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104. Antibiotic X-5108. VII. Absolute Stereochemistry of 8-Amino-3-methoxy-2,4-dimethyl-4,6-octadienal, a Compound Derived from Antibiotic X-5108 and Mocimycin [1]

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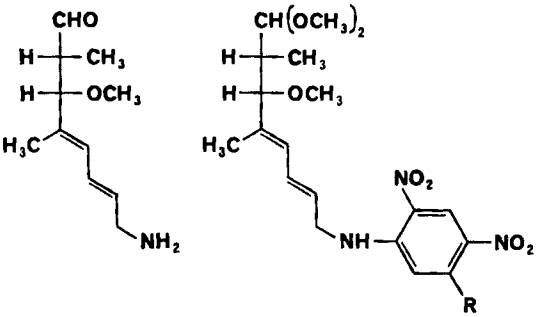
(15. III. 74)

Zusammenfassung. 6-Bromo-4-fluoro-1,3-dinitrobenzol ist ein wertvolles Reagens zur Herstellung kristalliner Derivate von Aminen, Phenolen und Alkoholen. Die resultierenden 5-Bromo-2,4-dinitrophenylverbindungen können zur Charakterisierung und Kristallstrukturanalyse durch Röntgendiffraktion dienen.

Aus den Antibiotika X-5108 und Mocimycin haben wir kürzlich ein neuartiges Octadienal isoliert, das mit 6-Bromo-4-fluoro-1,3-dinitrobenzol reagiert und in das Dimethylacetal umgesetzt wurde. Das resultierende Derivat wurde auf kristallanalytischem Wege als 8-(5-Bromo-2,4-dinitroanilino)-3(*S*)-methoxy-2(*R*),4-dimethyl-4(*trans*),6(*trans*)-octadienal-dimethylacetal identifiziert.

We have recently isolated octadienal **1** from both antibiotic X-5108 and mocimycin [2] [3].

The gross-structure of **1**, containing a Δ^6-*trans* configuration, was readily assigned on the basis of ^{1}H-NMR. spectra and a *threo*-configuration[1]) could be deduced by determination of the ratio of stretching-vibration intensities associated with bonded *versus* non-bonded hydroxyl groups of 8-acetamido-3-methoxy-2,4-dimethyl-4,6-octadienol, a derivative of **1**. The absolute configuration of **1** and the Δ^4 configura-



1 **2a**: R = H
2b: R = Br

tion, however, were not readily ascertained. Crystalline derivatives of **1** were prepared but only **2a** proved suitable for Roentgen analysis which led to configuration **1** or its enantiomer [3].

