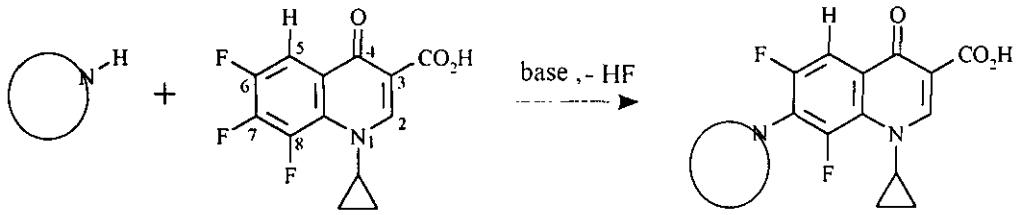
SYNTHESIS OF 1,2,3,4,5,6-HEXAHYDROPYRROLO[3,4-*c*]PYRROLE DIHYDROBROMIDE AND 1,2,3,5-TETRAHYDRO-2-[(4-METHYL-PHENYL)SULFONYL]PYRROLO[3,4-*c*]PYRROLE

Heiner Jendralla*[,a] and Gerd Fischer[b]

Hoechst AG, Allgemeine Pharma Forschung, Entwicklungsgruppe Synthese [a] und SBU Antiinfektiva [b] , Postfach 800320, D-65926 Frankfurt / Main 80, Germany

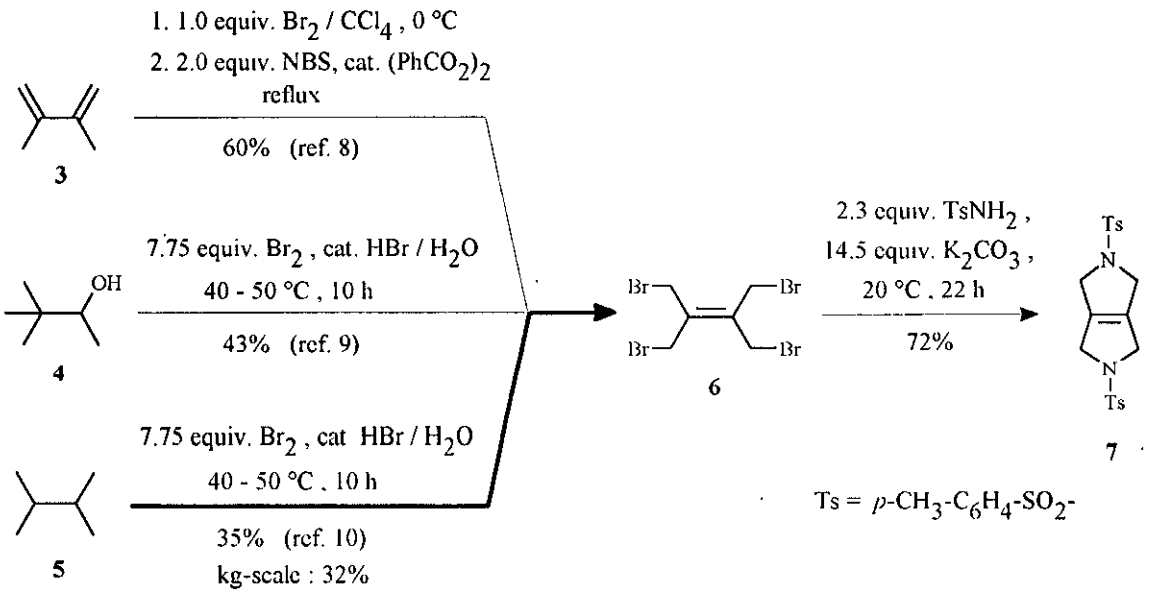
Abstract ---------- Synthesis of the pyrrolo[3,4-*c*]pyrrole derivatives (**8**) and (**9**) is reported. Nucleophilic aromatic substitution of the 7-fluoride of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**1**) by **8** under basic conditions followed by *N*-methylation, gives the quinolone antibacterial agent (**11**) (KR 10755, HK 3140)

