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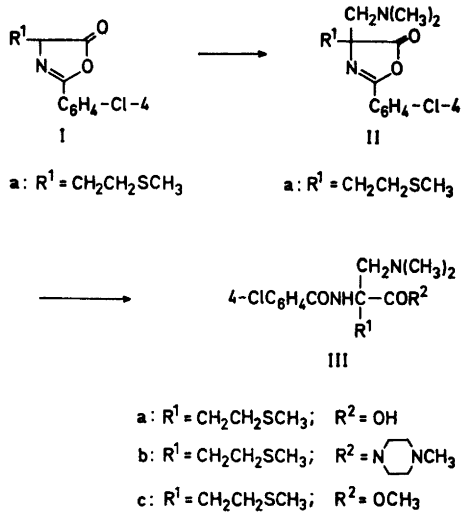

Synthesis of 2-*p*-Chlorophenyl-4-(2-methylthioethyl)-4-dimethylaminomethyloxazolin-5-one — a Reactive Mannich Base

HANS JØRGEN PETERSEN

Leo Pharmaceutical Products, 2750 Ballerup, Denmark

In a previous paper[1] the preparation of a number of 4-monosubstituted 2-*p*-chlorophenyloxazolin-5-ones (I) was reported, involving heating of the requisite α-*p*-chlorobenzamido acids in acetic anhydride.* With secondary amines, *e.g.* dimethylamine, and formaldehyde (aqueous solutions) in methanol or ethanol (I) underwent a Mannich reaction at the 4-position followed by alcoholysis of a hitherto not isolated intermediate (II), resulting in diamino acid esters (III) ($R^2 = OCH_3$ or OC_2H_5). The present communication describes the synthesis of a compound of class II (IIa) from the corresponding (IIIa).

* A low-temperature modification of this classical procedure was successfully employed for converting α-*p*-chlorobenzoyl-L-histidine in trifluoroacetic anhydride at 0° into a reactive oxazolin-5-one derivative which yielded racemic products with an unaffected imidazole ring.

The esters (III) proved to be rather refractory to aminolysis and saponification, in the latter case often suffering a certain amount of destruction. With the methionine azlactone (Ia) a Mannich reaction was conducted in 2-trifluoroethanol. The weakly alkaline conditions brought about a concerted reaction, in one step affording (IIIa), isolated as the hydrochloride in high yield. Thus, the difficulties in obtaining the pure diamino acid *via* methyl or ethyl esters were overcome as the result of a simultaneous smooth hydrolysis of the intermediate 2-trifluoroethyl ester.

The mixed anhydride from (IIIa) and isobutyl chloroformate was prepared in acetone-methylene chloride. When treated with dry hydrogen chloride, the crystalline hydrochloride of (IIa) was obtained. While this work was in progress a general method for oxazolin-5-one preparation by the mixed anhydride reaction has appeared.[2] (IIa) – in accordance with the postulated intermediacy in the proposed reaction sequence – was completely converted to (IIIb) and to (IIIc),[1] when dissolved in *N*-methylpiperazine and in methanol, respectively. An authentic sample of (IIIb) was prepared by reacting the mixed anhydride from (IIIa) and isobutyl chloroformate with an excess of *N*-methylpiperazine in acetone.

A certain stability of (IIa) in aqueous medium was demonstrated by the fact that treatment of an aqueous solution

of (IIIa), hydrochloride with the water-soluble 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide metho-*p*-toluenesulfonate caused precipitation of (IIa), tosylate.[3-4] Under identical conditions (III) ($R^1 = C_6H_5$, $R^2 = OH$),[1] prepared like (IIIa), gave rise solely to (I) ($R^1 = C_6H_5$), indicating a retro-Mannich reaction.

The IR-spectra (KBr) of (IIa), hydrochloride and tosylate, were consistent with the proposed structure, displaying characteristic oxazolin-5-one bands in the 1817 – 1820 and 1652 – 1655 cm^{-1} regions.

None of the compounds prepared showed any significant pharmacological activity.[5]

Experimental. Melting points are uncorrected. IR-spectra were recorded with a Perkin-Elmer PE 21 spectrophotometer, NMR-spectra with a Varian A60A spectrometer. (TMS as internal standard. Chemical shifts given in ppm δ scale, coupling constants J in cps.)

