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THE STEREOCHEMISTRY OF SPIROPIPERIDINE CYCLIZATIONS[1]

(HISTRIONICOTOXIN, PART I)

MICHAEL GLANZMANN, CHATCHANOK KARALAI, BERND OSTERSEHLT, UWE SCHÖN, CHRISTIANE FRESE, and EKKEHARD WINTERFELDT*

Institut für Organische Chemie der Universität Hannover,
Schneiderberg 1 B, D-3000 Hannover, West Germany

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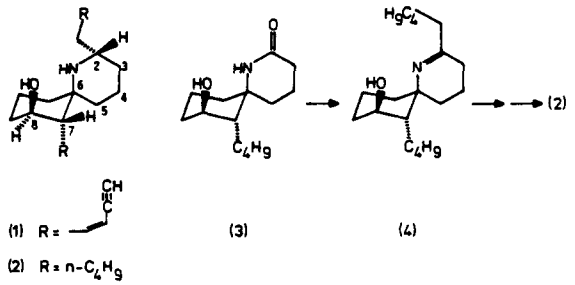
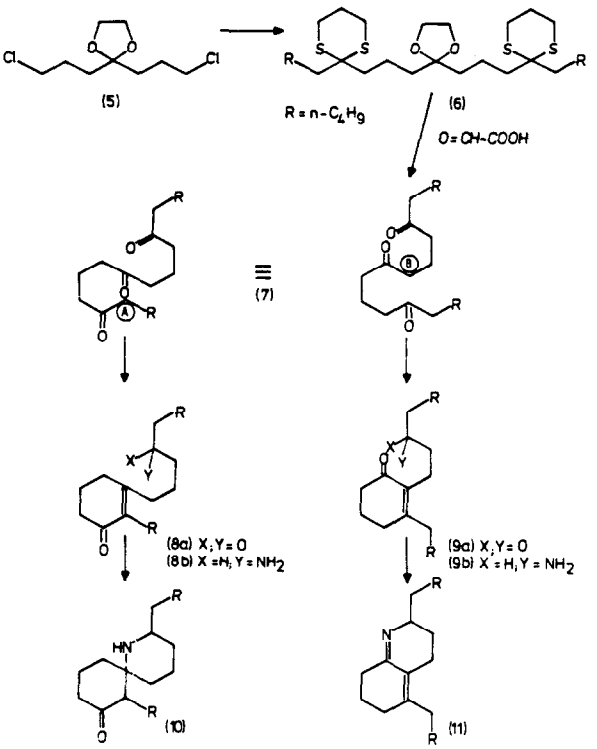
Abstract - The spirocyclization of straight-chain triketo-intermediates, similar to possible biogenetic precursors of histrionicotoxin, is shown to be stereoselective, generating the non-natural configuration at C-2. Aiming at an sp^2-center in this position, triketo-brassylic ester was treated with ammonia at room temperature and was shown to cleanly and efficiently yield a spiroketone.

The unusual structure of histrionicotoxin (1) and perhydrohistrionicotoxin (2)[2] as well as their interesting physiological activity[3] has led to various investigations aiming at spiropiperidines in general[4]. In a number of laboratories this work culminated in a total synthesis of perhydrohistrionicotoxin[5] and very recently one of these routes were adapted for a synthesis of pure enantiomers, too.[6] Many of the synthetic routes however, stop at Kishi's intermediate (3) which via (4) in a special aluminum-hydride reduction is giving rise to a 7 : 3 mixture[6] of perhydrohistrionicotoxin (2) and 2-epi-perhydrohistrionicotoxin, thus documenting the installation of the correct configuration at C-2 to be one of the key problems in this field.

