The Synthesis and Stereochemistry of (±)-(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]-isoquinoline Hydrochloride (Taclamine Hydrochloride[1]), a Novel Psychotropic Agent

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Received September 28, 1973

FRANÇOIS T. BRUDERLEIN, LESLIE G. HUMBER, and KAREL PELZ. Can. J. Chem. **52**, 2119 (1974).

Two synthetic routes to (±)-(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline hydrochloride (**1**) (taclamine hydrochloride) are described. Configurational assignments have been made on the basis of n.m.r. spectral interpretations and mechanistic considerations.

FRANÇOIS T. BRUDERLEIN, LESLIE G. HUMBER et KAREL PELZ. Can. J. Chem. **52**, 2119 (1974).

Deux synthèses du chlorhydrate de la (±)-(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido-[2,1-*a*]isoquinoline (**1**) (chlorhydrate de taclamine) sont présentées. L'interprétation des mécanismes de formation et de la spectroscopie r.m.n. permettent d'en déterminer la stéréochimie.

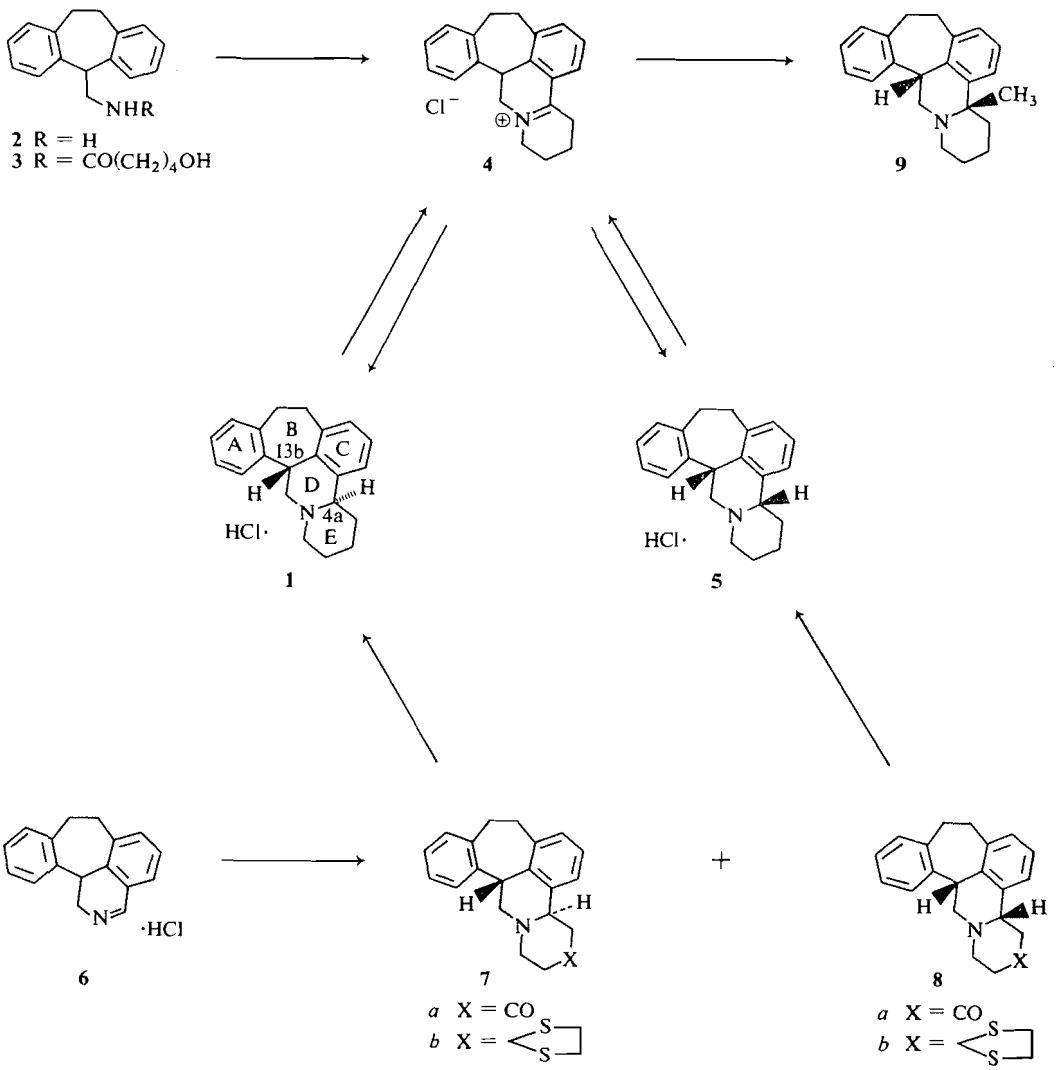
(±)-(4a,13b-*trans*)-2,3,4,4a,8,9,13b,14-Octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline hydrochloride (**1**) (taclamine hydrochloride) is a novel psychotropic agent exhibiting actions characteristic of anti-anxiety drugs in experimental animals. Preliminary pharmacological results have been described (1) and a full paper is in preparation. In this report we describe the synthesis and stereochemistry of taclamine hydrochloride.

