Some Reactions of 1-Methyl-(2-phenylethyl)-1,2,3,4-tetrahydropyridines with Organic Azides. Synthesis of 1-Methyl-(2-phenylethyl)piperidylidene-2-sulfonamides

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The 1,3-dipolar cycloaddition reaction of 1-methyl- and 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridines **7** with organic azides **8** afforded the respective 1-substituted-piperidylidene-2-sulfon(cyan)amides **9**. Nitration of the 1-(2-phenylethyl) analogue **9o** yielded the 1-[2-(4-nitrophenyl)ethyl] derivative **9r** which on reduction with palladium-on-charcoal and hydrazine gave the 1-[2-(4-aminophenyl)ethyl] analogue **9s**.

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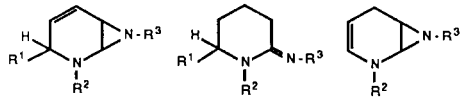
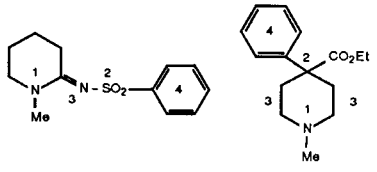
The 1,3-dipolar cycloaddition reaction of organic azides with cyclic dienamines and enamines is an attractive method for the synthesis of pharmacologically interesting heterocycles. In earlier studies we showed that the regiospecific 1,3-dipolar cycloaddition reaction of 1,2-dihydropyridines with azides afforded stable isolabile 2,7-diazabicyclo[4.1.0]hept-4-enes **1** which could be elaborated to the piperidylidene-2-sulfon(cyan)amide analogues **2** [1,2]. Similar reactions employing 1,4-dihydropyridines gave 2,7-diazabicyclo[4.1.0]hept-3-enes **3** that exhibited



1 **2** **3**



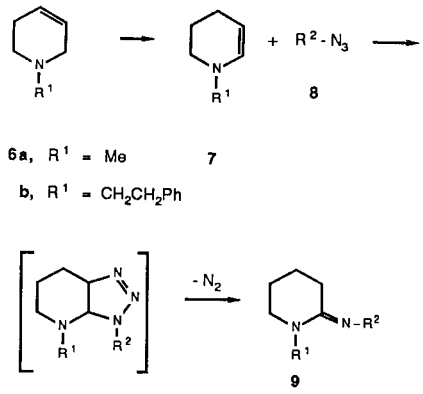
4 **5**

1 - 3, R^1 = H, *n*-Bu, Ph; R^2 = H, Me; R^3 = $SO_2Me(Ph)$, CN

analgesic activity [3]. The 1-methylpiperidylidene-2-benzenesulfonamide structure **4** bears some structural similarity to the analgesic drug meperidine **5** which possesses the four characteristic structural features common to the major analgesic agents morphine, *N*-methylmorphinan, *N*-methyl-6,7-benzomorphan and methadone [4]. These include 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 from the central carbon atom; and 4), a phenyl ring system attached directly to the central carbon atom. These structural comparisons of **4** with **5** would require the sulfonyl sulfur atom to serve as a central carbon atom and the C=N moiety of **4** to act as a two carbon spacer. We now describe a facile procedure for the synthesis of 1-methyl(arylalkyl)piperidylidene-2-sulfon(cyan)amides **9** [5].

Reaction of 1-methyl-1,2,3,4-tetrahydropyridine **7a**, prepared by isomerization of 1-methyl-1,2,5,6-tetrahydropyridine **6a** using potassium tert-butoxide [6], with methanesulfonyl azide **8** (R^2 = $MeSO_2$) in dry ether proceeded rapidly at 25° with evolution of nitrogen gas to yield 1-methylpiperidylidene-2-methanesulfonamide **9a** (R^1 = Me, R^2 = $MeSO_2$) in 82% yield. Similar reactions with other azides afforded **9b-9l** in 65 to 89% yield (see Table I for R^2-substituents). Reduction of **9q** with 10%

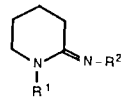
Scheme I



palladium-on-charcoal and 85% hydrazine hydrate in 95% ethanol [7] at 25° gave the 3-amino derivative **9m** (78% yield). A similar reduction of the 2-O_2N substituent of **9h**, which required more vigorous conditions, was carried out using 10% palladium-on-charcoal and 95% hydrazine hydrate at reflux temperature for 24 hours to yield the 2-NH_2 analogue **9n** (19% yield).

