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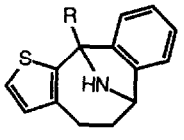
A NOVEL REARRANGEMENT FORMING 4,5,6,11-TETRA-HYDROBENZO[6,7]CYCLOOCTA[1,2-b]THIOPHEN-6,11-IMINES

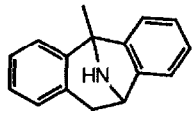
Ralph P. Robinson*, Kathleen M. Donahue, and Nicholas A. Saccomano
Pfizer Central Research, Groton, Connecticut, U.S.A. 06340

Abstract: *Exposure of the spirocyclic isoindolines* **9** *and* **16** *and the spirocyclic ether* **23** *to HBr gas in methylene chloride at 0°C leads to the formation of the bridged heterocycles* **10**, **17**, *and* **24** *respectively. These novel rearrangements probably occur via retro-Mannich fragmentation and subsequent intramolecular Mannich reaction on the thiophene ring.*

In this communication we report on the discovery and mechanism of a novel rearrangement reaction which provides access to the hitherto unknown 4,5,6,11-tetrahydrobenzo[6,7]cycloocta[1,2b]-thiophen-6,11-imine ring system (**1**)[1]. In addition to the mechanistic questions raised, impetus to study this reaction has derived from the relationship of the products **1** to the well-known dibenzo-[a,d]cycloheptenimine, MK-801 (**2**). The latter is an extremely potent anticonvulsant and neuroprotective agent whose biological activity is mediated primarily via blockade of ion channels linked to the N-methyl-D-aspartate (NMDA) subclass of excitatory amino acid receptor[2].



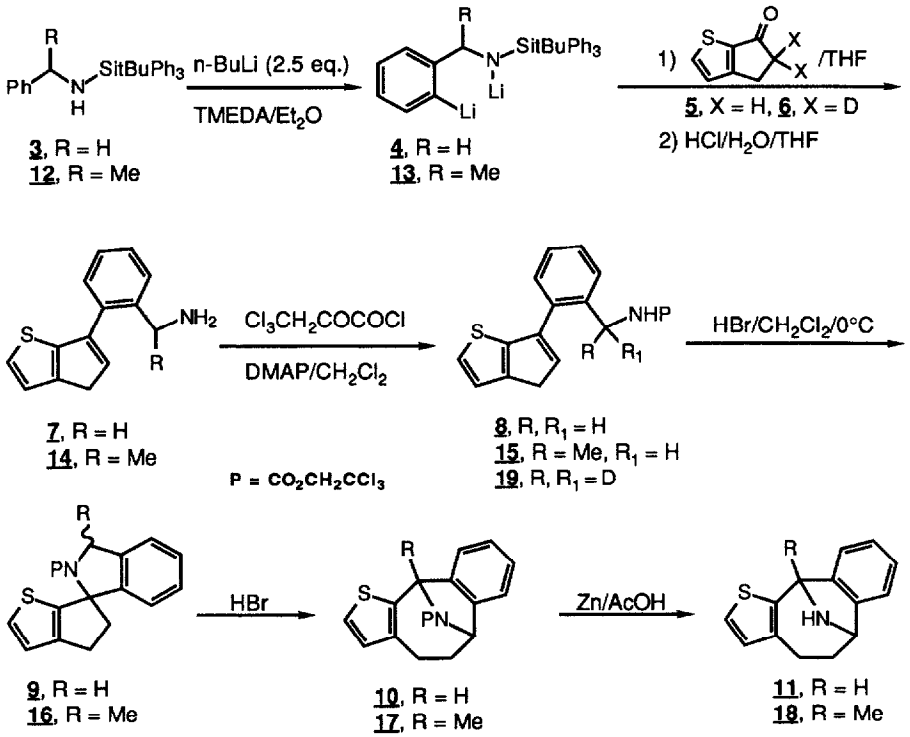
1



2

The discovery of the rearrangement arose from an effort to prepare the spirocyclic isoindoline **9** via cyclization of the protected amino olefin **8** (Scheme 1). Noteworthy in the synthesis of **8** is the double deprotonation of N-t-butyl-diphenylsilylbenzylamine (**3**)[3] which proceeded smoothly to yield **4**, a convenient equivalent of *ortho*-lithio benzylamine[4]. Unfortunately, the reaction of **4** with the ketone **5**[5] gave **7** in only 20% yield and was accompanied by extensive enolization[6]. However the use of the dideuteroketone **6** in the reaction did lead to some improvement in yield especially in the analogous formation of **14** from **13** (28% vs.7%)[7]. With **7** in hand, cyclization to provide the spirocycle **9** was expected to take place without incident as it had in the preparation of other isoindoline derivatives[6]. Thus, a solution of **7** in methylene chloride was cooled to 0°C and treated first with 2,2,2-trichloroethyl chloroformate in the presence of 4-dimethylaminopyridine to generate **8** *in situ*. Subsequent treatment of the solution with HBr gas at 0° led to rapid consumption of **8** by TLC. Although the initial product was presumably the desired spirocycle **9**, it was evident that this was being converted to a second product **10** on prolonged exposure to the acid. This conversion was complete in 2h after which **10** was isolated in 69% yield using flash chromatography on silica gel. The reaction of **10** with Zn in acetic acid afforded the amine **11**[8], the structure of which was confirmed by an X-ray crystal structure analysis of the hydrobromide salt[9].

