2'-Hydroxy-2-propyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (6c) Hydrobromide. A solution of 0.51 g (1.5 mmol) of **5d** oxalate in 8 mL of 48% aqueous HBr was heated at 100 °C for 2 h and evaporated to dryness. The resulting residue was dissolved in methanol, treated with decolorizing carbon, filtered, concentrated in vacuo, and recrystallized from methanol–ether to give 0.27 g (57%) of **6c**·HBr: mp 173–175 °C; ^{1}H NMR (methanol-d_4) δ 6.7–7.5 (m, 3 H, aromatic), 4.7 (m, 1 H, CHN), 1.2–3.7 (m, 13 H, aliphatic), 1.0 (t, 3 H, methyl). Anal. ($C_{15}H_{22}BrNO$) C, H, N.

Acknowledgment. This research was supported by the National Institutes on Drug Abuse through Grant DA01366. The authors thank Dr. Arthur Jacobson of NIH for obtaining analgesic data and for helpful discussions.

Some Reactions of 1,4-Dihydropyridines with Organic Azides. Synthesis of 2,7-Diazabicyclo[4.1.0]hept-3-enes with Analgesic and Antiprotozoal Activity

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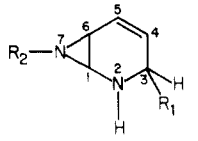
Received June 2, 1980

The 1,3-dipolar cycloaddition reaction of 1,4-dihydropyridines, **2**, with organic azides, **3**, afford 2,7-diazabicyclo-[4.1.0]hept-3-enes, **4**, which exhibit significant analgesic and antiprotozoal activities. The most active analgesics, **4a** and **4c**, were more potent than aspirin or dextropropoxyphene. Diazabicyclo[4.1.0]hept-3-enes **4a–e** exert potent antiprotozoal activity, inhibiting growth of *Trichomonas vaginalis* at concentrations of less than 10 μg/mL of medium. The broad spectrum pharmacological screen also revealed moderate hypoglycemic (**4a**), antiinflammatory (**4c**), antidepressant (**4d** and **4e**) and antihistaminic (**4f**) activities.

In an earlier study[1] we showed that the regiospecific 1,3-dipolar cycloaddition reaction of 1,2-dihydropyridines with organic azides afforded 7-substituted 2,7-diazabicyclo[4.1.0]hept-4-enes, **1**, which exhibited significant anal-



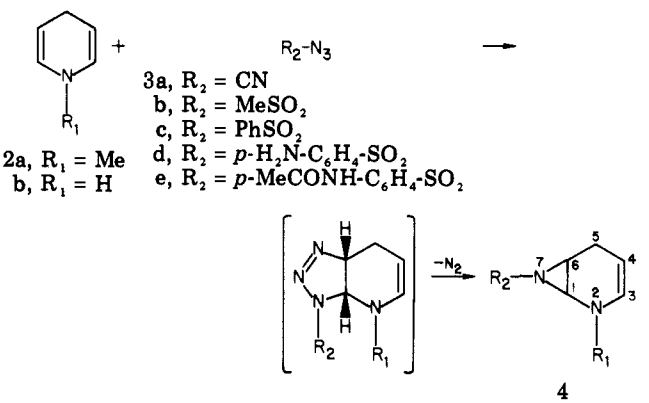
1, R_1 = *n*-Bu, Ph; R_2 = CN, MeOCO, $MeSO_2$, $PhSO_2$, *p*-H_2N-C_6H_4-SO_2, *p*-MeCONH-C_6H_4-SO_2

gesic,[2] antibacterial and antifungal[3] activities. It was, therefore, of interest to prepare similar bicyclic ring structures in which 1,2,3-triazoline or aziridine is fused to a tetrahydropyridine ring. We now describe the synthesis and analgesic–antiprotozoal activity of the previously unknown 7-substituted 2,7-diazabicyclo[4.1.0]hept-3-enes, **4**.