Table I

Physical Constants of 1-Substituted-piperidylidene-2-sulfon(cyan)amides **9**



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No.	R^1	R^2	Method of Preparation	Yield %	Mp, °C	Formula	Analysis % Calcd./Found C	H	N
9a	Me	$MeSO_2$	A	82	130-131	$C_7H_{14}N_2O_2S$	44.19 44.04	7.42 7.19	14.72 14.85
9b	Me	$PhSO_2$	A	71	104	$C_{12}H_{16}N_2O_2S$	57.12 56.80	6.39 6.57	11.10 11.14
9c	Me	4-Me-C_6H_4-SO_2	A	78	110-111	$C_{13}H_{18}N_2O_2S$	58.63 58.32	6.81 6.77	10.52 10.60
9d	Me	4-Cl-C_6H_4-SO_2	A	73	106-107	$C_{12}H_{15}N_2O_2SCl$	50.25 49.94	5.27 5.21	9.77 9.71
9e	Me	4-MeO-C_6H_4-SO_2	A	70	103-105	$C_{13}H_{18}N_2O_3S$	55.30 55.10	6.43 6.35	9.92 9.91
9f	Me	4-O_2N-C_6H_4-SO_2	A	65	147-148	$C_{12}H_{15}N_3O_4S$	48.48 48.21	5.09 5.00	14.13 13.88
9g	Me	3-O_2N-C_6H_4-SO_2	A	65	136-137	$C_{12}H_{15}N_3O_4S$	48.48 48.40	5.09 5.11	14.13 14.09
9h	Me	2-O_2N-C_6H_4-SO_2	A	67	126-127	$C_{12}H_{15}N_3O_4S$	48.48 48.19	5.09 4.99	14.13 14.19
9i	Me	4-MeCONH-C_6H_4-SO_2	A	79	222-223	$C_{14}H_{19}N_3O_3S$	54.35 54.01	6.19 6.31	13.58 13.48
9j	Me	4-H_2N-C_6H_4-SO_2	A	89	187-188	$C_{12}H_{17}N_3O_2S$	53.91 53.55	6.41 6.24	15.72 15.64
9k	Me	3-pyridyl-SO_2	A	79	96-97	$C_{11}H_{15}N_3O_2S$	52.16 51.93	5.97 5.99	16.59 16.63
9l	Me	CN	A	81	98	$C_7H_{11}N_3$	61.29 60.98	8.08 7.94	30.63 30.31
9m	Me	3-H_2N-C_6H_4-SO_2	B	78	165	$C_{12}H_{17}N_3O_2S$	53.91 53.63	6.42 6.38	15.72 15.70
9n	Me	2-H_2N-C_6H_4-SO_2	C	19	114	$C_{12}H_{17}N_3O_2S$	53.91 53.52	6.42 6.32	15.72 15.50
9o	$PhCH_2CH_2$	4-Cl-C_6H_4-SO_2	D	25	110-111	$C_{19}H_{21}N_2O_2SCl$	60.55 60.25	5.62 5.66	7.43 7.24
9p	$PhCH_2CH_2$	4-H_2N-C_6H_4-SO_2	D	29	170-171	$C_{19}H_{23}N_3O_2S$	63.84 63.51	6.49 6.32	11.75 11.47
9q	$PhCH_2CH_2$	3-pyridyl-SO_2	D	23	105-106	$C_{18}H_{21}N_3O_2S$	62.95 62.55	6.16 6.10	12.23 12.19
9r	4-O_2N-$C_6H_4CH_2CH_2$	4-Cl-C_6H_4-SO_2	E	61	157-158	$C_{19}H_{20}N_3O_4SCl$	54.09 53.82	4.78 4.76	9.96 9.82
9s	4-H_2N-$C_6H_4CH_2CH_2$	4-Cl-C_6H_4-SO_2	B	67	128-130	$C_{19}H_{22}N_3O_2SCl$	58.23 57.86	5.66 5.85	