Scheme 1



3, R = H
12, R = Me

4, R = H
13, R = Me

7, R = H
14, R = Me

8, R, R1 = H
15, R = Me, R1 = H
19, R, R1 = D

9, R = H
16, R = Me

10, R = H
17, R = Me

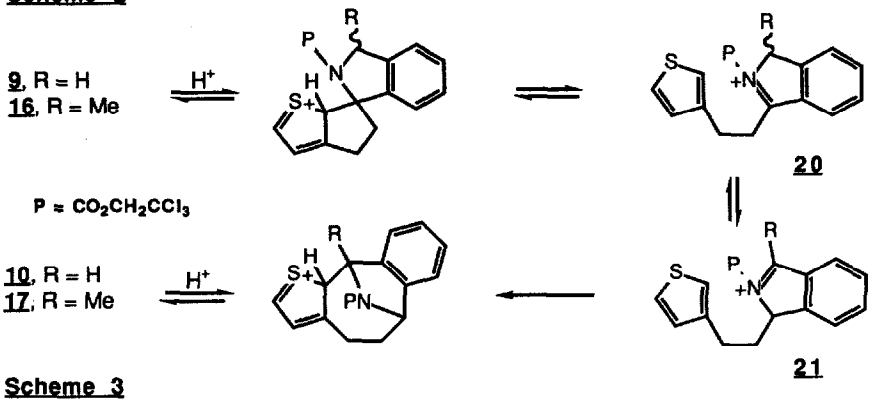
11, R = H
18, R = Me

The possible intermediacy of the spirocycle **9** in the transformation of **8** into the 4,5,6,11-tetrahydrobenzo[6,7]cycloocta[1,2b]thiophen-6,11-imine **10** was confirmed by the formation of **10** during reaction of an authentic sample of **9** (obtained by cyclization of **8** on silica gel) with HBr as before. Rearrangement of the carbamate **15** was also observed, affording **17** (79% from **14**) and subsequently the bridged amine **18**[10] on removal of the 2,2,2-trichloroethyloxycarbonyl protecting group. This was a significant result since it was now possible to make compounds analogous to MK-801 bearing a methyl group at the doubly benzylic bridgehead position.

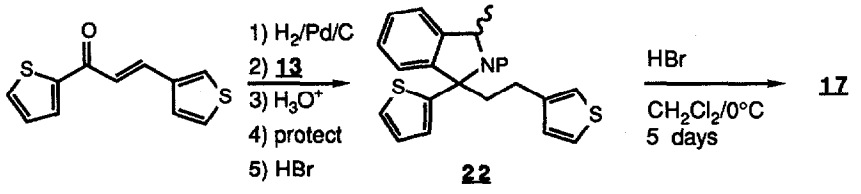
The mechanism of the rearrangement is thought to involve a novel retro-Mannich fragmentation of the spirocycle to provide the protonated isoindole **20** as an intermediate (Scheme 2). This tautomerizes to **21** which then undergoes intramolecular Mannich cyclization to the bridged carbamate **10** or **17**. In agreement with this mechanism is the loss of deuterium during HBr-catalysed rearrangement of **19** and the production of racemic **17** from optically active **16** (prepared from (R)-(+)-α-methylbenzylamine). Furthermore, the isoindoline **22** also yields **17** on exposure to HBr (Scheme 3). Here, loss of thiophene from **22** in a retro-Mannich step must occur, giving rise to the protonated isoindole **20**. Interestingly, this reaction is very slow, taking 5 days at 0°C for complete conversion to

the bridged product **17**. The higher rate of the conversion of **16** into **17**, probably results from the relief of ring strain in the fused five-membered ring on formation of **20**.

Scheme 2

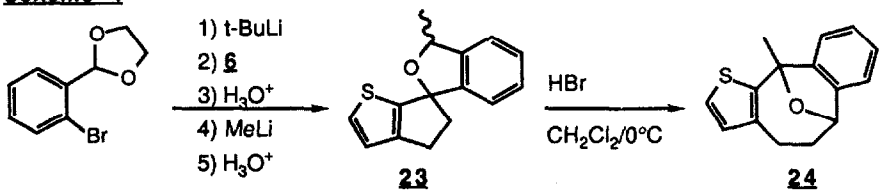


Scheme 3



Also noteworthy is the rearrangement of the spirocyclic ether **23** which gave the bridged heterocycle **24**[11] in 66% yield (after chromatography) following exposure to HBr gas for 1.25h under the usual conditions (Scheme 4). We presume that a mechanism entirely analogous to that shown in Scheme 2 is operative.

