Synthesis of a Novel Cyclic Sulfone Dihydropyridine: An Investigation of the Isomerization Reaction Converting an Exocyclic Double Bond Isomer into a 1,4-Dihydropyridine

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An eight membered cyclic sulfone 1,4-dihydropyridine, RWJ 22726, **1**, with remarkable cardiovascular activity was prepared by isomerization of an exocyclic double bond isomer using various reaction conditions. Under acidic and thermal isomerization conditions, an equilibrium mixture of products in an optimum ratio of 1:3.5 in favor of the desired 1,4-dihydropyridine was obtained. Equilibration using basic reaction conditions could not be effected. Complete conversion to the 1,4-dihydropyridine during the isomerization reaction was ultimately achieved by selective precipitation of the hydrochloride salt of the desired isomer.

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Introduction.

In recent y ears the syntheses of 1,4-dihydropyridine derivatives have been the focus of intensive efforts by medicinal chemists due to the large numbers of these compounds that exhibit cardiovascular activity [3]. This important biological activity results from the ability of these compounds to inhibit cellular calcium ion influx through the voltage-dependent calcium channel which effectively inhibits the excitation-contraction coupling in vascular smooth muscle [4]. Compounds that behave in this manner are known as calcium channel or calcium entry blockers. Many calcium channel blockers are useful as smooth muscle relaxants and have been used in the treatment of angina pectoris and hypertension [3].

Recent pharmacological investigations evaluating the cardiovascular properties of RWJ 22726, **1**, indicated that this compound was a substantially more potent and longer acting antihypertensive agent in addition to being a more active, potent, and selective coronary vasodilator than the known calcium entry blocker nifedipine [5]. Of specific interest was the fact that **1** may also have a decreased liability with regard to causing constipation. Constipation is a clinical liability of most calcium channel blockers especially in elderly patients. Due to the intense interest in the biological properties of **1**, an investigation into the efficient synthesis of this compound was initiated.

Calcium channel blockers of the 1,4-dihydropyridine class are typically prepared by employing the Hantzsch synthesis which involves the condensation of an aldehyde with two equivalents of a ß-ketoester and one equivalent of ammonia [6]. In many cases, modifications of this procedure are used to allow for the synthesis of unsymmetrical 1,4-dihydropyridines. These procedures may involve the condensation of an aldehyde with an aminoenone and a compound with a doubly activated methylene group or the condensation of an α,ß-unsaturated ketone with an aminoenone [7]. Typically, these reactions proceed smoothly to give the desired 1,4-dihydropyridines, however, several examples have recently appeared in the literature in which unusual exocyclic double bond isomers of the expected compounds were isolated in low to moderate yields [8]. The formation of these isomeric compounds was attributed to the relief of steric congestion about the dihydropyridine ring and to stabilization due to conjugation of the exocyclic double bond with a carbonyl group in the substituent side-chain [8c,d]. Most importantly, the biological activity of these compounds was determined to be significantly lower than that of the related 1,4-dihydropyridines [8c,g].

Results and Discussion.

During the course of our study on the synthesis of the cyclic sulfone 1,4-dihydropyridine calcium channel blocker RWJ 22726, **1**, we encountered similar problems with respect to the formation of an exocyclic double bond isomer of the desired compound. Pharmacological analysis revealed that the biological activity of this compound was substantially less than the corresponding 1,4-dihydropyridine. Details of a study on the isomerization reaction, converting the undesired exocyclic isomer to the desired 1,4-dihydropyridine, are reported herein.