The synthesis of taclamine·HCl **1** has been accomplished through two independent pathways (see Scheme 1). In the first, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylmethylamine (**2**) (2) was condensed with δ-valerolactone to give the hydroxyamide **3**, which on treatment with phosphorous oxychloride undergoes a double cyclization to afford the pentacyclic pyridoisoquinolinium salt **4**. Reduction of **4** with hydrogen and platinum, or, with sodium borohydride generates the 4a,13b-*cis* isomer of taclamine free base which was converted to the hydrochloride salt **5**. On the other hand, reduction of **4** with zinc and hydrochloric acid affords predominately the 4a,13b-*trans* isomer, **1**. (See discussion of stereochemistry below.) The isomeric nature of the two reduction products was confirmed by the oxidation of each, with mercuric acetate, to the common precursor, the pyridoisoquinolinium salt **4**.

The second pathway for the synthesis of taclamine·HCl involved the addition of methyl vinyl ketone to 1,7,8,12b-tetrahydrobenzo-[1,2]-cyclohepta[3,4,5-*de*]isoquinoline hydrochloride (**6**) (3). A mixture of the 4a,13b-*trans*- and 4a,13b-*cis*-pentacyclic amino ketones **7***a* and **8***a*, respectively, were formed in a ratio of 6:1. The mixture was readily separated into its components by column chromatography and the amino ketones **7***a* and **8***a* were converted to **1** and **5**, respectively, through desulfurization of the corresponding ethylenethioketal derivatives, **7***b* and **8***b*. The pure ethylenethioketal derivatives, **7***b* and **8***b* were also obtained by column chromatographic separation of the mixture of **7***b* and **8***b* obtained by direct treatment of the amino ketone mixture (**7***a* and **8***a*) with ethanedithiol and boron trifluoride etherate.

Configurational assignments at the 4a and 13b centers of **1** and **5** were made by interpretation of their n.m.r. spectra and, independently, by a consideration of the stereochemical controls operative in the reductions of the iminium salt **4**. Thus, the isomer **5** obtained via catalytic hydrogenation of **4** is assigned a 4a,13b-*cis* relative configuration since examination of molecular models shows that the substrate for reduction, **4**, contains an iminium center, which causes rings C, D, and E to be virtually coplanar while the phenyl ring A is located on the α-side at the

[1]Nonproprietary name selected by the U.S. Adopted Names Council. This compound has also been designated AY-22,214.



SCHEME 1

CDE plane and is oriented to it by an angle of about 100°. Absorption to the catalyst will take place from the less-hindered β-face of the molecule whence hydrogen will be delivered, generating a 4a,13b-*cis* relative configuration. The other isomer, **1**, obtained by zinc and hydrochloric acid reduction consequently is assigned a 4a,13b-*trans* relative configuration.