Chemistry. The 1,3-dipolar cycloaddition reaction of *N*-methyl-1,4-dihydropyridine (**2a**) with 1 equiv of cyanogen azide (**3a**) at 25 °C proceeds rapidly with evolution of nitrogen to yield 2-methyl-7-cyano-2,7-diazabicyclo-[4.1.0]hept-3-ene (**4a**) in 99% yield. The reaction of 1,4-dihydropyridines, **2**, with organic sulfonyl azides, **3b–e**, is general as illustrated by Scheme I and summarized in Table I. On the other hand, reaction of 1,4-dihydropyridines, **2**, with the less reactive[4] methoxycarbonyl and benzoyl azide did not occur. No product resulting from the 1,3-dipolar cycloaddition of **3a** to both the C2–C3 and C5–C6 olefinic bonds of **2a** was produced, since reaction of **2a** with 5 equiv of **3a** also afforded **4a** in 99% yield. 2-Methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (**4a**) does not react further with cyanogen azide (**3a**).

Pharmacology. The compounds synthesized using the 1,3-dipolar cycloaddition reaction described in the previous

Scheme I



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section were tested for analgesic activity using the phenylquinone writhing test[5] and for antiprotozoal activity using the tube dilution technique.[6]

Discussion

The 2,7-diazabicyclo[4.1.0]hept-3-enes, **4**, all exhibit significant analgesic activity, irrespective of the nature of the R_2 substituent. The position of the olefenic double bond and the presence of a N-2 methyl substituent do not appear to have a significant effect on activity, since the structurally related 2,7-diazabicyclo[4.1.0]hept-4-enes, **1**, exhibit similar analgesic activities for the same N-7 substituents.[2] The mechanism by which compounds **4** exhibit analgesic activity has not been investigated. It is not known whether these compounds act as prostaglandin synthetase inhibitors.

A study, using 2-mercaptoethanol as a model nucleophile, was carried out to determine the reactivity of 2,7-diazabicyclo[4.1.0]hept-3-enes, **4**, toward nucleophiles. No reaction was observed when a solution of **4d** in aceto-

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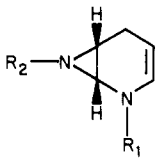
Table I. Some Synthetic and Pharmacological Data of 2,7-Diazabicyclo[4.1.0]hept-3-enes



compd	R_1	R_2	yield, %	mp, °C	formula[a]	analgesic act., inhib act. on phenylquinone writhing: dose, mg/kg sc	analgesic act., inhib act. on phenylquinone writhing: % inhibn	min inhib concn (MIC), μg/mL, of medium of each compd that inhibited 90% of growth of *Trichomonas vaginalis*
4a	Me	CN	99	67-69	$C_7H_9N_3$	64	86	<10
4b	Me	$MeSO_2$	97	69-72	$C_7H_{12}N_2O_2S$	128	50	<10
4c	Me	$PhSO_2$	98	57-59	$C_{12}H_{14}N_2O_2S$	64	92	<10
4d	Me	p-H_2N-C_6H_4-SO_2	97	188-190	$C_{12}H_{15}N_3O_3S$	128	97[b]	<10
4e	Me	p-MeCONH-C_6H_4-SO_2	94	176-179	$C_{14}H_{17}N_3O_3S$	128	95	<10
4f	H	$PhSO_2$	53	108	$C_{11}H_{12}N_2O_2S$	128	47	nt[c]
aspirin						50	50	
dextropropoxyphene						56	50	

[a] All new compounds were analyzed for C, H, and N, and the results were within 0.4% of theory. [b] The percent inhibition at doses of 4, 8, 16, 32, and 64 mg/kg sc was 23, 40, 45, 69, and 78%, respectively. [c] nt, not tested.

nitrile–aqueous phosphate buffered to pH 7.4 was treated with 2-mercaptoethanol at 37 °C for 24 h. In a related experiment it was also shown that no reaction occurred when a solution of **4d** and 2-mercaptoethanol in the presence of a catalytic quantity of piperidine using benzene as solvent was heated at reflux for 24 h. It is therefore reasonable to conclude that *N*-cyano- and *N*-sulfonylaziridines, **4**, do not act as biological alkylating agents.