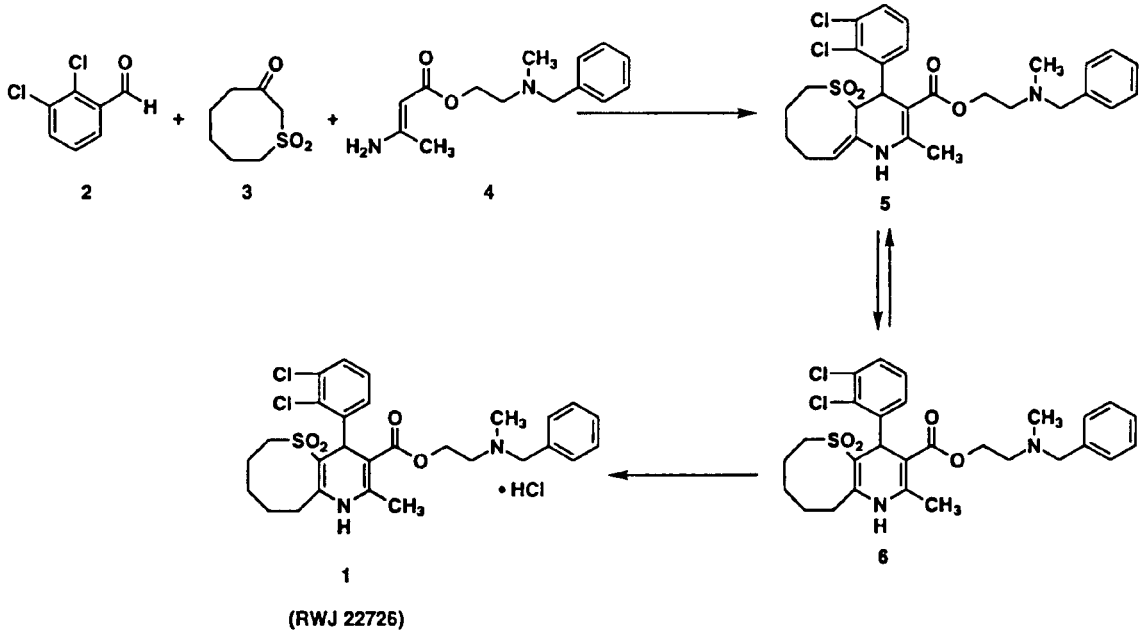
The compound of interest was prepared using a modification of the Hantzsch synthesis and involved condensation of 2,3-dichlorobenzaldehyde (**2**) with thiacyclooctan-3-one 1,1-dioxide (**3**) and 2-(*N*-benzyl-*N*-methyl)aminoethyl 3-aminocrotonate (**4**). Although **2** was commercially available, syntheses of the other two components in this reaction were required. Sulfone **3** was obtained *via* a five step protocol which involved: 1) condensation of ethyl 2-mercaptoacetate and ethyl 5-bromovalerate to afford ethyl 5-(carboethoxymethylmercapto)valerate; 2) Dieckmann cyclization and decarboxylation of the resulting diester

to provide thiacycloheptan-3-one; 3) peroxide mediated oxidation to give thiacycloheptan-3-one 1,1-dioxide [9] (~29% overall yield for 3 steps); 4) stannic chloride catalyzed ring expansion with ethyl diazoacetate [10]; and 5) hydrolysis with subsequent decarboxylation to give **3**. The synthesis of **4** was accomplished in 70% yield by a one-pot reaction involving condensation of diketene with *N*-benzyl-*N*-methylethanolamine followed by reaction with ammonia [11]. The Hantzsch reaction of **2**, **3**, and **4** gave the undesired exocyclic double bond isomer *N*-benzyl-*N*-methylaminoethyl 10-(2,3-dichlorophenyl)-3,4,5,7,10,10a-hexahydro-8-methyl-1,1-dioxo-2*H*-thiacycloocteno[3,2-*b*]pyridine-9-carboxylate (**5**) in 60% isolated yield as described in Scheme 1 [12]. Previous analog work from these laboratories has shown that exocyclic double bond isomers are obtained with both seven and eight member sulfones when the central phenyl ring is substituted with 2-nitro, 2-trifluoromethyl, or 2,3-dichloro groups [10].

relationship requiring an assignment of a trans configuration. The exocyclic double bond was assigned an *E* geometry due to the known instability of trans double bonds in eight membered rings to acidic reaction conditions [13] and due to the lack of evidence for formation of other isomeric products in the thermodynamically controlled isomerization reactions.

While the mechanism of the Hantzsch reaction has been investigated in detail, an explanation for the isolation of isomers of the aforementioned type was not addressed [14]. Patterson [8d] suggested that sterically bulky substituents on the central ring account for the formation of the unusual isomers while Taylor [8c] further interpreted the formation of the unusual double bond isomers as being the result of relief of steric congestion between the substituents in the 3, 4, and 5 positions. Interestingly, in previously reported examples of 1,2,3,4-tetrahydropyridines, the side chain adjacent to the double bond always contained a functional group that provided stabilization

Scheme 1



The molecular structure of **5** was established by ^1H and ^{13}C nmr spectroscopy and by analogy to previously reported compounds of similar structure [8c]. The ^1H and ^{13}C nmr spectra of the isomers differed substantially. Most notable, the exocyclic double bond isomer **5** exhibited a diagnostic doublet of doublets at δ 5.10 downfield from tetramethylsilane in the ^1H nmr and the carbons in the exocyclic double bond were uniquely distinguished in the ^{13}C spectra at δ 94.6 and 110.9. Lack of coupling between the C-3 and C-4 protons indicated an orthogonal

due to conjugation. The example reported herein does not meet this requirement. Although we believe that the fused eight-membered ring substituent in **5** is large enough to cause substantial steric congestion in this bicyclic system, the importance of the sulfone functional group must also be recognized. Cyclic and acyclic sulfones are known to prefer isomerization distal to the sulfone group due to low resonance and the destabilizing electron withdrawing properties of this functional group [15]. We postulate that the relatively high yield of **5** obtained in the studied reac-

tion is a consequence of both steric and stereoelectronic effects.