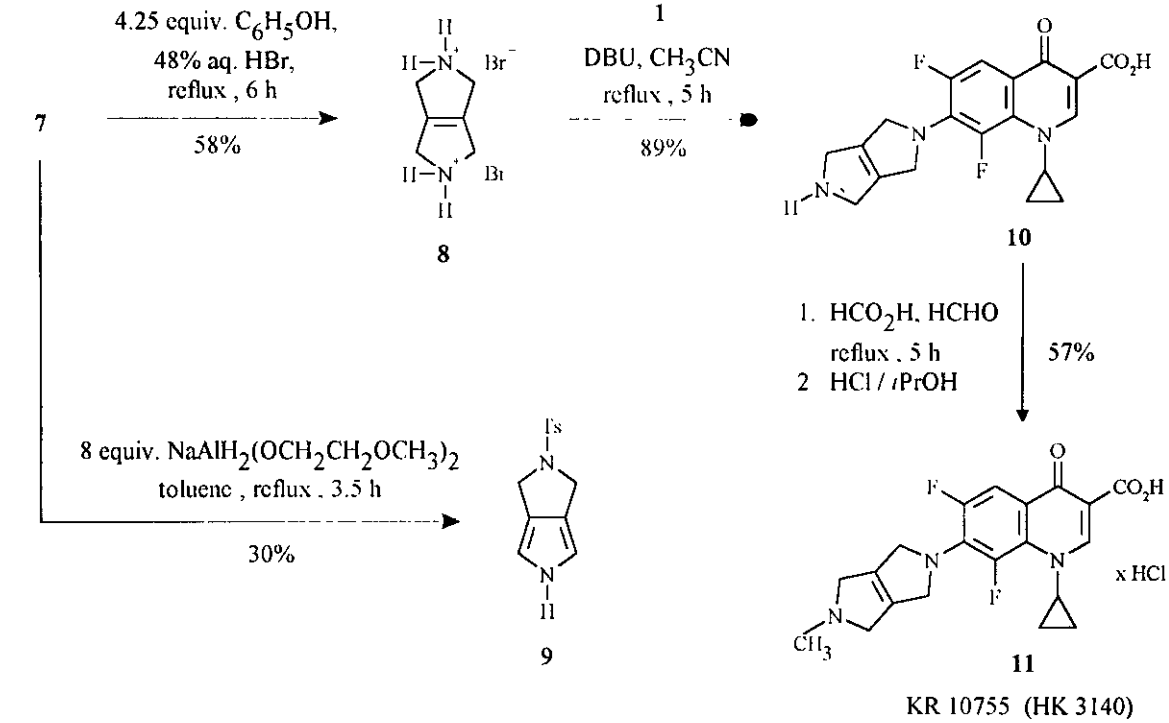
A majority of currently marketed quinolone antibiotics contain an unsubstituted or substituted piperazine at C-7 of the quinolone nucleus. These agents possess excellent activity against Gram-negative bacteria but only fair activity against important Gram-positive pathogens [1] Simultaneous presence of a cyclopropyl substituent at N-1, a fluorine at C-6 and a chlorine, fluorine or trifluoromethyl at C-8 of the quinolone nucleus has been found to increase *in vitro* potency against Gram-positive organisms and overall *in vivo* efficacy,[2] but the (most efficient) fluorine at the 8-position is often associated with a number of undesirable effects such as increased phototoxicity and cytotoxicity [2b,3] A plethora of sometimes new[4] nitrogen-heterocycles have been reacted with trifluorocarboxylic acid (**1**) in order to optimize the Gram-positive activity and *in vivo* efficacy of **2** and to minimize its adverse effects [5]



1 **2**

In 1990, in a cooperation with the Korea Research Institute of Chemical Technology (KRICT), we worked on a process for the large scale preparation of KR 10755 (**11**).[6] In the course of this work, we prepared the heterocycles (**8**)[6] and (**9**)[7],[8] the former compound on a kg-scale.