Scheme 4



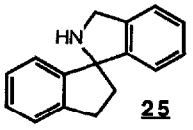
We are continuing to explore the scope and mechanism of this intriguing reaction. Further results will be detailed in a full paper at a later date.

Notes and References

1) The related tetrahydrodibenzo[a,d]cycloocta-5,12-imines are known: Evans, B.E., Anderson, P.S., Christy, M.E., Colton, C.D., Remy, D.C., Rittle, K.E., Englehardt, E.L., *J. Org. Chem.*, **1979**, *44*, 3127.

2) a) Wong, E.H.F., Kemp, J.A., Priestley, T., Knight, A.R., Woodruff, G.N., Iversen, L.L., *Proc. Natl. Acad. Sci., U.S.A.*, **1986**, *83*, 7104. b) Kemp, J.A., Foster, A.C., Wong, E.H.F., *Trends Neurosci.*, **1987**, *10*, 294.

3) Overman, L.E., Okazaki, M.E., Mishra, P., *Tetrahedron Lett.*, **1986**, *27*, 4391.
4) While N,N-dimethylbenzylamine and N-methylbenzylamine have been successfully lithiated at the *ortho* position, *ortho* metalation of benzylamine has never been carried out. One alternative is the the *ortho* lithiation of N-pivaloylbenzylamine. However, this is not entirely satisfactory due to the occurance of significant α-metalation (Simig, G., Schlosser, M., *Tetrahedron Lett.*, **1988**, *29*, 4277 and references sited therein). More satisfactory is the dilithiation of N-trimethylsilylbenzylamines (Burns, S. A., Corriu, R. J. P., Huynh, V., Moreau, J. J. E., *J. Organomet. Chem.*, **1987**, *333*, 281 and Polniaszek, R. P., Kaufman, C. R., *J. Am. Chem. Soc.*, **1989**, *111*, 4859).
5) MacDowell, D. W. H., Patrick, T. B., Frame, B. K., Ellison, D. L., *J. Org. Chem.*, **1967**, *32*, 1226.
6) Additions of **4** to various other carbonyl compounds took place in higher yields: e.g. 1-indanone (32%), cyclohexanone (57%), benzaldehyde (83%). Efficient conversions of the resulting amino carbinols (or amino olefins) to the isoindolines **25**-**27** were achieved by the sequence: 1) $Cl_3CH_2COCOCl$/ DMAP, 2) HBr gas, 3) Zn / AcOH.



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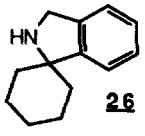

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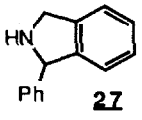

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7) Jacobs, S.A., Cortez, C., Harvey, R.G., *J. Chem. Soc., Chem. Commun.*, **1981**, 1215. Some deuterium is encorporated at the olefinic position in the products **7** and **14**. However, this is lost by exchange during the rearrangement step using HBr.
8) An oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.10 (m, 4 H), 6.88 (d, J = 5 Hz, 1 H), 6.69 (d, J = 5 Hz, 1 H), 5.28 (s, 1 H), 4.80 (t, J = 3 Hz, 1 H), 2.62 (dt, J = 15, 3 Hz, 1H), 2.42 (br s, 1 H), 2.18-1.86 (m, 3 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ 142.4, 142.3, 141.6, 136.4, 131.5, 127.6, 127.2, 122.5, 121.8, 120.3, 63.1, 60.9, 37.1, 25.6. MS: m/z (relative percent) 227 (100), 212 (81). Mp: (hydrobromide) 268-274°C (dec.).
9) We express our gratitude to Dr. Jon Bordner for the X-ray crystallographic analysis on the hydrobromide of **11**.
10).An oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.21 (m, 3 H), 7.07-7.04 (m, 1 H), 6.88 (d, J = 5 Hz, 1 H), 6.67 (d, J = 5 Hz, 1 H), 4.80 (t, J = 3 Hz, 1 H), 2.64 (dt, J = 15, 3 Hz, 1 H), 2.35 (br s, 1 H), 2.18-1.84 (m, 3 H), 1.97 (s, 3 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ 148.1, 145.1, 142.8, 137.6, 131.7, 127.8, 127.0, 121.7, 121.2, 119.5, 65.2, 62.6, 36.8, 26.7, 26.0. MS: m/z (relative percent) 241 (100), 226, (44). Mp: (hydrochloride) 265-268°C.
11) A waxy solid, mp 100-107°C: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.23 (m, 3 H), 7.10-7.06 (m, 1 H), 6.95 (d, J = 5 Hz, 1 H), 6.71 (d, J = 5 Hz, 1 H), 5.63 (t, J = 3 Hz, 1 H), 2.71 (dt, J = 15, 3 Hz, 1 H), 2.46-2.28 (m, 1 H), 2.12-1.91 (m, 2 H), 2.07 (s, 3 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ 144.7, 144.5, 141.5, 138.6, 131.4, 128.1, 127.3, 120.5, 120.4, 84.2, 82.8, 35.6, 25.6, 25.3. MS: m/z (relative percent) 242 (92), 213 (100), 199 (98).

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