Numerous isomerization experiments were conducted in an effort to efficiently convert **5** into the desired 1,4-dihydropyridine **6**. The results of these experiments are compiled in Table 1. Several of these experiments gave important results and deserve comment. Mild acids were unable to effect isomerization unless heated (entries a-d), while stronger acids provided equilibrium mixtures of the undesired isomer **5** and the desired 1,4-dihydropyridine **6** (entries f-m). Isomerization, however, was not observed when catalytic amounts of hydrochloric acid were used (entry e). The optimum ratio of **5**:**6** (1:3.5) was achieved using a homogeneous solution of aqueous acid (entry i). Complete equilibration in these experiments was verified by individually reacting pure samples of **5** and **6** under identical conditions until a consistent product distribution was established (entries f and g). Isomerization could not be effected under basic conditions with either triethylamine in ethyl acetate solution or by reaction of **5** with one equivalent lithium diisopropylamide (LDA) followed by quenching with saturated ammonium chloride solution (entries n and o). Thermally induced isomerization could only be achieved in solvents with relatively high boiling points such as toluene or xylenes (entries p, q, and r). Notably, thermal equilibration under optimum conditions produced the same product ratio as achieved using a homogeneous solution of aqueous acid.

Greatest success in these isomerization reactions was achieved by taking advantage of the observations that the hydrochloride salt of **5** was soluble in methylene chloride while the hydrochloride salt of **6** was insoluble in methylene chloride. Consequently, when a solution of **5** in methylene chloride was cooled to 5° and then reacted with four equivalents of concentrated hydrochloric acid followed by warming to 25°, virtually complete conversion to the hydrochloride salt **1** was effected (entry u). Subsequent neutralization of **1** with aqueous sodium bicarbonate or sodium hydroxide solution readily provided **6** in 65-75% isolated yield. Isomerization of **5** in methylene chloride solution by reaction with a saturated solution of gaseous hydrogen chloride (1.1 equivalents) in ethyl acetate allowed for the direct preparation and isolation of **1** in 75% yield (entry v). Interestingly, replacement of methylene chloride with ethyl acetate in this experiment resulted solely in the isolation of the hydrochloride salt of **5** in 84% yield (entry t). Utilization of the aforementioned procedures allowed for the large scale synthesis of the desired 1,4-dihydropyridine **1**.

Table 1
Isomerization Studies

Entry	Starting Material	Reagent [a]	Solvent [b]	Time [c] (hours)	Temperature (°C)	Product Ratio [d] (**5** : **6**)
a	**5**	silica gel	$EtOAc/CH_2Cl_2$	96	25	1:0
b	**6**	silica gel	$EtOAc/CH_2Cl_2$	96	25	0:1
c	**5**	*p*-TsOH [e]	acetic acid	24	25	1:0
d	**5**	*p*-TsOH [e]	acetic acid	1	reflux	1:1 [f]
e	**5**	HCl [e]	methanol	5.5	reflux	1:0
f	**5**	HCl	methanol	2	25	1:2.5
g	**6**	HCl	methanol	24	25	1:2.5
h	**5**	HCl	methanol	5.5	reflux	1:2 [f]
i	**5**	HCl	tetrahydrofuran	24	25	1:3.5
j	**5**	HCl	dimethyl sulfoxide	72	25	1:2.5 [f]
k	**5**	H_3PO_4	tetrahydrofuran	24	25	1:0
l	**5**	H_3PO_4	tetrahydrofuran	34	reflux	1.2 :1
m	**5**	H_2SO_4	tetrahydrofuran	24	25	2.5:1
n	**5**	LDA/NH_4Cl [g]	tetrahydrofuran	0.5	0	1:0
o	**5**	triethylamine [g]	ethyl acetate	12	reflux	1:0
p	**6**	——	isopropanol	48	reflux	0:1
q	**5**	——	toluene	32	reflux	1:2
r	**5**	——	xylene	48	reflux	1:3.5
s	**5**	HCl	ethyl acetate	24	25	50:1
t	**5**	$HCl_{(g)}$ [g]	ethyl acetate	1	25	100: <1
u	**5**	HCl	methylene chloride	24	25	1:26
v	**5**	$HCl_{(g)}$ [g]	methylene chloride	1	25	<1:75

[a] Excess reagent (4-33 equivalents) was used except where noted. [b] All reactions were conducted in a concentration range of 0.01-0.2 *M* dependent upon substrate solubility in the solvent. [c] Reactions were monitored over the entire course of the reaction to verify equilibration. [d] Product ratios were determined by hplc (See general isomerization procedure in the experimental section). [e] Catalytic amount of reagent used. [f] Some decomposition of reactants observed. [g] 1.1 equivalents of reagent used.

