NITROGEN AND SULFUR HETEROCYCLES.

45.* DUAL REACTIVITY OF 1,2-DIOXO-3a-ALKYL-7-CHLOROIMIDAZOLIDINO[3,2-f]-PYRIDO[2,3-b]-1,4-THIAZINES

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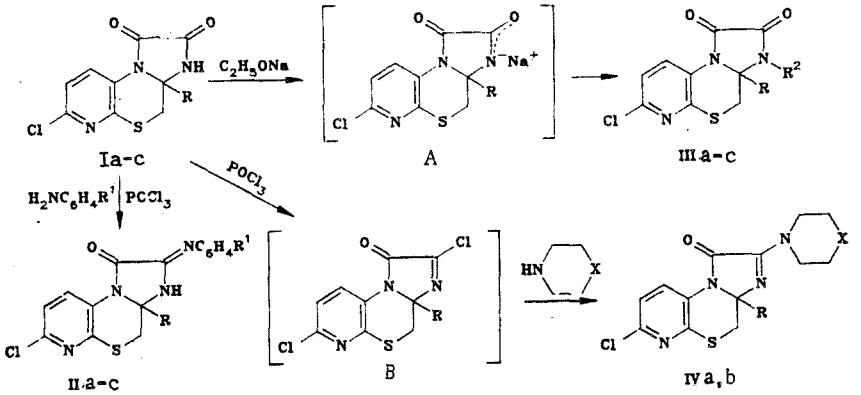
1,2-Dioxo-3a-alkyl-7-chloroimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines react with o- and p-nitroanilines, alkyl and acyl halides, and heterocyclic amines to give $C_{(2)}$- and $N_{(3)}$-substituted 3a-alkyl-7-chloroimidazolidino[3,2-f]pyridol[2,3-b]-1,4-thiazines.

We have previously devised methods for the synthesis of derivatives of the novel heterocyclic system imidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine, by reacting oxazolidino[3,2-f]-pyrido[2,3-b]-1,4-thiazines with ammonium acetate, or N-(pyrid-3-yl)oxamate esters with ammonia in glacial acetic acid [1]. While extending these investigations in order to discover novel biologically active compounds, some chemical reactions of 1,2-dioxoimidazolidino[3,2-f]-pyrido[2,3-b]-1,4-thiazines (Ia-c) have been examined.

We here show that these imidazolidino-compounds (Ia-c), being cyclic lactams, are able to react to give products derived from both the lactam and lactim forms, depending on the reaction conditions. For instance, reaction of (Ia-c) with o- and p-nitroanilines in the presence of phosphoryl chloride under the conditions described in [2] gives the corresponding nitrophenyliminoimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines (IIa-c) (Table 1), which are derived from the lactam form. Alkylation of (Ia-c) with alkyl halides, and acylation with acyl halides also affords lactam derivatives, but substituted at the nitrogen in the 3-position of the imidazolidine ring. Thus, reaction of (Ib) with sodium ethoxide followed by treatment of the intermediate enolate A with methyl iodide gives 3-N-methylimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine (IIIa), while treatment of the enolate A with 3-bromo- or 3-chloropropionyl chloride in ether gives the 3-halopropionyl derivatives (IIIb) and (IIIc).



Ia-c; A; IIIa-c; IIa-c; B; IVa,b

Ia, IIa,b R=CH_3; Ib IIc IIIa-c, IVb R=C_2H_5; Ic IVa R=C_3H_7; IIa,c R^1=*p*-NO_2; b R^1=*o*-NO_2; IIIa R^2=CH_3; b R^2=$COCH_2CH_2Cl$; c R^2=$COCH_2CH_2Br$; IVa X=N—CH_3; b X=O

Derivatives of the lactim form, specifically the 2-amino-compounds (IVa, b) (Table 1), were obtained by reaction of (Ia, b) with phosphoryl chloride in the presence of dimethylaniline, followed by reaction of the resulting 2-chloro-compounds B (without isolation in the

*For Communication 44, see [1].

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TABLE 1. Properties of (IIa-c), (IIIa-c), and (IVa, b)