Hexahydropyrrolo[3,4-*c*]pyrrole dihydrobromide (**8**) was prepared according to the scheme Three procedures have so far been reported for the synthesis of tetrakis(bromomethyl)ethylene (**6**).[9~11] Although the preparation[9] from 2,3-dimethyl-1,3-butadiene (**3**) gives the best yield, we considered it unsuitable for a large scale since allylic bromination is highly exothermic and toxic solvent CCl_4 is not acceptable on a large scale and is not easily replaced. The exothermic nature of this reaction is particularly hazardous in this particular case because of the large amounts of hydrogen bromide evolved and the tendency of the product (**6**) to sublime into a reflux condenser and to plug it if it is not efficiently flushed back into the reaction vessel by the refluxing solvent. Preparations of **6** from pinacolyl alcohol (**4**)[10] and 2,3-dimethylbutane (**5**)[11] are conducted in the absence of solvents, respectively, and are virtually equivalent as regards their yields, reagents, reaction conditions, and probably also their reactive intermediates.[10,11] Five equivalents of bromine are needed theoretically for the oxidative introduction of four bromine atoms and the double bond into hydrocarbon (**5**) We opted for **5** as the starting material because of its lower price and especially the totally non-exothermic nature of the reaction A 32% yield of purified tetrabromide (**6**) was obtained on a 13 kg scale. Reaction of **6** with 2 3 equiv. of *p*-toluenesulfonamide and excess K_2CO_3 in DMF at ambient temperature provided bicyclic sulfonamide (**7**) in 72% yield on a 13 kg scale. Cleavage of the tosyl group by refluxing in a mixture of 48% aqueous HBr and phenol furnished dihydrobromide (**8**) (mp 293 - 303 °C, decomp.) in 58% yield on a 3 kg scale. An attempt to induce detosylation of **7** by Red-Al® in refluxing toluene gave 1,2,3,5-tetrahydro-2-tosylpyrrolo [3,4-*c*]pyrrole (**9**) as the main product, that was isolated in 30% yield after chromatography

Trifluorocarboxylic acid (**1**) was prepared according to the literature procedure.[12] A batch of 10 kg of 2,3,4,5-tetrafluorobenzoic acid furnished 5 75 kg of **1**, corresponding to an overall yield of 39.4%.

Coupling of 1 mol of **1** with 1.02 mol of **8** in the presence of 3 7 mol of 1,8-diazabicyclo[5.4 0]undec-7-ene (DBU) in refluxing acetonitrile gave the substitution product (**10**) in 89% yield Methylation of the secondary amino group of **10** in refluxing formic acid / formaline solution, followed by formation of the hydrochloride furnished the antibacterial agent (**11**) (KR 10755 , HK 3140 [6]) in 57% yield.

In summary, we have described the preparation of pyrrolo[3,4-*c*]pyrrole derivatives (**8**) and (**9**) in three steps from 2,3-dimethylbutane. A synthesis of **8** according to this scheme has been performed on a kg-scale. It was used to furnish the substituted quinolone acid (**11**)

EXPERIMENTAL

Mps were determined on a Büchi 535 capillary melting point apparatus (according to Dr. Tottoli) and are uncorrected. Hplc analyses were performed with a Spectra Physics SP 4200 Pump / 8750 Organizer (10 µl injection loop) with SP 8700 Solvent Delivery System and Spectra 100 UV-Vis Detector Tlc analyses were performed on 5 x 10 cm glass plates pre-coated with silica gel 60F-254 (E-Merck), visualizing the spots at 254 nm. **8** is not uv-active and may be detected in the iodine-chamber or with ninhydrin-spray plus heating to give a yellow-brown dye. Glc analyses were performed with a Varian Model 3700 Gas Chromatograph with split-injection (at 240 °C), utilizing a 30m x 0 25mm fused silica column DB 5 at 220 °C, 1.0 bar He as a carrier gas, detector (FID) 280 °C. Ms were obtained by "fast atom bombardment" positive ionization (+FAB) utilizing *p*-nitro-benzylalcohol (NBA) on a VG ZABSEQ, and by "dissociation chemical ionization" (DCI) utilizing *iso*butane on a Kratos MS 80

