HETEROCYCLES, Vol 16, No 7, 1981

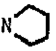
THE REACTIONS OF LITHIUM ESTER ENOLATES WITH N-(ω-BROMOALKYL)PHTHALIMIDES

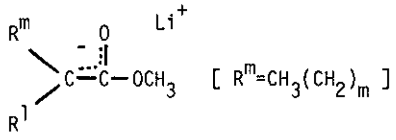
Shunsuke Naruto*, Keiko Shimakawa, Hiroyuki Mizuta, Hitoshi Uno
and Haruki Nishimura
Research Laboratories, Dainippon Pharmaceutical Co., Ltd.
Suita, Osaka 564, Japan

Abstract —— In the titled reactions, N-(ω-bromoalkyl)phthalimides were ambident electrophiles. The carbanion of straight chain ester enolates(I, R^1=H) attacked the carbonyl carbon atom of phthalimide moiety to give several types of compounds.

During the course of our synthetic studies on biologically interesting ω-amino acids, it was found that a phthaloyl group is not always suitable for terminal N-protective group in the reactions of lithium ester enolates(I) with N-(ω-bromoalkyl)phthalimides(II). This communication deals with such reactions whose products depended on a steric factor of I and also on an alkyl chain length of II.

An α-branched lithium ester enolate(Ia) which was obtained from the corresponding methyl ester in tetrahydrofuran(THF) by lithium diisopropylamide(LDA) in the usual way was treated with IIb and IIc in THF at -65° to 0° to give the expected colorless oily IIIb and IIIc1) in 88% and 60% yields, respectively. On the other hand, treatments of straight chain lithium ester enolates(I, R^1=H, m=0, 1, 2) with II(n=2, 3, 4, 5) under the same conditions described above gave compounds(V, VII, X and XI) instead of the expected products(III, R^1=H).

Firstly, the reaction of Ib with IIb gave a pyrrolidine derivative(Va), colorless oil, in 50% yield. Compound Va lacked the characteristics of phthalimide group in its nmr(unsymmetrical multiplets of four aromatic protons at δ 7.3-7.9) and ir($\nu_{C=O}^{neat}$ 1730, 1690 and 1620 cm^{-1}) spectra. The nmr spectrum of Va exhibited eleven protons of a partial structure $CH_3CH_2CH_2CHCOOCH_3$ and eight protons appeared at δ 3.68, 3.12 and 1.92 in ratio of 2:2:4. The latter splitting pattern indicated the presence of a partial structure -CO-N which was substantiated by a base peak at m/z 70 in the mass spectrum of Va. Catalytic hydrogenation of Va on PtO$_2$ in ethanol afforded two colorless oily diastereoisomers. The isomers, more polar erythro- and less polar threo-dihydroalcohol(VIa and VIb), were distinguished by nmr in which methoxyl signal of VIa and VIb appeared at δ 3.44 and 3.70, respectively. However, each doublet assigned to benzylic methine proton of both isomers



