# Derivatives of Benzo[4,5]cyclohepta[1,2-*b*]thiophene. 2. Synthesis of (±)-6,t-8b,9,10,11,12,13,t-13a-Octahydro-5*H*-7-thia-12a-azabenzo[*f*]-naphth[1,2,3-*cd*]azulene (QM-7184) [1]



Enrique Arribas and Salvador Vega* [2]

Instituto de Química Médica, C.S.I.C.,
Juan de la Cierva, 3, Madrid-6, Spain

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The synthesis of (±)-6,t-8,9,10,11,12,13,t-13a-octahydro-5*H*-7-thia-12a-azabenzo[*f*]naphth[1,2,3-*cd*]azulene (III) (QM-7184) by two independent pathways is described. Configurational assignments have been made on the basis of nmr spectral interpretations.

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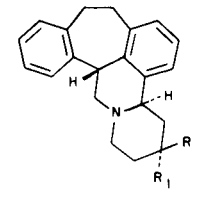
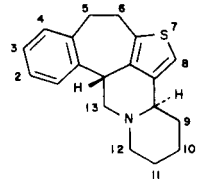
Some years ago, a novel class of pentacyclic compounds with a benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline skeleton in their molecules, was shown to possess useful psychopharmacological properties. Typical examples of these compounds are butaclamol (I) an antipsychotic drug whose efficacy in man has been demonstrated and taclamine (II) a psychotropic agent exhibiting actions characteristic of antianxiety drugs in experimental animals [3-5].



I R = t-butyl, $R_1$ = OH
II R = $R_1$ = H



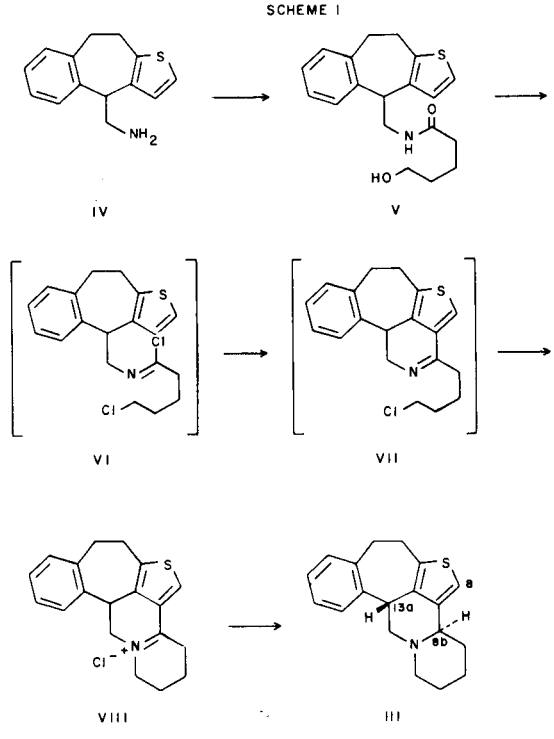
III
QM-7184

Our interest in the search of potential CNS agents prompted us to investigate the synthesis of a series of new derivatives of benzo[4,5]cyclohepta[1,2-*b*]thiophene which is a thiophene isostere system of dibenzo[a,d]cycloheptene from which both taclamine and butaclamol have been prepared.

As a part of this research program, we report here the synthesis of the title compound III, a thiophene isostere of taclamine and the first representative of the novel 7-thia-12a-azabenzo[*f*]naphth[1,2,3-*cd*]azulene ring system.

The pentacyclic ring of QM-7184 was constructed through two independent pathways. In the first (Scheme 1), a modification of the procedures reported [5] for the preparation of taclamine was used. Thus, amino derivative IV [1] was acylated with δ-valeroacetone or ethyl δ-hydroxyvalerate to give the δ-hydroxivaleramide V in 65% yield. This amide, on treatment with phosphorus pentachloride underwent a double cyclization, probably through the intermediate halogen compounds VI and VII which have not been isolated but successively detected in the course of the reaction by thin layer chromatography

