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Reduction of O-Alkylated Imides[1]

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In our previous papers,[3] the reductions of cyclic vinylogous esters with lithium aluminum hydride and Raney-Ni catalyst were reported. On the other hand, studies on the syntheses of azaheterocyclic compounds were in progress in our laboratory.[4] Therefore, the reduction of the systems of vinylogous esters containing nitrogen atom, that is O-alkylated imides or azavinylogous esters, was examined.

The O-alkylated imides examined were the following three: O-ethyl succinimide (Ia), O-ethyl 4,4-dimethyl-glutarimide (Ib), and O-ethyl phthalimide (Ic).

Already in 1891,[5] Comstock, *et al.*, reported on the synthesis of Ia and the reaction of this compound with aniline. Photochemical reactions of Ia and Ic have also recently been presented in Tetrahedron Letters,[6] in which Ia and Ic were synthesized by the treatment of silver salt of corresponding imides with ethyl iodide in anhydrous chloroform for a long time at room temperature. But no literature on other O-alkylated imides is presented. We succeeded in the efficient synthesis of O-alkylated imides by refluxing a benzene solution of the corresponding imide-Ag salt and ethyl iodide for a short time. O-Alkylated imides could be distilled and were hydrolyzed spontaneously by acid to the starting imides. In the case of Ic, ethyl phthalamate formation couldn't be avoided. This ester was also readily converted to phthalimide by acid treatment.[7] Separation of Ic and ethyl phthalamate could be effected by recrystallization from acetone.

Using O-alkylated imides here obtained, hydride reductions were carried out. With sodium borohydride in ethanol at room temperature, all of the O-alkylated imides were reduced to the corresponding ethoxy lactams (II) in quantitative yields. These results are in contrast with the reactions of O-alkylated lactams,[8] which were reported to afford the corresponding amines. For IIa—c satisfactory elementary analyses were obtained, and physical data also

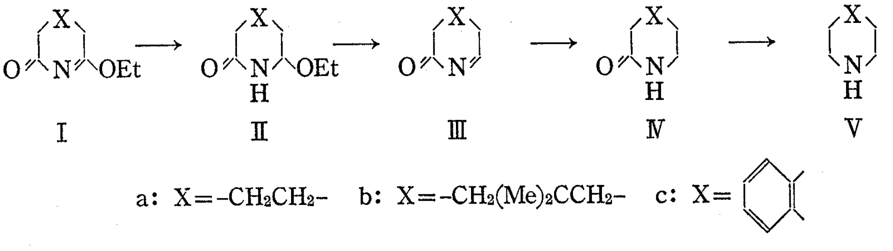

Chart 1

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[1] A part of this work was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April, 1974.

[2] Location: *Gofuku, Toyama.*

[3] Katsuhide Matoba and Takao Yamazaki, *Yakugaku Zasshi*, **93**, 1406 (1973), and references therein.

[4] Masanori Nagata, Masami Goi, Katsuhide Matoba, Takao Yamazaki, and R.N. Castle, *J. Heterocycl. Chem.*, **10**, 21 (1973), and references therein.

[5] S.J. Comstock and H.L. Wheeler, *Am. Chem. J.*, **13**, 522 (1891).

[6] *a*) T.H. Koch and K.H. Howard, *Tetrahedron Letters*, **1972**, 4035; *b*) T.H. Koch and R.J. Slusk, *ibid.*, **1970**, 2391.

[7] J.A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1901 (1963).

[8] R.F. Borch, *Tetrahedron Letters*, **1968**, 61.

supported their chemical structures. IIa—c were relatively stable, however when treated with acid, they decomposed into several kinds of water-soluble substances which exhibited many spots on thin-layer chromatogram (TLC).

IIa was reduced to lactam (IVa) with a large excess of sodium borohydride in ethanol under reflux or with lithium aluminum hydride in ether at room temperature. In the latter case, the formation of amine (Va) couldn't be avoided.

In a similar fashion, IIb could be reduced to IVb by refluxing an ethanolic solution of IIb with a large excess of sodium borohydride. With lithium aluminum hydride, it was converted to a mixture of IVb and Vb.

