Some Reactions of 1-Alkyl-1,2,3,4-tetrahydropyridines with Organic Azides. Synthesis of 1-Alkylpiperidylidene-2-sulfonamides

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The 1,3-dipolar cycloaddition reaction of 1-substituted-1,2,3,4-tetrahydropyridines **4a-d** with organic azides **5** afforded the respective 1-substituted-piperidylidene-2-sulfonamides **6**. In contrast, the reaction of (*E*)-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (**4e**) with 4-chlorobenzenesulfonyl azide yielded **6m** as well as 1-(4-chlorophenyl)sulfonimine-1,2,3,4-tetrahydropyridine (**7**) arising from addition of the azide to the (*E*)-1-(1-propenyl) substituent of **4e**.

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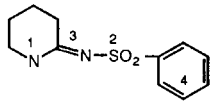
The 1-methylpiperidine ring system is a common structural moiety present in several classes of drugs that exhibit analgesic μ-receptor agonist activity such as morphine, *N*-methylmorphinan, *N*-methyl-6,7-benzomorphan and meperidine [1]. In an earlier study we reported a facile regiospecific 1,3-dipolar cycloaddition reaction of 1-methyl-1,2,3,4-tetrahydropyridine with benzenesulfonyl azide that yielded 1-methylpiperidylidene-2-benzenesulfonamide **1** which bears some structural similarity to the analgesic drug meperidine **2** [2]. The four characteristic structural features common to the major analgesics including meperidine are 1), a tertiary amino group with a methyl substituent; 2), a central carbon atom of which none of the valences are hydrogen; 3), a two carbon chain separating the tertiary nitrogen atom from the central carbon atom; and 4), a phenyl ring system attached directly to the central carbon atom [1]. These structural comparisons



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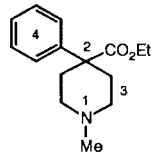

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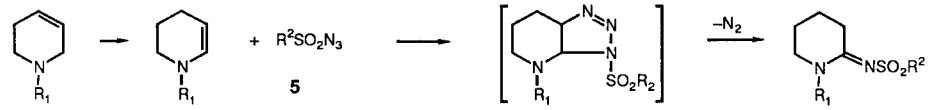
of **1** with **2** would require the sulfonyl sulfur atom to serve as a central carbon atom and the C=N moiety of **1** to act as a two carbon spacer. Replacement of the *N*-methyl group of analgesic μ-receptor agonists in the morphine class of compounds by a larger *n*-alkyl, *N*-allyl or *N*-cycloalkylalkyl substituent provides drugs that exhibit analgesic μ-receptor antagonist activity which are non-addictive such as Naloxone® [1,3-6]. We now describe a facile procedure for the synthesis of 1-substituted-piperidylidene-2-arylsulfonamides **6** with analgesic μ-receptor antagonist activity.

Reaction of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine **4a**, prepared by isomerization of 1-cyclopropylmethyl-1,2,5,6-tetrahydropyridine **3a** using potassium *t*-butoxide [7], with 4-chlorobenzenesulfonyl azide **5** (R^2 = 4-Cl-C_6H_4-) in dry ether proceeded rapidly at 25° with evolution of nitrogen gas to yield 1-cyclopropylmethyl-piperidylidene-2-(4-chlorophenyl)sulfonamide **6a** (R^1 = cyclopropylmethyl, R^2 = 4-Cl-C_6H_4-) in 56% yield. Similar reactions of **4a** with **5** (R^2 = 4-H_2N-C_6H_4- and 3-pyridyl) afforded **6b** and **6c** in 52 and 57% yield, respectively. A variety of other 1-substituted-piperidylidene-2-sulfonamides **6** possessing other R^1-substituents such as cyclobutylmethyl, *n*-Pr and *i*-Bu were also synthesized in order that the effect which these R^1-substituents have upon analgesic μ-receptor antagonist activity could be investigated. Thus, reaction of **4b-d** with **5** as described above yielded the respective analogues **6d-l** in 37-91% yield as summarized in Table I.

The base catalyzed isomerization of 1-(2-propenyl)-1,2,5,6-tetrahydropyridine **3e** using potassium *t*-butoxide afforded (*E*)-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (**4e**) in 60% yield. The 1-(1-propenyl) substituent of **4e** possesses the *E*-stereochemistry since the N-CH=C*H* and

Scheme I



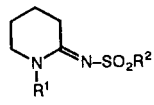
3 **4** **5** **6**

3-4a, R^1 = –CH_2–cyclopropyl; **3-4b**, R^1 = –CH_2–cyclobutyl; **3-4c**, R^1 = *n*-Pr;

