The Synthesis of 1,4-Ethano-1,2,3,4-tetrahydroisoquinolines as Rigid Analogues of Adrenergic Agents

Frank W. Muellner and Ludwig Bauer*

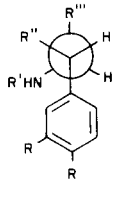
Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy,
University of Illinois at Chicago, Health Sciences Center,
P. O. Box 6998, Chicago, Illinois 60680

Received May 10, 1983

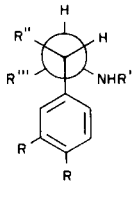
The Diels-Alder addition of benzyne and 4,5-dimethoxybenzyne to 1-(2-*trans*-phenylvinyl)-2-pyridone and 1-benzyl-3-benzyloxy-2-pyridones provided members of the 1,4-etheno-3-oxo-1,2,3,4-tetrahydroisoquinoline system. Catalytic reduction of these adducts yielded the corresponding tricyclic lactams. Lithium aluminum hydride reduction of these lactams produced a number of 1,4-ethano-1,2,3,4-tetrahydroisoquinolines.

J. Heterocyclic Chem., **20**, 1581 (1983).

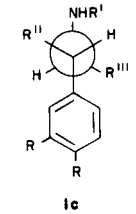
The nature of agonist-receptor interactions have been studied to determine the stereochemical requirements for biological responses. Elucidation of the mechanism of action of biologically active molecules and the design of new agonists and antagonists are the benefits from such investigations. The use of analogues of the agonist, where a certain conformation is locked in place, may provide more definite information concerning this stereochemical requirement. Amphetamine (**1**, R = R′ = R″ = H, R‴ = CH_3), ephedrine, (**1**, R = H, R′ = R‴ = CH_3, R″ = OH), dopamine (**1**, R = OH, R′ = R″ = R‴ = H) can exist in either two folded conformations (**1a** and **1b**), or an extended form **1c**. Quantum mechanical calculations of the conformations of amphetamine and dopamine have shown that the most stable conformation is the folded conformation [1]. Another study concluded that the most stable conformation of gaseous amphetamine is the folded form, but in aqueous media, a strong preference for the extended conformation was observed [2].



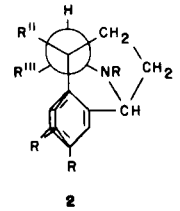
1a



1b



1c



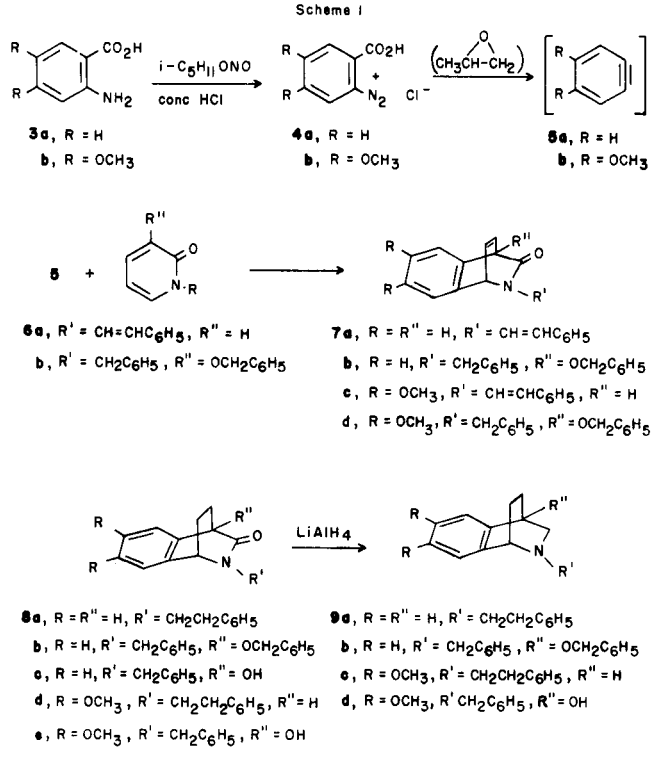
2

Compounds **2** resemble closest one of the folded forms of **1**. Besides the folded *vs* extended form, the plane of the aromatic ring to that of the ethylamine side chain of **1** has also come under discussion. Free rotation of the aryl group could provide additional conformers. The relationship of the arene to the side chain in dopamine has been discussed [3]. In compounds described here, the relative position of the arene is also fixed and their structure is portrayed more realistically as **9** which is equivalent to **2** (R‴ = H).