As an intermediate from II to IV or V, imino ketone (III) may exist. As an evidence for the above speculation, the substance considered to be III was isolated from Ia. Kept at room temperature for about one year, IIa changed partly into IIIa, which was a crystalline substance of a relatively high melting point and exhibited a carbonyl band at 1690 cm^{-1} in its infrared (IR) spectrum. In its nuclear magnetic resonance (NMR) spectrum, a signal assigned to a vinylic proton was observed at 4.63τ. However, the conversion of this imino ketone to IVa with sodium borohydride couldn't be attempted because of its small quantity.

On the other hand, IIc could be converted neither to IVc nor to Vc under the same conditions that were employed for reductions of IIa and IIb. As a product from Ic by the lithium aluminum hydride reduction in ether, only 3-hydroxy-phthalimidine could be isolated in poor yield. The mechanism for the formation of this product is obscure.

Ia could be reduced only to IIa in the presence of Adams' catalyst or Raney-Ni, but the reaction rate was very slow and the yield was poor.

Experimental

All the melting points and boiling points are uncorrected. The following equipments were used: IR spectra, Hitachi Grating Infrared 215 spectrophotometer; UV spectra, Hitachi EPS-2T spectrophotometer; NMR spectra, JEOL C-60H spectrometer with tetramethylsilane as an internal reference unless otherwise mentioned; Mass spectra, JMS-01SG(JEOL). The TLC values were obtained with Kiesel gel G nach Stahl-(Merck) as adsorbent using $CHCl_3$–acetone as developer. The spots were detected by spraying with 1% ceric sulfate-10% sulfuric acid and heating. For column chromatography silicagel (200 mesh, Wako) were used. Gas-liquid chromatography (GLC) was performed with a Shimazu gas chromatograph Model GC-3AF. The column was packed with 5% SE-30 and carrier gas was N_2 (40 ml/min). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Unless otherwise stated, all the solvents were evaporated under reduced pressure.

O-Ethyl Succinimide (Ia)——Succinimide-Ag salt, prepared from succinimide (20 g, 200 mmoles) and $AgNO_3$ (35 g, 270 mmoles), was dispersed in benzene (200 ml), and water contaminated in crystals was removed by azeotropic distillation. Ethyl iodide (70 g, 560 mmoles) was added to this cooled mixture, followed by refluxing for 4 hr. After removal of AgI by filtration, the solvent was evaporated. The resultant residue was distilled to give Ia (16.5 g, 65% from succinimide), bp 90° (2 mmHg) (lit,[5] bp 144—146° (20 mmHg)). IR $\nu_{max}^{liq.}$ cm^{-1}: 1745, 1710, 1570. UV (in EtOH): only end absorption. GLC (at 135°) t_R: 3.7 min. NMR (in CCl_4) τ: 8.60 (3H, t, J=7.0 cps, $-CH_2-C\underline{H}_3$), 7.39 (4H, nearly s, $-CH_2-CH_2-$), 5.57 (2H, q, J=7.0 cps, $-C\underline{H}_2-CH_3$). *Anal.* Calcd. for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.39; H, 7.03; N, 11.15.

O-Ethyl 4,4-dimethyl-glutarimide (Ib)——Similar treatment of 4,4-dimethyl-glutarimide-Ag salt (12 g, 48 mmoles) to the case for the preparation of Ia afforded Ib (7.5 g, 92% from salt), bp 108—110° (5 mmHg). GLC (at 130°) t_R: 7.2 min. IR $\nu_{max}^{liq.}$ cm^{-1}: 1695, 1583. NMR (in CCl_4) τ: 8.96 (6H, s, geminal $-CH_3$), 8.67 (3H, t, J=7.0 cps, $-CH_2-C\underline{H}_3$), 7.95—7.45 (4H, m, $2\times-CH_2-$), 5.66 (2H, q, J=7.0 cps, $-C\underline{H}_2-CH_3$). Ib turned gradually into 4,4-dimethyl-glutarimide at room temperature, therefore, a sample analytically pure couldn't be obtained.