Diazabicyclo[4.1.0]hept-3-enes, **4a–e**, are also active antiprotozoal agents effective against *Trichomonas vaginalis*. In contrast, 2,7-diazabicyclo[4.1.0]hept-4-ene, **1** (R_1 = *n*-Bu; R_2 = CN), was inactive.[2]

Other broad spectrum pharmacological screening results indicated that **4a** (100 mg/kg sc) was a slightly active hypoglycemic agent, lowering blood glucose by 19 and 18%, respectively, 2 and 4 h after treatment.[7] The N-7 benzenesulfonyl product **4c** (64 mg/kg sc) was a slightly active antiinflammatory agent, inhibiting carrageenan-induced rat paw edema by 50% 3 h after injection of carrageenan.[8] Compounds **4d** and **4e** exhibited antidepressant activity (128 mg/kg sc), inhibiting tetrabenazine-induced ptosis 44 (30 min), 23.5 (1 h), and 11 (30 min), and 23.5% (1 h), respectively.[9] The N-7 benzenesulfonyl product **4f** (0.1 mg/kg bath solution) provided a 25% antagonism of the response to histamine in the isolated guinea pig ileum and was considered to be a slightly active antihistaminic agent.[10]

Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solutions in $CDCl_3$ with Me_4Si as internal standard with a Varian EM-360A spectrometer. Infrared spectra (potassium bromide unless otherwise noted) were taken on a Perkin-Elmer 267 spectrometer. Mass spectra were measured with an AEI-MS-50 mass spectrometer. All of the products described gave rise to a single spot on TLC using three different solvent systems of low, medium, and high polarity. No residue remained after combustion of the products.

Caution: Cyanogen azide is a hazardous material! It should be handled only in solution. Concentration to pure material will result in detonation by heat or shock.

The broad spectrum pharmacological testing was performed by Bio-Research Laboratories, Montreal, Quebec, under an agreement between Canadian Patents and Development Limited (CPDL) and Bio-Research Laboratories.

2-Methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (4a). General Procedure. A solution of cyanogen azide (**3a**; 0.32 g, 4.7 mmol) in 30 mL of acetonitrile, prepared from cyanogen bromide (0.50 g, 4.7 mmol) and sodium azide (1.53 g, 23.5 mmol) as reported previously,[11,12] was added slowly with stirring to a solution of 1-methyl-1,4-dihydropyridine[13] (**2a**; 0.45 g, 4.7 mmol) in 75 mL of ether at 25 °C. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed at 25 °C for 2 h. Removal of the solvent in vacuo afforded **4a**: yield 0.625 g (99%); IR 2190 (CN), 1665 cm^{-1} (C=C); NMR δ 2.2–2.68 (m, 2 H, C_5 H), 2.9–3.26 (m, 2 H, C_1 H and C_6 H), 3.3 (s, 3 H, Me), 5.32–5.7 (m, 1 H, C_4 H), 6.25 (d of d of d, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 2 Hz, $J_{3,5}$ = 2 Hz, 1 H, C_3 H). Exact mass for $C_7H_9N_3$: calcd, 135.0796 found (high-resolution MS), 135.0797. Anal. ($C_7H_9N_3$) C, H, N.

2-Methyl-7-(methanesulfonyl)-2,7-diazabicyclo[4.1.0]-hept-3-ene (4b). A solution of methanesulfonyl azide (**3b**; 0.387 g, 3.2 mmol) in 50 mL of ether was added to a solution of 1-methyl-1,4-dihydropyridine (**2a**; 0.304 g, 3.2 mmol), and the reaction was completed as described under General Procedure to yield **4b**: yield 0.582 g (97%); IR 1670 cm^{-1} (C=C); NMR δ 2.05–2.55 (m, 2 H, C_5 H), 3.0–3.4 (m, 8 H, $MeSO_2$, MeN, C_1 H and C_6 H), 5.2–5.52 (m, 1 H, C_4 H), 6.1 (d of d of d, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 2 Hz, $J_{3,5}$ = 2 Hz, 1 H, C_3 H). Exact mass for $C_7H_{12}N_2O_2S$: calcd, 188.0619; found (high-resolution MS), 188.0614. Anal. ($C_7H_{12}N_2O_2S$) C, H, N.

2-Methyl-7-(benzenesulfonyl)-2,7-diazabicyclo[4.1.0]-hept-3-ene (4c). A solution of benzenesulfonyl azide (**3c**; 0.58 g, 3.2 mmol) in 75 mL of ether was added to a solution of 1-methyl-1,4-dihydropyridine (**2a**; 0.30 g, 3.2 mmol) in 75 mL of ether with stirring, and the reaction was completed as described under General Procedure to give **4c**: yield 0.784 g (98%); IR 1665

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(C=C) and 1140 cm^{-1} (SO_2NH_2); NMR δ 2.1–2.5 (m, 2 H, C_5 H), 3.02–3.42 (m, 2 H, C_1 H and C_6 H), 3.1 (s, 3 H, Me), 5.16–5.5 (m, 1 H, C_4 H), 6.06 (d of d of d, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 2 Hz, $J_{3,5}$ = 2 Hz, 1 H, C_3 H), 7.55 (m, 3 H, meta and para phenyl hydrogens), 8.06 (m, 2 H, ortho phenyl hydrogens). Exact mass for $C_{12}H_{14}N_2O_2S$: calcd, 250.0776; found (high-resolution MS), 250.0780. Anal. ($C_{12}H_{14}N_2O_2S$) C, H, N.

