Heterocyclic Variants of 1,5-Benzodiazepine System. VII. Synthesis of Substituted 2a-Phenyl-4-methylsulfonyl-2-methoxy-1,2,2a,3-tetrahydroazeto[1,2-*a*][1,5]benzodiazepin-1-ones

Roberto Martínez* [1]

Instituto de Química [2], Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.

Paulina E. Hernández and Enrique Angeles

FES-Cuautitlán, Universidad Nacional Autónoma de México, Campo 1, Química Orgánica, Cuautitlán Izcalli, Estado de México, México.

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The preparation of novel 2a-phenyl-4-methylsulfonyl-2-methoxy-1,2,2a,3-tetrahydroazeto[1,2-*a*][1,5]-benzodiazepin-1-ones is described. The structure of all the products was corroborated by ir, mass spectrometry and ^1H and ^{13}C-nmr.

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Since the introduction of Librium in 1960 [3] and the posterior detection of its mode of action *via* γ-aminobutyric acid receptor ($GABA_AR$), the benzodiazepines have stimulated the exploitation of the chemistry of this class of compounds. Some of the most interesting novel developments are the benzodiazepines containing an additional heterocyclic ring fused to the different faces of the diazepine ring nucleus [4]. In our continuing search for central nervous system drugs [5], the β-lactam moiety has been integrated into the benzo diazepine system by regiospecific cicloaddition of substituted acetyl chloride to 4-aryl-2-methylthio-3*H*-1,5-benzodiazepines [6]. In this work, we report the extension of this synthetic strategy to a synthesis of substituted 2a-phenyl-4-methylsulfonyl-2-methoxy-1,2,2a,3-tetrahydroazeto-[1,2-*a*][1,5]benzodiazepin-1-ones, **III** (Scheme 1).

Our key intermediates, **I**, were prepared similarly to literature methods [7]. Treatment of 2-methylthio-4-(R-phenyl)-3*H*-1,5-benzodiazepines **I** (**a** = H, **b** = *p*-F, **c** = *p*-Cl, **d** = *p*-Br, **e** = *p*-Me, **f** = *p*-OMe, **g** = *p*-Ph, **h** = *m*-Br) with