SCHEME I

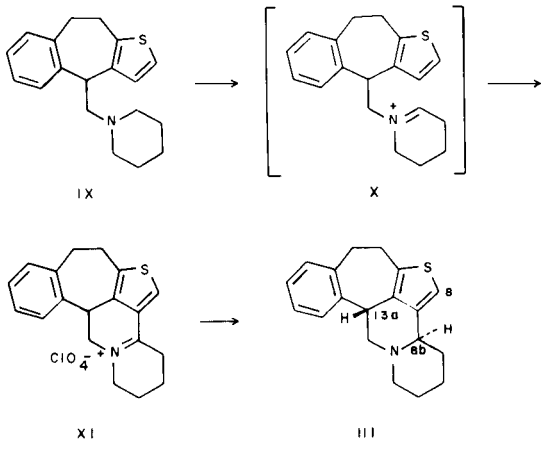


IV V VI VII VIII III

($R_f$ 0.8 and 0.5, respectively), to afford the pentacyclic iminium salt VIII. Reduction of VIII with sodium borohydride, or zinc and hydrochloric acid generated in both cases the 8b-13a-*trans* isomer free base III which was converted to the corresponding hydrochloride salt.

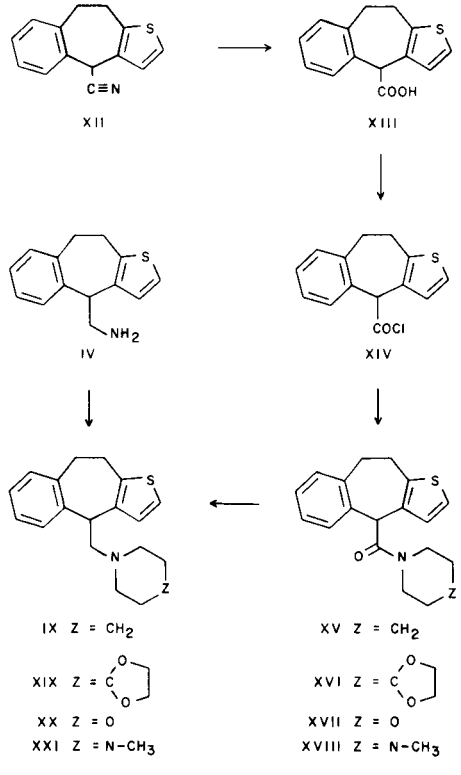
The second pathway for the synthesis of QM-7184 (Scheme 2) involved an oxidative cyclization of piperidine derivative IX carried out with mercuric acetate in dilute acetic acid. The oxidation of cyclic tertiary amines by mercuric acetate is a well known reaction [6] which has been largely utilized mainly in the chemistry of indole and isoquinoline alkaloids [7]. In our case, with the use of the method described by Wenkert and Wicberg [8] it was possible to isolate the perchlorate of the iminium salt XI which was converted to III through its reduction with sodium borohydride.

SCHEME 2



Scheme 3 illustrates the synthetic routes for *N*-(4-methyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-piperidine (IX). It was directly prepared by alkylation of amine IV with 1,5-dibromopentane in acetone or acetonitrile in the presence of potassium carbonate [9]. However, a better yield could be obtained by reduction of amide XV with an equimolar mixture of lithium aluminum hydride and aluminum chloride [10]. Intermediate XV was prepared in three steps by alkaline hydrolisis of carbonitrile XII [1] to the acid XIII followed by halogenation and reaction with piperidine. The use of this last method also

SCHEME 3



permitted the preparation of aminocompounds XIX-XXI, which were obtained to open a possible route for the synthesis of thiophene analogs of butaclamol (I).

The structure of III was established on the basis of the following evidences. Firstly, cyclization of compound V on the thiophene ring was demonstrated by examination of the $^1$H- and $^{13}$C-nmr spectra of III. The signal at $\delta$ 6.70, a singlet corresponding to the thiophene proton at position 8, as well as its integration in respect to that of the benzene protons (1:4), showed, as expected, that III came from the salt cyclized on the thiophene ring. Besides, in the coupled $^{13}$C-nmr spectrum, the coupling of the carbon atom at position 8 with a proton could be observed, while the carbon atom at position 8a appeared as a singlet.