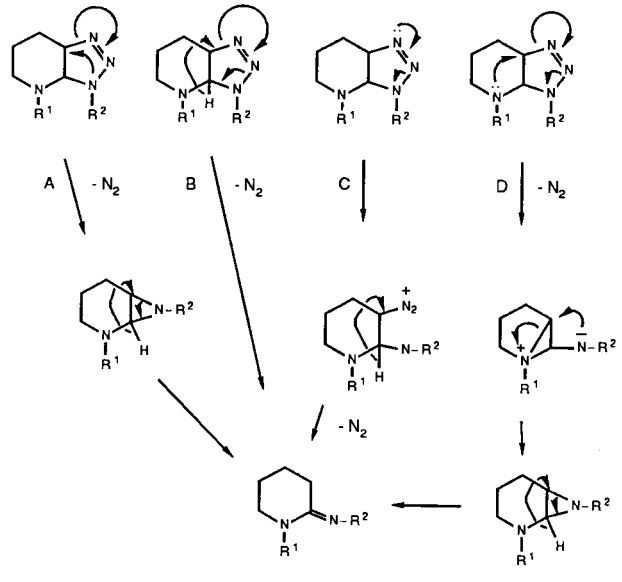
Reaction of **7b** with azides **8** (R^2 = 4-Cl-C_6H_4-SO_2, 4-H_2N-C_6H_4-SO_2 and 3-pyridylsulfonyl) afforded the respective 1-(2-phenylethyl)piperidylidene-2-(4-chlorophenyl, 4-aminophenyl and 3-pyridyl)sulfonamides **9o**, **9p** and **9q** in 25, 29 and 23% yield, respectively. Unreacted azide **8** was isolated in 66, 62 and 68% recovery, respectively.

Replacement of the *N*-methyl substituent present in narcotic analgesics as morphine by a *N*-(2-phenylethyl) or *N*-[2-(4-aminophenyl)ethyl] substituent results in an enhanced analgesic activity [4]. The 1-[2-(4-aminophenyl)ethyl] analogue **9s** would therefore be expected to have a greater potency than the 1-methyl analogue **9d**. Nitration of the 1-(2-phenylethyl) derivative

9o with fuming nitric acid yielded the 1-[2-(4-nitrophenyl)-ethyl] analogue **9r** (61%) which on reduction with 10% palladium-on-charcoal and 85% hydrazine hydrate afforded the 1-[2-(4-aminophenyl)ethyl] derivative **9s** (67% yield).

If the intermediate triazoline adduct formed by reaction of **7** with **8** is the product of electronic control the nitrogen atom bearing the sulfono (cyano) group should be directed to the carbon of the olefinic bond of **7** bearing the enamine ring nitrogen [8]. Loss of nitrogen from the triazoline intermediate may occur by a number of possible mechanisms as illustrated in Scheme II. Elimination of nitrogen from the triazoline adduct could give rise to the unstable 2,7-diazabicyclo[4.1.0]heptane (Path A) which could undergo C-1 hydrogen migration to afford **9**. In earlier studies we isolated stable 2,7-diazabicyclo[4.1.0]-hept-4-enes **1** [1,2] and hept-3-enes **3** [3] which on reduction with 10% palladium-on-charcoal and hydrogen gas afforded piperidylidene-2-sulfon(cyan)amides **2**. This

Scheme II



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pathway would require that the hept-4-ene and hept-3-ene olefinic bond stablize the bicyclic ring system. Alternatively, the triazoline adduct may fragment by loss of nitrogen with concomitant rearrangement to yield **9** (Path B). A mechanism analogous to this has been used to explain the formation of 1,3-dimethylpiperidylidene-2-tosylsulfonamide from the reaction of 1,6-dimethyl-1,2,3,4-tetrahydropyridine with tosyl azide [9]. Zwitterionic intermediates, analogous to those outlined in Path C, have been proposed for reactions of azides with olefins [10] and dienes [11]. Finally, there is the possibility that elimination of nitrogen occurs by the mechanism outlined in Path D. At the present time no particular pathway can be favored in the absence of isolation or detection of one of the possible intermediates.

Pharmacological testing using the analgesic phenylquinone writhing assay [12] indicates that the piperidylidene-2-sulfon(cyan)amides **9** exhibit significant analgesic activity [13].

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide unless otherwise indicated) were taken on a Perkin-Elmer 267 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. 1-Methyl- **7a** and 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine **7b** were prepared by base catalyzed isomerization of **6a** and **6b**, respectively using the procedure of Bovin [6]. The azides **8** were prepared by the reaction of the respective sulfonyl chloride with sodium azide using the procedure described by Stout *et al.* [14]. 4-Aminobenzenesulfonyl azide was prepared by acid hydrolysis of 4-acetamidobenzenesulfonyl azide [15]. Warning: Cyanogen azide is a hazardous material. It should be handled only in solution. Concentration to pure material will result in violent detonation by heat or shock [16].

