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Rearrangement in Dihydroresorcinol Derivatives. VI.[1] Schmidt Rearrangement of 3-Chloro-2-cyclohexen-1-ones

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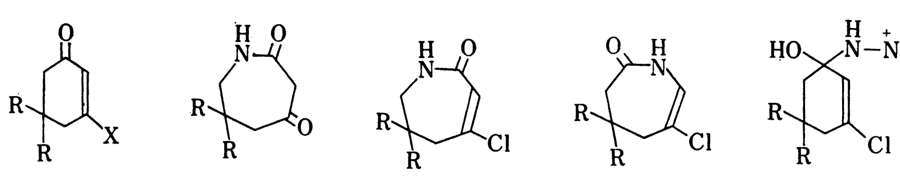
The previous reports have revealed that in the Beckmann[3] rearrangement of dihydro resorcinol derivatives with polyphosphoric acid (PPA) the migration of alkyl site (C-6) takes place exclusively, that is, the Beckmann rearrangement of 3-alkoxy (I: X=O-alkyl) and 3-chloro-2-cyclohexen-1-one oximes (I: X=Cl) gives the derivatives of hexahydroazepine-2,4-dione (II and III) in good yields. In the present paper it has been shown that in Schmidt rearrangement of 3-chloro-2-cyclohexen-1-one (I: X=Cl) with PPA migration of the alkyl site and the double bond site are competitive and thus nearly equal amounts of 4-chloro-1,5,6,7-tetrahydro-2H-azepin-2-one (III) and 6-chloro-2,3,4,5-tetrahydro-1H-azepin-2-one (IV) are obtained.

Treatment of (Ia: R=CH_3, X=Cl) with sodium azide in PPA at 120° for 2 hr gave a 36% yield of IIIa and a 32% yield of IVa. Structures of IIIa and IVa were deduced from examination of their spectra. The ultraviolet (UV) spectra of IIIa and IVa show absorptions at 226 mμ and 246 mμ, respectively. It is reasonable that the former absorption is ascribed to a NH-CO-CH=C- system (220 mμ region) and the latter to a CO-NH-CH=C- system (240 mμ region).[4] The nuclear magnetic resonance (NMR) spectrum of IIIa exhibits τ 2.80 (1H, b-s, NH), 3.80 (1H, s, CH=), 7.02 (2H, d, CH_2N, J=6 cps), 7.49 (2H, s, CH_2C), and 8.95 (6H, s, gem-diCH_3). The signal (doublet) at τ 7.02 changes to a singlet on treatment with D_2O. On the other hand, the NMR spectrum of IVa exhibits τ 2.10 (1H, s, NH), 3.75 (1H, d, CH=), 7.55 (4H, s, CH_2CO and CH_2C=), and 8.85 (6H, s, gem-diCH_3). The former structure was unequivocally established by direct comparison with the authentic specimen of IIIa prepared by the Beckmann rearrangement of (Ia oxime: R=CH_3, X=Cl).[3b] By similar reaction to that employed for IIIa and IVa, IIIb and IVb were obtained from (Ib; R=H, X=Cl) in 15% and 11% yields, respectively.



Ia, b IIa, b IIIa, b IVa, b A

X=O-alkyl or Cl

a: R=CH_3
b: R=H

Chart 1

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[1] Part V: Y. Tamura, Y. Yoshimura and Y. Kita, *Chem. Pharm. Bull.* (Tokyo), **19**, 1068 (1971).

[2] Location: *6-5, Toneyama, Toyonaka, Osaka.*

[3] *a*) Y. Tamura, Y. Kita, Y. Matsutaka and M. Terashima, *Chem. Ind.* (London), **1970**, 1350; *b*) Y. Tamura, Y. Kita and M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **19**, 529 (1971).

[4] R.H. Mazur, *J. Org. Chem.*, **17**, 823 (1952).

The rearrangement of I (X=Cl) to III and IV is supposed to proceed through a tetrahedral intermediate (A).[5] It is known that in the reaction of 3-chloro-2-cyclohexen-1-one derivatives, substitution of the chlorine atom with nucleophiles such as sodium azide,[6] amine,[6a,7] and active methylene[6a,8] takes place preferentially in basic medium, while condensation of the carbonyl group with hydroxylamine and semicarbazide is accelerated in acidic medium.[9] Therefore, the formation of A by preferential attack of sodium azide to the carbonyl group of I (X=Cl) in PPA medium is well acceptable.

Experimental

Boiling and melting points were uncorrected. The NMR spectra were measured on a Hitachi Perkin-Elmer H-60 type (60 Mc) spectrometer with tetramethylsilane as internal reference and infrared (IR) spectra on a Hitachi EPI-G2 spectrophotometer and UV spectra on a Hitachi EPS-3T spectrophotometer.

Schmidt Rearrangement of 5,5-Dimethyl-3-chloro-2-cyclohexen-1-one——To a stirred mixture of 5,5-dimethyl-3-chloro-2-cyclohexen-1-one (Ia: R=CH_3, X=Cl) (0.792 g) and PPA (25 g) was added in portions NaN_3 (0.325 g) over a period of 40 min. The mixture was heated at 120° for 2 hr with occasional shaking. It was then cooled and poured into a mixture of crushed ice and water (25 ml), and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina (25 g). The column was treated successively with pet. ether (30 ml), C_6H_6 (60 ml), 80% C_6H_6–20% EtOAc (50 ml) and MeOH (50 ml). The first compound was eluted with C_6H_6 and was recrystallized from ligroin to give 0.252 g (32%) of IVa, mp 95—96°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3390, 1665, 1295. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 246 (3.98). *Anal.* Calcd. for $C_8H_{12}ONCl$: C, 55.33; H, 6.97; N, 8.07. Found: C, 55.29; H, 6.97; N, 8.14. The second compound was eluted from the column with 80% C_6H_6–20% EtOAc and was recrystallized from pet. ether to give 0.281 g (36%) of IIIa, mp 84.5—85.5° (lit.[3b] 84.5—85.5°). The latter material (IIIa) was identified with the authentic specimen by IR and NMR comparison.

Schmidt Rearrangement of 3-Chloro-2-cyclohexen-1-one——To a stirred mixture of 3-chloro-2-cyclohexen-1-one (Ib: R=H, X=Cl) (1.30 g) and PPA (35 g) was added in portions NaN_3 (0.715 g) over a period of 20 min. The mixture was heated at 120 ° for 1 hr with occational shaking. It was then cooled and poured into a mixture of crushed ice and water (35 ml), and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*, giving 0.895 g of yellow crystals. The crude crystals were distilled, 90—120° (0.05 mmHg) (bath temp.), to give 0.489 g of pale yellow prisms, mp 90—101°. The yellow prisms (0.180 g) were submitted to a preparative thin-layer chromatography on alumina with 50% C_6H_6–50% EtOAc. The fast moving fraction gave 54 mg (11%) of crude IVb, mp 48—75°, and was recrystallized from pet. ether to give colorless crystals, mp 80—84°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3395, 1660. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 248 (4.02). *Anal.* Calcd. for C_6H_8ONCl: C, 49.49; H, 5.54; N, 9.62. Found: C, 49.35; H, 5.49; N, 9.45. The slow moving fraction gave 58 mg (15%) of crude IIIb, mp 118—124°, and was recrystallized from ligroin to give colorless crystals, mp 128—129.5° (lit.[3b] 128.5—129°). The latter material was identified with the authentic specimen by IR and NMR comparison.

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9) This work was presented at Meeting of Kinki Branch, Phrmaceutical Society of Japan, Kyoto, November 1968.