Entry into the tricyclic 1,4-ethano-1,2,3,4-tetrahydroisoquinoline system has been demonstrated by two major routes. The method developed initially in this laboratory utilized the Diels-Alder cycloaddition of *N*-substituted pyridones with benzyne to furnish the unsaturated lactams **7** [4,5]. The Diels-Alder route has subsequently been applied to the synthesis of a number of tricyclic unsaturated lactams **7** [6-10]. Several reductions on **7** lead to the bridged reduced isoquinolines, **8** and **9**. An alternate sequence of reactions involves first the synthesis of *cis*-1-amino-4-carboalkoxyltetralins, and their subsequent thermal ring closure to provide the bridged lactams, **8** [11]. Whenever applicable, the shorter Diels-Alder method is the synthetic method of choice for **8** and **9**, and is the only method whereby the unsaturated lactams **7**, are prepared readily.

We have investigated the Diels-Alder addition of benzyne and 3,4-dimethoxybenzyne to 1-(2-*trans*-phenylvinyl)-2-pyridone (**6a**) and 1-benzyl-3-benyloxy-2-pyridone, (**6b**). The benzyne intermediates **5**, were generated in one of two ways. One of these consisted of the diazotization of an anthranilic acid **3** with isopentyl nitrite *in situ* in the presence of the pyridone. In the other method, the *o*-carboxydiazonium chloride, **4**, was isolated. To generate the benzyne (**4**) the elements of HCl are "neutralized" by reaction with propylene oxide to form the thermally unstable *o*-diazonium carboxylate *in situ* which loses carbon dioxide and nitrogen to furnish **5**. Since **6** is present, the Diels-Alder reaction can then take place quickly. The adducts, **7**, were isolated by repeated column chromatography. Due to their thermal instability, **7** could not be distilled or sublimed [4].

Scheme I



Catalytic reduction of **7** provided the expected saturated lactams, **8**, which were reduced further by lithium aluminum hydride to afford the target amines, **9**. Both steps proceeded in good yields. The reduction of the alkene in **7b** and **7d** over palladium was accompanied by hydrogenolysis of the benzyl ether. There was isolated the saturated ether **8b**, and also the alcohols, **8c** and **8e**. The alkene was reduced quickly and with time *O*-debenzylation became the dominant reaction. At room temperature no *N*-debenzylation was observed.

EXPERIMENTAL

Melting points were determined on a Mel-Temp block and are uncorrected. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian T-60 A spectrometer equipped with a Nicolet Instrument Corp. TT-7 Fourier transform accessory. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. The following abbreviations were used: s, singlet; d, doublet; t, triplet; and m, multiplet. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Mass spectra were obtained by Mr. Richard Dvorak at 70 eV from a Varian MAT 112S mass spectrometer. In general, relative abundances are reported for fragments over 10% of the base peak.

All solvents were reagent grade and distilled prior to use. Dimethylformamide and 3-hydroxy-2-pyridone were purchased from Aldrich Chemical Co. and used without further purification. Alumina F-20 was obtained from Alcon Chemicals. "Baker Analyzed" reagent. Silica Gel (60-200 mesh) was used for column chromatography. Silica Gel (230-400 mesh) was purchased from Merck and used for flash chromatography [17]. Thin layer chromatograms (tlc) were obtained on 6 × 6 cm strips of Eastman Chromagram silica gel sheets (No. 13181) mixed with a fluorescent indicator. Developing solvents were chloroform (solvent A), petroleum ether-ethyl acetate, 9:1 (solvent B), ethyl acetate (solvent C) and ethylene chloride (solvent D).

