α,β-BUTENOLIDES

V.* REACTION OF α,β-DIBROMO-γ-(α'-CARBETHOXYACETONYL)-$\Delta^{\alpha,\beta}$-BUTENOLIDE WITH AMINES

I. K. Kalnin' and É. Yu. Gudrinietse

UDC 547.722.3.4.6'852

α,β-Dibromo-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolide (I) reacts with amines in diethyl ether solution to give α-bromo-β-amino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolides (II). Compounds II are converted to α-bromo-β-amino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-crotonolactams (IV) on reaction with amines. The corresponding arylhydrazones (VI and VII) are obtained by the reaction of I and II with p-nitro- and 2,4-dinitrophenylhydrazines. Compound I reacts with phenylhydrazine to give furopyridazine VIII.

Despite the fact that the $\Delta^{\alpha,\beta}$-butenolide ring is encountered in many biologically active compounds [2-5] and in natural substances [6,7], the chemical properties of $\Delta^{\alpha,\beta}$-butenolide derivatives have received extremely little study. The reactions of α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolide derivatives with amines arouses interest, for products with different structures are formed in these reactions [8-12]. The reactions of α,β-dihalo-$\Delta^{\alpha,\beta}$-butenolides with amines can proceed in the following directions: opening of the butenolide ring to form the corresponding amide, nucleophilic substitution of the halogen by an amine residue, and addition of the amine to the C=C bond of the $\Delta^{\alpha,\beta}$-butenolide ring [13].

In the present research we have studied the reaction of α,β-dibromo-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolide (I) [14] with amines. In addition to the reactions noted above, I can react with an acetoacetic ester residue [15].

Replacement of the bromine by an amine residue to give α-bromo-β-amino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolides (IIa-*l*) (see Table 1) occurs with a twofold quantity of primary and secondary amines in diethyl ether at 5-10°C. In contrast to [8, 11, 12], substitution of bromine occurs in the β position, which we explain by the minimum electron density on the corresponding carbon atom [16]. The acetoacetic ester residue does not participate in these reactions, as confirmed by the positive color reaction with ferric chloride [17].

The absorption bands of the carbonyl group of the $\Delta^{\alpha,\beta}$-butenolide ring are observed at 1720-1735 cm^{-1} in the IR spectra of crystalline II (see Table 2). The decrease in the carbonyl frequency is explained by the presence of an α,β-unsaturated β-amino ketone grouping in the molecules of II [18, 19]. The decrease in the carbonyl frequency is apparently also caused by intermolecular hydrogen bonds, for an increase in it is observed in the IR spectra of dioxane solutions of II (see Table 2). The IR spectra of II contain an intense absorption band at 1600-1645 cm^{-1}, which probably arises as a consequence of overlapping of the absorption bands of the C=C bonds of the $\Delta^{\alpha,\beta}$-butenolide ring and the acetoacetic ester residue. The inflection at 1739-1746 cm^{-1} in the IR spectra of IIa-e, IIi, and II*l* can be assigned to the ester carbonyl group. This absorption is also observed in the IR spectra of dioxane solutions (see Table 2).

$\Delta^{\alpha,\beta}$-Butenolides II are converted to the corresponding $\Delta^{\alpha,\beta}$-crotonolactams (IV) (see Table 1) in dioxane solution at room temperature on reaction with a twofold quantity of primary amines. We have previously [1] proposed a conjectural mechanism for opening of the $\Delta^{\alpha,\beta}$-butenolide ring in reactions with

---

*See [1] for communication IV.

Riga Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 867-871, July, 1972. Original article submitted June 22, 1971.

TABLE 1. $\Delta^{\alpha,\beta}$-Butenolides (IIa-*l*) and $\Delta^{\alpha,\beta}$-Crotonolactams (IVa-e)