The i.r. spectra of **1** and **5** as their free bases show only weak absorption in the Bohlmann band region at 2700–2800 cm^{-1} and the low intensity of these bands makes their use unreliable for configurational assignments. The n.m.r. spectra, in contrast, show pronounced differences which can be readily interpreted. The preferred conformation of the 4a,13b-*trans* isomer **1** is shown in Fig. 1*A* in the form of the base along with the Newman projection obtained by viewing the C_{14}—C_{13b} axis. Of particular significance are the dihedral angles of 35 and 146° between the C_{13b}-proton and those at C_{14}. The C_{13b}-proton should consequently appear as a triplet in the isomer obtained by metal–acid reduction. Experimentally the n.m.r. spectrum of the metal–acid reduction product shows a one-proton band as a triplet centered at 4.9 δ which is assigned to the benzylic C_{13b}-proton and allows a 4a,13b-*trans* configurational

assignment for taclamine·HCl, **1**. Similarly, examination of the preferred conformation of the free base of the 4a,13b-*cis* isomer, **5**, (see Fig. 1*B*) reveals that the dihedral angles in question are 20 and 90°, and consequently the C_{13b}-proton should appear as a doublet as is observed experimentally, centered at 4.5 δ.

The assignment of 4.9 and 4.5 δ bands in the n.m.r. spectra to the 13b-protons of **1** and **5**, respectively, is confirmed by the appearance of a 4.4 δ band in the spectrum of the 4a-methyl derivative **9**. Compound **9** was obtained by the reaction of methyl magnesium iodide with the iminium salt **4**, and is expected to be formed by attack of the Grignard reagent from the least hindered β-face of the molecule, generating a 4a,13b-*cis* relationship of the groups at these centers. Thus, the absorption of the C_{13b}-proton of **9** (4.4 δ) occurs at about the same position as that of the corresponding proton in the *cis* isomer **5** (4.5 δ). The large downfield shift of the C_{13b}-proton, to 4.9 δ, in the *trans* isomer **1** is probably due to the deshielding of this proton by the nitrogen lone pair in **1** (see Fig. 1*A*).

The configurational assignments for the amino ketones **7***a* and **8***a* are consistent with their conversions to **1** and **5**, respectively. In addition the n.m.r. absorption of the C_{13b}-proton appears as a triplet in **7***a*, and as a doublet in **8***a* consistent with the patterns seen for *cis* isomers in this series (*viz.* **1** and **8***b*) and for *trans* isomers (*viz.* **5** and **7***b*).

Experimental

Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of Ayerst Research Laboratories. The n.m.r. spectra were recorded on a Varian A-60-A instrument. All new compounds gave i.r. and n.m.r. spectra consistent with their respective structures.

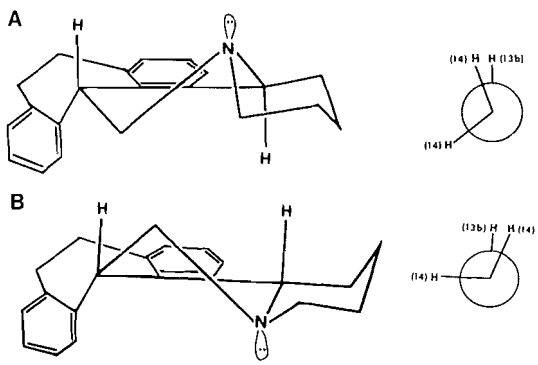


FIG. 1. Molecular models of **1** and **5**.

N-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-5-hydroxyvaleramide (3)

A mixture of **2** (2) (20 g, 0.09 mol) and δ-valerolactone (12.5 g, 0.125 mol) was heated for 3 h at 150°. After cooling, the solid was recrystallized from benzene to give 24 g (83%) of **3**, m.p. 104–106°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 78.23; H, 7.74; N, 4.36.

1,2,3,4,8,9,13b,14-Octahydro[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolinium Chloride (4)

Method A

To a solution of **3** (24 g, 0.074 mol) in 400 ml of toluene, phosphorus oxychloride (150 ml) was added and the reaction mixture was refluxed for 3 h. After cooling, petroleum ether (b.p. 60–80°) was added and the solvent was decanted. The residual oil was dissolved in benzene, quickly washed with water, a 10% aqueous sodium hydroxide solution and water again, dried, and finally refluxed for 40 min. The precipitate was recrystallized from acetone to give 10.1 g (42%) of **4**, m.p. 220–223°; u.v. (EtOH) λ 283 (ε 10 660); i.r. (Nujol) 3350 (OH), 1645 cm^{-1} (C=N). This compound could be obtained only in a hydrated form for which good analysis could not be obtained.