Removal of "solvents *in vacuo*" implies distillation of those solvents at temperature of 95° (steam bath) or less on a water aspirator (20-30 Torr) by means of a flash evaporator.

1-Benzyl-3-benzyloxy-2-pyridone (**6b**).

The alkylation reported by Nedenskov [13], used DMSO as solvent and gave us a black polymer. The following method was found to be reproducible. Sodium (11.5 g, 0.5 mole) was dissolved in anhydrous ethanol (100 ml) and then DMF (100 ml) was added. Most of the ethanol was then removed, *in vacuo*. An additional 200 ml of DMF was added, followed by 3-hydroxy-2-pyridone (22.2 g, 0.2 mole). Benzyl chloride (59.5 ml, 0.5 mole) was then added dropwise (0.5 hour) with stirring. The mixture was refluxed for 4 hours, then cooled and poured onto ice-water. The solid was collected, washed with water, and recrystallized from ethanol-water (2:1), 38.6 g, 66% yield, mp 112-114°, (lit [13] mp 115-116°), tlc, R_f = 0.12 (solvent A); ^{1}H nmr (DMSO-d_6): δ 5.01 (s, NCH_2), 5.12 (s, OCH_2), 6.14 (dd, H-5, $J_{4,5}$ = 7 Hz, $J_{5,6}$ = 7 Hz), 6.92 (dd, H-4, $J_{4,5}$ = 6 Hz, $J_{4,6}$ = 1 Hz), 7.30-7.92 (m, H-6 and $2C_6H_5$).

Diels-Alder Reaction of Benzyne **5a** with **6b**, Method A.

In this method, benzyne is generated *in situ* from anthranilic acid. This method was originally reported by Borne and coworkers [6]. Mariano and coworkers used this method for the addition of benzyne to 1-(2-*trans*-phenylvinyl)-2-pyridone **6a**, where they used a very large quantity of solvent for chromatography. Simplification of the separation, for this reaction procedure, is reported.

To a refluxing solution of **6b** (26.2 g, 0.09 mole) and isopentyl nitrite (16.1 ml, 0.12 mole) in methylene chloride (200 ml), was added a solution of anthranilic acid (12.3 g, 0.09 mole) in acetone (90 ml) over 1.5 hours. Three additional portions of isopentyl nitrite (4 ml, 0.03 mole, each) were added over 0.5, 1, and 1.5 hours. The reaction mixture was evaporated to dryness *in vacuo* and yielded a black residue. In order to remove polar, volatile impurities, the residue was boiled down twice with toluene (100 ml, each time). The residue was chromatographed on alumina (400 g, column size 5 cm × 40 cm) prepared in toluene. Elution with toluene (500 ml), provided a mixture of starting pyridone and adduct. These fractions were rechromatographed on silica gel (200 gm, column size 5 cm × 40 cm prepared in chloroform. Elution with chloroform (600 ml), afforded the adduct 1,4-etheno-2-benzyl-3-oxo-4-benzyloxy-1,2,3,4-tetrahydroisoquinoline, **7b**, 3.85 g, 10% yield, mp 85-87°, tlc, R_f = 0.80 (solvent A); ^{1}H nmr (deuteriochloroform): δ 4.44-5.67 (a series of complex multiplets, OCH_2, NH_2, CHN), 6.44-8.00 (m, $2C_6H_5$, arom, CH=CH); ms: m/e 235 (11), 234 (59), 115 (12), 92 (16), 91 (100), 65 (11).

Anal. Calcd. for $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81. Found: C, 81.74; H, 5.82; N, 3.72.

1,4-Etheno-2-(2-*trans*-phenylvinyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (**7a**).

Starting from 17.7 g of **6a** [12] and using Method A, **7a** was prepared in 25% yield, 6.15 g, mp 206-207° (lit [8] mp 208-210°), tlc, R_f = 0.68 (solvent A).