Secondly, due to the particular complexity of the $^1$H-nmr spectrum of III, the configurational assignments at the 8b and 13a centers could not be made by application of the criteria employed in the case of taclamine [5], based, in a great part, on the direct interpretation of its $^1$H-nmr spectroscopic data. However, this difficulty could be circumvented by running the $^1$H-nmr spectrum of III in the presence on increasing amounts of Eu(fod)$_3$, a paramagnetic induced-shifts reagent. As it is known [11], these complexes displace the signals of nitrogen heterocyclic protons associating to the nitrogen atom by its electronic lone pair. In general, the magnitude of these shifts increase with the increasing of lanthanide concentration, being the protons nearest the association point the most shifted.

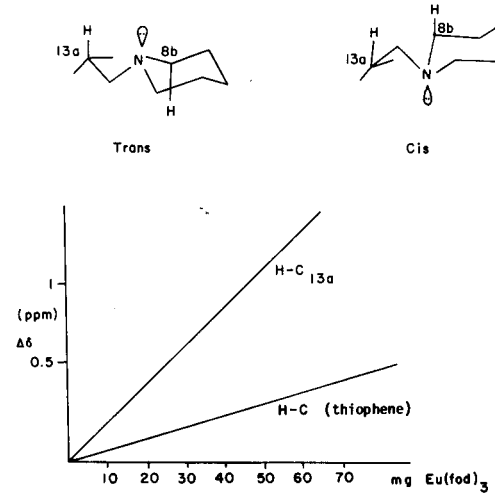


FIGURE 1

As illustrated in Figure 1, if compound III were the *cis*-isomer, both protons at 8b and 13a would be opposite to the Eu(fod)$_3$ complex and their chemical shifts should not vary in respect to those of other molecular protons which are little or nothing affected by the reagent. In the case of the *trans*-isomer, the 13a proton would be on the same side

of the molecule than the $Eu(fod)_3$ and therefore a strong shift of its signal should be expected.

In fact, taking as a reference the thiophene proton for which $\Delta\ \delta$ must be similar in both isomers, a large downward shift of the 13a proton signal could be observed and based on this evidence the 8b-13a-*trans* relative configuration was assigned to III.

## EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were taken on a Perkin-Elmer Model 257 instrument. The $^1$H-nmr spectra were measured with a Varian EM-390 spectrometer using TMS as internal reference. The $^{13}$C-nmr spectra were recorded on a Bruker WP-80 instrument using TMS as internal reference. Mass spectra were obtained on a Varian MAT-711 spectrometer.

*N*-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-methyl)-δ-hydroxivaleramide (V).

Method A.

A mixture of the amine IV [1] (20 g, 0.043 mole) and δ-valerolactone (6 g, 0.06 mole) was heated for 3 hours at 150°. After cooling, the resultant oil was treated with ethyl acetate and hexane, crystallizing V as a white solid (7 g, 65%), mp 114-115° (benzene); ir (nujol: 3250-3450 $cm^{-1}$ (OH), 3330 $cm^{-1}$ (NH), 1640 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 1.6 (m, 4, O-C-$CH_2CH_2$-C), 2.1 (m, 3, $CH_2$-C=O and OH), 3.15 (m, 4, $CH_2$-$CH_2$), 3.7 (m, 4, $CH_2$-O and $CH_2$N), 4.35 (t, J = 8.1 Hz, 1, CH-C), 5.65 (br s, 1, NH), 6.96 (d, J = 5.4 Hz, 1, S-C=CH), 7.15 (d, J = 5.4 Hz, 1, S-CH=C), 7.3 (s, benzene).

*Anal.* Calcd. for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.03; N, 4.25; S, 9.71. Found: C, 69.07; H, 7.10; N, 4.30; S, 10.04

Method B.

A solution of the amine IV (10 g, 0.043 mole) and ethyl-δ-hydroxivalerate [12] (8 g, 0.05 mole) in xylene (10 ml) was refluxed for 16 hours. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate gave 7 g (65%) of the compound V identical with that described above.