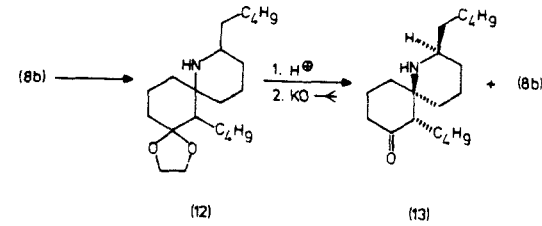


When we started work in this class of compounds a few years ago we were mainly interested in the stereochemistry of the spirocyclization of straight-chain intermediates of type (7) as this according to Witkop's biogenetic reasoning[2b] should be an equivalent of the possible common precursor for histrionicotoxin as well as gephyrotoxin type alkaloids.



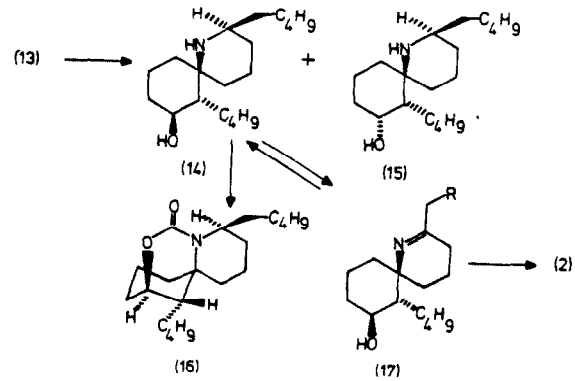
This triketone intermediate may be prepared in a few simple steps via triketal (6) which is generated in a thioketal alkylation from dichloro-ketal (5) - a starting material available on kg scale from butyrolactone.[7] Glyoxylic-acid-hydrolysis transforms the protected triketone derivative (6) into the symmetric triketone (7) which in principle may be isolated but which on prolonged treatment with acid cyclizes to the hard to separate mixture of the non symmetric cyclohexenones (8a) and (9a); as can be easily proven by the subsequent formation of the basic compounds (8b) and (11) on reductive amination.[8] These fortunately differ considerably in polarity as (9b) does cyclize spontaneously under the reaction conditions generating the much less polar conjugated imine (11). (8b) and (11) can be easily separated and they represent the carbon-framework of histrionicotoxin - as well as gephyrotoxin - or pumiliotoxin-alkaloids, thus proving that a polycarbonyl-intermediate of type (7) can easily cyclize to give rise to both types of alkaloids. This obviously is due to the fact that C-H-bond acidity and nucleophilicity in CH_2-group-(A) is very similar to (B) [see formula (7)]. Selective histrionicotoxin cyclization therefore would demand for extra acidification in (A) [see below].

Concentrating on the histrionicotoxin series the spirocyclization of (8b) was studied next. As was also reported by Corey and Balanson[5f] normal Michael cyclization does not work and so we decided to shift the Michael equilibrium by ketalization[8] and were pleased to note that on heating in toluene one spiroketal mainly was obtained. This one stereoisomer quickly can be classified as the product of thermodynamic control as preparation of the same compound in benzene gives rise to a mixture of stereoisomers which on further heating in toluene is focused again into this one stereoisomer. Without determining its configuration the ketal-group was hydrolyzed with hydrochloric acid in a tetrahydrofuran-acetonitrile mixture with only a very small amount of the easy to separate ring open material (8b) being formed in an accompanying retro-Michael-reaction. Interestingly the resulting ketone turns out to be a mixture of stereoisomers again, but according to our expectations subsequent treatment with potassium-tert.butoxide clearly converted this into (13) as the thermodynamic stable main product of the spirocyclization process, proving the relative configurations



at C-2, C-6 and C-7 to be introduced in a stereoselective manner.

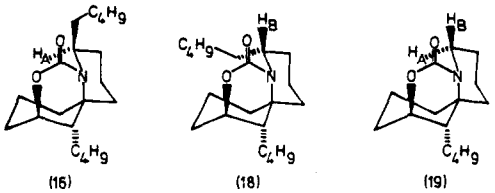
The relative configuration given in (13) can be proven the following way:



Lithium-aluminum-hydride reduction of (13) gives rise to two spirocarbinols, one of them (14) cyclizing readily with phosgene to yield the cyclic urethane (16) and thus proving the cis-relationship of hydroxy- and amino-group. As this same aminocarbinol is together with perhydrohistrionicotoxin also obtained from imine (17) - kindly provided by Dr. A.Brossi - on borohydride reduction, the 2-epi-configuration (14) for this alcohol as well as configuration (13) for the thermodynamic stable ketone obtained on ketal-hydrolysis is proven.