4,5-Dimethoxyanthranilic Acid Hydrochloride.

Nitration of veratric acid produced 6-nitroveratric acid mp 187-191° (lit [14] mp 189-190°). 4,5-Dimethoxyanthranilic acid was prepared by catalytic hydrogenation (50 psi, Pd on activated carbon, 1 hour) of 6-nitroveratric acid [15], in 95% ethanol, but the amine turned greenish-brown quickly. It was more readily handled and stored as the hydrochloride which was prepared by addition of an equivalent amount of concentrated hydrochloric acid, before filtering off the catalyst. The reaction mixture warmed after the addition of the acid, allowing the catalyst to be filtered off, before the salt precipitated. After filtration the filtrate was cooled and the salt was collected and washed with cold ethanol, mp 234-237°. The salt could be stored without decoloration.

Diels-Alder Reaction of 4,5-Dimethoxybenzyne with **6a**. Method B.

The 4,5-dimethoxyanthranilic acid was converted to 2-carboxy-4,5-dimethoxybenzenediazonium chloride by the method reported by Goering and coworkers [16]. 4,5-Dimethoxyanthranilic hydrochloride (15.5 g, 0.07 mole) was suspended in absolute ethanol (260 ml) and cooled to 5°. Isopentyl nitrite (10 ml, 0.07 mole) was then added and stirred for 1 hour, after which anhydrous ether (260 ml) was added and then stirred for an additional 0.5 hour. The salt **4b** was collected, washed with cold anhydrous ether, dried at the pump for 0.5 hour, giving 15.3 g (94%), and was then used immediately.

To a solution of **6a** (5.91 g, 0.03 mole) in ethylene chloride (160 ml) was added the 2-carboxy-4,5-dimethoxybenzenediazonium chloride **4b** (7.34 g, 0.03 mole) and propylene oxide (6.76 ml, 0.13 mole). The mixture was refluxed for 2.5 hours, when the evolution of gas ceased [barium hydroxide test for carbon dioxide]. The reaction mixture was evaporated to dryness, *in vacuo*, and was boiled down twice with toluene, *in vacuo*, (100 ml, each time). The residue was chromatographed as in Method A first on alumina, then on silica gel, to afford 1,4-etheno-2-(2-*trans*-phenylvinyl)-3-oxo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**7c**) which was recrystallized from absolute ethanol, 0.2 g, 2% yield, mp 146-150°, tlc R_f = 0.09 (solvent B); ^{1}H nmr (deuteriochloroform): δ 3.84 (s, $2OCH_3$), 4.62 (m, CHCO), 5.72 (m, CHN), 6.18 (d, CH=C*H*Ar, J = 15 Hz), 6.78-7.63 (m, NCH=C, C-CH=CH-C, ArH); ms: m/e 334 (M^+ + 1, 10), 333 (M^+, 46), 215 (28), 189 (12), 188 (100), 145 (23), 117 (13), 115 (22), 102 (20), 90 (12), 50 (11).

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.31; H, 5.81; N, 4.05.

1,4-Etheno-2-benzyl-3-oxo-4-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahyroisoquinoline (**7d**).

Starting from 8.73 g (0.03 mole) of **6b** and 7.33 g (0.03 mole) of **4b**, **7d** was prepared using Method B, and was recrystallized from absolute ethanol, 1.19 g, 9% yield, mp 129-133°, tlc, R_f = 0.40 (solvent A); ^{1}H nmr (deuteriochloroform): δ 3.73, 3.83 (2s, $2OCH_3$), 4.75-5.64 (a series of complex multiplets, OCH_2, CHN), 6.49 (s, arom), 6.65-7.70 (m, $2C_6H_5$, arom, CH=CH); ms: m/e 336 (M^+ -$CH_2C_6H_5$, 1), 295 (17), 294 (83), 204 (28), 203 (100), 175 (27), 160 (11), 132 (12), 92 (13), 91 (100), 65 (16), 28 (12).