Tetrakis(bromomethyl)ethylene (6). The reaction is conducted in a 150 l enameled cone-reactor that has a connection of at least 20 cm inner diameter to a glass reflux condenser (volume 100 l, heat exchange on circular concentric glass cooling coils) cooled by circulating brine of -15 °C The flow of this cooling liquid is adjusted to provide a temperature of -7 °C in the condenser that assures maximum condensation of Br_2 vapours but avoids crystallization of Br_2 (mp -7.3 °C). The top of the reflux condenser is connected to four consecutive scrubbers (each of 500 l volume) The first and the second scrubber are filled with 100 l of ice-water, the third and fourth scrubber with 5% aqueous $NaHSO_3$ solution. The first scrubber should be kept at 10 to 20 °C by continuous addition of ice or by a cooling device

The reactor is charged at 0 °C with 13.1 l (8 66 kg, 100 5 mol) of 2,3-dimethylbutane (**5**) , then 40.0 l (124.4 kg, 778.4 mol, 7.75 equiv) of Br_2 , followed by 1 5 l of 48% aqueous HBr (~ 13 26 mol HBr). The manhole is closed gastight and the stirred contents are heated to gentle reflux. The optimum inner temperature (42 - 46 °C) is adjusted according to the following criteria: During the reaction a yellow-brown solid mainly consisting of product (**6**) sublimes into the connection of reactor and reflux condenser. Plugging of the connection must be avoided. Increased bromine reflux achieved by elevating the reactor temperature by ~2 °C, serves to flush the solid back into the reactor. On the other hand, the temperature should not be unduly elevated so as to minimize the amount of Br_2 that escapes condensation. The reaction is **not** exothermic at any time. After 10 h at reflux, the contents are cooled to +5 °C and allowed to stir overnight (13 h) under N_2. 36 l of ice-water are added within 10 min, followed by ~77 l of 40% aqueous $NaHSO_3$ solution within 3 - 4 h. The reaction with the bisulfite solution is exothermic. Maximum mantle cooling is applied and the addition is adjusted to maintain the reaction temperature below +25 °C. At the

equivalence point of the Br_2 reduction, a redox electrode (that indicated +750 to +850 mV for the original reaction mixture and ~ +100 mV for the bisulfite solution) indicates a steep decline to 350 to 450 mV, and the addition of bisulfite is stopped. The stirrer is shut off and the crude product is allowed to settle as a brown, very sticky solid at the bottom of the reactor After 1 h the aqueous supernatant is removed and 25 l of *tert*-butyl methyl ether is added to the residue. The suspension is allowed to stir at 20 °C overnight, affording a more crystalline solid. It is suction-filtered, washed with 2 x 7 l of bisulfite solution and dried at 40 °C in vacuo to give 16 9 kg of crude **6**[13,14] as a pale-yellow powder, mp 140-150 °C. With an Ultra Turrax it is finely suspended in 25 l of ethyl acetate (EtOAc) and then refluxed for 30 min The suspension is stirred 2 h at 0 °C. The solid is collected by suction-filtration and dried in vacuo to give 12.8 kg (32%) of nearly colourless crystals, mp 156-158 °C (lit., 158-159 °C[9] , 156-157 °C[10]), ^{1}H-nmr as described.[10] Glc (inj. of 10% $CHCl_3$ solution): t_{ret} 5.25 min; single peak