2-Methyl-7-[(*p*-aminobenzene)sulfonyl]-2,7-diazabicyclo[4.1.0]hept-3-ene (4d). A solution of (*p*-aminobenzene)sulfonyl azide (**3d**; 0.63 g, 3.2 mmol) in 75 mL of ether was added slowly to a solution of 1-methyl-1,4-dihydropyridine (**2a**; 0.30 g, 3.2 mmol) in 75 mL of ether with stirring, and the reaction was completed as described under General Procedure to afford **4d**: yield 0.82 g (97%); IR 3480, 3380 (NH_2), 1650 cm^{-1} (C=C); NMR δ 2.0–2.46 (m, 2 H, C_5 H), 2.9–3.3 (m, 2 H, C_1 H and C_6 H), 3.08 (s, 3 H, Me), 4.9 (br s, 2 H, NH_2, exchanges with deuterium oxide), 5.14–5.5 (m, 1 H, C_4 H), 6.12 (d, $J_{3,4}$ = 8 Hz, 1 H, C_3 H), 6.75 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8 Hz, 2 H, $C_{3'}$ H and $C_{5'}$ H), 7.7 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8 Hz, 2 H, $C_{2'}$ H and $C_{6'}$ H). Exact mass for $C_{12}H_{15}N_3O_2S$: calcd, 265.0885; found (high-resolution MS), 265.0888. Anal. ($C_{12}H_{15}N_3O_2S$) C, H, N.

2-Methyl-7-[(*p*-acetamidobenzene)sulfonyl]-2,7-diazabicyclo[4.1.0]hept-3-ene (4e). A solution of (*p*-acetamidobenzene)sulfonyl azide (**3e**; 0.77 g, 3.2 mmol) in 100 mL of chloroform was added slowly with stirring to a solution of 1-methyl-1,4-dihydropyridine (**2a**; 0.30 g, 3.2 mmol) in 75 mL of chloroform, and the reaction was completed as described under General Procedure to yield **4e**: yield 0.925 g (94%); IR 3380 (NH), 1710 (CO), 1655 cm^{-1} (C=C); NMR δ 2.1–2.55 (m, 2 H, C_5 H), 2.21 (s, 3 H, COMe), 2.9–3.3 (m, 2 H, C_1 H and C_6 H), 3.17 (s, 3 H, NMe), 5.2–5.55 (m, 1 H, C_4 H), 6.12 (d of d of d, $J_{3,4}$ = 8 Hz, $J_{3,5}$ = 2 Hz, $J_{3,5}$ = 2 Hz, 1 H, C_3 H), 7.6–8.1 (m, 4 H, phenyl hydrogens), 9.14 (br s, 1 H, NH, exchanges with deuterium oxide). Exact mass for $C_{14}H_{17}N_3O_3S$: calcd, 307.0991; found (high-resolution MS), 307.0996. Anal. ($C_{14}H_{17}N_3O_3S$) C, H, N.