Anal. Calcd. for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.90; N, 3.28. Found: C, 76.23; H, 6.13; N, 3.14.

General Catalytic Hydrogenation of Diels-Alder Adducts (**7**).

The catalyst (10% palladium on carbon, 0.1 g) was suspended in a solution of the Diels-Alder adduct, **2** (0.022 mmole) in methanol (150 ml) and reduced by hydrogen in a Parr apparatus (24 hours). The mixture was filtered through Celite and the solvent was removed *in vacuo*. The brown crystals were collected, dried, and recrystallized from cyclohexane, yielding **8**, as white crystals.

Using this procedure the following compounds were prepared.

1,4-Ethano-2-(2-phenylethyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline (**8a**).

Reduction of **7a** followed the general procedure outlined above, produced **8a** in 47% yield, mp 126-127° (lit [6] mp 127-129°), tlc, R_f = 0.30 (solvent A); ^{1}H nmr (deuteriochloroform): δ 1.43-14.41 (a series of complex multiplets, CHN, $2CH_2CH_2$, CHCO), 6.57-7.74 (complex multiplets, arom, C_6H_5); ms: m/e 277 (M^+, 48), 186 (100), 145 (25), 141 (11), 130 (60), 129 (96), 128 (41), 117 (14), 115 (23), 104 (12), 91 (20), 77 (14).

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.08; H, 6.98; N, 4.98.

1,4-Ethano-2-benzyl-3-oxo-4-benzyloxy-1,2,3,4-tetrahydroisoquinoline (**8b**).

Reduction of **7b** following the general procedure shown above produced a mixture of **8b** and **8c**, where the extent of hydrogenolysis of the *O*-benzyl group depended on reaction time. After 16 hours, 80% of the **8b** was obtained, after 36 hours, 80% of **8c** was formed. Separation of **8a** and **8b** was carried out as follows. After evaporation of the ethanol, the residue was triturated with cyclohexane. It was found that the alcohol **8c** was insoluble in cyclohexane. Separation of the ether **8b** was accomplished by simple filtration. Evaporation of the cyclohexane filtrate yielded the ether **8c** (89%), mp 105-107°, tlc, R_f = 0.433 (solvent A); ms: m/e 369 (M^+, 19), 264 (19), 263 (62), 248 (30), 236 (38), 172 (15), 146 (64), 145 (99), 144 (85), 131 (10), 129 (10), 128 (13), 117 (66), 116 (15), 115 (42), 92 (25), 91 (100), 77 (11), 65 (34). This solid was reduced in the next step to **9b**.

1,4-Ethano-2-benzyl-3-oxo-4-hydroxy-1,2,3,4-tetrahydroisoquiinoline (**8c**).

This alcohol was isolated, after 36 hours of reduction in 25% yield, mp 146-148°, tlc, R_f 0.17 (solvent A); ^{1}H nmr (deuteriochloroform): δ 1.26-2.05 and 4.25-4.48 (2 series of complex multiplets, CH_2CH_2, CHN, OH), 4.58 (s, NCH_2), 7.03-7.53 (complex multiplet, arom, C_6H_5); ms: m/e 279 (M^+, 7), 251 (24), 147 (85), 146 (100), 145 (91), 144 (18), 132 (31), 131 (88), 129 (14), 128 (23), 127 (56), 119 (10), 117 (50), 116 (26), 115 (59), 104 (20), 103 (24), 92 (17), 91 (90), 89 (17), 84 (11), 78 (11), 77 (34), 65 (36).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.47; H, 6.21; N, 4.96.

1,4-Ethano-2-(2-phenylethyl)-3-oxo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8d**).