3-4d, R^1 = *i*-Bu; **3e**, R^1 = –CH_2–CH=CH_2; **4e**, R^1 = (E)-CH_3–CH=CH–

Table I

Physical Constants of 1-Substituted-piperidylidene-2-arylsulfonamides **6**



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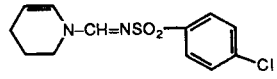

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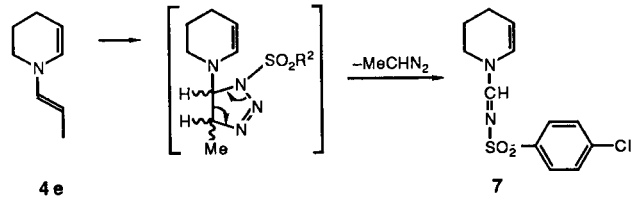
No.	R^1	R^2	Yield %	Mp, °C	Formula	Analysis % Calcd./Found C	H	N
6a	c-$C_3H_5CH_2$- [a]	4-Cl-C_6H_4-	56	114-115	$C_{15}H_{19}ClN_2O_2S$	55.12	5.86	8.57
						54.90	5.86	8.44
6b	c-$C_3H_5CH_2$-	4-H_2N-C_6H_4-	52	165	$C_{15}H_{21}N_3O_2S$	58.61	6.89	13.67
						58.23	6.87	13.29
6c	c-$C_3H_5CH_2$-	3-pyridyl	57	89	$C_{14}H_{19}N_3O_2S$	57.31	6.53	14.32
						56.94	6.44	13.98
6d	c-$C_4H_7CH_2$- [b]	4-Cl-C_6H_4-	68	113	$C_{16}H_{21}ClN_2O_2S$	56.38	6.21	8.22
						56.32	6.35	8.16
6e	c-$C_4H_7CH_2$-	4-H_2N-C_6H_4-	86	216-217	$C_{16}H_{23}N_3O_2S$	59.79	7.21	13.07
						59.65	7.31	12.96
6f	c-$C_4H_7CH_2$-	3-pyridyl	91	56-57	$C_{15}H_{21}N_3O_2S$	58.61	6.89	13.67
						58.25	6.95	13.51
6q	*n*-Pr	4-Cl-C_6H_4-	68	107-108	$C_{14}H_{19}ClN_2O_2S$	53.41	6.08	8.90
						53.61	6.17	8.90
6h	*n*-Pr	4-H_2N-C_6H_4	65	178-179	$C_{14}H_{21}N_3O_2S$	56.92	7.17	14.22
						57.04	7.26	14.05
6i	*n*-Pr	3-pyridyl	64	109-110	$C_{13}H_{19}N_3O_2S$	55.49	6.81	14.93
						55.27	6.84	14.77
6j	*i*-Bu	4-Cl-C_6H_4-	37	106	$C_{15}H_{21}ClN_2O_2S$	54.78	6.44	8.52
						54.81	6.49	8.48
6k	*i*-Bu	4-H_2N-C_6H_4-	49	184-185	$C_{15}H_{23}N_3O_2S$	58.22	7.49	13.58
						58.37	7.63	13.57
6l	*i*-Bu	3-pyridyl	42	66-67	$C_{14}H_{21}N_3O_2S$	56.92	7.17	14.22
						56.57	7.24	13.97
6m	(*E*)-CH_3CH=CH-	4-Cl-C_6H_4-	43	106-107	$C_{14}H_{17}ClN_2O_2S$	53.75	5.48	8.96
						53.39	5.49	8.96
7	–	–	20	55	$C_{12}H_{13}ClN_2O_2S$	50.62	4.60	9.84
						50.37	4.64	9.63

[a] Cyclopropylmethyl. [b] Cyclobutylmethyl.

N-C*H*=CH- protons which appeared at δ 4.32 and 6.0, respectively exhibited a *trans*-coupling constant of 15 Hz. Reaction of **5e** with one equivalent of 4-chlorobenzenesulfonyl azide yielded a mixture of **6m** (43%) and **7** (20%) resulting from addition to the tetrahydropyridine C5-C6 and 1-(1-propenyl) olefinic bonds, respectively. A plausible mechanism for the formation of **7** could involve addition of 4-chlorobenzenesulfonyl azide (**5**, R^2 = 4-Cl-C_6H_4-) to the (*E*)-1-(1-propenyl) substituent of **4e** to form an unstable triazoline adduct from which diazoethane is expelled as indicated in Scheme II. This mechanism is consistent with that proposed for the formation of *N*-methyl-*N*-phenyl-*N'*-tosylsulfonylimine, obtained from the reaction of tosyl azide with 1-(*N*-methylaniline)-2-benzoylethylene [8]. A similar reaction of **4e** with two equivalents of 4-chlorobenzenesulfonyl azide yielded **6m** and **7** in 43 and 16% yield, respectively.