Summary.

In conclusion, various conditions for the isomerization of an undesirable exocyclic double bond isomer of a novel cyclic sulfone 1,4-dihydropyridine were investigated. Although isomerization using basic reaction conditions was unsuccessful, acidic and thermal isomerization conditions provided equilibrium mixtures of desired product and starting material. Optimum results were achieved by taking advantage of the differential solubility of the hydrochloride salt of the desired product in methylene chloride.

EXPERIMENTAL

All reactions were conducted under a nitrogen atmosphere unless otherwise indicated. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Reagents and solvents were used as purchased unless otherwise indicated. Proton and carbon nmr spectra were recorded on a General Electric Model QE-300 spectrometer at 300 MHz and 75 MHz, respectively. Microanalyses were performed on a Perkin-Elmer Model 2400 CHN Elemental Analyzer and infrared spectra were recorded on a Nicolet 5DBX FT-IR spectrometer. Mass spectra were obtained with a Finnigan MAT Model 8230 mass spectrometer. All reactions were monitored by tlc wherever possible.

N-Benzyl-*N*-methylaminoethyl 10-(2,3-Dichlorophenyl)-3,4,5,-7,10,10a-hexahydro-8-methyl-1,1-dioxo-2*H*-thiacyclooctено-[3,2-*b*]pyridine-9-carboxylate (**5**).

A 5.0 l flask was charged with **2** (70.0 g, 400 mmoles), **3** (69.0 g, 392 mmoles), **4** (99.4 g, 400 mmoles) and 2.25 l 2-propanol. The reaction mixture was then heated at reflux for 14 hours and then slowly cooled to room temperature at which time an off white solid precipitated. The solids were isolated by filtration and dried under vacuum to give 133 g (60% yield) of product; ^{1}H nmr (deuteriochloroform): δ 1.54 (m, 1H), 1.71-2.17 (m, 4H), 2.04 (s, 3H), 2.24 (m, 1H), 2.49 (s, 3H), 2.57 (t, 2H, J = 5.9 Hz), 3.02 (dd, 1H, J = 9.0, 15.7), 3.30 (dd, 1H, J = 9.0, 16.2 Hz), 3.35 (d, 2H, J = 1.85 Hz), 4.13 (s overlapping m, 1H), 4.13 (m overlapping s, 2H), 5.10 (dd, 1H, J = 7.0, 10.4 Hz), 5.52 (s, 1H), 6.27 (s, 1H), 6.91 (d, 1H, J = 6.4 Hz), 7.06 (t, 1H, J = 7.9 Hz), 7.27 (m, 6H); ^{13}C nmr (deuteriochloroform): δ 20.6, 21.3, 24.7, 26.9, 34.0, 42.5, 54.5, 56.0, 57.8, 61.9, 62.3, 94.6, 110.9, 127.1, 127.4, 127.7, 128.3, 129.0, 129.5, 131.5, 133.7, 139.2, 142.5, 149.8, 166.9; ir (potassium bromide): 3357, 2953, 1688, 1607, 1525 cm^{-1}; ms: m/z 563 (MH$^+$).

Anal. Calcd. for $C_{28}H_{32}N_2O_4Cl_2S$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.45; H, 5.52; N, 4.59.

N-Benzyl-*N*-methylaminoethyl 10-(2,3-Dichlorophenyl)-3,4,5,-6,7,10-hexahydro-8-methyl-1,1-dioxo-2*H*-thiacycloocteno[3,2-*b*]pyridine-9-carboxylate (**6**).