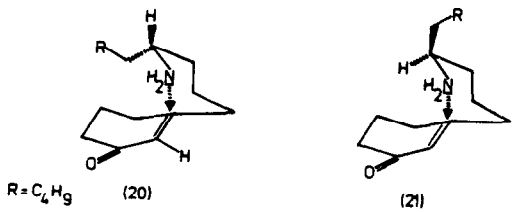
Hypohalogenide treatment and subsequent elimination transforms (14) into (17) which on aluminum-hydride reduction has been shown to yield perhydrohistrionicotoxin as the main product[*]. For comparison the cyclic urethane (18) of perhydrohistrionicotoxin was prepared, too and it is worth mentioning that this functionality is extremely useful for a quick and easy decision on the configuration at C-2.

[*] This material proved to be identical (IR, DC, MS) with a sample kindly provided by Prof. Y.Kishi.

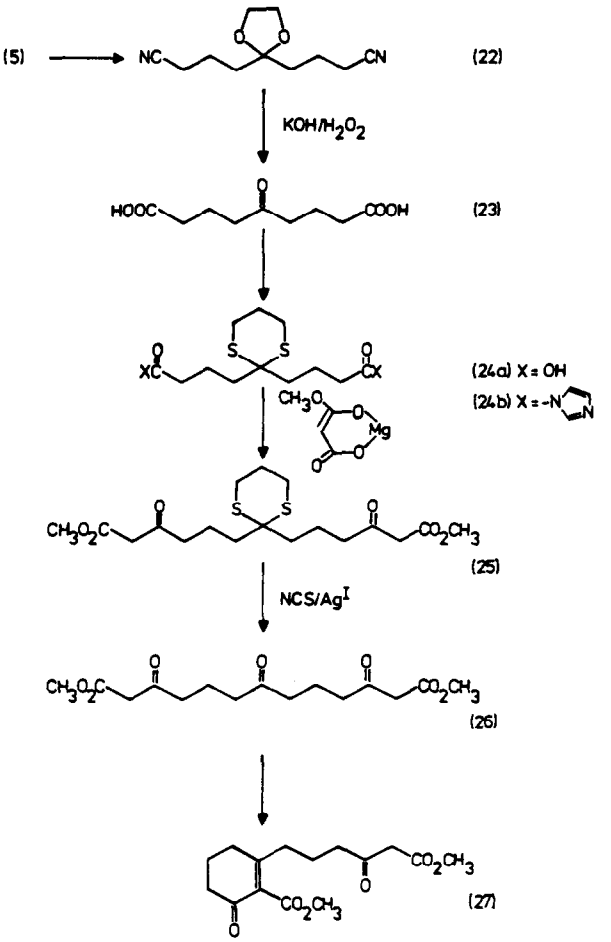


While the axial α-proton H_A in (16) shows up as a broad multiplet between 4.2 and 3.9 ppm the corresponding ß-proton H_B in the perhydro-histrionicotoxin-derivative (18) gives rise to a narrow triplet at 4.4 ppm shifted downfield by the adjacent carbonyl-group. To prove this interpretation the cyclic urethane (19) which can be easily prepared from 2-des-pentyl-perhydro-histrionicotoxin[+] was investigated, too. In this case there is the advantage of both protons AB being present in the same molecule and thus giving rise to an easy to analyze AB-pattern. In this urethane the non-deshielded axial α-proton is appearing even at 2.7 ppm as a broad triplet, well separated from the equatorial proton at 4.3 ppm.