Pharmacological testing using the analgesic phenylquinone writhing assay [9] indicated that **6a** acts as an analgesic μ-receptor antagonist [10].

Scheme II



4e **7**

EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide unless otherwise indicated) were taken on a Perkin-Elmer or Nicolet 5DX FT spectrometer. Nuclear magnetic resonance spectra were determined for solutions in deuteriochloroform unless otherwise stated with TMS as internal standard using a Bruker AM-300 or Varian EM-360A spectrometer. All the products described gave rise to a single spot on tlc using three different solvent systems of low, medium and high polarity. Preparative thin layer chromatography (tlc) was performed on 20 x 20 cm silica gel G plates, 0.75 mm in thickness. The 1-substituted-1,2,3,4-tetrahydropyridines **4a-e** were prepared by base catalyzed isomerization of **3a-e**, respectively using the procedure of Beeken and Fowler [7]. The azides **5** were prepared

by the reaction of the respective sulfonyl chloride with sodium azide using the procedure described by Stout *et al.* [11].

1-Cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (**6a**). General Procedure.

A solution of 4-chlorobenzenesulfonyl azide (0.34 g, 1.56 mmoles) in 10 ml of ether was added dropwise to a solution of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (**4a**), 0.21 g, 1.53 mmoles) [7] in 20 ml of ether at 25° with stirring. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 hour and the solvent was removed *in vacuo*. The yellow solid obtained was purified by preparative tlc with ether as development solvent to yield **6a** (Rf 0.37, 0.26 g, 56%) as a white solid; ir: 1575 (C=N) cm^{-1}; ^1H nmr: δ 0.18-1.36 (m, 5H, cyclopropyl hydrogens), 1.65-2.05 (m, 4H, C-4H, C-5H), 2.96-3.28 (m, 2H, C-3H), 3.31-3.61 (m, 4H, C-6H, -C*H*$_2$-cyclopropyl), 7.42 (d, $J_{2,3} = J_{5,6} = 9$ Hz, 2H, C-3H, C-5H phenyl hydrogens), 7.89 (d, $J_{2,3} = J_{5,6} = 9$ Hz, 2H, C-2H, C-6H phenyl hydrogens). Extraction of the band having Rf 1.0 with 75 ml hot acetone yielded 4-chlorobenzenesulfonyl azide (0.081 g, 26% recovery) which was identical (^1H nmr and micro tlc) to the authentic sample.

The 1-substituted-piperidylidene-2-sulfonamides **6b-l**, which were also prepared using this general procedure, were purified as illustrated below: **6b** and **6e** (recrystallization from acetone); **6c, 6q** and **6i** (neutral aluminum oxide column chromatography with acetone as eluant); **6d** and **6j** [preparative tlc using ether as development solvent, **6d** (Rf 0.44) and **6j** (Rf 0.39)]; **6f** (sublimation, 0.1 Torr, 65°); **6h** (recrystallization from carbon tetrachloride-acetone); **6k** [preparative tlc using ether:acetone (2:1 v/v) as development solvent, Rf 0.31]; **6l** [preparative tlc using ether:acetone (5:1 v/v) as development solvent, Rf 0.39].

Some spectral data for selected compounds **6** are presented below.

1-Cyclobutylmethylpiperidylidene-2-(4-aminophenyl)sulfonamide (**6e**).

This compound had ir: 1565 (C=N), 3380 and 3460 (NH_2) cm^{-1}; ^1H nmr: δ 1.54-2.08 (m, 10H, C-4H, C-5H, cyclobutyl methylene hydrogens), 2.39-3.07 (m, 3H, C-3H, cyclobutyl methine hydrogen), 3.22-3.50 (m, 2H, C-6H), 3.60 (d, $J_{CHCH_2} = 7$ Hz, 2H, -C*H*$_2$-cyclobutyl), 5.43 (br s, 2H, NH_2, exchanges with deuterium oxide), 6.78 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-3H, C-5H phenyl hydrogens), 7.54 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-2H, C-6H phenyl hydrogens).

1-*n*-Propylpiperidylidene-2-(3-pyridyl)sulfonamide (**6i**).

This compound had ir: 1560 (C=N) cm^{-1}; ^1H nmr: δ 0.86 (t, J = 7 Hz, 3H, Me), 1.34-2.11 (m, 6H, C-4H, C-5H, C*H*$_2$CH$_3$), 3.00-3.26 (m, 2H, C-3H), 3.26-3.61 (m, 4H, C-6H, C*H*$_2$CH$_2$CH$_3$), 7.40 (d, $J_{4,5} = 8$ Hz of d, $J_{5,6} = 5$ Hz, 1H, pyridinyl C-5H), 8.23 (d, $J_{5,6} = 5$ Hz of d, $J_{4,6} = 2$ Hz, 1H, pyridinyl H-6), 8.75 (d, $J_{4,5} = 8$ Hz of d, $J_{4,6} = 2$ Hz of d, $J_{2,4} = 2$ Hz, 1H, pyridinyl H-4), 9.17 (d, $J_{2,4} = 2$ Hz, 1H, pyridinyl H-2).