Scheme 1

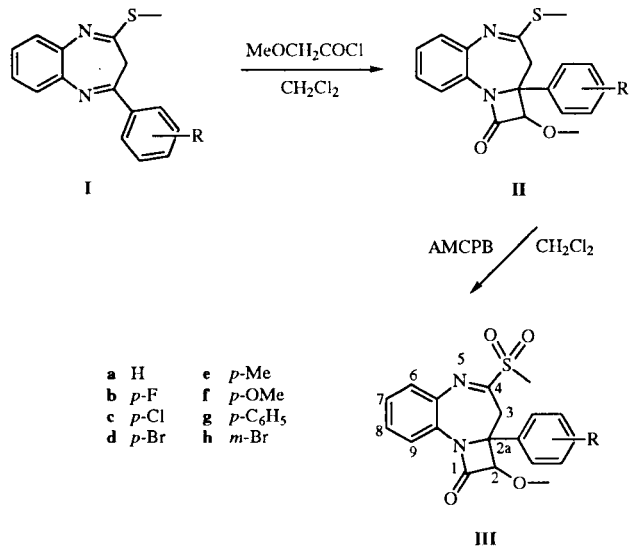

Table 1

Physical, Analytical and IR Data for Compounds **IIa-h**

Compound No.	R	Yield %	Mp, °C	Molecular Formula	Analysis, % C	H	C=O cm^{-1}
a	*p*-H	57.0	149-151	$C_{19}H_{18}N_2O_2S$	67.43	5.37	1748
					67.40	5.33	
b	*p*-F	51.0	136-138	$C_{19}H_{17}FN_2O_2S$	64.03	4.81	1760
					63.98	4.79	
c	*p*-Cl	56.0	148-149	$C_{19}H_{17}ClN_2O_2S$	61.28	4.60	1766
					61.20	4.57	
d	*p*-Br	61.0	165-167	$C_{19}H_{17}BrN_2O_2S$	54.68	4.12	1757
					54.78	4.09	
e	*p*-Me	44.0	144-145	$C_{20}H_{20}N_2O_2S$	68.16	5.72	1747
					68.10	5.68	
f	*p*-OMe	50.0	113-115	$C_{20}H_{20}N_2O_3S$	65.20	5.48	1759
					65.0	5.45	
g	*p*-C_6H_5	60.0	178-179	$C_{25}H_{22}N_2O_2S$	72.44	5.35	1760
					72.40	5.31	
h	*m*-Br	65.0	167-168	$C_{19}H_{17}BrN_2O_2S$	54.68	4.12	1755
					54.78	4.10	

Table 2

^{1}H-NMR Data (ppm, δ) for Compounds **IIa-h** in Deuteriochloroform

Compound No.	R	H-3a [a]	H-3b [a]	H-2	OCH_3	SCH_3	H-9 [b]
a	*p*-H	3.75	3.03	4.57	3.28	2.24	8.32
b	p-F	3.72	3.32	4.54	3.31	2.27	8.31
c	*p*-Cl	3.73	3.04	4.55	3.32	2.27	8.31
d	*p*-Br	3.72	3.03	4.54	3.33	2.27	8.30
e	*p*-CH_3	3.76	3.02	4.52	3.30	2.28	8.31
f	*p*-OCH_3	3.73	2.98	4.47	3.28	2.25	8.29
g	*p*-C_6H_5	3.75	3.01	4.50	3.29	2.26	8.34
h	*m*-Br	3.68	3.02	4.54	3.31	2.27	8.27

[a] Doublet (J = 14 Hz). [b] Multiplet.

derivatives **II** the presence of a three-proton singlet at δ 3.28-3.33 confirmed the incorporation of an aliphatic methoxy group; a downfield one-proton singlet at δ 4.47-4.57 was assigned to the methine proton attached to the carbon bearing the methoxy group. Likewise another three-proton singlet at δ 2.24-2.28 was assigned to the *S*-methyl protons. Two doublets at δ 2.98-3.32 (J = 14 Hz) and δ 3.68-3.76 (J = 14 Hz) respectively were assigned to the methylene protons joined to C-3 whereas a multiplet at δ 8.27-8.34 was assigned to the aromatic proton joined to C-9. The remaining aromatic protons in compounds **II** appeared as unresolved multiplet at δ 6.76-7.38. Further evidence of the structure of **II** is derived from their mass spectral data. All the compounds showed the molecular ion and their base peak is formed by the loss of a methoxyketene unit [9].

Table 3

^{13}C-NMR Data (ppm, δ) for Compounds **IIa-h** in Deuteriochloroform

Compound No.	R	C-1	C-4	C-9	C-2	C-2a	OCH_3	C-3	SCH_3
a	*p*-H	164.9	163.0	121.5	91.0	67.2	58.5	48.1	14.2
b	*p*-F	164.8	162.8	121.4	90.9	67.1	58.6	48.1	14.2
c	*p*-Cl	164.7	162.7	121.4	91.0	67.2	58.8	47.9	14.2
d	*p*-Br	164.7	162.6	121.4	91.0	67.2	58.8	47.9	14.2
e	*p*-CH_3	164.9	163.0	121.5	91.1	67.5	58.6	48.0	14.2
f	*p*-OCH_3	164.9	163.1	121.7	91.3	67.3	58.5	48.3	14.2
g	p-C_6H_5	164.9	163.0	121.6	91.2	67.6	58.7	48.0	14.2
h	*m*-Br	164.8	162.8	121.7	91.0	67.6	58.8	47.7	14.3