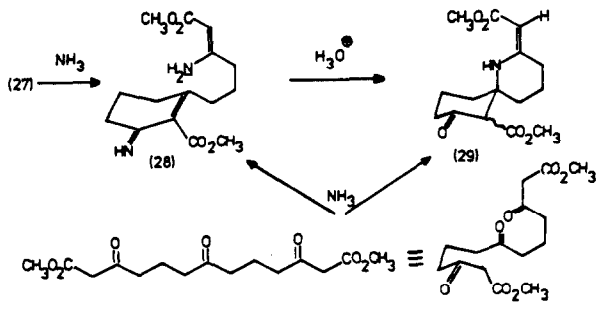
These results prove that without extra acidification by R,spiro-type compounds as well as hydroquinolines are formed in equal amounts on cyclization [see (7)] and that sp^3-hybridization at carbon-atom-2 gives rise in this process to the nonnatural 2-epi-configuration. This can be explained by strong steric interactions of the pentyl-group with the cyclohexenone-system in Michael-addition transition state (20), as compared to the situation in (21) which is giving rise to (13).



For a regioselective and stereoselective approach to histrionicotoxin-type-compounds, R should activate the neighbouring CH_2-group and C-2 should be an sp^2-center in the spiro-cyclization-step. This was the reason to prepare triketone (26) in the following way:



The thioketalization of (23) prior to formation of the imidazolide intermediate turned out to be necessary to avoid enollactone-formation in the ß-ketoester synthesis.[9] Deprotection yielded (26) which as predicted under very mild conditions cyclized with excellent regio-selectivity to generate (27) exclusively, in 80% isolated yield. On treatment with ammonia this cyclohexenone-derivative was very smoothly transformed into (28). Leaving this compound in dilute acid at room temperature very quickly gave rise to spiroketone (29), thus proving spirocyclization to be an extremely easy process with an sp^2-center at C-2.



[+] A sample of this material was also kindly provided by Dr. A.Brossi.

Owing to enolization at the ß-ketoester group the configuration of this compound was not investigated in detail[*] but as a number of chemoselective as well as stereoselective reactions were feasible, making (29) a quite attractive intermediate we considered the direct transformation of triketone (26) into (29), hopefully generating this spiro-compound under very mild biogenetic conditions.
When (26) was left at room temperature in dioxane saturated with ammonia it was quickly and cleanly converted into two products which proved to be identical with the monocyclic imine (28) and the desired spiro-ketone (29). To convert this mixture into pure (29) it was treated with aqueous acid as shown above and to our great delight (29) was obtained in high yield. This result proves that a simple triketone easily generates a spiro-piperidine bearing the necessary functionality for further elaboration into histrionicotoxin-type compounds.

EXPERIMENTAL

Infrared spectra were taken on Perkin-Elmer 467 and UV spectra on a Beckman DB-GT. ^{1}H-NMR spectra were taken with tetramethylsilane as reference on a Bruker WH-90 and mass spectra were recorded on a CH-5 instrument. High resolution measurements were done with a Varian MAT 711 instrument at 70 eV. TLC-separations were run on Macherey-Nagel (0.5 mm)- or Woelm (0.25 mm)-plates and melting points were determined on a Kofler bank.

6,10,14-Triketo-nonadecane (7):

95.2 g freshly distilled 2-amyl-1,3-dithiane is dissolved in 1 l dry tetrahydrofuran and at -30°C treated with 305 ml of a 1.65M solution of butyllithium in n-hexane. The mixture is left overnight at -25°C and then 56.8 g of chloroketale (5) are added and standing at -25°C is continued for another 12 h. After raising the temperature to +20°C and standing at this temperature for 12 h the reaction mixture is poured into water, extracted with chloroform and the solvent evaporated at reduced pressure. The remaining residue (yield: 74%) is hydrolyzed the following way: 14 g are dissolved in a 10 : 1 mixture of acetonitrile and concentrated HCl (800 ml) after addition of 13 g glyoxylic-acid hydrate the hydrolysis is run at room temperature (DC-control). A sample is taken, washed with saturated sodiumbicarbonate-solution, evaporated and crystallized from ether, m.p. 106°C; IR ($CHCl_3$): 1700, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.25 - 2.55 [12] m, 1.10 - 2.00 [16] m, 0.78 - 1.00 [6] m; MS: m/e 310 (M^+, 10), 292 (31), 254 (26), 239 (30), 236 (54), 221 (54), 197 (38), 169 (97), 151 (47), 149 (100), 99 (92), 97 (61), 95 (43). Found: C, 73.40; H, 11.06. Calc.for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04.