4-Carboxy-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (XIII).

A well stirred mixture of the nitrile XI [1] (30 g, 0.13 mole), potassium hydroxide (49.5 g , 0.88 mole), ethanol (300 ml) and water (75) ml was heated under reflux for 48 hours. The ethanol was evaporated and the residue was diluted with water and extracted with ether. The aqueous phase was acidified with 20% hydrochloric acid and the precipitated solid was filtered, washed with water and dried to give the acid XIII (30.5 g, 96%), mp 197-198° (benzene); ir (nujol): 1690 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 3.1 (m, 4, $CH_2$-$CH_2$), 4.86 (s, 1, CH), 6.8 (d, J = 5.4 Hz, 1, S-C=CH), 7.0 (d, J = 5.4 Hz, 1, S-CH=C), 7.2 (s, 4, benzene), 10.4 (br s, 1, COOH).

*Anal.* Calcd. for $C_{14}H_{12}O_2S$: C, 68.84; H, 4.95; S, 13.10. Found: C, 68.95; H, 5.00; S, 13.21.

4-Chlorocarbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (XIV).

A mixture of the acid XIII (3.2 g, 0.013 mole), thionyl chloride (3.1 g, 0.026 mole) and benzene (55 ml) was refluxed for 24 hours. Benzene and excess of thionyl chloride were then distilled off and the residue was recrystallized from cyclohexane (2.9 g, 85%), mp 115-116°; ir (nujol) 1785 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 3.0 (m, 4, $CH_2$-$CH_2$), 5.1 (s, 1, CH), 6.8 (d, J = 5.4 Hz, 1, S-C=CH), 7.0 (d, J = 5.4 Hz, 1, S-C=CH), 7.2 (s, 4, benzene).

*Anal.* Calcd. for $C_{14}H_{11}ClOS$: C, 64.03; H, 4.22; S, 12.19; Cl, 13.46. Found: C, 64.28; H, 4.40; S, 12.00; Cl, 13.21.

*N*-(4-Carbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)amines (XV-XVIII).

General Procedure.

To a solution of the acid chloride XIV (5.2 g, 0.02 mole) in benzene (100 ml) sodium carbonate (0.5 g) and the corresponding amine (0.02 mole) were added. The mixture was stirred for 24 hours and then diluted with ethyl acetate. The inorganic solid was filtered and the filtrate was successively washed with 2*N* hydrochloric acid, 15% sodium hydroxide and water and dried (magnesium sulfate). The solvent was evaporated and the residue was purified by crystallization. By this method the following compounds were prepared:

*N*-(4-Carbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)piperidine (XV).

This compound was obtained in 77% yield from piperidine, mp 113-114° (ether-petroleum ether); ir (nujol): 1630 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 1.5 (m, 6, $CH_2$-$CH_2$-$CH_2$), 3.0 (m, 4, $CH_2$-$CH_2$), 3.6 (m, 4, $2CH_2N$), 5.3 (s, 1, CH), 6.85 (d, J = 5.4 Hz, 1, S-C=CH), 7.1 (d, J = 5.4 Hz, 1, S-CH=C), 7.27 (s, 4, benzene).

*Anal.* Calcd. for $C_{19}H_{21}NOS$: C, 73.31; H, 6.75; N, 4.50; S, 10.29. Found: C, 73.52; H, 6.70; N, 4.48; S, 10.06.

*N*-(4-Carbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-4-piperidinone Ethylene Ketal (XVI).

This compound was obtained in 77% yield from 4-piperidinone ethylene ketal, mp 165-166° (benzene-cyclohexane); ir (nujol): 1625 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 1.4 (br s, 4, 2N-C-$CH_2$), 2.8 (m, 4, $CH_2$-$CH_2$), 3.6 (m, 4, 2N-$CH_2$), 3.8 (s, 4, $2CH_2$-O), 5.15 (s, 1, CH), 6.70 (d, J = 5.4 Hz, 1, S-C=CH), 6.93 (d, J = 5.4 Hz, 1, S-CH=C), 7.1 (s, 4, benzene).