Comp.	NRR′	R″	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
					Br	N	Br	N	
IIa	$NHCH_3$	—	107—109[a]	$C_{11}H_{14}BrNO_5$	25,2	4,6	25,3	4,4	48
IIb	NHC_2H_5	—	104—106[b]	$C_{12}H_{16}BrNO_5$	24,1	4,3	24,0	4,2	53
IIc	NHC_3H_7-*n*	—	103—105[b]	$C_{13}H_{18}BrNO_5$	23,1	4,0	23,0	4,0	53
IId	NHC_3H_7-*i*	—	123—124[b]	$C_{13}H_{18}BrNO_5$	23,1	3,9	23,0	4,0	75
IIe	NHC_4H_9-*n*	—	108—109[a]	$C_{14}H_{20}BrNO_5$	22,2	4,0	22,1	3,9	57
IIf	$NHCH_2CH_2OH$	—	97—98[b]	$C_{12}H_{16}BrNO_5$	22,9	3,9	23,0	4,1	57
IIg	$NHCH_2C_6H_5$	—	133—134[b]	$C_{16}H_{16}BrNO_5$	20,9	3,7	20,9	3,7	54
IIh	NHC_6H_5	—	122—123[a]	$C_{17}H_{18}BrNO_5$	21,2	3,7	20,2	3,5	58
IIi	$N(CH_3)_2$	—	118—119[a]	$C_{12}H_{16}BrNO_5$	23,9	4,2	23,0	4,3	78
IIj	$N(C_2H_5)_2$	—	88—89[a]	$C_{14}H_{20}BrNO_5$	22,2	4,0	22,1	3,9	54
IIk	$N(CH_2)_5$	—	99—100[b]	$C_{15}H_{20}BrNO_5$	20,8	3,7	20,8	3,6	72
II*l*	$N(CH_2)_4O$	—	131—132[c]	$C_{14}H_{18}BrNO_6$	21,4	3,8	22,2	3,9	77
IVa	NHC_3H_7-*i*	CH_3	129—131[a]	$C_{14}H_{21}BrN_2O_4$	22,2	7,5	22,2	7,8	57
IVb	NHC_3H_7-*i*	C_3H_7-*i*	128—129[b]	$C_{16}H_{25}BrN_2O_4$	20,2	7,1	20,6	7,2	61
IVc	NHC_4H_9-*n*	CH_3	128—130[d]	$C_{15}H_{23}BrN_2O_4$	21,4	7,4	21,3	7,5	53
IVd	$N(CH_2)_5$	CH_3	142—143[c]	$C_{16}H_{23}BrN_2O_4$	20,7	7,3	20,7	7,2	55
IVe	$N(CH_2)_5$	C_4H_9-*n*	98—99[e]	$C_{19}H_{29}BrN_2O_4$	18,4	6,5	18,9	6,5	50

---

[a] From benzene. [b] From acetone–hexane (1 : 2). [c] From ethanol. [d] From acetone–hexane (1 : 3). [e] From carbon tetrachloride–hexane (1 : 2).

TABLE 2. IR Spectra of $\Delta^{\alpha,\beta}$-Butenolides (IIa-*l*) and $\Delta^{\alpha,\beta}$-Crotonolactams (IVa-e)

Comp.	Solids			Dioxane solutions	
	1800—1600 cm^{-1}	δ_{NH}, cm^{-1}	ν_{NH}, cm^{-1}	1800—1600 cm	δ_{NH}, cm^{-1}
IIa	1745, 1730, 1632				
IIb	1743,* 1722, 1612	1562	3277		
IIc	1746,* 1720, 1643,* 1617	1588	3268		
IId	1743,* 1723, 1608	1566	3265	1772, 1732, 1636	1550
IIe	1743,* 1717, 1644,* 1613	1566	3245	1770, 1732, 1640	1550
IIf	1727, 1630	1553	3270		
IIg	1720, 1619	1557	3257		
IIh	1733, 1638,* 1619	1583	3178		
IIi	1739, 1734,* 1623			1781, 1742, 1638	
IIj	1720, 1636,* 1595			1783, 1745, 1617	
IIk	1727, 1638,* 1608			1767, 1725, 1617	
II*l*	1745, 1723, 1622			1770, 1723, 1621	
IVa	1739, 1633, 1592	1541	3316, 3059	1749, 1635, 1594	1521
IVb	1719, 1625, 1590	1545	3233, 3050		
IVc	1723, 1632, 1608	1539	3314, 3072		
IVd	1718, 1642, 1595				
IVe	1720, 1644, 1603				

---

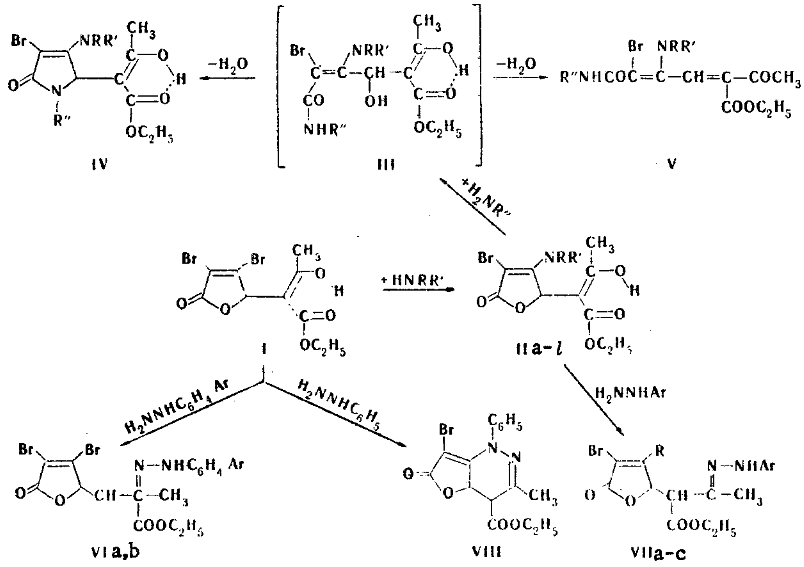
*Shoulder.

