SYNTHESIS OF N-SUBSTITUTED 2-BENZOXALONES

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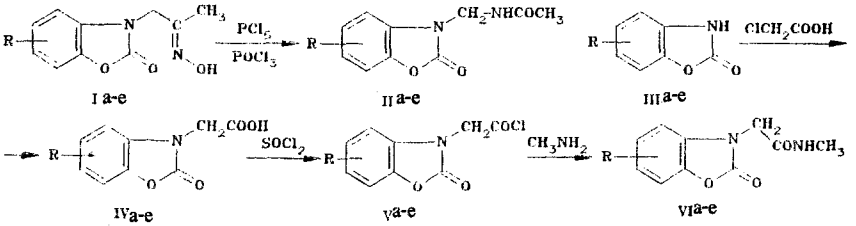
3-Acetylaminomethyl-2-benzoxazolones are obtained by Beckmann rearrangement of the anti-oximes of 3-acetonyl-2-benzoxazolones. The isomeric 3-(N-methylcarbamoylmethyl)-2-benzoxazolones are synthesized by alkylation of 2-benzoxazolone with chloroacetic acid, followed by reaction of the 3-carboxymethyl-2-benzoxazolones obtained with thionyl chloride and methylamine.

It is well known that halogen-substituted 2-benzoxazolones possess marked antibacterial and fungicidal properties [1, 2]. In particular, 5-chloro-2-benzoxazolone (Paraflex) is a compound with central muscle-relaxing action [3, 4]. It was found also that N-substituted 2-benzoxazolones frequently have a higher biological activity [5].

In this connection we undertook the synthesis of some new N-substituted halogen-containing benzoxazolones, in particular using oximes of 3-acetonyl-2-benzoxazolone (I), described by us previously [6], to which was assigned the anti configuration on the basis of IR spectra. It could be expected that 3-(acetylaminomethyl)-2-benzoxazolones (II) would be formed by Beckmann rearrangement.

If the oximes I were to have the syn configuration the formation of 3-(N-methylcarbamoylmethyl)-2-benzoxazolones (VI) would be expected.



Ia-e IIa-e IIIa-e IVa-e Va-e VIa-e

I—VI a R=H, b R=5-Cl, c R=6-Cl, d R=6-Br, e R=5-Cl—6-Br

By reacting oximes I with a mixture of $POCl_3$ and PCl_5 at room temperature we obtained amides IIa-e (Table 1). In their IR spectrum, apart from the vibrational band of the carbonyl group in the oxazolone ring at 1770 cm^{-1}, the band of amide I at 1720 cm^{-1} as well as the vibrational NH band in the region of 3225 cm^{-1} were observed. In the PMR spectrum of compound IIb (in DMSO), apart from the distinctive group of signals from the three aromatic protons, a singlet from the three protons of the acetyl group (1.80 ppm), a doublet from the two protons of the methylene group (5.00 ppm), and a broadened triplet from the amide proton at 8.86 ppm were observed. On recording the spectrum in D_2O solution the latter disappeared, and the doublet from the methylene protons changed to a singlet.

The unstable molecular ion of amide IIb formed by electron impact mainly undergoes McLafferty rearrangement [7] (Scheme 1) with separation of a molecule of N-acetylmethyleneimine leading to the pseudo-molecular ion of 5-chloro-2-benzoxazolone, which loses subsequently two CO molecules. At the same time cleavage of the N—CH_2 bond is observed, with the formation of the fairly stable ion 72. Also the ions (M—CH_2CO) 42 and 43 indicate the presence of the acetylamino group in the IIb molecule. The ions mentioned above constitute more than 60% of all the ions of the spectrum.

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TABLE 1. Properties of Compounds IIa-e, IVa-e, Va-e, VIa-e

Compound*	mp, deg C	Found N, %	Empirical formula	Calculated N, %	Yield, %
IIa	143—144	13,5	$C_{10}H_{10}N_2O_3$	13,6	87
IIb	217—218	11,6	$C_{10}H_9ClN_2O_3$	11,6	76
IIc	182—183	11,5	$C_{10}H_9ClN_2O_3$	11,6	81
IId	194—195	9,9	$C_{10}H_9BrN_2O_3$	9,9	78
IIe	253—254	8,8	$C_{10}H_8BrClN_2O_3$	8,8	87
IVa	179—180	[8]	—	—	68
IVb	207—208	[9]	—	—	65
IVc	230—231	[8]	—	—	56
IVd	232—233	5,1	$C_9H_5BrNO_4$	5,1	79
IVe	384—385	4,3	$C_9H_4BrClNO_4$	4,6	76
Va	116—117	6,8	$C_9H_6ClNO_3$	6,6	92
Vb	150—151	5,8	$C_9H_5Cl_2NO_3$	5,7	77
Vc	140—141	5,4	$C_9H_5Cl_2NO_3$	5,7	70
Vd	129—130	4,8	$C_9H_5BrClNO_3$	4,8	85
Ve	214—215	4,2	$C_9H_4BrCl_2NO_3$	4,3	80
VIa	189—190	13,8	$C_{10}H_{10}N_2O_3$	13,6	90
VIb	183—184	11,5	$C_{10}H_9ClN_2O_3$	11,6	85
VIc	207—208	11,5	$C_{10}H_9ClN_2O_3$	11,6	76
VId	240—241	9,7	$C_{10}H_9BrN_2O_3$	9,9	80
VIe	215—216	8,7	$C_{10}H_8BrClN_2O_3$	8,8	82

*Mass spectrum (peaks listed with intensity >5%), m/z (relative intensity, %) for compound IIb: 240 (6), 171 (33), 170 (10), 169 (100), 115 (10), 113 (30), 78 (28), 72 (6), 63 (8), 43 (10), 42 (16); for compound VIb: 242 (17), 240 (56), 185 (32), 184 (18), 183 (100), 182 (25), 156 (10), 154 (28), 138 (14), 102 (10), 75 (10), 58 (42).