7-(Benzenesulfonyl)-2,7-diazabicyclo[4.1.0]hept-3-ene (4f). A solution of 1,4-dihydropyridine[13] (**2b**; 1.21 g, 15 mmol) in 20 mL of ether was added dropwise with stirring to a solution of benzenesulfonyl azide (**3c**; 5.49 g, 30 mmol) in 100 mL of ether at 0 °C and then for 6 h at 25 °C. The reaction mixture was washed with water (75 mL), the ether layer was dried (Na_2SO_4), and the ether was removed in vacuo to yield 6.5 g of a pale yellow oil. A portion of this oil (0.65 g) was purified by preparative TLC on ten 8 × 8 in. silica gel G plates, 1.0-mm in thickness, using benzene–ether (2:1, v/v) as development solvent. Extraction of the fraction having R_f 0.45 using hot methanol (100 mL) gave 0.185 g of **4f**: total yield 1.85 g (52.8%); IR 3315 (NH) and 1655 cm^{-1} (C=C); NMR δ 2.0–2.44 (m, 2 H, C_5 H), 2.5–2.9 (m, 2 H, C_1 H and C_6 H), 5.1–5.4 (m, 1 H, C_4 H), 6.0–6.35 (m, 1 H, C_3 H), 7.3–7.7 (m, 3 H, meta and para phenyl hydrogens), 7.8–8.1 (m, 2H, ortho phenyl hydrogens), 9.6 (br s, 1 H, NH, exchanges with deuterium oxide). Exact mass for $C_{11}H_{12}N_2O_2S$: calcd, 236.0619; found (high resolution MS), 236.0622. Anal. ($C_{11}H_{12}N_2O_2S$) C, H, N.

Pharmacological Methods. Analgesic activity was evaluated by the phenylquinone writhing test.[5] Five male Swiss albino mice weighing 18–22 g were used in each group. The test compound, suspended in a solution of physiological saline and Tween 80 surfactant, was administered subcutaneously, and 30 min later each mouse received a 0.03% phenyl-*p*-benzoquinone solution in a volume of 0.1 mL/10 g of body weight intraperitoneally. The total number of writhes exhibited by each animal in the test group was recorded and compared to that of a vehicle-treated control group. The percent change is calculated according to the following equation: % change = (no. of writhes in treated group/no. of writhes in control group) × 100 − 100. A compound causing a 30–50% reduction is considered to be slightly active, whereas one causing a greater than 50% reduction in the number of writhes is an active analgesic agent.

Antiprotozoal activity was determined by the method of Diamond and Burtgis[6] using the tube dilution technique with *Trichomonas vaginalis* as the test organism growing in modified TYM basal medium. The test compound was added to the liquid medium to give the desired concentration in micrograms per milliliter of medium. Each tube was then innoculated with a known number of trophozoites (1 × 10^5/mL) grown in the same medium for 48 h. The innoculated media were incubated for 24 and 48 h at 35 °C.

To enumerate the total population of parasites, an aliquot of each test culture was diluted in saline containing formaldehyde (1%). Cell counting was performed with the aid of a Speirs–Levy eosinophil counting chamber. The results are expressed as the minimal inhibitory concentration, which was taken as the lowest concentration of each compound that inhibited 90% of growth. Table I summarizes the pharmacological results obtained in the above assays.

Treatment of 2-Methyl-7-[(*p*-aminobenzene)sulfonyl]-2,7-diazabicyclo[4.1.0]hept-3-ene (4d) with 2-Mercaptoethanol. In Phosphate Buffer at pH 7.4. Solutions of 2-mercaptoethanol (22.3 mg, 0.286 mmol) in 1 mL of distilled water, monobasic sodium phosphate monohydrate (15.8 mg) in 1.7 mL of water, dibasic sodium phosphate heptahydrate (59 mg) in 3.3 mL of water, and 3.5 mL of acetonitrile (to effect dissolution of **4d**) were added to 2-methyl-7-[(*p*-aminobenzene)sulfonyl]-2,7-diazabicyclo[4.1.0]hept-3-ene (25 mg, 0.094 mmol). The pH of the resultant solution was 7.4. This solution was maintained at 37 ± 0.5 °C for 24 h. Examination of this solution using micro silica gel G plates with methylene chloride–acetone (1:1, v/v) as development solvent did not show the presence of any product other than **4d** and 2-mercaptoethanol. Removal of the water in vacuo gave a gummy residue for which the ^{1}H NMR spectra and the TLC chromatogram (as above) showed the presence of only **4d** and 2-mercaptoethanol.

In Benzene at Reflux. A solution of **4d** (36 mg, 0.136 mmol), 2-mercaptoethanol (10.61 mg, 0.136 mmol), and one drop of piperidine in 10 mL of benzene was heated under reflux for 24 h. Removal of the benzene and piperidine in vacuo gave a gummy residue for which the ^{1}H NMR spectrum and TLC chromatogram (as above) showed the presence of only **4d** and 2-mercaptoethanol.

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant MA-4888) for financial support of this work and to T. A. Ondrus for carrying out the reaction of 1,4-dihydropyridine with benzenesulfonyl azide.