2,5-Bis[(4-methylphenyl)sulfonyl]-1,2,3,4,5,6-hexahydropyrrolo[3,4-*c*]pyrrole (7). 17 0 kg (42.5 mol) of tetrabromide (**6**) and 17.0 kg (99.3 mol, 2.3 equiv) of *p*-toluenesulfonamide are added to 220 l of DMF contained in a 500 l stainless steel reactor to obtain a clear yellow solution 95.0 kg (687.4 mol) of K_2CO_3 is added within 15 min to give a weakly exothermic reaction The mixture is stirred for 22 h at 21 °C under N_2. Tlc (cyclohexane / EtOAc 3·1, R*f* 7 0 33, **6** 0.64, $TsNH_2$ 0 14) The mixture is transferred within 1 h into 680 l of water, that is stirred at 21 °C in a 1000 l reactor. Due to the heat of mixing the temperatur rises to 30 °C where it is kept by slight cooling. The precipitate is collected by centrifugation and washed with 4 x 150 l of water It is centrifuged to dryness, then resuspended in 130 l of EtOAc and stirred for 1 h at 21 °C. The solid is collected by centrifugation and dried for 4 d at 30 °C in vacuo, initially with introduction of 200 l N_2 / h, to obtain 12.8 kg (72%) of a colourless powder, mp 267 °C decomp. (onset at ~250 °C), 0.2 % H_2O (Karl-Fischer titration); ^{1}H-nmr (270 MHz, $CDCl_3$) δ 2.43 (6H, s), 4 00 (8H, s), 7 32 (4H, d, *J*=8.8 Hz), 7.69 (4H, d, *J*=8.8 Hz); Anal. Calcd for $C_{20}H_{22}N_2O_4S_2$ · C 57 40, H 5.30, N 6.69, S 15.32. Found. C 57.10, H 5.45, N 6 50, S 15.40.

1,2,3,4,5,6-Hexahydropyrrolo[3,4-*c*]pyrrole dihydrobromide (8). 8 5 kg (20.3 mol) of bis(tosylamide) (**7**) and 8 13 kg (86.4 mol, 4 25 equiv) of phenol are added into 46 l of 48% aqueous HBr, contained in an enameled 200 l reactor. The stirred mixture is heated within 2 h to 110 °C, where gentle reflux of the clear solution starts, and is kept at reflux for 6 h . It is then cooled to 25 °C and allowed to stand overnight under N_2 without stirring. The (upper) aqueous phase is siphoned off from the viscous layer into a 100 l separatory funnel and is stirred there with 40 l CH_2Cl_2. The phases are separated and the CH_2Cl_2 layer is

added to the viscous phase in the reactor, leading to a clear two-phase solution that is transferred into the separatory funnel. 10 l of 12% aqueous HBr is added and the mixture is stirred. The (lower) aqueous layer is separated. The combined aqueous phases are washed with 2 x 40 l of CH_2Cl_2. A precipitate of product (**8**), that is occasionally observed during these washings, can be redissolved by the addition of 1 l of water. 1.3 kg of charcoal is added to the aqueous phase, the mixture is stirred for 30 min and allowed to stand overnight. The mixture is suction-filtered through a clarifying pad and the filtrate is concentrated to 25 l in vacuo. The concentrated solution (from which some product has already crystallized) is poured with stirring within 10 min into 80 l of EtOH pre-cooled to 0 °C 40 l of iPr_2O is added and the suspension is stirred 12 h at 0 °C. The solid is collected by suction-filtration, washed with 40 l of EtOH / iPr_2O (1:1), and dried at 30 °C in vacuo to furnish 3.2 kg (58%) of colourless crystals, mp 293-303 °C decomp. , H_2O: 0.3% (K F.), tlc [$CHCl_3$ / MeOH / 28% NH_4OH (6 4.1)] R*f* 0.26 , no uv-active spot, ^{1}H-nmr (270 MHz, D_2O) δ: 4.15 (8H, s), 4:70 (4H, s); ^{13}C-nmr (67 93 MHz, D_2O) δ: 51.4 , 138.8; ir (KBr) ν. 3240-2200 (s, br), *1568 (m), 1463 (m), 1376 (s), 1328 (m), 1209 (m), 846 (m)* cm^{-1}, capillary electrophoresis [70 cm x 75 μm, K_2HPO_4 in 10% *i*PrOH (20 mmol, pH 2.60) , 18 kV, injection: electrokinetic 20 kV / 3 sec, det. uv 200 nm]: *tret* 4 80 min , purity > 96% ; potentiometric titration of HBr. 96-97% dihydrobromide , 3-4% monohydrobromide ; potentiometric titration of Br^- with $AgNO_3$ 100-101% of theory.

