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A NOVEL 1,4 ARYLRADICAL REARRANGEMENT[1].

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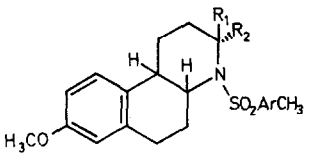
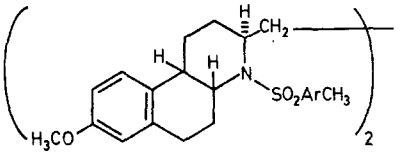
Radical rearrangements involving transannular 1,4 arylshifts are scarcely known[4,5]. In this communication we report a novel rearrangement of a α-halomethyl-piperidino-N-p-toluene-sulfonamide which proceeds quantitatively via an unique reaction-path.

In the course of investigations aiming at the total synthesis of functionally substituted heterocyclics by means of a cyclo-addition reaction[6,7] the dichloromethyl derivative 1 was prepared from the corresponding Δ 9,11-trichloromethyl adduct[6] by catalytic hydrogenation (Pt/EtOH), while the monochloromethyl derivative 2 was obtained from n-Bu_3SnH reduction of 1. Alternatively 1 could be dehydrochlorinated to the vinylchloride 3[6].



1 R_1=H , R_2=$CHCl_2$
2 R_1=H , R_2=CH_2Cl
3 R_1R_2= , =CHCl
4 R_1=CH_2OH , R_2=H
5 R_1=CH_2Cl , R_2=H
6 R_1=CH_2Br , R_2=H
10 R_1=CH_3 , R_2=H
11 R_1=H , R_2=CH_3



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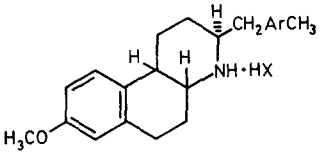


8 X=Cl
9 X=Br

With respect to the stereochemistry of 2, it was concluded from an extensive NMR-analysis of 1 the ring junction to be cis and the chloromethyl sub-

stituent having an axial configuration.

Vinylchloride 3 could be converted[6] into alcohol 4 which upon reaction with thionyl chloride and phosphorus tribromide gave the corresponding chloromethyl derivative 5 (mp 126-128°) and the bromomethyl derivative 6 (mp 125-127°) respectively. The spectral properties of 5 differed from those of 2 (mp 113-116°), thereby establishing the stereochemistry of the chloromethyl group and consequently also of the bromomethyl group.

During the preparation of alcohol 4 from vinylchloride 3 (B_2H_6-H_2O_2/NaOAc) small quantities of two other products were isolated: the dimer 7 (yield: 0.4%; mp 224-226.5°; mass: molecular ion $^m/e$ 768) and the α-benzyl substituted piperidine -HCl salt 8 (yield: 6.5%; mp 252-257°; IR (KBr): 2500-3000 cm^{-1} (NH^+); NMR ($CDCl_3$): δ 7.07 s 4 protons (phenyl), 3.70 s ($OC\underline{H}_3$), 2.27 s ($ArC\underline{H}_3$), the formation of which could not be explained initially in a satisfactory manner, although the isolation of 7 pointed to a radical mechanism.