Table 4

Physical, Analytical and IR Data for Compounds **IIIa-h**

Compound No.	R	Yield %	Mp, °C	Molecular Formula	Analysis, % C	H	C=O[1] cm^{-1}
a	*p*-H	73.6	170-171	$C_{19}H_{18}N_2O_4S$	61.61 61.57	4.90 4.85	1753
b	*p*-F	81.0	204-206	$C_{19}H_{17}FN_2O_4S$	58.75 58.69	4.41 4.38	1769
c	*p*-Cl	54.0	188-189	$C_{19}H_{17}ClN_2O_4S$	56.43 56.39	4.24 4.21	1770
d	*p*-Br	69.6	[a]	$C_{19}H_{17}BrN_2O_4S$	50.79 50.82	3.82 3.80	1751
e	*p*-Me	61.4	[a]	$C_{20}H_{20}N_2O_4S$	62.48 62.42	5.25 5.21	1766
f	*p*-OMe	77.7	217-219	$C_{20}H_{20}N_2O_5S$	59.98 59.92	5.04 4.98	1764
g	*p*-C_6H_5	85.5	[a]	$C_{25}H_{22}N_2O_4S$	67.24 67.16	4.97 4.94	1768
h	*m*-Br	72.4	[a]	$C_{19}H_{17}BrN_2O_4S$	50.79 50.81	3.82 3.78	1770

[a] Decompose.

methoxyacetyl chloride in dried dichlorometane, in the presence of triethylamine, afforded **IIa-h** (Scheme 1). Structural assignment of derivatives **II** was made on spectroscopic grounds. In the infrared spectra of **II** the appearance of absorption bands at 1747-1766 cm^{-1} was consistent with the presence of a β-lactam group [8]. In the ^{1}H-nmr spectra of

The synthesis of **IIIa-h** was achieved by a regiospecific oxidation with *m*-chloroperoxybenzoic acid, in the presence of dichloromethane, of compounds **II**. In agreement with the suggested structure the ir spectra (chloroform) of all the compounds **III** exhibited a characteristically band for the β-lactam group at 1753-1770 cm^{-1} together with a band at

Table 5

^{1}H-NMR Data (ppm, δ) for Compounds **IIIa-h** in Deuteriochloroform

Compound No.	R	H-3a [a]	H-3b [a]	H-2	OCH_3	SO_2CH_3	H-9 [b]
a	*p*-H	4.79	2.90	4.64	3.33	2.88	8.49
b	*p*-F	4.72	2.93	4.62	3.33	2.98	8.45
c	*p*-Cl	4.72	2.93	4.62	3.34	3.00	8.45
d	*p*-Br	4.80	2.92	4.63	3.33	2.91	8.48
e	*p*-CH_3	4.73	2.95	4.64	3.33	2.98	8.58
f	*p*-OCH_3	4.75	2.90	4.58	3.31	2.96	8.46
g	*p*-C_6H_5	4.55	2.84	4.51	3.16	2.81	8.28
h	*m*-Br	4.47	2.89	4.48	3.10	2.73	8.22

[a] Doublet (J = 14 Hz). [b] Multiplet.

Table 6

^{13}C-NMR Data (ppm, δ) for Compounds **IIIa-h** in Deuteriochloroform

Compound No.	R	C-1	C-4	C-9	C-2	C-2a	OCH_3	C-3	SO_2CH_3
a	*p*-H	164.5	161.5	121.2	92.0	65.8	59.0	38.8	37.1
b	*p*-F	165.2	164.3	121.2	92.0	65.0	59.0	38.5	36.9
c	*p*-Cl	164.2	161.1	121.6	92.1	65.2	58.2	38.3	36.9
d	*p*-Br	164.4	161.5	121.3	92.3	65.6	59.2	38.6	37.1
e	*p*-CH_3	164.9	163.4	120.9	91.1	65.2	58.8	37.8	37.1
f	*p*-OCH_3	164.9	163.5	120.6	91.4	65.1	58.5	37.9	37.0
g	*p*-C_6H_5	165.1	164.3	121.1	91.9	65.2	59.0	39.0	37.0
h	*m*-Br	168.9	163.9	121.0	91.5	65.0	58.7	37.7	36.6