*Anal.* Calcd. for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79; S, 8.66. Found: C, 68.32; H, 6.36; N, 3.65; S, 8.77.

*N*-(4-Carbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-morpholine (XVII).

This compound was obtained in 90% yield from morpholine,mp 151-152° (ether-petroleum ether); ir (nujol); 1630 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriohchloroform): δ 3.1 (m, 4, $CH_2$-$CH_2$), 3.6 (br s, 8, 2N-$CH_2$-O), 5.28 (s, 1, CH), 6.87 (d, J = 5.4 Hz, 1, S-C=CH), 7.14 (d, J = 5.4 Hz, 1, S-CH=C), 7.3 (s, 4, benzene).

*Anal.* Calcd. for $C_{18}H_{19}NO_2S$: C, 69.00; H, 6.07; N, 4.47; S, 10.22. Found: C, 68.82; H, 6.12; N, 4.30; S, 10.36.

*N*-(4-Carbonyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-4-methylpiperazine (XVIII).

This compound was obtained in 85% yield from 4-methylpiperazine, mp 111-112° (ether-petroleum ether); ir (nujol): 1630 $cm^{-1}$ (C=O); $^1$H-nmr (deuteriochloroform): δ 2.2 (br s, 7, N-$CH_3$ and $2CH_2$-N), 3.1 (m, 4, $CH_2$-$CH_2$), 5.3 (s, 1, CH), 6.86 (d, J = 5.4 Hz, 1, S-C=CH), 7.11 (d, J = 5.4 Hz, 1, S-CH=C), 7.3 (s, 4, benzene).

*Anal.* Calcd. for $C_{19}H_{22}N_2OS$: C, 69.93; H, 6.74; N, 8.58; S, 9.82. Found: C, 69.89; H, 6.74; N, 8.39; S, 9.80.

*N*-(4-Methyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)piperidine (IX).

Method A.

A mixture of amine IV (1.7 g, 7.5 mmoles), 1,5-dibromopentane (1.7 g, 7.5 mmoles) and acetone (30 ml) was refluxed for 24 hours. After cooling potassium carbonate (1 g, 7.5 mmoles) was added and the mixture was refluxed again for 48 hours. The solvent was evaporated under reduced pressure and the residue treated with 10% hydrochloric acid and extracted with ether. The acidic layer was made basic with ammonium hydroxide and extracted with ether several times. The combined ether extracts were washed with water, dried (magnesium sulfate) and concentrated to an oil (0.8 g, 36%) which was transformed in the corresponding hydrochloride salt, mp > 300° (water).

*Anal.* Calcd. for $C_{19}H_{24}ClNS$: C, 68.37; H, 7.24; N, 4.19; Cl, 10.59.

Found: C, 68.30; H, 7.37; N, 4.23; Cl, 10.77.

The free base had $^1$H-nmr (deuteriochloroform): δ 1.4 (br s, 6, $CH_2$-$CH_2$-$CH_2$), 2.5 (m, 4, 2N-$CH_2$), 2.9 (d, J = 7.4 Hz, 2, C-$CH_2$-N), 4.25 (t, J = 7.4 Hz, 1, CH), 6.9 (d, J = 5.4 Hz, 1, S-C=CH), 7.06 (d, J = 5.4 Hz, 1, S-CH=C), 7.28 (s, 5, benzene).

Method B.

The amide XV (2.6 g, 6.4 mmoles) dissolved in dry ether (20 ml) was added over 15 minutes to a suspension of lithium aluminum hydride (0.26 g, 6.8 mmoles) and aluminum chloride (0.94 g, 7.0 mmoles) in ether (25 ml). The mixture was refluxed for 2 hours, then allowed to remain at room temperature for 60 hours. Concentrated hydrochloric acid (2.3 ml) and water (20 ml) were added and the ether was removed by distillation. The remaining aqueous mixture was heated until all solids were dissolved, filtered and cooled to yield the hydrochloride salt of IX (1.4 g, 73%) identical with that described above.

*N*-(4-Methyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-4-piperidinone-Ethylene Ketal (XIX).