Aminocyclohexenone (8b):

If the reaction described above is run to completion a mixture of the two cyclohexenones (8a) and (9a) is formed [yield 79%; UV (CH_3OH: 247 nm; IR ($CHCl_3$): 1710, 1655, 1620 cm^{-1}; MS: m/e 292 (M^+, 80)] which is not separated but dissolved in 150 ml dry methanol, 50 g ammoniumacetate are added and the solution treated with 1.3 g pure sodiumcyanoborohydride for 6 h at room temperature, poured into saturated sodium-bicarbonate solution and extracted with ether. After evaporation the polar aminocyclohexenone (8b) is separated from (11) by chromatography on aluminumoxide (neutral, grade I, ether/methanol) yielding (8b) in 30% yield. UV (CH_3OH): 244 nm; IR ($CHCl_3$): 1655, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 3.34 - 2.95 [1] m, 2.48 - 2.09 [4] m, 2.07 - 1.05 [22] m, 1.00 - 0.72 [6] m.
For characterization this aminocyclohexenone is transformed into its N-acetate by leaving overnight in acetic-acid-anhydride. m.p. 68°C; IR ($CHCl_3$): 3440, 1660, 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 5.84 [1] d (J = 8 Hz, 3.70 - 4.07 [1] m, 2.12 - 2.70 [6] m, 1.80 - 2.10 [2] m, 2.02 [3] s, 1.10 - 1.75 [18] m, 0.75 - 1.10 [6] m; MS: m/e 335 (M^+, 100), 292 (51), 276 (47), 264 (71), 233 (38), 220 (41), 205 (63), 193 (82), 114 (82), 100 (70). Found: 335.2833 (mass spectroscopy). Calc.for $C_{21}H_{37}NO_2$: 335.2824.

2-Epi-8-oxo-perhydrohistrionicotoxin (13):

300 mg of aminocyclohexenone (8b) are dissolved in 450 ml dry benzene and after addition of 300 mg ethyleneglycol and 200 mg p-toluene sulfonic acid the mixture is slowly distilled. After evaporation of 400 ml benzene the remaining residue is diluted with ether and washed with saturated sodium-bicarbonate. The residue after evaporation to dryness is dissolved in 60 ml of a 10 : 1 mixture of tetrahydrofuran and acetonitrile and treated with 3 ml concentrated aqueous HCl for 30' at 65°C. The reaction mixture is poured into saturated sodium-bicarbonate and extracted with ether. For epimerization the reaction product is heated for three hours in 200 ml of a 5% solution of potassium-tert.butoxide in tert.-butanol, poured into saturated sodiumchloride solution and again extracted with ether. The raw material (88% yield) is separated by TLC to yield (13) as main product: IR ($CHCl_3$): 3010 - 2865, 1698 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.96 - 2.72 [1] tr (J = 7.2 Hz), 2.62 - 2.12 [3] m, 2.10 - 1.04 [24] m, 1.01 - 0.77 [6] tr (J = 7 Hz); MS: m/e 293 (M^+, 28), 250 (66), 236 (17), 222 (18), 206 (27), 194 (19), 180 (72), 167 (43), 96 (100). Found: 293.2718 (mass spectroscopy). Calc.for $C_{19}H_{35}NO$: 293.2718.