2-p-Chlorophenyl-4-(2-methylthioethyl)-oxazolin-5-one (Ia). *N-p*-Chlorobenzoyl-L-methionine (m.p. 103 – 105°) (4.3 g, 15 mmol) in acetic anhydride (30 ml) was heated to 125 – 130°C for 10 min. The mixture was evaporated in high vacuum at 30°C. Extraction with ether-petroleum ether, 1:10, and evaporation left the azlactone as an oil (4.0 g, 98 %), showing IR-absorption bands ($CHCl_3$) at 1835 and 1657 cm^{-1}.

N-p-*Chlorobenzoyl-α-dimethylaminomethylmethionine (IIIa), hydrochloride.* (Ia) (12.3 g, 46 mmol) was added to a solution of aqueous (38 %) dimethylamine (9.0 ml) and aqueous (35 %) formaldehyde (4.4 ml) in 2-trifluoroethanol (55 ml) while stirring at 0°C. After 2 h the mixture was allowed to assume room temperature and stand for 18 h. After evaporation the residue was stirred with ice water (70 ml), 2 N sodium hydroxide (8 ml) and ether (70 ml). After separation the aqueous layer was shaken with ether, acidified with 4 N hydrochloric acid (11.5 ml) and extracted twice with ether. The crude product was salted out as an oil with sodium chloride and dried under high vacuum. Extraction with acetone (150 ml) and evaporation of the filtrate left (IIIa), hydrochloride as a solid (12.1 g, 70 %), which according to thin layer chromatography in 3 systems was essentially pure. The crystalline hydrochloride, m.p. 176 – 80°C (dec.), was obtained from acetone-ether. (Found: C 47.28; H 6.00; N 7.15. Calc. for $C_{15}H_{21}ClN_2O_3S$,HCl: C 47.24; H 5.82; N 7.34.) IR absorptions (KBr) were found at 3350, 1725 and 1662 cm^{-1}. NMR signals (D_2O): SCH_3: 2.01, s, 3H. $-S-CH_2CH_2C$: *ca*: 2.40, m, 4H. $N(CH_3)_2$: 2.96, s. 6H. $-CCH_2-N$. ABq 3.86, d, $J = 14$, 1H and 4.07, d, $J = 14$, 1H. ClC_6H_4-: 7.44, d, $J = 8.5$, 2H and 7.79, d, $J = 8.5$, 2H.

(IIIa), picrate (from the hydrochloride): m.p. 166 – 70°C(dec). (Found: C 43.76; H 4.33; N 12.02. Calc. for $C_{21}H_{24}ClN_5O_{10}S$: C 43.94; H 4.21; N 12.20.)

2-p-Chlorophenyl-4-(2-methylthioethyl)-4-dimethylaminomethyloxazolin-5-one (IIa), hydrochloride. (IIIa) hydrochloride (3.2 g, 8.4 mmol), dissolved in acetone (8 ml) and methylene chloride (12 ml) at – 15°C was reacted with triethylamine (2.30 ml) and isobutyl chloroformate (1.20 ml). After stirring for 15 min at – 2°C methylene chloride (90 ml) was added, followed by 2 N hydrogen chloride in dry tetrahydrofuran (5.5 ml). While stirring at – 5°C for 30 min a crystalline material gradually precipitated. Filtration and wash with methylene chloride and ether left (IIa), hydrochloride (2.48 g, 81 %), m.p. 171 – 172°C (unchanged after recrystallization from glacial acetic acid-ether). (Found: C 49.50; H 5.73; N 7.74; Cl 19.53. Calc. for $C_{15}H_{19}ClN_2O_2S$,HCl: C 49.59; H 5.55; N 7.71; Cl 19.52.) The IR spectrum (KBr) had absorptions at 1817 and 1652 cm^{-1}.

(IIa), hydrochloride (200 mg) was stirred with methanol (25 ml) over-night. After partial evaporation and addition of water and 2 N sodium hydroxide crude (IIIc) precipitated. After recrystallization from aqueous methanol it proved identical with an authentic sample,[1] m.p. 78 – 79.5°C.

2-p-Chlorophenyl-4-(2-methylthioethyl)-4-dimethylaminomethyloxazolin-5-one (IIa), tosylate. (IIIa), hydrochloride (762 mg, 2 mmol) in water (30 ml) at 0°C was treated with 1-cyclohexyl-3-(2-morpholinyl-(4)-ethyl)-carbodiimide metho-*p*-toluenesulfonate (1.00 g, 2.4 mmol), adjusting the pH to 3 with 4 N hydrochloric acid. After 3 h at 0°C the precipitate was filtered and washed with water and ether to yield (IIa), tosylate (440 mg, 44 %), m.p. 156 – 158°C (dec.) after recrystallization from acetone-ether. (Found: C 52.95; H 5.57; N 5.30; S 12.87. Calc. for $C_{22}H_{27}ClN_2O_5S_2$: C 52.94; H 5.45; N 5.61; S 12.85.) IR absorptions (KBr) were found at 1820 and 1655 cm^{-1}.