A solution of **5** (11.27 g, 20.0 mmoles) in methylene chloride (85.0 ml) was cooled to 5° and then reacted with concentrated hydrochloric acid (6.66 ml, ~12 *N* 80.0 mmoles). The reaction mixture was vigorously stirred for 3.5 hours. The reaction was then quenched by addition of a solution of sodium hydroxide (42.0 ml, 2.0 *N*, 84.0 mmoles) until *p*H ~12 was achieved. The mixture was then concentrated under reduced pressure followed by addition of ethyl acetate (20 ml) and methylene chloride (20 ml). After stirring at room temperature for 18 hours, a milky white suspension resulted. The solids were isolated by filtration, washed with methanol, and dried under reduced pressure to provide 7.30 g (65% yield) of product, mp 180-182°; ^{1}H nmr (deuteriochloroform): δ 1.54 (m, 1H) 1.64-1.94 (m, 5H), 2.17 (s, 3H), 2.26 (m, 1H), 2.30 (s, 3H), 2.45 (m, 1H), 2.98 (dt, 1H, J = 4.3, 14.3 Hz), 3.47 (s, 3H), 3.54 (m, 1H), 4.15 (t, 2H, J = 6.2 Hz), 5.62 (s, 1H), 6.09 (s, 1H), 7.08 (overlapping dd, 1H, J = 1.0, 7.8 Hz), 7.25 (m, 6H), 7.42 (d, 1H, J = 7.8 Hz); ^{13}C nmr (deuteriochloroform): δ 19.2, 21.4, 24.3, 27.6, 29.6, 40.0, 42.7, 55.5, 61.5, 61.9, 62.5, 103.1, 112.7, 127.3, 128.6, 129.4, 129.6, 131.2, 131.9, 134.0, 139.4, 145.8, 146.3, 148.6, 167.0; ir (potassium bromide): 3336, 2926, 1697, 1641, 1493 cm^{-1}; ms: m/z 563 (MH$^+$).

Anal. Calcd. for $C_{28}H_{32}N_2O_4Cl_2S$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.21; H, 5.61; N, 4.81.

N-Benzyl-*N*-methylaminoethyl 10-(2,3-Dichlorophenyl)-3,4,5,-6,7,10-hexahydro-8-methyl-1,1-dioxo-2*H*-thiacycloocteno[3,2-*b*]pyridine-9-carboxylate Hydrochloride (**1**).

a. Synthesis from **6**.

A saturated solution of hydrogen chloride in ethyl acetate (4.8 ml, 4.05 *N*, 19.4 mmoles) [16] was added dropwise to a solution of **6** (9.95 g, 17.7 mmoles) in methylene chloride (170 ml) over a period of 5 minutes. The reaction mixture was then stirred for 10 minutes after which a white precipitate formed. The resulting suspension was stirred for 18 hours to insure complete reaction of the starting material. The solids were isolated by filtration under nitrogen, washed with hexanes, and dried under vacuum at 55° for 18 hours to give 9.76 g (92% yield) of the final product as a white solid, mp 210-212°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.28-1.91 (m, 6H), 2.19 (m, 1H), 2.28 (s, 3H), 2.62 (m, 3H), 3.00-3.46 (m, 2H), 3.36 (s, 3H), 4.30 (m, 4H), 5.42 (s, 1H), 7.32 (dd, 1H, J = 5.3, 8.0 Hz), 7.42 (m, 5H), 7.58 (m, 2H), 9.55 (s, 1H), 11.04 (s, 1H); ir (potassium bromide): 3175, 3092, 2955, 1707, 1643, 1493 cm^{-1}; ms: m/z 563 (MH$^+$).

Anal. Calcd. for $C_{28}H_{33}N_2O_4Cl_3S$: C, 56.05; H, 5.54; N, 4.67. Found: C, 56.01; H, 5.34; N, 4.42.

b. Direct Synthesis from **5**.

A saturated solution of hydrogen chloride in ethyl acetate (5.6 ml, 4.5 *N*, 25.0 mmoles) was added to a solution of **5** (11.27 g, 20.0 mmoles) in methylene chloride (170 ml) over a period of 5 minutes. After stirring for 1 hour at room temperature the product was isolated by filtration, washed with hexanes, and dried under reduced pressure at 80° for 24 hours to provide 8.95 g (75% yield) of **1** as a white solid, mp 207-210°. This material provided satisfactory ^{1}H nmr, ir, ms and elemental analysis data similar to that described in the previous example.

General Isomerization Procedure.

A solution of **5** or **6** (564 mg, 1.00 mmole) dissolved in the solvent of choice (5.00-18.0 ml) was reacted with concentrated acid (4-33 equivalents). The reaction mixture was stirred at either room temperature or reflux and the progress of the reaction was determined by removal of a sample aliquot followed by analysis using reverse phase hplc. A 10 cm Whatman Partisil 5 ODS-3 C_{18} reverse phase RAC II column was used for the

analysis in conjunction with a mobile phase which consisted of a 65:35 mixture of methanol and buffer solution. The buffer solution consisted of a 0.05 *N* ammonium acetate solution adjusted to *p*H 5.5 with acetic acid. The products were observed using an ultraviolet detector set at a wavelength of 210 nm.

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