1-Isobutylpiperidylidene-2-(4-chlorophenyl)sulfonamide (**6j**).

This compound had ir: 1570 (C=N) cm^{-1}; ^1H nmr: δ 0.83 (d, J = 7 Hz, 6H, CH*Me*$_2$), 1.48-2.23 (m, 5H, C-4H, C-5H, C*H*Me$_2$), 2.91-3.48 (m, 6H, C-3H, C-6H, NC*H*$_2$CH), 7.40 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-3H, C-5H phenyl hydrogens), 7.86 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-2H, C-6H phenyl hydrogens).

(*E*)-1-(1-Propenyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (**6m**) and 1-(4-chlorophenyl)sulfonimine-1,2,3,4-tetrahydropyridine (**7**).

A solution of 4-chlorobenzenesulfonyl azide (0.355 g, 1.63 mmoles) in ether (10 ml) was added dropwise to a solution of **4e** (0.20 g, 1.63 mmoles) in ether (20 ml) at 25° with stirring. Evolution of nitrogen gas began 15 seconds after the final addition of the azide. The reaction was allowed to proceed for 1 hour, the solvent was removed *in vacuo* and the resulting viscous green oil was purified by preparative tlc using ether:petroleum ether (4:1 v/v) as development solvent. Extraction of the band having Rf 0.27 with 50 ml hot acetone yielded **6m** (0.22 g, 43%) as a white solid; ir: 1540 (C=N) and 1600 (C=C) cm^{-1}; ^1H nmr: δ 1.65-2.23 (m, 7H, C-4H, C-5H, CH*Me*), 3.02-3.32 (m, 2H, C-3H), 3.32-3.80 (m, 2H, C-6H), 5.30 (d, $J_{CH=CH} = 15$ Hz of q, $J_{CHMe} = 6$ Hz, 1H, C*H*Me), 7.32 (d, $J_{CH=CH} = 15$ Hz, 1H, C*H*=CHMe), 7.43 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-3H, C-5H phenyl hydrogens), 7.92 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-2H, C-6H phenyl hydrogens). Extraction of the band having Rf 0.48 with hot acetone (50 ml) afforded **7** (92 mg, 20%) as a white solid; ir: 1600 (C=N); ^1H nmr: δ 1.80-2.31 (m, 4H, C-3H, C-4H), 3.58-3.85 (m, 2H, C-2H), 5.20-5.44 (m, 1H, C-5H), 6.42 (d, $J_{5,6} = 8$ Hz, 1H, C-6H), 7.41 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-3H, C-5H phenyl hydrogens), 7.84 (d, $J_{2,3} = J_{5,6} = 8$ Hz, 2H, C-2H, C-6H phenyl hydrogens), 8.24 (s, 1H, C*H*=N). Extraction of the band having Rf 0.85 with hot acetone (50 ml) gave 4-chlorobenzenesulfonyl azide (18 mg, 5% recovery) which was identical (micro tlc and ^1H nmr) with an authentic sample.

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REFERENCES AND NOTES

[1] "Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry", R. F. Doerge, ed, 8th Ed, J. B. Lippincott Co., Philadelphia, 1982.

[2] A preliminary account of this work was published, B. K. Warren and E. E. Knaus, *J. Heterocyclic Chem.*, **19**, 1259 (1982).

[3] A. A. Kurland and L. McCabe, *J. Clin. Pharmacol.*, **16**, 66 (1976).

[4] B. A. Judron, D. U. Himmelburger and A. Goldstein, *Clin. Pharmacol. Ther.*, **27**, 492 (1980).

[5] K. Unna, *J. Pharmacol. Exp. Ther.*, **79**, 27 (1943).

[6] H. F. Fraser and L. S. Harris, *Ann. Rev. Pharmacol.*, **7**, 277 (1967).

[7] P. Beeken and F. W. Fowler, *J. Org. Chem.*, **45**, 1336 (1980).

[8] R. Fusco, G. Bianchetti, D. Pocur and R. Ugo, *Chem. Ber.*, **96**, 802 (1963).

[9] H. O. Collier, L. C. Dineen, C. A. Johnson and C. Schneider, *Brit. J. Pharmacol. Chemother.*, **32**, 295 (1968).

[10] E. E. Knaus, B. K. Warren and T. A. Ondrus, U. S. Patent, 4,468,403, August 28, 1984.

[11] D. M. Stout, T. Takaya and A. I. Meyers, *J. Org. Chem.*, **40**, 563 (1975).