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REARRANGEMENT OF SPIRO[BENZOCYCLOBUTENE-1,3'-PIPERIDINES]

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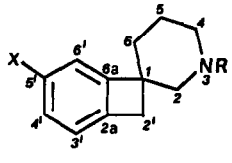
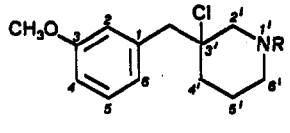
Summary: An unexpected rearrangement of spiro[benzocyclobutene-1,3'- piperidines] is reported. A reaction mechanism is proposed.

Aryl substituted piperidines are of pharmacological interest in medicinal chemistry.[1] In this context a series of conformationally restricted phenyl piperidines, namely spiro[benzocyclobutene-1,3'-piperidines] 1a - 1g have been synthesized. Upon treating the methyl ether[2] 1a or 1c with $AlCl_3$ in CH_2Cl_2 at room temperature,[4] the expected phenol 1b or 1d was not isolated. Instead, three new products 2, 3 and 4 were formed in an approximate ratio of 90 : 8 : 2. Their structural assignment is based on ^1H and ^{13}C-NMR data[5], particularly the coupling pattern of the aryl protons and the chemical shifts of the aryl and piperidine ring carbons.



1

	X	R
1a	OCH_3	CH_2Ph
1b	OH	CH_2Ph
1c	OCH_3	Prop
1d	OH	Prop
1e	OCH_3	H
1f	H	$(CH_2)_4$-p-FC_6H_4
1g	OCH_3	$(CH_2)_3$-CO-p-FC_6H_4



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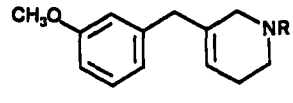

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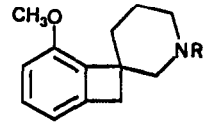

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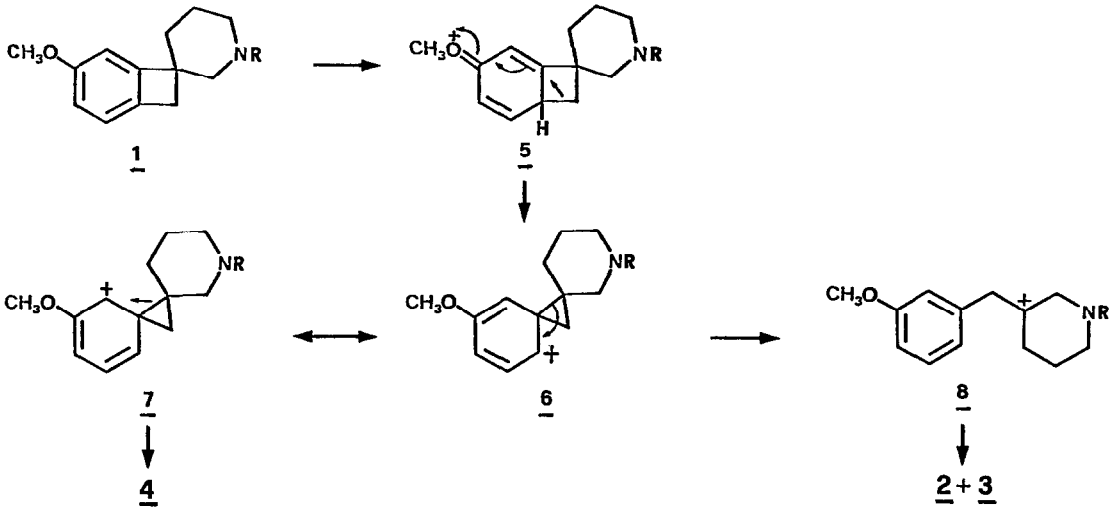
A variation of the substitution pattern 1a - 1g led in general to analogous rearrangement products. The 3° chloride 2 was always obtained in yields ≥ 90%. Addition of 1 equivalent dry HCl to the reaction mixture increased the reaction rate by a factor of ~ 5. No significant influence on product formation or distribution was noted. - Furthermore, no reaction was observed for the substrate 1f without an oxygen substituent under the reaction conditions used.[4] Treatment of the chloride 2 under identical reaction conditions did not yield 4, a possible Friedel-Crafts alkylation product; only unchanged starting material was recovered. Also, no reaction took place when any of the compounds 1a - 1g were exposed to HCl in CH_2Cl_2 at room temperature. A stronger acid species than HCl, therefore, is required (e.g. $H^+AlCl_4^-$ or $H^+AlCl_2(OH)_2^-$) to effect the observed reaction, the mechanism of which is proposed subsequently. Protonation of 1a is directed by the methoxy substituent and leads to an intermediate such as 5. Rearrangement[6] of 5 to the bis-spirocyclopropyl derivatives 6⟷7 and subsequent cyclopropyl ring opening in the two possible pathways are in agreement with the isolated products 2, 3 and 4.

