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THE STEVENS REARRANGEMENT OF ISOQUINOLINIUM SALTS.A NOVEL SYNTHESIS OF 1-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINES.

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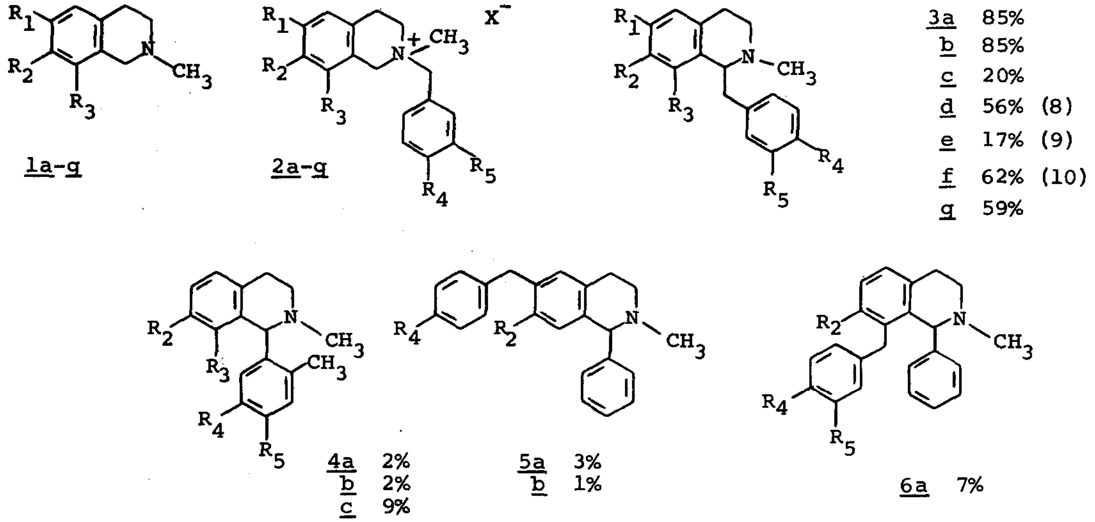
In connection with a study of 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids (1), we have investigated the phenyllithium induced Stevens rearrangement (2) of differently substituted 1,2,3,4-tetrahydroisoquinolinium salts 2a-g as a novel method for the preparation of these compounds (3). Starting materials 2a-g were prepared from the corresponding tetrahydroisoquinolines 1a-g by reaction with appropriate benzyl halides in benzene. The rearrangement was then carried out by treating suspensions of the isoquinolinium salts in ether with 2 equivalents of phenyllithium for up to 5 hr at room temperature. The major products of these rearrangements were the expected compounds 3a-g. The yields (4) are indicated in Scheme I. The structural assignments of 3a-g are supported by elemental analysis and spectroscopical data (5). The one-proton quartets in the nmr spectra of 3a-g indicate the C-1 position of the benzyl substituent (e.g. at δ 4.04 for 3a and 3.98 for 3b); the mass spectra show, in addition to the weak M-1 peaks, the expected base peaks which arise from the loss of the benzyl substituent at C-1 (e.g. m/e 206 for 3a, 3b, and 3e).

In some cases we isolated the by-products by preparative thin layer chromatography (6). The structures and yields of these by-products are shown in Scheme I. Compounds 4a-c were formed by Sommelet-Hauser rearrangement (2,7) of 2a-c. The structural assignments are supported by nmr spectra which exhibit three-proton singlets for the N-CH_3 and arom. CH_3 groups (e.g. at δ 2.41 and 2.36 for 4b). Furthermore, the signal of the C-1 proton appears as a singlet (e.g. at δ 4.91 for 4b). In the aromatic region, compound 4b exhibits an ABX- and AB-

Scheme I



a, $R_1=R_4=R_5=H$, $R_2=R_3=OCH_3$; b, $R_1=R_5=H$, $R_2=R_3=R_4=OCH_3$; c, $R_1=R_2=R_3=H$, $R_4=R_5=OCH_3$; d, $R_1=R_3=R_5=H$, $R_2=R_4=OCH_3$; e, $R_1=R_2=R_4=R_5=OCH_3$, $R_3=H$; f, $R_1=R_2=R_3=R_4=OCH_3$, $R_5=H$; g, $R_1=R_2=R_5=H$; $R_3=R_4=OCH_3$.