TABLE 3. Arylhydrazones VIa,b and VIIa-c

Comp.	R	Ar	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
					Br	N	Br	N	
VI a		$NO_2C_6N_4$-*p*	126—128[a]	$C_{16}H_{15}Br_2N_3O_6$	31,6	8,5	31,7	8,3	53
VI b		2,4-$(NO_2)_2C_6H_3$	147—148[b]	$C_{16}H_{14}Br_2N_4O_8$	29,0	10,2	29,0	10,2	79
VII a	$NHCH_3$	C_6H_5	129—130[b]	$C_{17}H_{20}BrN_3O_4$	19,5	10,4	19,5	10,2	68
VII b	NHC_3H_7-*i*	C_6H_5	131—132[b]	$C_{19}H_{24}BrN_3O_4$	18,6	9,7	18,3	9,5	93
VII c	$N(CH_2)_5$	C_6H_5	135—136[c]	$C_{21}H_{26}BrN_3O_4$	17,2	9,2	17,2	9,1	81

---

[a] From chloroform–carbon tetrachloride–hexane (2 : 1 : 1). [b] From ethanol. [c] From acetone–hexane (1 : 2).



amines. Compound III is formed as an intermediate product and can be converted to IV or V by splitting out of a water molecule. The compounds obtained do not add bromine but give a positive color reaction with ferric chloride, thus confirming structure IV.

The absorption bands of the carbonyl groups of the $\Delta^{\alpha,\beta}$-crotonolactam at 1718-1740 cm^{-1}, of the chelate of the acetoacetic ester residue at 1625-1645 cm^{-1}, of the C=C bonds of the $\Delta^{\alpha,\beta}$-crotonolactam at 1572-1616 cm^{-1}, and of the stretching and deformation vibrations of the N−H bonds at 3233-3316 cm^{-1} and 1539-1545 cm^{-1} are observed in the IR spectra of crystalline IV (see Table 2). The IR spectrum of IVa in dioxane is similar to the spectrum of the crystalline substance.

The corresponding arylhydrazones (VI and VII) (see Table 3) are obtained in the reaction of I and II with p-nitro- and 2,4-dinitrophenylhydrazines in ethanol at room temperature. Splitting out of hydrogen bromide with closing of the tetrahydropyridazine ring (VIII) also occurs in the reaction of I with phenylhydrazine. Compounds II do not react with phenylhydrazine to give the corresponding tetrahydropyridazine derivatives, which indicates the absence of a bromine in the β position. This reaction also confirms our assumption that the bromine in the β position is replaced in the reactions of I with amines.

The absorption bands of the carbonyl groups of the $\Delta^{\alpha,\beta}$-butenolide ring are observed at 1736-1769 cm^{-1} in the IR spectra of VI-VIII (see Table 4). The absorption bands of the ester carbonyl group appear at 1714-1736 cm^{-1}, those of the C=C bonds of the $\Delta^{\alpha,\beta}$-butenolide ring appear at 1620-1641 cm^{-1}, and those of the C=N bonds appear at 1594-1609 cm^{-1}. The IR spectra of VI and VII also contain deformation and stretching vibrations of the N−H bonds at 1517-1561 cm^{-1} and 3269-3370 cm^{-1}, which are absent in the IR spectrum of VIII.

EXPERIMENTAL

α-Bromo-β-amino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolides (IIa-*l*). A 0.01-mole sample of amine was added slowly with constant stirring at 5-10° to a solution of 1.9 g (5 mmole) of α,β-dibromo-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolide (I) [14] in 250 ml of diethyl ether, and stirring was continued for

TABLE 4. IR Spectra of Arylhydrazones VIa,b and VIIa-c

Comp.	$\nu_{C=O}$, cm^{-1}		$\nu_{C=C}$, cm^{-1}	$\nu_{C=N}$, cm^{-1}	ν_{NO_2}, cm^{-1}	δ_{NH}, cm^{-1}	ν_{NH}, cm^{-1}
VIa	1763	1725	1641	1596	1535	1556	3379
VIb	1764	1738	1620	1594	1541, 1509	1561	3320
VIIa	1741	1732	1633	1609	—	1522	3365
VIIb	1739	1714	1625	1607	—	1556, 1517	3316, 3269
VIIc	1736	1716	1620	1598	—	1561*	3340

---

*Shoulder.

