Tetrahedron Letters No. 32, pp. 2853-2856, 1970. Pergamon Press. Printed in Great Britain.

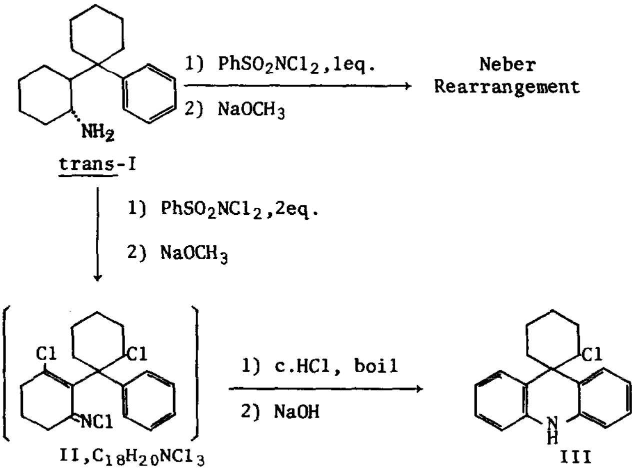
A NEW INTRAMOLECULAR CYCLIZATION OF HALAMINES. I.
CONVERSION OF DL-trans-2(1-PHENYLCYCLOHEXYL)CYCLOHEXYLAMINE TO SPIRO[ACRIDANE-9,1'-(2-CHLORO)CYCLOHEXANE]

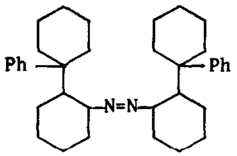
Tanezo Taguchi, Yoichi Shimizu[1] and Yuichi Kawazoe
Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan

(Received in Japan 3 June 1970; received in UK for publication 9 June 1970)

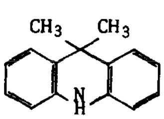
It has been known that the reactions of N,N-dichloro-sec-alkylamines with sodium methoxide followed by treatment with aqueous hydrochloric acid yield α-aminoketone hydrochlorides through the Neber rearrangement[2].

The procedure was applied to the N-chloro derivative which was derived from DL-trans-2(1-phenylcyclohexyl)cyclohexylamine(trans-I) on treatment with N,N-dichloro benzenesulfonamide(dichloramine-B)[3]. As a result , the change in molar ratio of trans-I and dichloramine-B used was found remarkably effective in altering the mode of reaction. When 1 molar equivalent of dichloramine-B was used to trans-I, the reaction proceeded as usual to afford finally the Neber rearrangement product(N-benzoyl derivative;m.p.203-205°(ethanol)) together with a less amount of DL-trans,trans-2.2'-azo(1-phenylcyclohexyl)cyclohexane(IV),m.p.167-168°(petroleum ether). On the other hand, when 2 molar equivalents of dichloramine-B were used, the reaction caused an intramolecular condensation in company with aromatization to yield an acridane derivative(III) as an end product. This report records the latter abnormal case.





IV

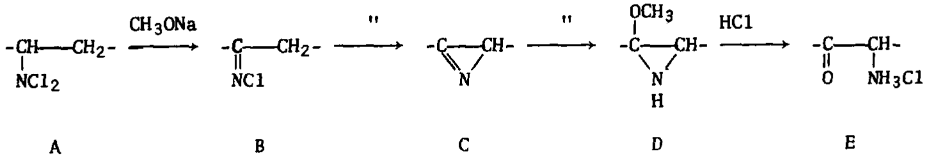


V

The starting material(trans-I)[4] was prepared by fractionation of a mixture of trans- and cis-I which was obtained by the Ladenburg reduction of DL-2(1-phenylcyclohexyl)cyclohexanone[5] oxime. To trans-I(16.6 g.,65 mmoles) dissolved in anhydrous benzene(50 ml.), a solution of dichloramine-B (29.4 g.,130 mmoles) in the same solvent (50 ml.) was added dropwise at 5° and stirred for 2 hr. at room temperature. After filtration of precipitated benzenesulfonamide, sodium (4.5 g.,200 mmoles) dissolved in dehydrated methanol (50 ml.) was introduced dropwise to the solution with stirring and refluxed for 30 min.. The reaction mixture was washed with 2N-hydrochloric acid, 2N-sodium hydroxide and water successively and evaporated to dryness to leave colorless needles (chloroform / petroleum ether), m.p.177-178°, yield 8.6 g. (39 %), $C_{18}H_{20}NCl_3$ (M^+ 355, a satisfactory elemental analysis) (II). In the mass spectrum of II, the appearance of $^{m}/e$ 355(p), 357(p+2), 359(p+4) and 361(p+6) in the intensity ratio of 27:27:9:1 indicated the existence of three chlorine atoms, one of which was characterized as an active chlorine by $^{m}/e$ 320 (M - Cl, base peak), 284 (M - HCl, - Cl) and 248 (M - 2HCl, - Cl) and by the help of the potassium iodide-starch test. The nmr (60 MHz, $CDCl_3$) and ir (neat) spectra of II exhibited signals at τ2.59 (s,5H,aromatic), 5.25 (t,1H, =CHCl) and 6.7-9.3 (br m,14H,ring $-CH_2-$) and at 1630 cm^{-1} (C=N). Any methine signal except one at τ5.25 did not appear in the nmr spectrum. All these observations suggest, though not definitely clear, 2(2-chloro-1-phenyl)cyclohexyl-3-chlorocyclohexenylidene chlorimine as the structure for II.