1371-1379 cm^{-1} asignable to the -SO_2 group. Its ^{1}H-nmr spectrum showed a singlet at δ 2.73-3.0 for the SO_2-methyl protons as well as one singlet at δ 3.34-3.1 for the *O*-methyl protons. Two one-proton signals at δ 2.90 (doublet, J = 14 Hz) and 4.75 (doublet, J = 14 Hz) were assigned to the methylene protons joined to C-3 whereas a singlet at δ 4.48-4.64 was assigned to the methine proton joined to C-2. The multiplet at δ 8.22-8.58 was assigned to the aromatic proton joined to C-9. The remaining aromatic protons in compounds **III** appeared as unresolved multiplet at δ 6.76-7.38. The ^{13}C-nmr spectrum showed 17 signals and DEPT experiment indicated that two of them correspond to CH_3, one to CH_2, seven to CH and seven to Cq. ^{1}H-^{13}C correlation (HETCOR) allowed us the identification of eleven signals: δ 37.0 (CH_3-SO_2), 37.9 (C-3), 58.5 (CH_3O-C2), 65.0 (C2a), 91.4 (C2), 113.9 (C3', C5'), 120.6 (C9), 127.8 (C2',C6'), 163.5 (C4) and 164.9 (C=O, amide). The mass spectrum of compounds showed their molecular ions and its fragmentation is according to the assigned structure.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H, ^{13}C and ^{1}H-^{13}C nmr spectra were determined on Varian Gemini 200 and Varian-VXR-300S spectrometers FT-300 instruments. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Jeol SX-100 mass spectrometer.

Compounds **Ia-h** have been prepared following a reported procedure [7]. The structures of compounds **Ia-h** were supported by ir, ^{1}H-nmr and mass spectral data which are similar to those reported.

Synthesis of 2a-(R-phenyl)-4-methylthio-2-methoxy-1,2,2a,3-tetrahydroazeto[1,2-*a*][1,5]benzodiazepin-1-ones, **IIa-h.**

General Procedure (R = H).

To a solution of **Ia** (0.53 g, 2.0 mmoles) dissolved in 50 ml of dichloromethane was added 6 mmoles (0.65 g) of methoxyacetyl chloride. The mixture was stirred for 10 minutes and a solution of triethylamine (0.61 g, 6 mmoles) in 2 ml of dichloromethane was added dropwise, with stirring, during 15 minutes. The reaction mixture was heated for 12 hours, then it was allowed to cool. The resulting solution was washed with a 5% aqueous hydrochloric acid (2 x 50 ml), water (2 x 50 ml), dried over anhydrous sodium sulfate and concentrated (rotatory evaporator) to afford a yellow oil that was purified by column chromatography (fluorosil, dichloromethane) to give 0.39 g (57%) of **IIa,** mp 149-151°. The physical, analytical and spectral data for the synthesized compounds **IIa-h** are recorded on Tables 1,2 and 3.

Synthesis of 2a-(R-phenyl)-4-methylsulfonyl-2-methoxy-1,2,2a,3-tetrahydroazeto[1,2-*a*][1,5]benzodiazepin-1-ones, **IIIa-h.**

General Procedure (R = H).

A solution of 0.76 g (2.2 mmoles) of *m*-chloroperoxybenzoic acid in 10 ml of dichloromethane was added dropwise to a cold solution (0-5°) of **IIa** (0.39 g, 1 mmole) in 10 ml of dichloromethane. The reaction mixture was stirred at this temperature for 10 minutes. The solution was then washed with saturated aqueous sodium bicarbonate (2 x 20 ml) and water (2 x 20 ml), dried (sodium sulfate), and concentrated(rotatory evaporator) to afford a colorless solid that was purified by column chromatography (fluorosil, hexane/ethyl acetate, 70:30) to give 0.27 g (74%) of **IIa**, mp 170-171°. The physical, analytical and spectral data for the synthesized compounds **IIIa-h** are recorded in Tables 4, 5 and 6.

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[1] Author to whom correspondence should be addressed.
[2] Contribution No. 1411 from Instituto de Química, UNAM.
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