Anal. Calcd. for $C_{21}H_{22}ClN{\cdot}1\frac{1}{2}H_2O$: C, 71.88; H, 7.17; Cl, 10.09; N, 3.99; H_2O, 7.7. Found: C, 71.44; H, 7.00; Cl, 9.94; N, 3.62; H_2O, 8.2.

Method B

Compound **5** (1.5 g, 0.005 mol), and mercuric acetate (9.3 g, 0.029 mol) were dissolved in a mixture of 15 ml of tetrahydrofuran, 12 ml of acetic acid, and 50 ml of water and heated on a steam bath for 1 h. The hot solution was filtered and the filtrate concentrated under vacuum, made basic with a 10% aqueous sodium hydroxide solution, and extracted with ether. The dried ethereal solution was then treated with gaseous hydrogen chloride and the precipitate was crystallized from acetone to give 0.9 g (60%) of **4**, identical with the sample obtained according to method A. The same product was also obtained using **1** as starting material.

(±)-(4a,13b-cis)-2,3,4,4a,8,9,13b,14-Octahydro-1H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinoline Hydrochloride (5)

Method A

Sodium borohydride (0.5 g, 0.013 mol) was added portionwise to a solution of **4** (1 g, 0.003 mol) in methanol and the mixture was refluxed for 1 h. The solvent was removed under vacuum, the residue treated with water, and extracted with ether to give 0.74 g (90%) of **5** free base, m.p. 132–134° (hexane); n.m.r. ($CDCl_3$) δ, 4.5 (d, 13b-H, J = 4 Hz).

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 86.98; H, 8.31; N, 4.63.

The corresponding hydrochloride melts at 235–236° (acetone).

Anal. Calcd. for $C_{21}H_{23}N{\cdot}HCl$: N, 4.30; Cl, 10.88. Found: N, 4.34; Cl, 11.19.

Method B

Catalytic hydrogenation of **4** (1.3 g, 0.004 mol) in 50 ml of ethanol in presence of 50 mg of platinum oxide at room temperature and under normal pressure gave, after removal of the solvent, dissolution in hexane, and

filtration through alumina, 0.9 g (84%) of **5** free base, identical with the product obtained using method A.

Method C

To a refluxing solution of **8***b* (2 g, 0.005 mol) in 200 ml of tetrahydrofuran, 20 g of Raney Ni were added portionwise. The mixture was stirred and refluxed for 4 h. The Ni was removed, washed with 100 ml of tetrahydrofuran, and the pooled solutions were concentrated to 150 ml, then poured into water and extracted with ether. After drying and evaporating the solvent an oil (1.5 g) which crystallized slowly was isolated. Recrystallization from hexane gave 1 g (65.5%) of pure **5** free base, identical with samples obtained using methods A or B.

1,2,4,4a,8,9,13b,14-Octahydro-3H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3-ones(7a and 8a)

A mixture of **6**·HCl (2) (32 g, 0.119 mol) and methyl vinyl ketone (26 g, 0.372 mol) was heated on a steam bath for 30 min. The mixture first became homogenous then gave a semisolid mass. This material was triturated with ether, dissolved in a 10% aqueous sodium hydroxide solution, and extracted with ethyl acetate. After drying and evaporating the solvent, crystallization from acetone–hexane gave 19 g (52.8%) of a mixture of 7*a* and **8***a*, m.p. 150–155°. Chromatography of this mixture on silica gel and eluting with chloroform–benzene (1:4) gave 2.8 g of **8***a*, m.p. 202–203° (acetone–hexane); n.m.r. ($CDCl_3$) δ 4.6 (d, 13b-H, J = 4 Hz).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.30; H, 7.17; N, 4.46.

Using $CHCl_3$ as eluant 16 g of 7*a*, m.p. 163–165° (acetone–hexane) were isolated; n.m.r. ($CDCl_3$) δ 4.8 (t, 13b-H, J = 10 Hz).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.08; H, 7.22; N, 4.41.