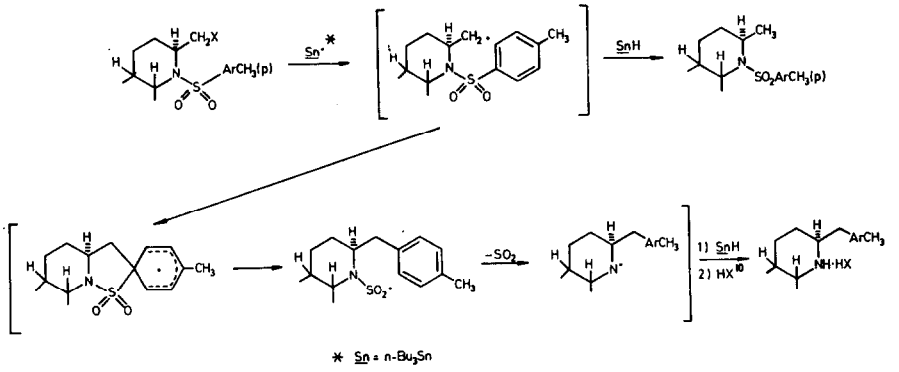
When, however, the β-chloromethyl compound 5 was treated with a 0.05 mol solution of nBu_3SnH[8] in refluxing anisole with azobisisobutyronitrile as a radical initiator, a relatively large amount (50%) of 8 was found, while none of the expected methyl derivative 10 could be detected. The yield of 9 was nearly quantitative[9] when a solution of 6 was refluxed in a 0.05 mol nBu_3SnH benzene solution. Upon work-up 88% of pure crystalline 9 (mp 278-282°) was obtained.

The radical character of this rearrangement was convincingly demonstrated upon carrying out the reaction of 6 in the presence of a radical inhibitor. Both the addition of galvinoxyl and hydroquinone led to a marked drop in the yield of 9 (respectively to 14 and 20%, determined via GLC). In a second experiment the reaction was carried out in pure nBu_3SnH to ensure optimum conditions for a normal hydrogen transfer from nBu_3SnH to the intermediate radical. In this experiment 30% of 10 (mp 144-147°; NMR ($CDCl_3$): δ 1.23 d (J=7 cps) CH-$C\underline{H}_3$) and 30% of 9 were obtained after work-up.

Finally when chloromethyl compound 2 was subjected to analogous reaction conditions (0.05 mol nBu_3SnH in refluxing anisole) 85% of methyl derivative 11 (mp 93-96°; NMR ($CDCl_3$): δ 1.32 d (J=7 cps) CH-CH_3) was obtained, although in this case too a rearranged product, the α-benzyl isomer of 8 was isolated in 8.5% yield.

The abovementioned results can be rationalized in terms of the following pathway: (Scheme A)

Scheme A



* Sn = n-Bu_3Sn

An examination of molecular models of 5 and 6 shows an approximate distance between the - equatorial - methylene radical and the migrating phenylcarbonatom of 2.3 Å. This small distance apparently allows interaction of the radical centre and the aromatic π-electronsystem. As in 2 - with the chloromethyl group axial - this distance is too large to account for a direct interaction of radical centre and aromatic ring, therefore a partial conformational isomerisation of the heterocyclic ring at the relatively high reaction temperature has to be assumed, which brings the chloromethyl group in the - equatorial - position required for a competitive rearrangement.

The remarkable ease of the reaction, the high yield and the multitude of variations possible in the heterocyclic ring could be of great interest in the synthesis of α-benzyl substituted piperidines. Studies concerning the influence of variation of substituents in the aryl sulfonamide ring,

as well as the application of the reaction on simple heterocyclics are currently on the way in this laboratory.

ACKNOWLEDGEMENT.

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REFERENCES AND FOOTNOTES.

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2. Part of forthcoming thesis of R. Loven, University of Amsterdam.
3. To whom all inquiries should be addressed.
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7. W.N. Speckamp, R.J.P. Barends (in part), A.J. de Gee (in part) and H.O. Huisman, Tetrahedron Letters no.5, p. 383-386, (1970).
8. a) For a review article about organotin hydrides see: H.G. Kuivila, Synthesis p 499 (1971).
   b) For rearrangements initiated by organotin hydrides see: H.G. Kuivila, Accounts Chem. Res. Vol.1, p 299 (1968).
9. For all GlC experiments the free oily amine was first obtained from the salt by alkaline treatment (GlC: all-glass apparatus, N_2 flow 50 ml/min, GasChromQ 100-120M, OV 17 1% analytical column).
10. $\underline{Sn}X + \underline{Sn}H \xrightarrow{\text{amine}} Sn\text{-}Sn + HX$
    See: W.P. Neumann, B. Schneider and R. Sommer, Liebigs Ann.Chem. 692 1 (1965).

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