O-Ethyl Phthalimide (Ic)——Phthalimide (10 g, 68 mmoles) was dissolved in 3% KOH solution (140 ml, 0.9 eq. mole). After $AgNO_3$ (13 g, 68 mmoles) was added, the pH of the solution was made 5.5 by the addition of 3% KOH solution. The Ag salt thus obtained was treated with ethyl iodide (26 g, 136 mmoles) in benzene in the manner similar to the case for the preparation of Ib. The resultant residue was a semisolid, which was recrystallized from acetone. Ic: mp 129—130° (prisms), 7.2 g (60.5%). GLC (at 200°) t_R: 2.8 min. Spectroscopic behavior (IR, UV and NMR) of this sample were identical with those reported by Koch.[6] *Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.61; H, 5.26; N, 7.85.

From the mother liquor of Ic, ethyl phthalamate was obtained. 2.3 g (30.2%), mp 125—126° (needles from EtOH). GLC (at 200°) t_R: 1.9 min. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3180, 1710, 1655. UV λ_{max}^{EtOH} mμ: 224, 276. NMR (in $CDCl_3$) τ: 8.68 (3H, t, $J=7.0$ cps, $-CH_2-C\underline{H}_3$), 5.68 (2H, q, $J=7.0$ cps, $-C\underline{H}_2-CH_3$), 3.55 (2H, broad s, $-NH_2$), 2.76—2.05 (4H, m, aromatic H). This ester could be identified with the authentic sample.[7]

Ethoxy Lactam Compounds (II)——O-Alkylated imide Ia—c was dissolved in EtOH, and an excess amount (3 eq. mole) of $NaBH_4$ was added portionwise. After stirring for 3 hr at room temperature, AcOH and water were added to decomposed excess hydride. The product extracted with *n*-BuOH was mainly one spot on TLC plates. Yield was quantitative. IIa: TLC *Rf*: 0.4. bp 100° (3 mmHg). GLC (at 130°) t_R: 4.9 min. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250, 1695. NMR (in CCl_4) τ: 8.82 (3H, t, $J=7.0$ cps, $-CH_2-C\underline{H}_3$), 6.51 (2H, m, $-O-CH_2-$), 5.07 (1H, m, $-\dot{C}\underline{H}-NH-$), 0.75 (1H, broad s, $-NH-$). *Anal.* Calcd. for $C_6H_{11}O_2N+H_2O$: C, 48.96; H, 8.90; N, 9.52. Found: C, 48.86; H, 8.83; N, 10.03. IIb: TLC *Rf*: 0.5. bp 114° (7 mmHg). mp 62—65°. GLC (at 150°) t_R: 4.8 min. IR ν_{max}^{Nujol} cm^{-1}: 3200, 3100, 1665. NMR (in CCl_4) τ: 8.99, 8.91 ($2\times 3H$, $2\times s$, $2\times -CH_3$), 8.83 (3H, t, $J=7.5$ cps, $-CH_2-C\underline{H}_3$), 8.30 (2H, t. like, $-CH-C\underline{H}_2-$), 7.95 (2H, s, $-CH_2-CO-$), 6.90—6.00 (2H, m, $-O-CH_2-$), 5.33 (1H, t.d, $J=6.0$, 2.5 cps, $-\dot{C}H-$), 0.98 (1H, br.s, $-NH-$). *Anal.* Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.18. Found: C, 62.87; H, 10.17; N, 8.03. IIc: mp 98—111° (from acetone or benzene). TLC *Rf*: 0.75. GLC (at 160°) t_R: 2.7 min. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3100, 1715, 1705. NMR (in $CDCl_3$) τ: 8.81 (3H, t, $J=3.0$ cps, $-CH_3$), 6.75—6.20 (2H, m, $-O-CH_2-$), 4.08 (1H, s, $-O-\dot{C}H-$), 2.75—2.10 (4H, m, aromatic H), 1.58 (1H, broad s, $-NH-$). *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.50; H, 6.23; N, 7.65.