Compound	T_{mp}, °C*	R_f	Found, %					Empirical formula	Calculated, %					Yield, ** %
			C	H	Cl	N	S(Br)		C	H	Cl	N	S(Br)	
IIa	276—278	—	49,6	3,5	9,5	18,1	8,2	$C_{16}H_{12}ClN_5O_3S$	49,3	3,1	9,1	18,0	8,2	80
IIb	262—264	—	49,1	3,1	9,6	18,2	8,1	$C_{16}H_{12}ClN_5O_3S$	49,3	3,1	9,1	18,0	8,2	93
IIc	255—257	—	50,2	3,4	8,9	17,5	7,6	$C_{17}H_{14}ClN_5O_3S$	50,5	3,5	8,8	17,3	7,9	85
IIIa	260—262	0,7	48,3	4,0	12,1	13,9	10,7	$C_{12}H_{12}ClN_3O_2S$	48,4	4,1	11,9	14,1	10,8	72
IIIb	208—210	0,95	45,2	3,6	18,7	11,3	8,6	$C_{14}H_{13}Cl_2N_3O_3S$	44,9	3,5	18,9	11,2	8,6	57
IIIc	196—198	0,95	40,4	3,1	8,3	10,3	7,3 (19,1)	$C_{14}H_{13}BrClN_3O_3S$	40,2	3,1	8,5	10,0	7,7 (19,1)	52
IVa	99—101	0,48	53,7	5,7	9,4	18,3	8,4	$C_{17}H_{22}ClN_5OS$	53,7	5,8	9,3	18,4	8,4	40
IVb	124—126	0,5	51,4	4,7	9,9	15,8	9,3	$C_{15}H_{17}ClN_4O_2S$	51,1	4,8	10,1	15,9	9,1	44

*Compounds (IIa-c) were recrystallized from a mixture of DMF and water (1:2), (IIIa-c) and (IVa, b) from ethanol.
**The yields given for (IIIa-c) and (IVa, b) are calculated on the starting materials (Ia-c).

TABLE 2. Spectral Characteristics of (II-IV)

Compound	ν, cm^{-1}			λ_{max}, nm (log ε)	m/z (I_{rel}, %)*
	NH	C=N	C=O (amide)		
IIa	3300	1645	1700	208 (3,96), 255 (3,94), 240 sh. (3,69), 335 (4,10)	389 (71), 374 (64), 359 (40), 343 (16), 199 (26), 183 (100), 155 (36)
IIb	3300	1645	1720	—	—
IIc	3300	1640	1700	—	—
IIIa	—	—	1720, 1740	208 (3,93), 244 (4,11), 312 (3,77)	297 (100), 282 (61), 268 (95), 240 (45,5), 199 (60), 183 (29), 166 (9), 165 (11), 103 (11), 70 (43), 42 (19)
IIIb	—	—	1720, 1760	212 (3,72), 242 (3,85), 308 (3,53)	373 (16), 337 (23), 283 (45), 254 (28), 226 (8), 212 (48), 183 (13), 98 (12), 91 (10), 55 (100)
IIIc	—	—	1720, 1760	208 (4,09), 244 (4,20), 310 (3,87)	417 (7), 337 (27), 283 (39), 254 (25), 212 (34), 183 (13), 135 (9), 109 (10), 107 (12), 55 (100)
IVa	—	1610	1700	208 (4,16), 246 (4,15), 284 (4,08)	379 (3), 336 (4), 183 (5), 99 (6), 98 (6), 84 (72), 71 (100), 59 (27), 44 (32), 43 (24)
IVb	—	1610	1700	208 (4,06), 246 (4,04), 284 (3,96)	352 (44), 337 (30), 323 (100), 295 (5), 279 (4), 200 (5), 198 (9), 185 (17), 183 (48), 85 (12)

*The mass numbers (for isotopes ^{35}Cl and ^{79}Br) and the intensities of the molecular ion peaks, and of ions with $I_{rel} \geq 3\%$, are shown.

pure state) with morpholine or N-methylpiperazine, respectively. It is clear that under these conditions the reaction involves transfer of the reaction center, although the possibility of the involvement of the lactim forms of (Ib, c) cannot be excluded. We have reported [1] that the reaction of nucleophiles (ammonia, primary aliphatic and secondary cyclic amines) with oxazolidino[3,2-f]pyrido[2,3-b]- and oxazolidino[3,2-f]pyrimido[4,5-b]-1,4-thiazines results in fission of the oxazolidine ring only, or of the oxazolidine and thiazine rings simultaneously at bonds $C_{(2)}$-O and $N_{(10)}$-$C_{(3a)}$. Unlike these compounds, in their imidazolidine analogs the imidazolidine and thiazine rings remain intact, as shown by physicochemical methods (Tables 2-4).

The IR spectra of (II-IV) show strong absorption stretching vibrations of the carbonyl group in the imidazolidine ring $C_{(1)}$=O at 1700-1720 cm^{-1}, together with [in (IIIa-c)] $C_{(2)}$=O at 1749-1760 cm^{-1}. The IR spectra of (IIa-c) contain bands for the stretching vibrations of the NH groups at 3300 cm^{-1}, which are absent from the spectra of (III) and (IV). In the spectra of (II) and (IV), absorption is present for stretching vibrations of the C=N group at 1640-1645 cm^{-1} for the exocyclic C=N double bond (IIa-c) and at 1610 cm^{-1} for the endocyclic C=N bond (IVa, c). The PMR spectral data confirm the tricyclic structure of (II-IV).