1,2,3,5-Tetrahydro-2-[(4-methylphenyl)sulfonyl]pyrrolo[3,4-*c*]pyrrole (9). 100 ml (350 mmol, 8 equiv) of a commercial 70% solution of sodium bis(2-methoxyethoxy)-dihydroaluminate (Red-Al ®) in toluene is added within 5 min under N_2 to the suspension of 18 2 g (43.5 mmol) of ditosylate (**7**) in 90 ml of toluene. The mixture is refluxed for 3 5 h , then cooled to 0 °C. 90 ml of 10% aqueous NaOH is added dropwise with efficient cooling to control the vigorous H_2 -evolution and to keep the exothermic reaction below +25 °C. The organic phase is separated and the aqueous layer is extracted with 3 x 100 ml of CH_2Cl_2 . The combined organic solutions are washed with 50 ml each of 10% aqueous NaOH, water, and brine. The solution is evaporated in vacuo and the residue is flash-chromatographed with an eluent of 99.5% CH_2Cl_2 / 0.5% NEt_3 through 200 g of silica gel (35 - 70 μm) to give 3 4 g (30%) of a colorless solid, mp 176-178 °C; ^{1}H-nmr (60 MHz, $CDCl_3$) δ· 2 39 (3H, s), 4.43 (4H, s), 6.46 (2H, d, J = 2.5 Hz), 7.30 and 7.80 (4H, AB-system, J_{AB} = 8.0 Hz), 8.14 (1H, br m), ir (KBr) ν· 3450 (s), 1332 (m), 1314 (m), 1163 (s), 1100 (m), 1053 (m), 663 (s), 585 (s), 580 (s), 547 (s) cm^{-1}; ms (DCI) m/z (intensity): 263 (30%, $M+H^+$), *261 (100%, M^+-H), 107 (53%, M^+-Ts), 106 (35%, M^+-TsH)*, 80 (52%, $C_7H_6^+$); Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C 59.52, H 5.38, N 10.68, S 12.22. Found. C 59.90, H 5 15, N 10.45

1-Cyclopropyl-6,8-difluoro-7-{3,7-diazabicyclo[3.3.0]oct-1(5)-en-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (10). 33.0 ml (220.7 mmol, 3 72 equiv) of DBU is added to a suspension of 16.8 g (59 3 mmol, 1.00 equiv) of carboxylic acid (**1**) and 16 5 g (60.6 mmol, 1 02 equiv) of dihydrobromide (**8**) in 500 ml of CH_3CN to give a clear solution. After 5 h of reflux tlc (CH_2Cl_2 / MeOH / 25% NH_4OH 6.4·1) indicates virtually complete consumption of **8** (R_f = 0.11) and **1** (R_f = 0.79) and clean formation of **10** (R_f = 0.53). The mixture is cooled in an ice-bath for 30 min. The precipitate is filtered, washed with 300 ml of CH_3CN, 300 ml of water, 50 ml of CH_3CN, and 50 ml of iPr_2O, and dried in vacuo to give 19.7 g (89%) of a pale-yellow powder, mp 256-258 °C; ^{1}H-nmr (270 MHz, CF_3CO_2D) δ. 1.35-1.70 (4H, m, *c*-propyl-*H*), 4.42-4 60 (5H, m, 2 x NCH_2 and NC*H*), 4 95-5.10 (4H, m, 2 x NCH_2), 8.08 (1H, dd, $^3J_{H,F}$ = 14 Hz, $^5J_{H,F}$ = 1 Hz, H_{arom}), 8 51 (1H, br s, =C*H*), 9 28 (1H, s, N*H*), ir (KBr) ν: 3415 (m), 1725(m), 1626 (s), 1462 (s), 1402 (m), 1373 (m), 1350 (m), 1322 (m), 820 (m)cm^{-1}; ms (DCI) m/z (intensity): 374 (100%, M+H$^+$), 329 (6%, M+H$^+$-CO_2H), hplc (250 x 4.0 mm C18 Nucleosil 120 , 5μm ; eluent· H_2O / MeOH / CH_3CN / 85% aq H_3PO_4 = 120 : 60 : 30 · 1 , adjusted to pH 6.2 with NEt_3; 1.0 ml / min , 40 °C ; det 250 and 290 nm): t_{ret} 4.61 min , single peak