Imino Ketone from IIa (IIIa)——IIa (1 g) from Ia was kept at room temperature for about 1 year. During this period, IIIa gradually precipitated. This was recrystallized from EtOH. 100 mg, mp 155—157°. It was readily soluble in water, soluble in alcohols and sparingly soluble in acetone, $CHCl_3$ and pyridine. TLC *Rf*: 0.2. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3100, 1690. UV (in EtOH): only end absorption. NMR (in D_2O using 3-(trimethylsilyl)-propanesulfonic acid sodium salt as an internal standard) τ: 8.0—7.1 (4H, m, $-CH_2-CH_2-$), 4.62 (1H, m, vinylic H). *Anal.* Calcd. for $C_4H_5ON+2/5H_2O$: C, 53.20; H, 6.47; N, 15.51. Found: C: C, 53.06; H, 6.78; N, 15.24. Mass Spectrum *m/e*: 83 (M^+).

Lactam Compounds (IV)——a) From Ia with $NaBH_4$: IIa was treated with an excess amount (10 eq. mole) of $NaBH_4$ in EtOH. The mixture was refluxed for 6 hr. The product obtained after the manner of the preparation of II was found to be a mixture of the starting material and IVa, the latter of which was identified with the authentic sample by IR and GLC. Pyrrolidone: GLC (at 140°) t_R: 3.9 min. IR $\nu_{max}^{liq.}$ cm^{-1}: 3220, 1690.

b) From Ia with $LiAlH_4$: Ia (200 mg) was treated with $LiAlH_4$ (100 mg) in ether for 3 hr at room temperature. NH_4Cl (700 mg) in water was added to this reaction mixture under ice-cooling. Solvent was distilled off under an ordinary pressure to give a fluid liquid with amine-like odor. GLC (at 140°) t_R: 1 min (pyrrolidine), 3.9 min (pyrrolidone). After pyrrolidine was removed under reduced pressure, IR spectrum of this residue was nearly identical with that of pyrrolidone.

c) From Ib with $NaBH_4$: IIb was treated under the same conditions as those for a). The product obtained was about 1 : 1 mixture of IIb and 4,4-dimethyl-2-piperidone (IVb), the latter of which was purified by column chromatography on silica gel using acetone as an eluant. mp 96—98° (leaflet from *n*-hexane, lit.[9] thick oil). TLC *Rf*: 0.4. GLC (at 150°) t_R: 2.9 min. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1658. NMR (in CCl_4) τ: 8.98 (6H, s, geminal CH_3), 8.46 (2H, t, $J=7.0$ cps, $-\overset{|}{\underset{|}{C}}-C\underline{H}_2-CH_2-$), 8.02 (2H, s, $-CH_2-CO-$), 6.68 (2H, t.d, $J=7.0$, 2.5 cps, $-C\underline{H}_2-NH-$), 1.65 (1H, broad s, $-NH-$).

d) From Ib with $LiAlH_4$: Under the same conditions as those mentioned in b), Ib was reduced with $LiAlH_4$. GLC (at 150°) t_R: 1 min (4,4-dimethyl-piperidine), 2.9 min (4,4-dimethyl-2-piperidone). After piperidine was removed under reduced pressure, IR spectrum of the residue was almost identical with that of 4,4-dimethyl-2-piperidone.

3-Hydroxy-phthalimidine——Ic (200 mg) was added portionwise to a suspension of $LiAlH_4$ (200 mg) in ether. The colour of the reaction mixture changed from brown to black. The reduction product was obtained by usual work-up. TLC *Rf*: 0.3, mp 176—178°, about 50 mg. This product was identical with 3-hydroxy-phthalimidine prepared by the method reported in literature.[10]

The Catalytic Reduction of Ia——Ia (1 g) was reduced at H_2 atmosphere in the presence of Adams' catalyst or Raney-Ni in EtOH under an ordinary pressure for 5 hr. In both cases, the product was only IIa (0.2 g, 0.1 g respectively). A large amount of the starting material or its hydrolyzed product was obtained.

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