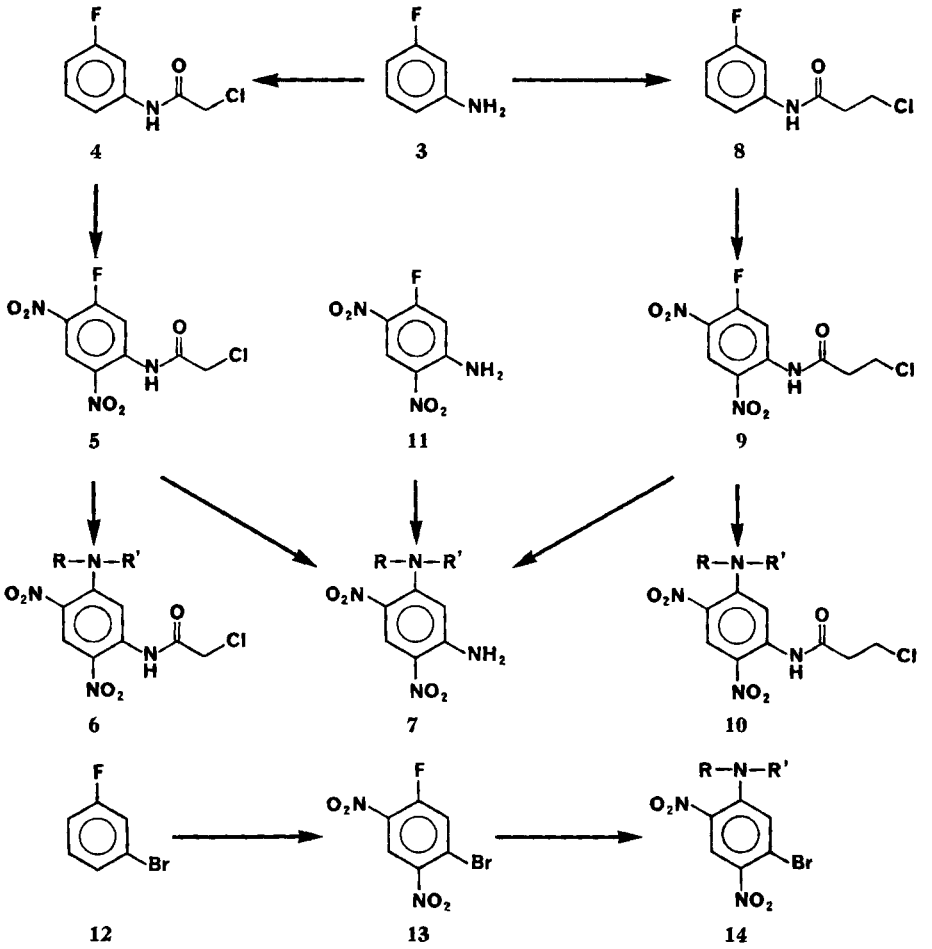
In view of the persistent ambiguity as to the chirality of **1**, a derivative of **1** was sought which contained a suitable anomalous scatterer. Encouraged by the quality of the **2a** crystals, a modification of **2a** which would contain a heavy atom but retain the basic structural features was proposed. To achieve this goal reagents **5**, **9** and **13** were prepared as outlined in *Scheme 1*.

Reagent **5** reacted readily with primary and secondary amines under established conditions [4] [5] to give **6**, but the reaction products always contained varying amounts of **7**. Reaction of amino acids with **5** yielded **6** as minor and **7** as major product readily separated by column chromatography. Derivatives of type **10** prepared by application of reagent **9** are somewhat less sensitive toward alkaline hydrolysis than **6**, usually resulting in **10** as major and **7** as minor component.

In an alternate approach to the preparation of a dinitrofluorobenzene reagent containing a heavy atom, **12** was nitrated to give **13**. Under conditions commonly used in the N-dinitrophenylation of amino acids and peptides [5] the fluorine substituent of **13** would be expected to be more reactive toward nucleophilic displace-

[1]) For use of *threo* and *erytrho* in this paper see *K. Mashens & N. Polgar*, J. chem. Soc Perkin I, *1973*, 109.

Scheme 1



ment than bromine due to the insignificant role of carbon-halogen bond breakage in the rate-determining steps. With poorly nucleophilic and sterically demanding amines in less polar solvents a reversal of the order of activity could be anticipated [6]. Indeed, reagent **13** yielded pure derivatives of type **14** with a number of amino acids tested and, under the conditions employed, no contamination by fluorine-containing analogs was observed. Thus, reaction of **1** with **13**, followed by acetalization [7] afforded **2b** whose configuration, *i.e.* 8-(5-Bromo-2,4-dinitroanilino)-3(*S*)-methoxy-2(*R*),4-dimethyl-4(*trans*),6(*trans*)-octadienal-dimethylacetal, was established by single-crystal Roentgen-diffraction analysis.

Possessing the known desirable properties of the 2,4-dinitrophenyl group, **13** proved to be a generally useful reagent for the preparation of derivatives of primary and secondary amines, phenols [8] and alcohols [9] suitable for chemical characterization and crystal-structure analysis by the heavy-atom method.

Experimental Part

Melting points were observed on a *Reichert Thermopan* hot stage and are uncorrected. Evaporations were conducted under reduced pressure. All crystalline compounds gave satisfactory elemental analyses.