1-Methylpiperidylidene-2-methanesulfonamide (**9a**). Procedure A.

A solution of methanesulfonyl azide (0.38 g, 3.14 mmoles) in 5 ml of ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (**7a**, 0.305 g, 3.14 mmoles) [6] 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*. Recrystallization from methylene chloride-ether afforded **9a** as a white solid (0.492 g, 82%); ir: 1590 (C=N) cm^{-1}; ^1H nmr: δ 1.69-2.0 (m, 4H, H_4, H_5), 2.93-3.24 (m, 8H, SO_2Me, N*Me*, H_3), 3.25-3.53 (m, 2H, H_6).

The 1-methylpiperidylidene-2-sulfon(cyan)amides **9b-l** were also prepared according to Procedure A except for the changes in procedure listed below. The azide **8** was dissolved in methylene chloride, rather than ether, for reactions involving the synthesis of **9f, 9q, 9i** and **9k**. Solutions of cyanogen azide and **7a** in acetonitrile, rather than ether, were used for the synthesis of **9l**. Products **9b-l** were purified by recrystallization or sublimation as described below: **9b** (methylene chloride-ether); **9c** (carbon tetrachloride); **9d** (carbon tetrachloride-petroleum ether); **9e** (sublimation, 0.1 Torr, 110°); **9f-h** (carbon tetrachloride-acetone); **9i-j** (methylene chloride); **9k** (carbon tetrachloride-hexane); and **9l** (ether-acetonitrile).

1-Methylpiperidylidene-2-(3-aminophenyl)sulfonamide (**9m**). Procedure B.

A solution of 85% hydrazine hydrate (0.5 ml) and 10% palladium-on-charcoal (30 mg) was added to a suspension of **9a** (0.20 g, 0.67 mmole) in 30 ml 95% ethanol at 0° with stirring. The reaction mixture was allowed to return to 25° with subsequent stirring for 16 hours. The reaction mixture was filtered and water (50 ml) was added. Extraction with methylene chloride (5 x 50 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gave a yellow solid. Recrystallization from carbon tetrachloride-acetone afforded **9m** (0.14 g, 78%) as pale yellow crystals; ir: 1590 (C=N), 3370 and 3470 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.55-1.86 (m, 4H, H_4, H_5), 2.74-3.07 (m, 2H, H_3), 3.07 (s, 3H, NMe), 3.19-3.57 (m, 2H, H_6), 5.48 (br s, 2H, NH_2, exchanges with deuterium oxide), 6.67-7.30 (m, 4H, phenyl hydrogens).

1-Methylpiperidylidene-2-(2-aminophenyl)sulfonamide (**9n**). Procedure C.

Palladium-on-charcoal (10%) (75 mg) and 95% hydrazine (1.0 ml) were

added to a suspension of **9h** (0.44 g, 1.48 mmoles) in 95% ethanol (45 ml) at 0° with stirring and the reaction mixture was heated at reflux for 12 hours. The reaction mixture was filtered and water (50 ml) was added to the filtrate. Extraction with methylene chloride (4 x 75 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gave a viscous green oil. This material was purified by preparative tlc, using 10 plates, with methylene chloride:acetone (5:1 v/v) as development solvent. Extraction of the lower 33% of the band having Rf 0.58 with 75 ml hot acetone gave **9n** as a pale brown solid (0.078 g, 19%); ir: 1570 (C=N), 3380 and 3480 (NH_2) cm^{-1}; ^1H nmr (acetone-d_6): δ 1.65-1.98 (m, 2H, H_4 or H_5), 1.98-2.21 (m, 2H, H_4 or H_5), 2.8-3.04 (m, 2H, H_3), 3.05 (s, 3H, NMe), 3.39-3.63 (m, 2H, H_6), 5.59 (br s, 2H, NH_2, exchanges with deuterium oxide), 6.54-7.0 (m, 2H, H_3 and H_5 phenyl hydrogens), 7.29 (d, $J_{4,5}$ = 8 Hz of d, $J_{3,4}$ = 8 Hz of d, $J_{4,6}$ = 2 Hz, 1H, H_4 phenyl hydrogen), 7.74 (d, $J_{5,6}$ = 8 Hz of d, $J_{4,6}$ = 2 Hz, 1H, H_6 phenyl hydrogen).