Reduction of **7c** following the general procedure for catalytic hydrogenation produced **8d** in 91% yield, mp 112-115°, tlc, R_f = 0.26 (solvent A); ^{1}H nmr (deuteriochloroform): δ 1.13-4.31 (a series of complex multiplets, CHN, $2CH_2CH_2$, CHCO), 3.85 (s, $2OCH_32$), 6.55, 6.82 (2s, arom), 7.19 (s, C_6H_5); ms: m/e 337 (M^+, 32), 246 (48), 205 (46), 190 (48), 189 (100), 175 (13), 174 (11), 91 (11), 30 (24).

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.49; H, 7.03; N, 3.94.

1,4-Ethano-2-benzyl-3-oxo-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8e**).

Reduction of **7d** (36 hours) produced **8e** in 67% yield, mp 157-159°, tlc, R_f = 0.31 (solvent A); ^{1}H nmr (deuteriochloroform): δ 1.43-2.04 (m, CH_2CH_2), 3.79, 3.91 (2s, $2OCH_3$), 4.27 (s, OH), 4.38 (m, CHN), 4.60 (s, CH_2N), 6.53, 7.17 (2s, arom), 7.25 (s, C_6H_5); ms: m/e 340 (5), 339 (M^+, 23), 311 (23), 207 (24), 206 (100), 205 (27), 192 (15), 191 (25), 175 (20), 164 (11), 91 (50), 65 (13), 28 (14), 18 (11).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.80; H, 6.50; N, 4.04.

General Lithium Aluminum Hydride Reduction of **8**.

A solution of **8** (0.009 mole) in anhydrous ether (50 ml) was added to a stirred suspension of lithium aluminum hydride (0.028 mole) in anhydrous ether (200 ml). The reaction mixture was refluxed for 22 hours, then cooled in an ice-bath and the reaction product and excess of hydride were decomposed by the dropwise addition, in this order, of water (1 ml), 15% sodium hydroxide (1 ml) and water (3 ml). After stirring for 0.5 hour the mixture was filtered swith suction and the granular precipitate was washed thoroughly with ether. The combined ether solutions were evaporated yielding a light yellow liquid. The free base was dissolved in ether and treated with hydrogen chloride gas. The solid hydrochloride, **9**, was recrystallized from benzene.

Using this procedure, the following compounds were prepared.

1,4-Ethano-2-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**9a**).

Reduction of **8a**, produced **9a** in 70% yield; mp 195-198° (lit [6] mp 142-144°], tlc, R_f = 0.07 (solvent D), ^{1}H nmr (deuteriochloroform): δ 1.05-4.58 (a series of complex multiplets, $CHNCH_2$, $2CH_2CH_2$, C-C*H*-Ar), 6.76-7.70 (complex multiplets, arom, C_6H_5); ms: m/e 263 (4.1), 234 (35), 172 (100), 143 (26), 128 (34), 115 (18), 105 (24), 91 (11), 77 (11), 65 (4.1), 44 (69), 36 (11), 28 (71).

Anal. Calcd. for $C_{19}H_{22}ClN$: C, 76.11; H, 7.40; N, 4.67; Cl, 11.82. Found: C, 76.25; H, 7.37; N, 4.60; Cl, 11.70.

1,4-Ethano-2-benzyl-4-benzyloxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**9b**).

From **8b**, there was isolated **9b** in 47% yield, mp 208-210°, tlc, R_f = 0.57 (solvent A); ^1H nmr (deuteriochloroform): δ 1.56-4.83 (a series of complex multiplets, NCH_2, OCH_2, CH_2CH_2, $CHNCH_2$), 6.97-7.82 (complex multiplet, arom, C_6H_5); ms: m/e 355 (M^+ -HCl, 1), 264 (15), 237 (17), 236 (85), 146 (13), 145 (93), 144 (70), 120 (17), 117 (30), 115 (17), 92 (15), 91 (100), 65 (16), 36 (11).

Anal. Calcd. for $C_{25}H_{26}ClNO$: C, 76.61; H, 6.69; N, 3.57; Cl, 9.05. Found: C, 76.60; H, 6.78; N, 3.53; Cl, 8.96.

1,4-Ethano-2-(2-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**9c**).