15 min. The precipitated amine hydrobromide was separated by filtration or washing with water, the ether was removed by distillation, and the residue was recrystallized (see Table 1).

α-Bromo-β-amino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-crotonolactams (IVa-e). A 4-mmole sample of amine was added to a solution of 1.1 g (3 mmole) of butenolide II in 30 ml of dioxane, and the mixture was held at room temperature for 24 h. The dioxane was removed by vacuum distillation. The resinous product hardened on treatment with diethyl ether and was removed by filtration and recrystallized (see Table 1). The compound is partially soluble in diethyl ether, and additional amounts of IV were obtained after removal of the ether by distillation and were recrystallized.

α,β-Dibromo-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolide Nitrophenylhydrazones (VIa, b). A solution of 3 mmole of nitrophenylhydrazine in 30 ml of glacial acetic acid was added to a solution of 1.1 g (3 mmole) of butenolide I in 10 ml of glacial acetic acid, and the mixture was held at room temperature for 30 min. The product was precipitated by the addition of water and recrystallized (see Table 3).

α-Bromo-β-alkylamino-γ-(α'-carbethoxyacetonyl)-$\Delta^{\alpha,\beta}$-butenolide Phenylhydrazones (VIIa-c). A 0.3-ml (3 mmole) sample of phenylhydrazine was added to a solution of 1.1 g (3 mmole) of butenolide II in 15 ml of ethanol, and the mixture was allowed to stand for 12-15 h. The product was precipitated by the addition of water and recrystallized (see Table 3).

1-Phenyl-3-methyl-4-carbethoxy-6-oxo-7-bromo-1,4,4a,6-tetrahydrofuro[3,2-c]pyridazine (VIII). A solution of 0.3 ml (3 mmole) of phenylhydrazine in 20 ml of ethanol was added to a solution of 1.1 g (3 mmole) of butenolide I in 30 ml of ethanol. Compound VIII began to precipitate after 2-3 h. The mixture was allowed to stand at 0-5° for 12 h, and the precipitate was removed by filtration and recrystallized from ethanol to give 60% of a product with mp 116-117°. IR spectrum (cm^{-1}): 1769 and 1731 ($\nu_{C=O}$), 1618 ($\nu_{C=C}$), and 1583 ($\nu_{C=N}$). Found: Br 20.9; N 7.5%. $C_{16}H_{15}BrN_2O_4$. Calculated: Br 21.1; N 7.4%.

LITERATURE CITED

1. I. K. Kalnin', É. Yu. Gudrinietse, and É. É. Liepin'sh, Izv. Akad. Nauk Latv. SSR, Ser. Khim., 103 (1971).
2. A. R. Pinder, Chem. Rev., 64, 551 (1964).
3. D. M. Green, A. G. Long, P. J. May, and A. F. Turner, J. Chem. Soc., 766 (1964).
4. G. Bach, J. Capitaine, and C. R. Engel, Can. J. Chem., 46, 733 (1968).
5. A. Lardon, K. Stöckel, and T. Reichstein, Helv. Chim. Acta, 52, 1940 (1969).
6. R. M. Mariarty, C. R. Romain, I. L. Karle, and J. Karle, J. Am. Chem. Soc., 87, 3251 (1965).
7. M. H. Benn and L. J. Yelland, Can. J. Chem., 46, 729 (1968).
8. E. Vinogradova and M. Shemyakin, Zh. Obshch. Khim., 16, 709 (1946).
9. R. E. Lutz, C. T. Clark, and J. P. Feifer, J. Org. Chem., 25, 346 (1960).
10. R. Lukeš and Z. Linhartova, Coll. Czech. Chem. Comm., 25, 502 (1960).
11. M. Semonský, A. Černy, B. Kakač, and V. Šubert, Coll. Czech. Chem. Comm., 28, 3278 (1963).
12. M. Semonský, A. Černy, R. Kotvá, V. Zikán, and B. Kakač, Coll. Czech. Chem. Comm., 33, 2698 (1968).
13. J. B. Jones and J. M. Young, Can. J. Chem., 44, 1059 (1966).
14. É. Yu. Gudrinietse, I. K. Kalnin', and Ya. Ya. Paulin'sh. Izv. Akad. Nauk Latv. SSR, Ser. Khim., 493 (1970).
15. O. Kuckert, Ber., 18, 619 (1885).
16. H. H. Wasserman and F. M. Precopio, J. Am. Chem. Soc., 76, 1242 (1954).
17. S. T. Ioffe, K. V. Vatsuro, and M. I. Kabachnik, Izv. Akad. Nauk SSSR, Ser. Khim., 2024 (1968).
18. H. Böhne and G. Willinger, Arch. Pharm., 302, 974 (1969).
19. L. Bellamy, Infra-Red Spectra of Complex Molecules, Methuen (1958).