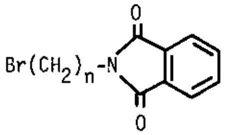
I

Ia $R^1=CH_3CH_2CH_2$, m=2

Ib $R^1=H$, m=2

Ic $R^1=H$, m=1

Id $R^1=H$, m=0



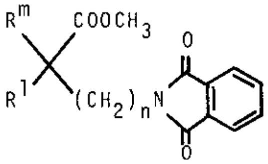
II

IIa n=5

IIb n=4

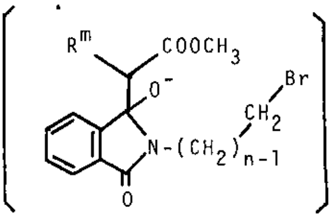
IIc n=3

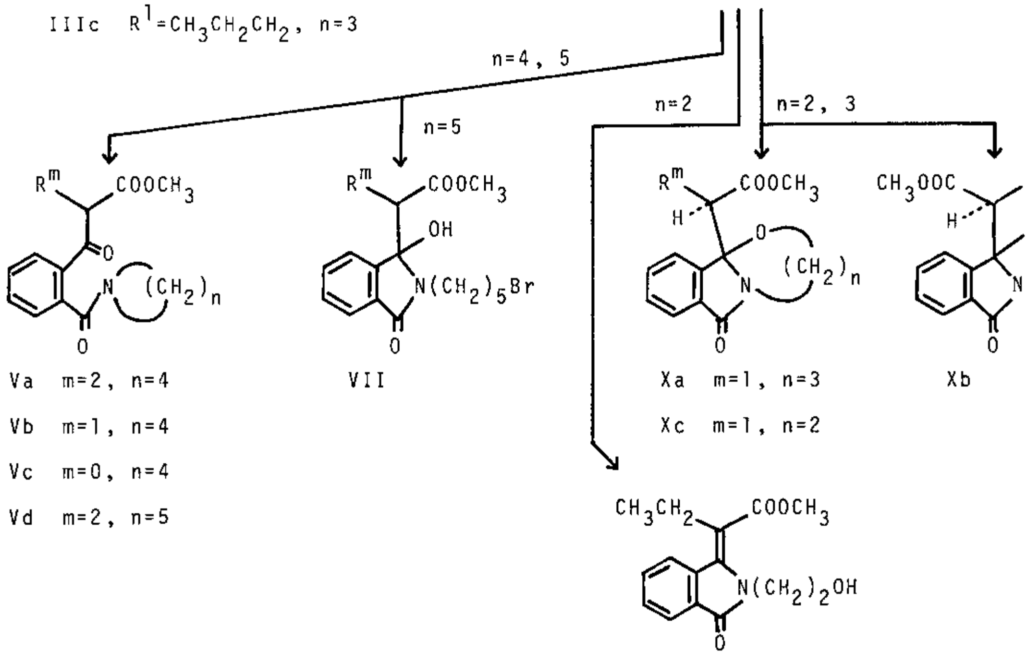
IId n=2



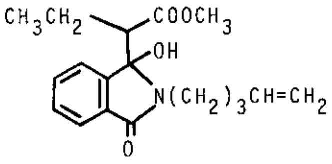
IIIb $R^1=CH_3CH_2CH_2$, n=4

IIIc $R^1=CH_3CH_2CH_2$, n=3

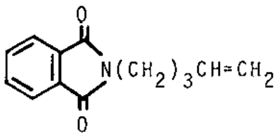




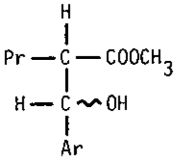
XI



VIII



IX



VI

$Pr=CH_3CH_2CH_2$

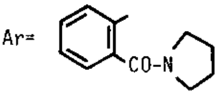
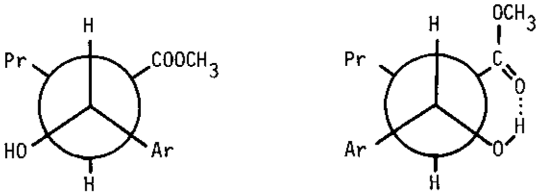


Fig. 1



VIa (erythro)   VIb (threo)

exhibited the same coupling constant(J=9 Hz). This contradictory fact is explained by taking account of a stabilization of threo-isomer with a hydrogen bond as shown in Fig. 1. The high field shift of methoxyl signal of erythro-isomer is also explained by Fig. 1 in which the methoxyl group located on an aromatic ring. These facts suggested that Va is a β-ketoester having the structure Va in consistent with the reaction mechanisms. In a similar manner, the reaction of Ic and Id with IIb gave Vb and Vc in 50% and 5%$^{2)}$ yields, respectively.

Secondly, the treatment of Ic with IIa gave an analogous piperidine derivative(Vd), colorless oil, in 39% yield, and an alcohol(VII), mp 130-131°, in 36% yield. The ir spectral data(3260, 1740, 1680 and 1660 cm^{-1} in KBr) of VII were in good agreement with those of 2-methyl-3-hydroxy-3-benzylphthalimidine$^{3)}$ except ester carbonyl bands at 1740 cm^{-1}. Thus it was suggested that VII was a product via the Grignard type reaction. On treatment of VII with two fold moles of LDA in THF at -65° to 0° gave methyl butylate, IIa(1% yield), VIII(40%), colorless oil, and IX(38%), colorless oil. This fact implies that VII is not an intermediate of Vd. Moreover, it is indicated that dehydrobromination is predominant and that a certain amount of VII decomposes to its starting materials under these reaction conditions.