In the case of (IIa) and (IIIa-c), the PMR spectra contain a quadruplet for the 4-H diastereotopic methylene protons at 3.3-4.2 ppm, $^2J_{4\text{-}CH_2} \sim 12.3$-12.8 Hz [3]. It must be pointed out that atom $C_{(3a)}$ remains asymmetrical when the ring is opened at the bond $C_{(2)}$—$N_{(3)}$, so that the signals for the protons at the $C_{(4)}$ atom in this instance will appear as a quartet. These signals will appear as singlets only when both the imidazolidine and thiazine rings are opened simultaneously. More reliable proof of the maintenance of the tricyclic structure in these compounds (II and III) is provided by the considerable differences in the chemical shifts of the 8-H pyridine ring protons (7.18-7.41 ppm) and the 9-H protons (8.37-8.53 ppm). The signal for the 9-H proton occurs at much lower field than that for the 8-H proton ($\Delta\delta \sim 0.95$-1.35 ppm), owing to the influence of the magnetic anisotropy of the $C_{(1)}$=O group, which is spatially adjacent to the 9-H proton and is firmly fixed on account of the ring. A marked difference in the values of the chemical shifts of these protons has been observed previously by us in the case of oxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines and their 4-chloro derivatives [4].

The mass spectra of (II-IV) show molecular ion peaks $M^{\pm}$ with m/z values of 389* (IIa), 297 (IIIa), 373 (IIIb), 417 (IIIc), 379 (IVa), and 352 (IVb), which are in agreement with the suggested structures. That the thiazine ring is retained in (II-IV) is shown by the presence in all the spectra of an intense ion peak with m/z 183, which is characteristic of the breakdown of oxazolidino[3,2-f]- and imidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines [1, 3], and is probably the pyrido[2,3-b]-1,4-thiazine cation Φ_1.

*Here and subsequently, the mass numbers given in the text are those for the isotopes ^{35}Cl and ^{79}Br.

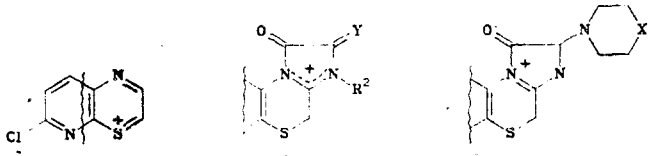
TABLE 3. PMR Spectral Data* for (IIa) and (IIIa-c), δ, ppm, J, Hz

Compound**	4-H	C_2H_5	$N_{(3)}$—R	8-H	9-H	4-H
IIa	3,34, 3,55	—	10.52	7,41	8,37	12.6
IIIa	3,64, 3,76	0,55 (CH_3), 2,09 (CH_2)	3,01	7,39	8,41	12,3
IIIb	3,40, 4,16	0,69 (CH_3), 2.40—2,80 (CH_2)	3,59, 3,88	7,18	8,50	12,8
IIIc	3,40, 4,16	0,70 (CH_3), 2,30—2,80 (CH_2)	3,71 (4H)	7,18	8,53	12,8

*In DMSO-D_6 for (IIa) and (IIIa), and in $CDCl_3$ for (IIIb) and (IIIc).

**For (IIa), the protons of the para-substituted benzene ring are seen in the spectrum as a symmetrical multiplet (4H) centered at 8.27 ppm, and for (IIIa-c) the diastereotopic methylene protons of the ethyl group are present as a complex multiplet.

A feature of the breakdown of these compounds, as in the case of the unsubstituted imidazolidino-compounds (Ia, b) [1] is the facile elimination of the substituent R from M^+ (or from the ion $[M - (R^2 - H)]^+$ in the case of (IIIb, c)). Breakdown of the imidazolidine ring takes place to a lesser extent, as shown in Table 4. The only exceptions are (IIIb) and (IIIc), in which the N-β-halopropionyl group may modify the breakdown sequence. The general nature of the fragmentation of (II-IV) and the unsubstituted imidazolidino-compounds (Ia, b) is evidence of the persistence therein of the imidazolidine moiety. The ease of elimination of the substituent R in these compounds appears to be due to stabilization of the charge in the imidazole ring of the $[M - R]^+$ ions formed (Φ_2 and Φ_3).



Φ_1 Φ_2 IIb, IIIa-c Φ_3 IVa,b

R^2=H, CH_3; X=N—CH_3, O; Y=O, NAr

In the case of the C-substituted compounds (IVa, b), the value of the ratio I_{Φ_2}/I_{M^+} is twice or more greater than the values for (II) and (III) (Table 4), perhaps as a result of the higher stability of the ion Φ_3, which has an oxoimidazolidine ring.