The amide XVI (0.5 g, 1.35 mmoles) dissolved in dry tetrahydrofurane (20 ml) was added over 15 minutes to a suspension of lithium aluminum hydride (0.32 g, 8.3 mmoles) in tetrahydrofurane (15 ml) at reflux under a nitrogen atmosphere. The mixture was refluxed for 24 hours and then was cooled and treated successively with water (0.32 ml), 15% sodium hydroxide (0.32 ml) and water again (0.95 ml). It was filtered and the filtrate concentrated to an oil (0.3 g, 63%), which crystallizes at 0°, mp 130-131° (ethanol); $^1$H-nmr (deuteriochloroform): δ 1.62 (t, J = 5.4 Hz, 4, 2C-$CH_2$-C), 2.55 (t, J = 5.4 Hz, 4, 2$CH_2$-N), 2.92 (d, J = 7.4 Hz, 2, C-$CH_2$-N), 3.1 (m, 4, $CH_2$-$CH_2$), 3.9 (s, 4, 2$CH_2$O), 4.25 (t, J = 7.4 Hz, 1, -CH-), 6.92 (d, J = 5.4 Hz, 1, S-C=CH), 7.07 (d, J = 5.4 Hz, 1, S-CH=C), 7.27 (s, 4, benzene).

*Anal.* Calcd. for $C_{21}H_{25}NO_2S$: C, 70.96; H, 7.09; N, 3.94; S, 9.00. Found: C, 71.18; H, 7.21; N, 3.84; S, 9.12.

In a similar manner the following compounds were prepared:

*N*-(4-Methyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-morpholine (XX).

This compound was obtained in 75% yield from amide XVII. The hydrochloride had mp 250° dec (chloroform-petroleum ether).

*Anal.* Calcd. for $C_{18}H_{22}ClNOS$: C, 64.38; H, 6.55; N, 4.17; Cl, 10.58. Found: C, 64.28; H, 6.62; N, 4.11; Cl, 10.54.

*N*-(4-Methyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene)-4-methylpiperazine (XXI).

This compound was obtained in 60% yield from amide XVIII, dihydrochloride, mp 250° dec (ethanol-petroleum ether).

*Anal.* Calcd. for $C_{19}H_{26}Cl_2N_2S$: C, 59.22; H, 6.75; N, 7.27; Cl, 18.44. Found: C, 59.14; H, 6.61; N, 7.30; Cl, 18.29.

5,6,9,10,11,12,13,13a-Octahydro-7-thia-12a-azoniabenzo[*f*]naphth[1,2,3-*cd*]azulene Chloride (VIII).

To a solution of amide V (2 g, 6 mmoles) in toluene (40 ml) phosphorous pentachloride (2.6 g, 13 mmoles) was added and the temperature of the reaction mixture was slowly increased over 1 hour until 80°. The progress of the reaction was minitored by tlc using silica gel 254 plates and ethyl acetate as eluent. When the temperature came up to 50° (30 minutes), the starting material was entirely transformed into another product of $R_f$ = 0.8 (probably compound VI). At 80°, a complete conversion of this product to a new one of $R_f$ = 0.5 (probably compound VII) was observed. The reaction mixture was kept at this temperature 12 hours more and then cooled. The precipitate oil was decanted, washed several times with petroleum ether and dissolved in benzene. The solution was washed with 10% sodium hydroxide and water, dried (magnesium sulfate) and finally refluxed for 1 hour. The precipitated solid was filtered and dried in a desiccator (0.5 g, 30%). Because of its hygroscopic properties compound VIII could not be obtained in a pure form and was used as such in the following step.

5,6,9,10,11,12,13,13a-Octahydro-7-thia-12a-azoniabenzo[*f*]naphth[1,2,3-*cd*]azulene Perchlorate (XI).

A mixture of amine IV (4 g, 13.4 mmoles), mercuric acetate (20 g, 67 mmoles) and 5% acetic acid solution (160 ml) was heated at 80-90° for 24 hours. The precipitate was filtered and the filtrate saturated with hydrogen sulphide. The mercuric sulphide was separated by filtration and the filtrate treated with 60% perchloric acid solution. The precipitated white solid was collected, and dried *in vacuo* (1.7 g, 32%). It was used as such in the reduction reaction.