2-Epi-perhydrohistrionicotoxin (14):

100 mg of ketone (13) dissolved in 100 ml dry ether was treated with 100 mg lithiumaluminumhydride for 30' at room temperature. After work-up the less polar material is separated by TLC and proved to be 30% of the reaction product. IR ($CHCl_3$): 3440 - 3065, 2935 - 2870, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.93 - 3.78 [1] s broad, 2.75 - 2.38 [1] m, 2.22 - 1.05 [27] m, 1.00 - 0.74 [6] m; MS: m/e 295 (M^+, 39), 294 (6), 278 (14), 266 (6), 252 (75), 238 (21) 234

[*] The presence of more than one olefinic proton may be explained by E- and Z-configuration of the exocyclic double bond as well as keto-enol-tautomerization.

(9), 224 (100), 222 (15), 206 (12), 196 (38), 194 (12), 183 (14), 181 (28), 180 (68), 167 (51), 154 (28), 149 (17), 140 (9), 124 (12), 110 (21), 96 (30). Found: 295.2873 (mass spectroscopy). Calc.for $C_{19}H_{37}NO$: 295.2874.

The more polar product turned out to be 2-epi-8-epi-perhydrohistrionicotoxin (15):

Yield: 60%. IR ($CHCl_3$): 3610, 2935 - 2860, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 4.2 - 3.96 [1] m, 2.71 - 2.41 [1] m, 1.85 - 1.02 [27] m, 0.94 - 0.68 [6] m; MS: m/e 295 (M^+, 37), 294 (6), 278 (14), 266 (5), 252 (100), 238 (17), 234 (7), 224 (41), 222 (11), 206 (7), 196 (24), 194 (9), 180 (58), 167 (36), 154 (19), 124 (7), 110 (11), 96 (18). Found: 295.2873 (mass spectroscopy). Calc.for $C_{19}H_{37}NO$: 295.2874.

1,2-Dehydro-perhydrohistrionicotoxin (17):

20 mg (14) dissolved in 20 ml dry ether is treated with one drop tert.butyl-hypochloride. After 30' at room temperature 20 mg potassium-tert.butoxide are added and the mixture stirred at room temperature for another 30 h. The reaction mixture is mixed with saturated sodium-chloride solution and extracted with ether. The product obtained after evaporation proved to be identical (TLC, MS, IR) with a sample of (17) provided by Dr. Brossi.

General procedure for preparation of cyclic urethanes (16), (18), and (19):

20 mg of the corresponding spirocarbinol dissolved in 3 ml dry toluene is treated with 50 mg diisopropylethylamine. After cooling to -78°C 0.3 ml of a solution of phosgene in toluene (20%) are added. The mixture is left overnight at room temperature, diluted with ether, washed with dilute citric-acid, saturated sodium-bicarbonate and finally saturated sodiumchloride solution. After evaporation the raw material is purified on TLC to yield the cyclic urethanes in yields ranging between 45 and 55%.

(16): IR ($CHCl_3$): 2960 - 2890, 1658, 1468, 1415 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 4.52 - 4.37 [1] tr, 4.20 - 3.90 [1] m, 2.07 - 1.10 [27] m, 1.02 - 0.75 [6] m; MS: m/e 321 (M^+, 3), 278 (3), 251 (19), 250 (66), 234 (2), 222 (3), 207 (24), 206 (100), 194 (5), 189 (8), 163 (8), 149 (25), 133 (19), 105 (8), 91 (13). Found: 321.2666 (mass spectroscopy). Calc.for $C_{20}H_{35}NO_2$: 321.2667.

(18): IR ($CHCl_3$): 2960 - 2860, 1658, 1464, 1412, 1264 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 4.5 - 4.3 [2] m, 2.10 - 1.11 [27] m, 1.01 - 0.86 [6] m; MS: m/e 321 (M^+, 4), 277 (3), 275 (2), 264 (2), 251 (20), 250 (70), 233 (2), 219 (4), 207 (24), 206 (100), 189 (8), 163 (9), 149 (19), 146 (5), 133 (20), 91 (15). Found: 321.2666 (mass spectroscopy). Calc.for $C_{20}H_{35}NO_2$: 321.2667.