Reduction of **8d** furnished **9c** in 50% yield, mp 189-193°; ^1H nmr (deuteriochloroform): δ 1.26-4.51 (a series of complex multiplets, $CHNCH_2$, $2CH_2CH_2$, CH-CHAr), 3.89, 3.91 (2S, $2OCH_3$), 6.73-7.36 (complex multiplet, arom, C_6H_5); ms: m/e 323 (M^+ -HCl, 1), 294 (14), 232 (35), 44 (100), 36 (14).

Anal. Calcd. for $C_{21}H_{26}ClNO_2$: C, 70.09; H, 7.28; N, 3.89. Found: C, 70.45; H, 7.21; N, 3.94.

1,4-Ethano-2-benzyl-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**9d**).

The salt of **9d** was prepared from **8e** in 64.5% yield, mp 241-243°, tlc, R_f = 0.51 (solvent C), ^1H nmr (deuteriochloroform): δ 1.53-4.29 (a series of complex multiplets, CHN, $-CH_2CH_2-$, CH_2NCH_2), 3.92, 3.99 (2s, $2OCH_3$), 6.74 (s, arom), 7.26-7.78 (m, C_6H_5, arom); ms: m/e 325 (M^+, 3), 297 (15), 296 (31), 232 (12), 207 (20), 206 (100), 205 (14), 191 (13), 176 (10), 175 (11), 120 (40), 91 (81), 65 (10), 38 (13), 36 (40).

Anal. Calcd. for $C_{20}H_{24}ClNO_3$: C, 66.39; H, 6.69; N, 3.87. Found: C, 66.29; H, 6.75; N, 3.84.

REFERENCES AND NOTES

[1] B. Pullman, J.-L. Coubeils, Ph. Courriere and J.-P. Gervois, *J. Med. Chem.*, **15**, 17 (1972).

[2] H. J. R. Weintraub and A. J. Hopfinger, *J. Theor. Biol.*, **41**, 53 (1973).

[3] A. S. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, **32**, 521 (1980).

[4] E. B. Sheinin, G. E. Wright, C. L. Bell and L. Bauer, *J. Heterocyclic Chem.*, **5**, 859 (1968).

[5] L. Bauer, C. L. Bell, G. C. Brophy, W. A. Bubb, E. B. Sheinin, S. Sternhell and G. E. Wright, *Aust. J. Chem.*, **24**, 2319 (1971).

[6] R. F. Borne, S.-J. Law, P. W. Wirth and J. C. Murphy, *J. Pharm. Sci.*, **66**, 594 (1977).

[7] A. P. Marchand and R. W. Allen, *Tetrahedron Letters*, 619 (1977).

[8] P. S. Mariano, P. L. Huesmann, R. L. Beamer and D. Dunaway-Mariano, *Tetrahedron*, **34**, 2617 (1978).

[9] M. J. O. Anteunis, F. A. M. Borremans, J. Gelan, A. P. Marchland and R. W. Allen, *J. Am. Chem. Soc.*, **100**, 4050 (1978).

[10] M. Kuzuya, M. Ishikawa, H. Hart and T. Okuda, *Tetrahedron Letters*, 523 (1979); *ibid.*, 1613 (1981).

[11] G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 491 (1971).

[12] P. S. Mariano, E. Krochmal, Jr. and A. Leone, *ibid.*, **42**, 1122 (1977).

[13] P. Nedenskov, N. Clauson-Kass, J. Lei, H. Heide, G. Olsen and G. Jansen, *Acta Chem. Scand.*, **23**, 1791 (1969).

[14] S. K. P. Sinha and D. N. Chaudhury, *J. Indian Chem. Soc.*, **47**, 925 (1970).

[15] C. A. Fetscher and M. T. Bogert, *J. Org. Chem.*, **4**, 71 (1939), reported yields between 10-70%.

[16] H. L. Goering, A. C. Backus, C.-S. Chang and D. Masilamani, *ibid.*, **40**, 1533 (1975).

[17] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).