Thirdly, the reaction of Ic with IIc afforded two tricyclic diastereoisomers, Xa(less polar isomer), colorless oil, and Xb(more polar isomer), mp 105-107°, in each 10% yield. Both isomers lacked the characteristics of hydroxyl and phthalimide groups in their spectral data. Their nmr spectra exhibited nine protons of a partial structure $CH_3CH_2CHCOOCH_3$ and six methylene protons appeared as a complex splitting pattern indicating that Xa,b had a moiety of $-OCH_2CH_2CH_2N<$ in a ring system$^{4)}$. Considering with the reaction mechanisms, it seems most reasonable to conclude that Xa,b have a tetrahydro-1,3-oxazino ring. As in the case of isomers(VIa and VIb), Xa and Xb were distinguished by nmr spectra which showed methoxyl signal at δ 3.88 and 3.43, respectively. Thus the higher methoxyl signal is attributed to the stereo structure Xb.

Finally, the treatment of Ic with IId gave an alcohol(XI), mp 109-110°, in 9% yield and a mixture of diastereoisomers in 20% yield whose nmr spectrum exhibited methoxyl signal at δ 3.68

and 3.76 in a ratio of 1:1. From the mixture, only one tricyclic isomer(Xc), mp 98-100° was isolated$^{5)}$. The nmr spectrum of Xc exhibited ethylene protons in a dihydrooxazolo ring at δ 3.4-4.4 appeared as a complex splitting pattern$^{4)}$ and one methoxyl signal at δ 3.76 indicating the stereo structure Xc. It has recently reported that the carbanion of lithium phenylacetylide attacked an imide carbonyl group of IId to give a similar dihydrooxazolo[2,3-a]isoindole derivative$^{6)}$. On the other hand, the presence of partial structures, $CH_3CH_2C(=C)COOCH_3$ and $-CO\underset{|}{N}CH_2CH_2OH$, in the alcohol(XI) were deduced from its ir(3360, 1700, 1670 and 1640 cm^{-1} in KBr) and nmr[δ in DMSO-d_6: 1.14^{t}(3H, J=7 Hz), 2.77^{q}(2H, J=7 Hz), 3.63^{m}(2H), 3.88^{s}(3H), 3.99^{t}(2H, J=6 Hz), 4.97^{t}(1H, J=5.5 Hz, exchangable by D_2O)] spectra. Thus the structure XI for the alcohol seems to be consistent with those data. Comparison of N-methylene proton signal of XI at δ 3.99 with those of N-(2-hydroxyethyl)phthalimide at δ 3.70(in DMSO-d_6) indicated Z-configuration of XI in which the N-methylene protons were deshielded by ester carbonyl group.

In these reactions of I with II, a steric factor of I determined where the new C-C bond is formed. This fact may be explained by taking account of the interaction of lithium ion with oxygen atom of carbonyl group. Presumably, this electrophilic assistance$^{7)}$ of lithium ion to oxygen atom is hindered in the case of α-branched ester enolates. It is assumed that the easiness of ring formation, cyclophilicity$^{8)}$, from a tentative intermediate IV determined the structure of products, since ring opening and/or closing reaction depended on alkyl chain length of II.

Acknowledgements We wish to thank Dr. M. Shimizu, Director of Research and Development Headquarters, Dainippon Pharmaceutical Co. Ltd.. Thanks are also due to the members of Analytical Center of these laboratories for microanalyses, nmr and mass spectrometric measurements.

References and Notes

1) All new compounds reported in this work gave satisfactory spectral[nmr(in $CDCl_3$ unless otherwise stated), ir, uv and mass] and analytical data.
2) In this case, about 90% of IIb was recovered from the reaction mixture.
3) K. Heidenbluth, H. Tönjes and R. Scheffler, J. Prak. Chem., 1965, 30, 204.
4) P. Aeberli and W. J. Houlihan, J. Org. Chem., 1969, 34, 165.
5) The other oily isomer could not isolated in pure form.
6) D. K. Olsen, B. E. Torian, C. D. Morgan and L. L. Braun, J. Org. Chem., 1980, 45, 4049.
7) B. Deschamps, Tetrahedron, 1978, 34, 2009.
8) Y. Kanaoka, "The Chemistry of Heterocycles", Vol. IV, eds. by T. Kametani, T. Mukai and S. Takano, Kagaku No Ryoiki, Zokan, 123, Nankodo, Tokyo, Kyoto, 1979, p 41.

Received, 9th March, 1981