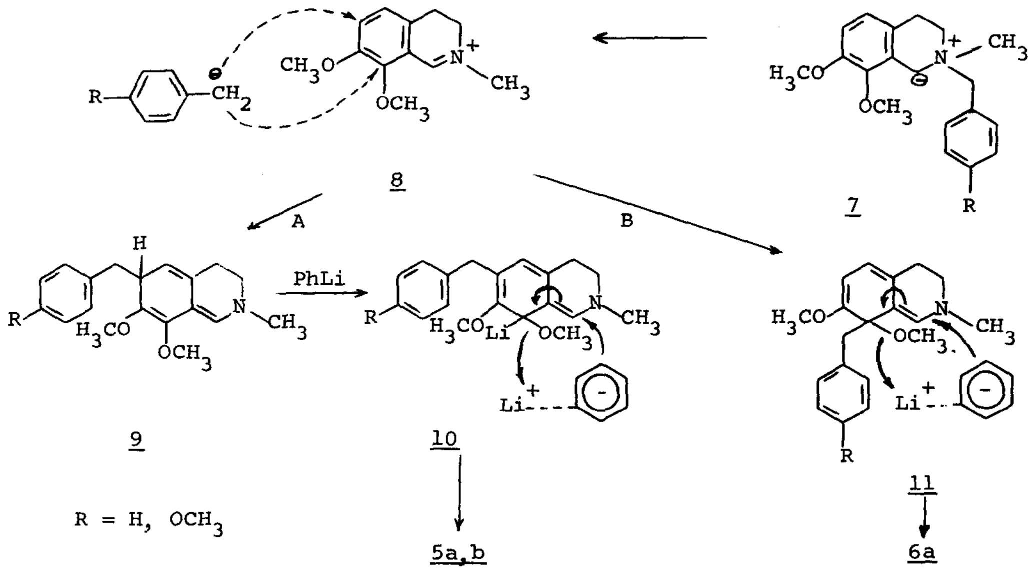
pattern.

When the rearrangement of 2b was carried out in liquid ammonia with sodium amide, the ratio of the products 3b and 4b changed as expected (2) in favor of 4b from 40:1 to 2:1 (25% yield) accompanied by the formation of the debenzylated product 1b in high yield (45%).

The mass spectra of the additional by-products (5a, 5b, and 6a) show low intensity molecular ion peaks at m/e 343 (5a, 6a) and m/e 373 (5b) and base peaks at m/e 266 (5a, 6a) and m/e 296 (5b). The base peaks corresponding to M-77 thus indicate the presence of a phenyl substituent at C-1. This interpretation is corroborated by the nmr signals of the C-1 protons which appear as singlets at δ 4.16 (5a, 5b) and δ 4.73 (6a). Two one-proton singlets at δ 6.07 and 6.77 for 5a and 5b are assignable to the aromatic para protons of the isoquinoline nucleus. In contrast, the nmr spectrum of 6a exhibits a complex pattern in the aromatic region. The methoxy group in 5a and 6a exhibits a three-proton singlet at δ 3.45 and 3.70, respectively. In the case of 5b two three-proton singlets at δ 3.46 and 3.74 are observed. One of these methoxy groups must be attached to the benzyl moiety since the spectrum also exhibits an AA'BB'-pattern in the aromatic region at δ 6.78 and 7.10.

A mechanistic rationale explaining the formation of these by-products is suggested in Scheme II. The intimate ion pair 8 (11) derived from the ylid 7 (12) can be recombined by route A to give 9 and by route B to give 11. This is followed by reaction of 9 and 11 with phenyllithium to give 5a, 5b and 6a (13), respectively. The formation of the debenzylated compound 1b and 4,4'-dimethoxydibenzyl (14), which were also identified as the by-products, results from attack of the benzyl carbanion moiety of 8 ($R=OCH_3$) on the still intact quaternary salt.

Scheme II



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2. D.J. Cram, "Fundamentals of Carbanion Chemistry", Organic Chemistry Series, Vol. 4, Academic Press, New York, N.Y., 1965, page 223. H.E. Zimmerman in "Molecular Rearrangements", P. DeMayo, Ed., Interscience Publishers,

New York, N.Y., 1963, page 378. Leading references can be found in both articles.

3. After completion of our work, R. Maeda and E. Ohsugi [*Chem.Pharm.Bull.*, **16**, 897 (1968)] reported the preparation of a 1-benzyl substituted octahydroisoquinoline by Stevens rearrangement.
4. The yields were determined by quantitative glpc. Separation was obtained on a 6 ft column using 1% Carbowax 20M + 0.5% KOH on Gas Chrom Z. The bands were matched with reference samples injected under same conditions.
5. Nmr spectra were obtained in $CDCl_3$ on a Varian Associates Spectrophotometer, Model HA-100, and chemical shifts are reported in δ using TMS as internal reference. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe.
6. Preparative tlc was carried out on silica gel DSF-5 or F_{254} (Merck) with benzene-ethylacetate (6:4) and $CHCl_3$-MeOH (95:5) as the mobile phase.
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8. The dextrorotatory free base corresponding to **3d** were described by J. Kunimoto, *Yakugaku Zasshi*, **82**, 981 (1962).
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10. The picrate is described by M. Tomita and K. Okui, *J.Pharm.Soc.Japan*, **76**, 632 (1956).
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12. The ylid (e.g. 7) as first intermediate was originally suggested by Stevens (11). It explains satisfactorily the formation of all products obtained.
13. The compound corresponding to **6a** in the rearrangement of **2b** could not be isolated. But the reaction mixture contained a compound in about 5% yield which in its behavior in glpc and on tlc was similar to **6a**.
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