Selective Deethoxycarbonylation of β-Ethoxycarbonylamino-α,β-Unsaturated Carboxylic Esters[*1]

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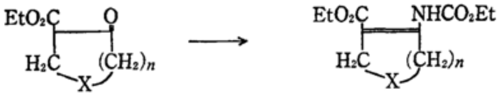
An ethoxycarbonyl group attached to a carbon atom is usually more easily hydrolysed in either an alkaline or an acidic medium than is an ethoxycarbonyl group attached to an amino group. We have, however, found that the hydrolysis of the compounds represented as having the general structure I with sodium ethoxide in ethanol occurs at different positions, depending on the nature of the group, G, intervening between ethoxycarbonyl and ethoxycarbonylamino groups.

$$EtO_2CNH\text{-}G\text{-}CO_2Et$$

(I)

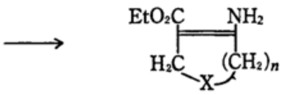
When G was a group containing a double bond between the two functional groups, as in the compound III, the ethoxycarbonyl group attached to the amino group was selectively hydrolysed to give IV, in which the ethoxycarbonyl group attached to the carbon atom remained unchanged.



(II) (III)

IIa_1: X=CH_2, $n=1$
IIa_2: X=CH_2, $n=2$
IIb_1: X=S, $n=1$
IIb_2: X=S, $n=2$

$IIIa_1$: X=CH_2, $n=1$
$IIIa_2$: X=CH_2, $n=2$
$IIIb_1$: X=S, $n=1$
$IIIb_2$: X=S, $n=2$



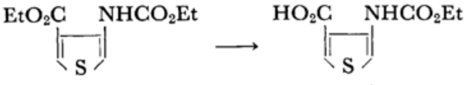
(IV)

IVa_1: X=CH_2, $n=1$
IVa_2: X=CH_2, $n=2$
IVb_1: X=S, $n=1$
IVb_2: X=S, $n=2$

Although β-amino-α, β-unsaturated carboxylic esters, such as IVa_1 and IVa_2, were also obtained from the corresponding β-ketoester II and ammonia according to the method of Prelog and Szpilfogel,[1] a similar reaction of 3-ethoxycarbonyl-4-ketotetrahydrothiophene IIb_1 resulted in the complete recovery of the starting material. However, IVb_1 was obtained in only a moderate yield by the alkaline hydrolysis of 3-ethoxycarbonyl-4-ethoxycarbonylamino-2,5-dihydrothiophene $IIIb_1$.

On the contrary, when G was a group containing a single bond between the two functional groups, as in the compound V[2] or VI,[2] the ethoxycarbonyl group attached to the carbon atom was selectively hydrolysed with sodium ethoxide in ethanol to give VII or VIII, in which the ethoxycarbonyl group attached to the amino group remained unattacked. The acid hydrolysis of V and VI, as usual, gave VII and VIII, respectively.

(V) (VII)



(VI) (VIII)

The starting materials, β-ethoxycarbonylamino-α, β-unsaturated carboxylic esters, III, were prepared in good yields by refluxing the corresponding β-ketoester, II, and urethane in the presence of *p*-toluenesulfonic acid.

[*1] Studies on the Syntheses of Heterocyclic Compounds. Part VII. Part VI: M. Fujimori, E. Haruki and E. Imoto, This Bulletin, in press.

[1] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1946).

Table 1. The preparation of III

Compound	Mp, °C	Yield, %	Formula		Analysis		
					C	H	N
IIIa$_1$	50—52	75	$C_{11}H_{17}O_4N$	Calcd Found	58.13 58.28	7.54 7.30	6.16 6.26
IIIa$_2$	46.5—48.5	81	$C_{12}H_{19}O_4N$	Calcd Found	59.73 59.71	7.94 8.18	5.81 6.02
IIIb$_1$	70—71.5	90	$C_{10}H_{15}O_4NS$	Calcd Found	48.97 48.87	6.17 6.17	5.71 5.80
IIIb$_2$	32—33	76	$C_{11}H_{17}O_4NS$	Calcd Found	50.96 51.03	6.61 6.59	5.40 5.24