Consequently, the main difference between the breakdown of imidazolidino[3,2-f] and oxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines, namely the greater stability of the imidazolidine ring to electron impact as compared with the oxazolidine ring [1], is also present in their C- and N-derivatives. These findings are in good agreement with the experimentally observed fact that the oxazolidinothiazine system is cleaved by nucleophiles, whereas the imidazolidinothiazine system is stable under these conditions. Introduction of substituents into the imidazolidine ring introduces a further mode of breakdown. For example, the introduction of a β-halopropionyl substituent into (IIIb, c) is responsible for the appearance of peaks for the ions $[M - HHal]^+$ (337), $[M = COCHCH_2Hal]^+$ (283), $\overset{+}{C}OCH_2CH_2Hal$ (91, IIIb, 135 IIIc); $\overset{+}{C}H_2CH_2Hal$ (63 IIIb, 197 IIIc), $\overset{+}{C}OCH{=}CH_2$ (55). The presence of the methylpiperazine ring in (IVa) results in the appearance in the spectrum of strong peaks for ions with m/z 99, 98, 83,

TABLE 4. Ratios of Intensities of M^+ Peaks and Some Characteristic Ions in the Mass Spectra of (I-V)*

Compound	I_{Φ_2}/I_{M^+}	$I_{[M-COCYNR]^+}/I_{M^+}$	I_{Φ_1}/I_{M^+}	Compound	I_{Φ_2}/I_{M^+}	$I_{[M-COCYNR]^+}/I_{M^+}$	I_{Φ_1}/I_{M^+}
Ib	0,4	0,2	0,5	IIIc	0,6	0,9	0,3
IIa	0,8	<0,1	1,4	IVa	2,0	0,3	2,0
IIIa	0,9	0,4	0,3	IVb	2,1	<0,1	1,0
IIIb	0,6	1,0	0,3	V	0	2,0	1,5

*Compound (V) is 3a-ethyloxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine [3].

and 71, due to its breakdown. The spectrum of (IIa) show peaks for the ions $[M - NO]^+$ (359) and $[M - NO_2]^+$(343), formed by elimination of the nitroso- and nitro-groups from the nitrophenylimino moiety.

EXPERIMENTAL

IR spectra were obtained as suspensions in Vaseline oil on a Perkin-Elmer 599 instrument, UV spectra (in alcohol) on a Perkin-Elmer 575 spectrophotometer, and NMR spectra on a Varian XL-200, internal standard TMS. Electron impact mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct introduction of the sample into the ion source. The purity of the compounds was confirmed by thin layer chromatography on Silufol UV-254 plates in the system benzene–ethyl acetate (1:1). The chromatograms were visualized in UV.

1-Oxo-2-(nitrophenylimino)-3a-alkyl-7-chloroimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines (IIa-c) were obtained from 3.7 mmole of (Ia) or (Ib) [1] and 3.7 mmole of the appropriate nitroaniline in the presence of 0.6 ml (6 mmole) of phosphoryl chloride, as described in [2].

1,2-Dioxo-3-methyl-3a-ethyl-7-chloroimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine (IIIa). To a solution of sodium ethoxide, obtained from 0.08 g (3.4 mmole) of sodium and 10 ml of absolute ethanol, was added 1.0 g (3.4 mmole) of (Ib), and the mixture stirred for 2 h at 18-20°C. The solid was filtered off, washed with ethanol, and dried to give 1.0 g (93%) of the sodio-derivative of (Ib), mp > 300°C. This compound (0.5 g, 1.6 mmole) was dissolved in 30 ml of ethanol, and 2.3 g (1.6 mmole) of methyl iodide added. After boiling for 20 min, the solid was filtered off, washed with water, and dried to give (IIIa).

1,2-Dioxo-3-N-(3'-halopropionyl)-3a-ethyl-7-chlorimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines (IIIb, c) were obtained similarly, for 0.5 g (1.6 mmole) of the enolate A and 3.2 mmole of β-bromo- or β-chloropropionyl chloride, except that the reaction was carried out in dry ether for 1 h.

1-Oxo-2-morpholino-3a-ethyl-7-chloroimidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazine (IVb). A suspension of 1.0 g (3.5 mmole) of (Ib) in 9 ml (98 mmole) of $POCl_3$ and 1.5 ml (11 mmole) of dimethylaniline was heated for 3 h at 100-105°C. The mixture was then poured onto ice, and the solid filtered off, washed with water, until neutral, and dried. The product (0.9 g) was dissolved in 20 ml of dry benzene, filtered, and the filtrate treated with 0.45 ml (5.1 mmole) of morpholine. The mixture was boiled for 0.5-1.0 h at 90°C, and the solution concentrated under reduced pressure to 1/3 of its volume. The solid which separated was filtered off, washed with water, and dried to give (IVb).

Compound (IVa) was obtained similarly.

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