1-Cyclopropyl-6,8-difluoro-7-{7-methyl-3,7-diazabicyclo[3.3.0]oct-1(5)-en-3-yl}-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride (11). To 16.4 g (43.9 mmol) of **10** is added 130 ml of 98% formic acid and 26 ml of 35% formaline, and the mixture is refluxed with protection from daylight for 5 h Volatiles are then evaporated in vacuo. 130 ml of *i*PrOH is added to the oily residue with stirring. After 15 min the precipitate is filtered. A solution of 11 g of HCl (gas) in 160 ml of *i*PrOH is added to the pale-yellow solid, and the mixture is refluxed for 4 h. The mixture is cooled to 20 °C. The precipitate is filtered, washed with 100 ml of 1 *N* isopropanolic HCl , with 120 ml of *i*PrOH, with 2 x 120 ml of iPr_2O, and dried in vacuo to furnish 10.6 g (57%) of a pale-yellow crystalline powder, mp 280-285 °C decomp. ; ^{1}H-nmr (270 MHz, DMSO-d_6) δ 1.10-1.30 (4H, m, *c*-propyl-*H*), 2.98 (3H, s, CH_3), 3 85-4.05 (2H, m, NCH_2), 4.10 (1H, m, NC*H*), 4.25-4.50 (2H, m, NCH_2), 4.62 (4H, br s, 2 x NCH_2), 7.77 (1H, dd, $^3J_{H,F}$ = 14 Hz, $^5J_{H,F}$ = 1 Hz, H_{arom}), 8.65 (1H, s, =C*H*), 11 93 (1H, br s, N$^+$*H*), 14.88 (1H, br s, CO_2H); ir (KBr) ν: 3520 (m), 3420 (m), 2750-2100 (m, br), 1727 (m), 1628 (s), 1520 (m), 1472 / 1463 / 1451 (s), 1375 (m), 1322 (m), 804 (m) cm^{-1}; ms (FAB) m/z (intensity): 388 (100%, M+H$^+$ of the free base), uv (H_2O, 17.4 μg / ml) λ (extinction coeff. ε [l mol^{-1} cm^{-1}]) 209 (1 50 x 10^4), 231 (1.28 x 10^4), 289 (3 96 x 10^4), 330 nm (1.15 x 10^4), faint absorption up to 420 nm ; hplc (cond. as described for **10**)· t_{ret} 7.10 min, 99 7% ; potentiometric titration of HCl : 104.7% of theory ; potentiometric titration of Cl$^-$ with 0.1 *N*

$AgNO_3$: 101.7% of theory , Anal Calcd for $C_{20}H_{20}N_3O_3ClF_2$. C 56 68 , H 4.76, Cl 8.36, F 8.96, N 9.91. Found: C 54.40, H 4.85, Cl 8.20, N 9.40

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13. If a significant amount of sublimed tetrabromide (**6**) remains in a reflux condenser, it is dissolved by refluxing EtOAc (10 l / kg) and collected by evaporation of the solvent
14. The only significant impurity gives ^{1}H-nmr singlets (60 MHz, $CDCl_3$) at δ 4.20 (CH_2Br) and 6.78 ($CHBr_2$) ppm and is thus identified as the hexabromide.

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