3-Fluorochloroacetanilide (**4**). A mixture of 3-fluoroaniline (11.1 g, 0.10 mol), pyridine (20 ml) and toluene (20 ml) was cooled to 0° and chloroacetyl chloride (15.8 g, 0.14 mol) in toluene (50 ml) was added dropwise over a period of 45 min. After 4 h at 0° pyridine hydrochloride was filtered off, the solids were washed with ethyl acetate, filtrate and washings were combined, washed with saturated saline, twice with saturated sodium hydrogencarbonate solution followed by water and concentrated to dryness. The residue dissolved in methanol (60 ml) was treated with charcoal (Norit A, 1.5 g) to yield **4** (skin irritant!) as tan prisms (10.3 g) after concentration to smaller volume and refrigeration. From the mother liquor additional quantities of **4** could be obtained which were purified by vacuum sublimation (4.6 g, total yield 79%), m.p. 123°.

5-Fluoro-2,4-dinitrochloroacetanilide (**5**). A mixture of conc. sulfuric acid (25 ml) and 90% nitric acid (10 ml) was cooled to – 20° and **4** (4.40 g, 0.023 mol) was added to the mechanically stirred solution within a few minutes. Vigorous stirring at – 20° was continued for 1.5 h, the suspension was cooled to – 30° and the reaction quenched with ice. The resulting crystals were washed extensively with ice-cold water and recrystallized from acetone to give colorless prisms (4.7 g, 72%), m.p. 131°.

5-Fluoro-2,4-dinitro-β-chloropropionanilide (**9**). A solution of 3-chloropropionyl chloride (3.18 g, 0.025 mol) in dioxane (15 ml) was added to a solution of 3-fluoroaniline (2.22 g, 0.020 mol) in pyridine (4 ml) and dioxane (8 ml) at 0° within 15 min. After continued stirring at 0° for 30 min and 1.5 h at room temperature the solution was concentrated to approximately one third of the original volume and ethyl acetate (15 ml) and saturated saline (5 ml) were added. The ethyl acetate phase and four additional ethyl acetate extracts were combined, washed with water, dried ($MgSO_4$) and concentrated to dryness. The residue was recrystallized from chloroform/ligroin to afford **8** as colorless prisms (3.62 g, 90%), m.p. 104°. Nitration was carried out as described for the preparation of **5** affording **9** as colorless prisms after crystallization from acetone, m.p. 138°, in 75% yield.

N-(5-chloroacetamido-2,4-dinitrophenyl)-DL-*valine* (**6**, R = H, R′ = —CH(COOH)—$CH(CH_3)_2$) *and N-(5-amino-2,4-dinitrophenyl)*-DL-*valine* (**7**, R = H, R′ = —CH(COOH)—$CH(CH_3)_2$). A solution of **5** (333 mg, 1.2 mmol) in methanol (2 ml) was added to a solution of DL-valine (117 mg, 1.0 mmol) and sodium hydrogencarbonate (252 mg, 3 mmol) in water (2 ml). After stirring for 24 h in the dark, the mixture was concentrated to remove methanol and partitioned between water (15 ml) and ether (20 ml). The filtered aqueous phase was extracted with ether (2 × 20 ml), freed of traces of ether, acidified with 1N hydrochloric acid (3 ml) and refrigerated overnight. The precipitate was filtered off, redissolved in a minimum amount of methyl ethyl ketone, diluted with chloroform and chromatographed with chloroform, followed by chloroform containing 5% acetone on a column of silicic acid (18 g, *Mallinckrodt*). Compound **6** was eluted first; crystallization from acetone afforded yellow prisms (62 mg, 17%), m.p. 178–180°. Continued column development with chloroform containing 5% acetone gave **7** (88 mg, 30%), m.p. 203–204°, identical with a sample prepared from DL-valine and **11** [10].

6-Bromo-4-fluoro-1,3-dinitrobenzene (**13**). Compound **12** was nitrated [11], the mixture was cooled to – 20°, poured on ice, the solids washed with water at 5° and crystallized from aqueous acetone. One additional crystallization from ether/ligroin gave colorless needles, 81%, m.p. 93°.