(19): IR ($CHCl_3$): 2955 - 2855, 1660, 1420, 1260, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 4.5 - 4.2 [2] m, 2.8 - 2.5 [1] tr broad, 2.21 - 1.14 [19] m, 1.05 - 0.79 [3] m; MS: m/e 251 (M^+, 55), 222 (4), 209 (22), 208 (77), 207 (7), 206 (12), 195 (20), 194 (28), 178 (34), 165 (27), 164 (75), 152 (74), 150 (23), 137 (31), 136 (36), 123 (18), 122 (22), 110 (15), 97 (100). Found: 251.1883 (mass spectroscopy). Calc.for $C_{15}H_{25}NO_2$: 251.1885.

5-Keto-azelaic-acid-thioketal (24a):

100 g 5-keto-azelaic-acid is dissolved in acetic-acid at 50°C (200 ml) 50 g propanedithiole and a few ml boron-trifluoride etherate are added and the mixture stirred for 1 h at 50°C. The precipitate is filtered, washed with ether, and dried in vacuum at 50°C. Yield: 131 g (91%); m.p. 153°C; IR (KBr): 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 2.93 - 2.71 [4] m, 2.35 [4] tr (J = 7 Hz), 2.09 - 1.60 [10] m; MS: m/e 292 (M^+, 40), 205 (100), 145 (25). Found: C, 49.31; H, 6.95. Calc.for $C_{12}H_{20}O_4S_2$ (292.08): C, 49.29; H, 6.89.

Di-imidazolide (24b):

5.6 g of diacid (24a) are mixed with 55 ml dry methylenechloride and 6.8 g carbonyldiimidazole are added in small portions. The solution gets clear in about two hours and is washed with cold 5% sodium-bicarbonate solution and dried. After evaporation CCl_4 is slowly added and 7.1 g (95%) of crystals are obtained. m.p. 132°C; IR (KBr): 1735, 1475, 1387, 1274, 1245 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 8.20 [2] s broad, 7.50 [2] tr (J = 1.5 Hz), 7.12 [2] dd (J = 1.5, 0.8 Hz), 2.97 [4] m, 2.85 [4] m, 2.00 [10] m. Found: C, 55.15; H, 6.25; N, 14.11. Calc.for $C_{12}H_{24}O_4S_2$ (292.41): C, 55.08; H, 6.16; N, 14.27.

3,7,11-Triketo-dimethyl-brassylate (26):

A solution of 23.4 g potassium salt of malonic-acid-mono-methylester in tetrahydrofuran (300 ml) is at 0°C mixed with 100 ml of a solution of isopropylmagnesiumbromide in tetrahydrofuran (3.6 g Mg, 14 ml isopropylbromide, 100 ml THF). After mixing both solutions the reaction is run at room temperature for another 30'. A solution of the diimidazolide (24b), prepared from 11 g (24a), 12.2 g carbonyldiimidazole and 30 ml tetrahydrofuran is added and stirring is continued for 12 h. After pouring into 2N H_2SO_4 and extracting with ether, the organic layer is washed with sodium-bicarbonate, dried and the solvent evaporated. Yield: 12.2 g (81%). For thioketale splitting the raw material is dissolved in 10 ml acetonitrile and added to a solution prepared from 17 g N-chloro-succinimide, 25 g silvernitrate, 360 ml acetonitrile and 90 ml water. After 15' at room temperature saturated sodium-hydrogensulfit- and sodium-chloride solution is added and after extraction and evaporation crystals of ß-ketoester (26) are obtained in 60% yield. m.p. 58 - 60°C (ether); IR (KBr): 1750, 1720, 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 3.75 [6] s, 3.45 [4] s, 2.6 [4] tr (J = 7 Hz), 2.4 [4] tr (J = 7 Hz), 1.85 [4] m; MS: m/e 296 (M^+, 12), 171 (65), 168 (15), 167 (25), 153 (20), 139 (50), 130 (95), 112 (35), 102 (35), 97 (30), 70 (25), 60 (55), 56 (100). Found: C, 57.23; H, 7.03. Calc.for $C_{15}H_{22}O_7$ (314.11): C, 57.31; H, 7.05.