1-(2-Phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (**9o**). Procedure D.

A solution of 4-chlorobenzenesulfonyl azide (0.60 g, 2.76 mmoles) in ether (10 ml) was added dropwise to a solution of **7b** (0.51 g, 2.73 mmoles) in 20 ml ether at 25° with stirring. Evolution of nitrogen gas began within 20 seconds after addition of the azide was complete. The reaction was allowed to continue for 1 hour, after which the solvent was removed *in vacuo* to give a viscous oil. Separation by preparative tlc, using twelve plates, with ether as development solvent gave **9o** (Rf 0.46, 0.25 g, 25%) as a white powder; ir: 1570 (C=N) cm^{-1}; ^1H nmr: δ 1.52-1.85 (m, 4H, H_4, H_5), 2.71-3.34 (m, 6H, H_3, H_6, CH_2CH_2Ph or CH_2CH_2Ph), 3.62 (t, J = 8 Hz, 2H, CH_2CH_2Ph or CH_2CH_2Ph), 6.92-7.33 (m, 5H, phenyl hydrogens), 7.44 (d, $J_{2,3}$ = 8 Hz, 2H, H_3 and H_5 4-chlorophenyl hydrogens), 7.93 (d, $J_{2,3}$ = 8 Hz, 2H, H_2 and H_6 4-chlorophenyl hydrogens). Extraction of the band having Rf 0.94 with 75 ml hot acetone yielded 4-chlorobenzenesulfonyl azide (0.395 g, 66% recovery) which was identical (^1H nmr and micro tlc) to the authentic sample.

The 2-(4-aminophenyl) analogue **9p**, which was also prepared according to Procedure D, was purified by recrystallization from carbon tetrachloride-acetone. The 2-(3-pyridyl) analogue **9q** was prepared in a similar manner with purification by preparative tlc, as described for **9o**, using ether as the development solvent (Rf 0.15).

1-[2-(4-Nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (**9r**). Procedure E.

A mixture of **9o** (1.17 g, 3.11 mmoles), 3 ml of 90% fuming nitric acid and 2 ml of nitric acid were stirred vigorously for 4 hours at 25°. The reaction mixture was poured onto ice-water (50 ml) and the *p*H of the mixture was adjusted to 9 using 1*N* sodium hydroxide. Extraction with methylene chloride (4 x 50 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gave a yellow gum which was purified by preparative tlc, using eighteen plates, with acetone-ether (1:2 v/v) as development solvent. Extraction of the band having Rf 0.88 with 100 ml hot acetone afforded **9r** as a pale yellow solid (0.73 g, 61%); ir: 1350, 1540 (NO_2) and 1570 (C=N) cm^{-1}; ^1H nmr: δ 1.53-2.01 (m, 4H, H_4, H_5), 2.85-3.52 (m, 6H, H_3, H_6, NCH_2CH_2 or NCH_2CH_2), 3.68 (t, J = 7 Hz, 2H, NCH_2CH_2 or NCH_2CH_2), 7.14-7.6 (m, 4H, H_3, H_5 4-chlorophenyl hydrogens, H_2, H_6 4-nitrophenyl hydrogens), 7.8-8.2 (m, 4H, H_2, H_6 4-chlorophenyl hydrogens, H_3, H_5 4-nitrophenyl hydrogens).

1-[2-(4-Aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (**9s**).

Reduction of **9r** (0.15 g, 0.36 mmole), using the methodology described under Procedure B, with a reaction time of 20 hours afforded **9s** as a pale brown solid (0.095 g, 67%); ir: 1575 (C=N), 3370 and 3440 (NH_2) cm^{-1}; ^1H nmr: δ 1.57-1.88 (m, 4H, H_4, H_5), 2.75 (t, J = 7 Hz, 2H, NCH_2CH_2 or NCH_2CH_2), 2.96-3.40 (m, 4H, H_3, H_6), 3.4-3.72 (m, 4H, NCH_2CH_2 or NCH_2CH_2, NH_2, exchanges with deuterium oxide), 6.6 (d, J = 8 Hz, 2H, H_3, H_5 4-aminophenyl hydrogens), 6.87 (d, J = 8 Hz, 2H, H_2, H_6 4-aminophenyl hydrogens), 7.48 (d, J = 8 Hz, 2H, H_3, H_5 4-chlorophenyl hydrogens), 7.96 (J = 8 Hz, 2H, H_3, H_6 4-chlorophenyl hydrogens).

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