1,2,4,4a,8,9,13b,14-Octahydrospiro[3H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3,2′-[1,3]dithiolanes] (7b and 8b)

A solution of a mixture of 7*a* and **8***a* (39 g, 0.129 mol) in 750 ml of acetic acid, 39 ml of ethanedithiol and 39 ml of boron trifluoride etherate was left overnight at room temperature. After pouring it into water and extracting with ether, the organic layer was neutralized with a 10% aqueous sodium carbonate solution, dried, and concentrated to give 37 g (76%) of a crystalline material, m.p. 218–220°. Chromatography of this mixture on silica gel using $CHCl_3$ as eluant gave **8***b*, m.p. 150° (methanol–hexane), followed by 7*b*, m.p. 225–230° (methanol–hexane) using methanol as eluant, in a ratio similar to that of the original mixture of 7*a* and **8***a*.

7*b*: n.m.r. ($CDCl_3$) δ 4.83 (t, 13b-H, J = 13 Hz).

Anal. Calcd. for $C_{23}H_{25}NS_2$: C, 72.78; H, 6.64; N, 3.69. Found: C, 72.88; H, 6.60; N, 3.39.

8*b*: n.m.r. ($CDCl_3$) δ 4.5 (d, 13b-H, J = 4 Hz).

Anal. Calcd. for $C_{23}H_{25}NS_2$: C, 72.78; H, 6.64; N, 3.69. Found: C, 72.68; H, 7.01; N, 3.56.

*(±)-(4a,13b-trans)-2,3,4,4a,8,9,13b,14-Octahydro-1H-benzo[6,7]cyclohepta[1,2,3-de]pyrido]2,1-a]isoquinoline hydrochloride (**1**)*

Method A

A suspension of **4** (2 g, 0.006 mol), 4 g of Zn dust in 150 ml of ethanol and 40 ml of concentrated hydrochloric acid was stirred and heated on a steam bath for 1 h. 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 extract was dried and concentrated to dryness. The crude base (1.2 g) was dissolved in 10 ml of benzene and absorbed on a column of 120 g of neutral alumina (activity II). By elution with hexane 325 mg (19.7%) of **5** free base, m.p. 132–134° was first isolated; elution with benzene gave 800 mg (48.5%) of **1** free base m.p. 90–92° (hexane); n.m.r. ($CDCl_3$) δ 4.9 (t, 13b-H, J = 14 Hz).

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.46; H, 8.13; N, 4.63.

The hydrochloride salt of **1** was crystallized from isopropanol–acetone, m.p. 270–272°.

Anal. Calcd. for $C_{21}H_{23}N$·HCl: C, 77.40; H, 7.42; N, 4.30; Cl, 10.88. Found: C, 77.56; H, 7.52; N, 4.30; Cl, 10.92.

Method B

In the same way as described for the preparation of **5** (method C), 7*b* (1.9 g, 0.005 mol) was treated with 20 g of Raney Ni to give 1.2 g (83%) of **1** free base, which was converted directly to the corresponding hydrochloride **1** identical with the product obtained by using the method above.

*(±)-(4a,13b-cis)-4a-Methyl-2,3,4,4a,8,9,13b,14-octahydro-1H-benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinoline (**9**)*

Compound **4** (4 g, 0.0114 mol) was added portionwise to a solution of methylmagnesium iodide in ether (100% excess) and the reaction mixture was refluxed for 40 min. The excess of the Grignard reagent was destroyed by adding slowly a saturated solution of ammonium chloride in water (150 ml). The organic phase was separated, dried, and concentrated to give 2.5 g of an oil, which was chromatographed over alumina (neutral, activity I) using benzene as eluant. After crystallization from hexane 2.3 g (66.3%) of **9**, m.p. 119–120°, were isolated; n.m.r. ($CDCl_3$) δ 1.3 (s, 4a-CH_3), 4.4 (d, 13b-H, J = 5 Hz).

Anal. Calcd. for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 87.00; H, 8.45; N, 4.76.

The corresponding hydrochloride melts at 270° (methanol–ether).

Anal. Calcd. for $C_{22}H_{25}N$·HCl: C, 77.71; H, 7.71; N, 4.72; Cl, 10.43. Found: C, 77.50; H, 7.75; N, 4.69; Cl, 10.58.

The authors wish to thank Miss R. Liechti, Mr. B. Berger, and Mr. N. Sideridis for their valuable technical assistance.

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