SCHEME



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References and Notes:

1. H.J.J. Loozen and F.T.L. Brands, Rec. Trav. Chim. Pays-Bas 100, 333 (1981). U. Hacksell, L.-E. Arvidsson. U. Svensson, J.L.G. Nilsson, D. Sanchez, H. Wickström, P. Lindberg, S. Hjorth and A. Carlsson, J.Med. Chem. 24, 1475 (1981). W. Arnold, J.J. Daly, R. Imhof and E. Kyburz, Tetrahedron Lett. 1983, 343.
2. Compound 1e was prepared as follows: 1-cyano-5-methoxybenzocyclo-butene[3] was treated with 1.5 equiv. ethyl acrylate in DMSO and 0.2 equiv. Me_3NBzOH at 100 °C for 2 hrs. Subsequent hydrogenation with Raney-Ni and reduction of the resulting spiro-piperidone with BMS led to 1e, m.p. 225 - 227 °C (HCl-salt). Analogous procedure for all other substrates 1. 1g, m.p. 176 - 178 °C (HCl-salt).
3. T. Kametani, M. Kajiwara, K. Fukumoto, Tetrahedron 30, 1053 (1974); P. Schiess, S. Rutschmann, V.V. Toan, Tetrahedron Lett. 23, 3665, 3669, (1982); P. Schiess, S. Rutschmann, Chimia 39, 213 (1985).
4. At room temperature a 5% solution of substrate 1, as HCl-salt, in CH_2Cl_2 is added under argon and stirring to 2.1 equivalents of $AlCl_3$. The reaction is monitored by TLC. When all the starting material has disappeared, the reaction mixture is diluted with CH_2Cl_2, quenched with ice cold 2N NaOH and immediately worked up as usual. Products were separated by MPLC. Traces of water (0.01 - 0.03%) were present under usual working conditions. Careful exclusion of water substantially slowed down the reaction rates.
5. All spectra in $CDCl_3$ except the ^{13}C-NMR of 3g ($DMSO-d_6$) 1g: ^1H-NMR: 7.00 (H-3); 6.80 (H-6); 6.75 (H-4); 3.73 (OCH_3); 2.87 & 2.83 (AB, J=14, H-2); 2.50 & 1.75 (m, piperidine-H). ^{13}C-NMR: 159.0 C(5); 153.5 C(6a); 133.7 C(2a); 124.3 C(3); 113.5 C(4); 107.6 C(6); 61.9 C(2'); 55.4 OCH_3; 54.2 C(6'), 48.3 C(1); 40.6 C(2); 34.2 C(4'); 24.0 C(5'). 2g: ^1H-NMR: 7.21 (t, J=8, H-5); 6.87 (H-2); 6.85 & 6.80 (H-4 & H-6); 3.80 (OCH_3); 3.14 & 3.09 (AB, J=14, C(1)-CH_2); 2.65, 2.50, 1.6-1.9 (m, piperidine H). ^{13}C-NMR: 159.2 C(3); 137.6 C(1); 128.7 C(5);123.5 C(6); 117.2 C(2); 112.0 C(4); 71.2 C(3'); 64.6 C(2'); 55.2 (OCH_3); 53.4 C(6'); 47.1 $\underline{C}H_2$-C(1); 38.1 C(4'); 22.9 C(5').3g: ^1H-NMR: 7.21 (ΣJ= 16, H-5); 6.76 (m, H-2, H-4, H-6); 5.49 (br, H-4'); 3.80 (OCH_3); 3.24 (H-2'); 2.87(H-6'); 2.17 (br, H-5'). ^{13}C-NMR:159.2 C(3); 141.0 C(1); 135.4 C(3'); 129.1 C(5); 120.9 & 120.4 C(6) & C(4'); 114.4 C(2); 111.2 C(4); 54.8 OCH_3; 54.7 C(2');49.2 C(6'); 41.1 $\underline{C}H_2$-C(1); 25.4 C(5'). 4b: ^1H-NMR: 9.70 (OH); 7.10 (dd, J= 8 & 7,H-4); 6.75 & 6.64 (H-3 & H-5); 2.93 & 2.87 (AB, J=14, H-2); 3.10, 3.03, 2.42, 2.10, 1.7-2.0 (m, piperidine H). ^{13}C-NMR: 151.1 C(6); 142.5 C(2a); 136.6 C(6a); 129.3 C(4); 115.0 C(3); 113.8 C(5); 63.6 C(2'); 53.4 C(6'); 49.2 C(3'); 41.0 C(2); 35.5 C(4'); 24.4 C(5').
6. For general electrophilic ring opening reactions of benzocyclobutenes, cf: L. Horner, P.V. Subramanian, K. Eiben, Liebigs Ann. Chem. 714, 91 (1968) and references therein; S. Rutschmann, Ph. D. Thesis, University of Basel 1982.

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