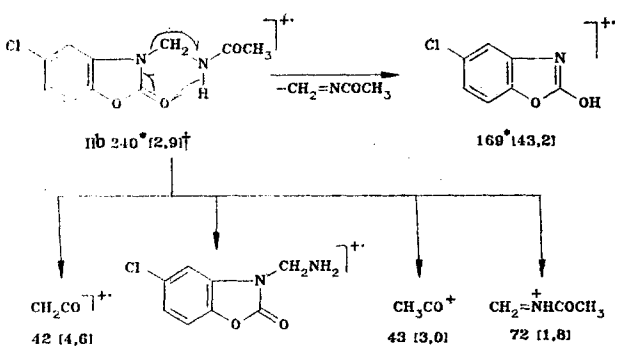
Thus, taking into account the trans-migration mechanism of the Beckmann rearrangement, our conclusions [6] about the configuration of oximes I have been confirmed chemically.

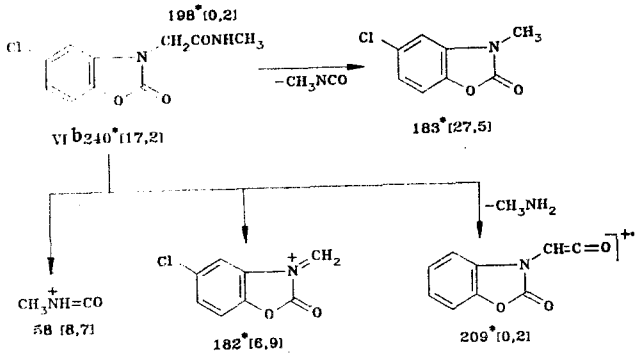
We obtained the isomers of the acetylamines II by alkylation of 2-benzoxazolones IIIa-e with chloroacetic acid, followed by conversion of the acids IVa-e obtained to the acid chlorides Va-e, and further to the N-methyl amides VIa-e [8, 9] (see Table 1). The IR spectra of compounds VI were very similar to the IR spectra of amides II described above, but in the PMR spectrum of compound VIb, apart from the distinctive group of signals of the three aromatic protons (at 7.15-7.85 ppm) and a broadened multiplet from the proton of the imino group at 8.5 ppm, a doublet from the three protons of the methyl group at 3.75 ppm and a singlet from the two protons of the methylene fragment at 4.76 ppm were observed.

In the mass spectrum of compound VIb can be seen intense peaks from the molecular ion, which mainly eliminates a methyl isocyanate molecule (Scheme 1) with the formation of the pseudo-molecular ion of 3-methyl-5-chloro-2-benzoxazolone. Simple cleavage in the molecular ion of the CH_2—CO bond also leads to the two fairly stable acyliminium ions 58 and 182-184. Finally, the loss from the molecular ion of methylamine (ion 209-211) indicates the presence of a methyl amide fragment in molecule VIb. The ions mentioned constitute more than 70% of all the ions of the spectrum, which indicates the high selectivity of fragmentation.

Thus, the mass spectrometric behavior of the isomeric amides II and VI is markedly different.

Scheme 1





*m/z listed [intensity, % Σ_{39}].
†Ions containining the ^{35}Cl isotope.

EXPERIMENTAL

IR spectra were recorded on a UR-10 instrument using a KBr disk; PMR spectra were recorded on a BS-487-C instrument (80 MHz) in DMSO solution (standard was TMS). Mass spectra were obtained on a Varian MAT-111 mass spectrometer with direct introduction into the ion source; ionization energy 80 eV.

The properties of compounds IIa-e, Va-e and VIa-e are given in Table 1.

3-Acetylaminomethyl-2-benzoxazolones (IIa-e). To a solution of 10 mmole phosphorus oxychloride and 10 mmole phosphorus pentachloride in 20 ml chloroform is added 10 mmole oxime Ia-e. The mixture is kept at room temperature for six days, and the precipitate formed is separated, washed with chloroform, and recrystallized from ethanol.

Acids IVa-e. These are obtained according to method [9].

3-(Chlorocarbonylmethyl)-2-benzoxazolones (Va-e). To a solution of 10 ml thionyl chloride in 20 ml benzene is added 10 mmole acid IV. This is heated for 30 min, cooled, supplemented with 30 ml petroleum ether, and kept in a refrigerator for 24 h. The precipitate formed is separated and recrystallized from benzene.

3-(Methylcarbamoylmethyl)-2-benzoxazolones (VIa-e). To a solution of 10 mmole of chloride Va-e in 10 ml benzene is added a solution of 10 mmole methylamine in 5 ml benzene. This is boiled for 1 h, cooled, and the precipitate formed is recrystallized from ethanol.

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