Cyclohexenone (27):

1 g of triketone (26) in 50 ml dry methanol is treated with 300 mg acetic-acid and 300 mg diisopropyl-ethyl-amine and left in the freezer for 10 days. The reaction mixture is dissolved in methylenechloride, washed with dilute HCl and sodium-bicarbonate solution. The residue obtained on evaporation may be directly used for the introduction of nitrogen [see (28)], but for characterization a sample was purified by reversed phase-chromatography (methanol/water 1 : 1). The combined fractions are again extracted with methylenechloride, dried ($MgSO_4$) and evaporated. UV (CH_3OH): 237 nm; IR ($CHCl_3$):

1750 - 1720, 1675, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 3.82 [3] s, 3.73 [3] s, 3.48 [2] s, 2.7 - 1.8 [12] m; MS: m/e 296 (M^+, 12), 265 (12), 264 (14), 233 (12), 232 (22), 164 (80), 163 (40), 149 (61), 136 (29), 79 (31), 77 (26), 59 (51), 55 (100). Found: 296.1258 (mass spectroscopy). Calc.for $C_{15}H_{20}O_6$: 296.1259.

Imine (28):

850 mg ammoniumnitrate are dissolved in 70 ml dry methanol and saturated with ammonia at 0°C. 3 g of cyclohexenone (27) dissolved in 10 ml dry methanol are added and the temperature is allowed to rise. The stream of ammonia is continued for another 5 h, the solvent evaporated and the residue dissolved in dry methylenechloride. After filtration the solution is again taken to dryness and then treated with ether. On evaporation of the ether one gets colourless crystals (2.2 g = 78%) of m.p. 147 - 152°C (decomposition). UV (CH_3OH): 297 nm (22 300); IR ($CHCl_3$): 3500, 3320, 1650, 1640, 1600, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 8.72 [1] broad, 6.4 [2] broad, 4.25 [1] s, 3.68 [3] s, 3.59 [3] s, 2.5 - 2.1 [6] m, 1.9 - 1.5 [6] m; MS: m/e 294 (M^+, 44), 236 (16), 208 (16), 204 (21), 180 (100), 179 (23), 168 (30), 154 (30), 148 (86), 140 (30). Found: 294.1579 (mass spectroscopy). Calc.for $C_{15}H_{22}N_2O_4$: 294.1579. Found: C, 61.19; H, 7.56; N, 9.46. Calc.for $C_{15}H_{22}N_2O_4$ (294.15): C, 61.21; H, 7.53; N, 9.52 (recrystallization for analysis was done from dioxane saturated with ammonia, to avoid hydrolysis of the imine).

Spiroketone (29):

1.55 g of imine (28) dissolved in 20 ml tetrahydrofuran is treated for 1.5 h at room temperature with 100 ml 0.1N HCl. After neutralization with saturated sodium-bicarbonate solution and extraction with methylenechloride one obtains 1.52 g (98%) of the spiroketone (29). UV (CH_3OH): 286 nm; IR ($CHCl_3$): 1740, 1712, 1650, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 9.15, 8.8 [1] broad, 4.5 - 4.3 [1], 3.8 - 3.6 [7] m, 2.5 - 2.2 [4] m, 2.05 - 1.5 [8] m; MS: m/e 295 (M^+, 18), 294 (30), 264 (18), 232 (19), 204 (19), 181 (24), 180 (90), 176 (22), 168 (31), 167 (31), 163 (25), 162 (30), 149 (50), 148 (72), 79 (40), 77 (36), 59 (50), 55 (100). Found: 295.1417 (mass spectroscopy). Calc.for $C_{15}H_{21}NO_5$: 295.1419.

For direct preparation from tri-keto-brassylate (26) 580 mg of this material are left at room temperature in 60 ml of a saturated solution of ammonia in dioxane for 15 h with further ammonia being bubbled through. The raw material obtained on evaporation is treated with acid as given under (29) to yield the spiroketone in 88% yield on chromatography (ether). Its identity with compound (29) described above was proven by comparison of IR- and MS-spectra as well as by TLC.

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