry of lithium aluminium hydride (0.2 g) in tetrahydrofuran (50 ml) was added *rel*-(4a*R*,7*S*,7a*R*,13*S*)-1,2,3,4,4a,5,6,7,7a,12-decahydro-7-phenylisoindolo[1,2-*d*]quinolizin-13-ium tosylate (**6**) (1 g, 2.1 mmol) in tetrahydrofuran (20 ml). The resulting mixture was heated at *ca.* 40 °C warmed for 30 min and to the resulting cooled solution water was carefully added dropwise until all the excess of lithium aluminium hydride had been consumed. The resulting solution was filtered and the solvent removed under reduced pressure to give an oil. Chromatography of the oil over silica using diethyl ether as the eluant gave a white solid. Recrystallisation from ether–light petroleum (b.p. 40–60 °C) (50:50) gave the *title compound* (**9**) as colourless needles (0.31 g, 48%), m.p. 135.5–136.5 °C; ν_{max}(Nujol) 1 600 cm^{-1}; δ(CDCl$_3$) 6.7–7.3 (9 H, m, ArH), 4.2 [1 H, d, ArCH$_{eq}$ C(H)Ph], 3.4 (1 H, m, ArCH$_2$C*H*Ph), 2.7 (1 H, s, ArC*H*N), 2.5 [1 H, dd, ArC*H*$_{ax}$C(H)Ph], 1.7–2.3 (12 H, m, aliphatic H); *m*/*z* 303 (*M*$^+$); δ_C(CDCl$_3$) 51.2 (C-5), 40.2 (C-6), 27.4 (C-7), 20.5 (C-8), 35.3 (C-9), 59.4 (C-10), 13.8 (C-11), 34.6 (C-12), 43.3 (C-13), and 38.2 (C-14) (Found: C, 87.1; H, 8.3; N, 4.6. $C_{22}H_{25}N$ requires C, 87.1; H, 8.25; N, 4.6%). The corresponding [5-^{2}H$_1$,14-^{2}H$_1$]derivative (**10**) was prepared in the same manner from the tosylate (**7**), *m*/*z* 305 (*M*$^+$).

Acknowledgements

We thank the SERC for the award of a research studentship (to C. J. R.).

References

1 T. A. Crabb, C. Roxburgh, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2431.

Paper 0/01545H
Received 5*th April* 1990
Accepted 12*th June* 1990