Table 2. Selective hydrolysis of III, V and VI

Compound	Mp (Bp, °C/mmHg)	Recryst. solvent	Yield, %	Formula		Analysis		
						C	H	N
IVa$_1$	58—60	Petroleum*1 ether	77	$C_8H_{13}O_2N$	Calcd Found	61.91 62.03	8.44 8.21	9.03 8.81
IVa$_2$	71—73	Petroleum ether	62	$C_9H_{15}O_2N$	Calcd Found	63.88 64.01	8.94 9.01	8.28 8.01
IVb$_1$	80—82	EtOH-H_2O	58	$C_7H_{11}O_2NS$	Calcd Found	48.55 48.23	6.40 6.40	8.09 7.74
IVb$_2$	(108—109/0.2)		65	$C_8H_{13}O_2NS$	Calcd Found	51.33 51.58	7.00 7.30	7.48 6.89*2
VII	124—125	Benzene	70	$C_9H_5O_4N$	Calcd Found	53.72 53.78	7.51 7.65	6.97 6.70
VIII	152—154	Benzene	73	$C_8H_9O_4NS$	Calcd Found	44.66 44.80	4.22 4.10	6.51 6.47

*1 Bp 40—60°C.

*2 Partly decomposed into 3-ethoxycarbonyltetrahydro-1,4-thiapyrone and ammonia.

Experimental[3]

β-Ketoester, II. Several β-ketoesters, 2-ethoxycarbonylcyclopentanone IIa$_2$,[4] 2-ethoxycabonylcyclohexanone (IIa$_2$),[5] 3-ethoxycabonyl-4-ketotetrahydrotiophene (IIb$_1$),[6] and 3-ethoxycarbonyltetrahydro-1,4-thiapyrone (IIb$_2$),[7] were sythesized by the methods given in the literature.

General Procedure for the Preparation of III. A mixture of 0.6 mol of II, 0.7 mol of urethane, and 1 g of *p*-toluenesulfonic acid dissolved in 100 m*l* of benzene was refluxed for 15 hr in a Soxhlet apparatus containing sodium sulfate in a thimble. The reaction mixture was then washed thoroughly with water to remove the *p*-toluenesulfonic acid and the excess urethane. After the evaporation of the solvent, a crude product was purified by chromatography using a column packed with alumina, plus chloroform - petroleum ether as an eluent, or by recrystallization from methanol-water (9: 1). The yield and properties for each compound are given in Table 1.

General Procedure for the Deethoxycarbonylation of III. A solution of 0.25 mol of sodium metal in 100 m*l* of ethanol containing 0.05 mol of III was refluxed for 17 hr. The cooled reaction mixture was diluted with water and then extracted with ether, after which the ethereal solution was treated with active charcoal and dried over sodium sulfate overnight. The solvent was removed, and the residue was recrystallized from an appropriate solvent or distilled under reduced pressure to give IV. The yield, properties, and recrystallizing solvent for IV are given in Table 2.

Hydrolysis of V or VI. After the treatment of 6 mmol of V or VI with 0.5 g of sodium metal in 50 m*l* of ethanol in the manner described above, the cooled reaction mixture was diluted with water, acidified with hydrochloric acid, and extracted with ether. The ethereal solution was then worked up in the usual manner and recrystallized from benzene. The products, VII and VIII, were obtained by refluxing V and VI respectively with 6 N hydrochloric acid for 8 hr. The analytical data and physical constants of VII and VIII are summarized in Table 2.

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2) The preparation of V and VI will be described in another paper.

3) All melting points are uncorrected.

4) P. S. Pinkney, " Organic Syntheses, " Coll. Vol. II, p. 116 (1943).

5) H. R. Snyder, L. A. Brooks and S. H. Shapiro, *ibid.*, Coll. Vol. II, p. 531 (1943).

6) G. B. Brown, B. R. Baker, S. Bernstein and S. R. Safir, *J. Org. Chem.*, **12**, 155 (1947).

7) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **70**, 1813 (1948).