(±)-6,t-8b,9,10,11,12,13,t-13a,-Octahydro-5*H*-7-thia-12a-azabenzo[*f*]-naphth[1,2,3-*cd*]azulene (III).

Method A.

Sodium borohydride (0.32 g, 8 mmoles) was added portionwise to a solution of the salt VIII (0.6 g, 2 mmoles) in methanol (30 ml) and the mixture was refluxed for 1 hour. The solvent was removed under vacuum, the residue treated with water, and extracted with ether. The organic phase was dried (magnesium sulfate), filtered and concentrated to give an oily residue which crystallized by addition of benzene and petroleum ether. It was recrystallized from petroleum ether to give 0.4 g (80%) of III as pale yellow prismatic crystals, mp 148-149°; ms: 295 ($M^+$); $^1$H-nmr (deuteriochloroform): δ 1.6 (m, 6, $CH_2$-$CH_2$-$CH_2$), 2.2 (m, 1, N-CH), 3.1 (m, 8, $CH_2$-$CH_2$ and 2$CH_2$-N), 4.6 (m, 1, CH), 6.7 (s, 1, thiophene), 7.2 (s, 4, benzene); $^{13}$C-nmr (deuteriochloroform): δ 114.0 (d, C-8), 136.6 (s, C-8a).

*Anal.* Calcd. for $C_{19}H_{21}NS$: C, 77.25; H, 7.16; N, 4.74. Found: C, 77.09; H, 6.98; N, 4.58.

The hydrochloride had mp 200° dec (ethanol)

*Anal.* Calcd. for $C_{19}H_{22}ClNS$: C, 68.77; H, 6.63; N, 4.22; Cl, 10.70. Found: C, 68.70; H, 6.66; N, 4.19; Cl, 10.63.

Method B.

A suspension of VIII (1.8 g, 6 mmoles), zinc dust (4 g) in ethanol (150 ml) and concentrated hydrochloric acid (10 ml) was stirred and heated on a steam bath for 1 hour. The ethanol was removed under vacuum and the remainder of the mixture was made basic with concentrated ammonium hydroxide and then extracted with benzene. The benzene extracts were dried (magnesium sulfate) and concentrated to dryness. The crude base was chromatographed on preparative tlc plates (silica gel and ethyl acetate-cyclohexane (1:1) as eluent) giving 1.1 g (62%) of III identical with the product obtained by the method described above.

Method C.

The perchlorate XI (0.9 g, 2.3 mmoles) dissolved in methanol (200 ml) was reduced with sodium borohydride (0.5 g, 9.4 mmoles) following the procedure used in A. It gave 0.11 g (17%) of pure III identical with samples obtained using methods A or B.

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## REFERENCES AND NOTES

[1] Preceeding paper see E. Arribas and S. Vega, *J. Heterocyclic Chem.*, in press.

[2] To whom correspondence should be addressed.

[3] F. Bruderlein, L. Humber and K. Voith, *J. Med. Chem.*, **18**, 185 (1975).

[4] K. Voith and F. Herr, *Psychopharmacologia*, **42**, 11 (1975).

[5] F. Bruderlein, L. Humber and K. Pelz, *Can. J. Chem.*, **52**, 2119 (1974).

[6] N. J. Leonard, A. S. Hay, R. Fulmer and W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

[7] R. N. Butler "Synthetic Reagents", Vol 4, J. S. Pizey, ed, Ellis Horwood, Chichester, 1981, p 97.

[8] E. Wenkert and D. K. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

[9] C. R. Ellefson and J. W. Cusie, *J. Med. Chem.*, **14**, 307 (1979).

[10] M. Kukla, J. L. Bloss and L. R. Brougham, *ibid.*, **22** 401 (1979).

[11] C. C. Hinckley, *J. Am. Chem. Soc.*, **91**, 5160 (1969).

[12] R. Robinson and L. H. Smith, *J. Chem. Soc.*, **1**, 373 (1937).