A suspension of II in conc. hydrochloric acid and ethanol (6:1) was boiled for 9 hr. and the resulting clear solution was evaporated to dryness to afford colorless plates (ethanol / ether), m.p.175°(decomp.), yield 94 %, $C_{18}H_{19}NCl_2$ (III-HCl) (a satisfactory elemental analysis). Treatment of the product (III-HCl) with aqueous sodium hydroxide gave a free base (III), m.p.64° (petroleum ether), $C_{18}H_{18}NCl$ (M^+ 283, a satisfactory elemental analysis). The structure of III was characterized as spiro[acridane-9,1'-(2-chloro)cyclohexane] on the basis of spectral data: nmr (60 MHz, $CDCl_3$) τ2.6-3.3 (m,8H,aromatic), 6.3 (br,1H,-NH-), 5.75 (t, 1H,=CHCl), 7.8-8.6 (m,8H,ring $-CH_2-$); ir (neat) 3360 cm^{-1} (-NH-). These spectroscopic values correspond well with those of acridane and 9,9-dimethylacridane (V). Morever, it supported the structural assignment of III that III formed a double salt with acridine[6], m.p. 213°(decomp.).

If a speculation is allowed at this stage of study, the reaction may be mechanistically interpreted as follows. On treatments with dichloramine-B (2 mol. equiv.)followed by sodium methoxide, trans-I suffered polychlorination and then dehydrochlorination to convert to II which resisted to further transformation causing the interruption of the Neber rearrangement. It has been convinced that the Neber rearrangement proceeds through the reaction sequence, A → B → C → D → E, where an azirine (C) is a key intermediate[2].



The transformation of II to the azirine derivative (corresponds to C) appears to bring disadvantages that steric strain extremely increased and overlaping of π-electrons is partially destroyed by the fusion of cyclohexene and azirine rings. This may be the cause that II rejected the transformation to the azirine derivative and accordingly the Neber rearrangement was interrupted

In the formation process of III from II stated above, the aromatization took place together with the intramolecular condensation as a result of dehydrochlorination. The aromatization bears a resemblance to the Semmler[7]-Wolff[8] aromatization reaction where, for example, cyclohexenone oxime converts to aniline by the action of hydrogen chloride in acetic anhydride and acetic acid[9]. No example of aromatization accompanied by condensation has been found in the Semmler-Wolff reaction. However, also the occurrance of condensation is naturally expected in the reaction of II, because II bears the chloroketimine group which can link to the benzene ring by dehydrochlorination. In this view, the reaction of II may be comprehensible as a special case of the Semmler-Wolff reaction.

The details will be reported in near future with the case of cis-I which appeared less reactive on the same treatment and showed something different from trans-I in the reaction feature. Also studies on the mechanism and the expansion of this reaction which are in progress will follow this report in publication.

REFERENCES

1. Present address: Sankyo Kasei Kogyo Co. Inc., Ohfuna, Kamakura, Japan.
2. H.E.Baumgarten and F.A.Bower, J.Am.Chem.Soc., 76, 4561 (1954); H.E.Baumgarten, J.M.Petersen and D.C.Wolf, J.Org.Chem., 28, 2369 (1963); C.O'Brien, Chem.Rev., 64, 81 (1964).
3. H.E.Baumgarten and E.P.William, " Organic Syntheses " Vol.41, John Wiley & Sons, Inc., New York, N.Y., 1963, p.82.
4. T.Kobayashi, A Master Degree Thesis submitted to Kyushu University, 1964. Paper in preparation.
5. T.Taguchi, K.Miyano, Y.Shimizu and Y.Kawazoe, Tetrahedron Letters, 4105 (1968).
6. K.Lehmstedt and H.Hundertmark, Ber., 62, 416 (1929).
7. W.Semmler, Ber., 25, 3352 (1892).
8. L.Wolff, M.Gabler and F.Heyl, Ann., 322, 362, 380 (1902).
9. M.V.Bhatt, Experientia, 13, 70 (1957).