Benzyl 5-bromo-2,4-dinitrophenyl ether. A mixture of benzyl alcohol (0.67 ml, 6.48 mmol), **13** (1.78 g, 6.72 mmol) and 6.7 ml of a solution prepared by diluting 1.39 ml (10 mmol) of triethylamine with dimethyl formamide to a volume of 10 ml was kept in the dark at room temperature overnight. The product separated as light-yellow needles and was recrystallized from acetone/ethanol (1.3 g, 3.7 mmol, 57%), m.p. 189–190, *m/e* (%) 324(7), 322(7) [*M* – NO], 91(100).

8-(5-Bromo-2,4-dinitroanilino)-3(S)*-methoxy-2*(R)*,4-dimethyl-4*(trans)*,6*(trans)*-octadienal dimethylacetal* (**2b**). Crude **1** (99 mg, 0.5 mmol) was dissolved in a mixture of dioxane (3.5 ml) and water (3.5 ml), sodium hydrogencarbonate (84 mg, 1 mmol) and **13** (160 mg, 0.6 mmol) were added and stirred in the dark overnight. The mixture was repeatedly extracted with ether, the com-

bined extracts were dried ($MgSO_4$), concentrated, redissolved in chloroform and chromatographed with chloroform on a column of silicic acid (15 g, *Mallinckrodt*). The pure fractions (Rf 0.79, TLC., silica gel; chloroform/ether 1:2 (*v/v*)) were combined and concentrated to dryness. The resulting oily aldehyde (120 mg) was dissolved in methanol (5 ml) and 2,2-dimethoxypropane (2 ml), bis-(*p*-nitrophenyl)-phosphate (50 mg) was added and the mixture was stirred for 3 h and refrigerated overnight. The mixture was neutralized by addition of Dowex 1 (HCO_3^-). The resin was filtered off and washed exhaustively with acetone. Filtrate and washings were combined, concentrated to dryness and crystallized from aqueous acetonitrile as yellow prisms (146 mg, 60%), m.p. 120–121°, $[\alpha]_D$ + 27.8 (c = 0.5, dioxane); *m/e* (%) 473, 471(3) [M – O], 75(100).

Determination of absolute configuration of **2b**. Diffraction data were collected on a *Hilger-Watts* diffractometer from a crystal with approximate dimensions of 0.10, 0.25, and 0.55 mm, with acetonitrile as monosolvate. For data collection the crystal was mounted in a sealed capillary to prevent loss of solvate. Crystals of **2b** exhibit space group $P2_12_12_1$ with unit cell dimensions a = 7.734(4), b = 11.016(4), c = 30.049(10) Å and d_{calcd} = 1.373 g cm^{-3} for Z = 4. Of 3019 accessible reflections with $\theta < 76°$, 2323 had intensities significantly greater than background ($I > 2.5\sigma(I)$) and these data were used for the analysis. The data were corrected for absorption (μ(Cu K_α) = 28.1 cm^{-1}). The structure was solved by *Patterson*- and *Fourier*-methods. Three electron density syntheses were required to locate all non-hydrogen atoms, including those of the solvate molecule.

The initial refinement was conducted by full matrix least squares with isotropic thermal parameters for all atoms. The refinement was continued by block diagonal least squares with anisotropic thermal parameters for all atoms. At the conclusion of this refinement the positions of the hydrogen atoms were calculated. The hydrogen atoms were included in all subsequent calculations, but their parameters were not refined. Up to this point the refinement had been carried out with the imaginary part of the anomalous dispersion correction set to zero. Structure factors were now calculated for both enantiomers taking into account both parts of the anomalous dispersion correction. The configuration of the enantiomer corresponding to the lower of the two weighted R values (0.063 and 0.074) was taken as the absolute configuration. Full matrix least squares, taking into account the complete anomalous dispersion correction, was used for the final refinement. The final unweighted discrepancy index was R = 0.041 for the 2323 observed reflections.

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