N-p-*Chlorobenzoyl-α-dimethylaminomethylmethionine-N'-methylpiperazide (IIIb).* To a solution of (IIIa), hydrochloride (3.05 g, 8 mmol) in acetone (55 ml) at – 10° were added triethylamine (2.24 ml) and isobutyl chloroformate (1.08 ml). The reaction mixture was kept for 15 min below – 4° and poured into a solution of *N*-methylpiperazine (8.8 ml) in acetone (90 ml) at 0°. After 2 h at 0° and

2 h at room temperature the mixture was evaporated, finally in high vacuum at 40°C. The residue was extracted with ether and filtered through activated charcoal on celite. Concentration and addition of petroleum ether afforded a crystalline product (2.85 g, 84 %), which after recrystallization from ether-petroleum ether had m.p. 130-32°C. (Found: C 56.04; H 7.40; N 12.91. Calc. for $C_{30}H_{31}ClN_4O_2S$: C 56.25; H 7.32; N 13.12.) IR bands (KBr) occurred at 3250, 1650 and 1617 cm^{-1}. NMR signals ($CDCl_3$): $S-CH_3$: 2.05, s, 3H. $N(CH_3)_2$: 2.23, s, 6H. $>NCH_3$: 2.31, s, 3H. $pip(CH_2)_4$: 2.47, m, 4H and 3.73. m, 4H. $S-CH_2CH_2-C$: *ca.* 2.30, m. 4H. $-C-CH_2-N$: ABq 2.93, d, $J=14.5$, 1H and 3.51, d, $J=14.5$, 1H. ClC_6H_4-: 7.43, d, $J=8.5$, 2H and 7.80, d, $J=8.5$, 2H. $-CONH$: 8.37, broad s, 1H.

(IIa), hydrochloride (200 mg) was gradually dissolved in *N*-methylpiperazine (5 ml) by heating to 50°. After exhaustive evaporation in high vacuum and work-up as described for (IIIb) an identical compound was obtained.

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Skeletal Rearrangements in Thienothiophenes under Electron Impact

ANDREAS BUGGE

Pharmaceutical Institute, University of Oslo, Oslo 3, Norway

Recent papers by de Jong *et al.*[1] and by Cooks and Bernasek[2] have prompted the author to submit his results on the skeletal rearrangements of thieno[2,3-b]thiophene (I) and thieno[3,2-b]thiophene (II)[3] under electron impact. The spectra were recorded on an AEI MS 902 mass spectrometer at 70 eV and at 16 eV. All voltages given are nominal values. The compounds were introduced through the all glass heated inlet system with source temperatures of 230° and 50°, but no significant dependence on the source temperature was observed. The major fragments were examined at high resolution. The only metastable visible in the spectra was at *m/e* 65.8 (*m/e* 140→ *m/e* 96). All the other metastable transitions were determined by the metastable defocusing technique.[4] The primary processes found in the low voltage spectra and confirmed by high resolution and metastable defocusing are shown in Fig. 1.

An examination of the 70 eV spectra of the isomeric compounds, or those recorded at low voltage, showed that the spectra were very similar except for small intensity variations on different runs. Of interest in this discussion are the fragments *m/e* 64 and *m/e* 76. The fragment *m/e* 64, $C_5H_4{\cdot}^+$, is present in the spectra of both compounds and is in both isomers found to originate from the molecular ion by the loss of CS_2. The fragment *m/e* 76 in both isomers was found to be a doublet containing $CS_2{\cdot}^+$ and $C_6H_4{\cdot}^+$ in the approximate ratio of 5:1. By lowering the energy of the electron beam to about 18 eV, only $CS_2{\cdot}^+$ was present, with no reduction in the intensity. In thieno[3,2-b]-thiophene metastable defocusing on $CS_2{\cdot}^+$ showed transitions from *m/e* 102 [$M-C_3H_2$] and the molecular ion (*m/e* 140), the latter of very low intensity. In thieno[2,3-b]-thiophene the transition from *m/e* 102 was absent, while the metastable from *m/e* 140 was of about twice the intensity of that observed for the other isomer.

The reduction of the intensity of *m/e* 76 in the low voltage spectra is surprisingly small compared with the other fragments,