to be the most active inhibitors in the whole series of SA. This result is in full agreement with the hypothesis of Bell and Roblin,[19] which affirms that the lower the acidity of the sulfonamide, the higher the antibacterial (and, in our case, the enzyme inhibitory) activity of both the anionic and the molecular forms.

Actually, the activity parameters of the anions of compounds 1 and 2 could be somewhat overestimated because of the approximation which assigns the whole activities of these compounds to their anionic forms, whose fractions are rather small in these cases. This point has been already discussed in a previous work,[9] and it can be concluded that a reasonable correction of ap_E and ap_G values, made by considering the contributions of the neutral forms of compounds 1 and 2, should be within the limits of the approximations introduced in the calculation of the anionic fractions.

The correlation between ap_E and ap_G and the relationships previously observed[7,9] between the antibacterial potencies of the different forms of SA and the measured spectroscopic values ν_S (SO_2) and δ (NH_2) suggest the occurrence of similar relationships between the enzyme inhibitory activities of the same forms and the spectroscopic indexes.

The correlation between ap_E and ν_S (SO_2) values results from eq 5, where compounds 4 and 8 are not considered

$$ap_E = -0.048\nu_S\ (SO_2) + 53.44 \quad (5)$$

$$n = 20;\ r = 0.871;\ s = 0.35;\ F = 56.47$$

because of the uncertain assignment of their ν_S (SO_2) frequencies, and from eq 6, where compounds **10**, **21**, and **22** are also discarded because of their large deviations from eq 5. Actually, amides **21** and **22** show too large inhibitory potencies (both in growth and enzymatic activity measurements) in relation to their structural indexes.

$$ap_E = -0.054\nu_S\ (SO_2) + 60.54 \quad (6)$$

$$n = 17;\ r = 0.932;\ s = 0.26;\ F = 99.08$$

The correlation between ap_E and δ (NH_2) values is shown by eq 7 and 8. Here again, compounds **10**, **21**, and **22** are not considered in eq 8.

$$ap_E = -1.68\delta\ (NH_2) + 8.81 \quad (7)$$

$$n = 22;\ r = 0.757;\ s = 0.42;\ F = 26.88$$

$$ap_E = -1.92\delta\ (NH_2) + 10.03 \quad (8)$$

$$n = 19;\ r = 0.818;\ s = 0.40;\ F = 34.42$$

Equations 5–8 point out the relationship between the enzyme inhibitory potency of SA and their electronic features, represented by spectroscopic indexes.[10,11] The negative slopes of these equations assign the highest activity to those SA forms which show the highest electronic richness both on the SO_2 oxygens and on the p-NH_2 group.

Conclusion

It appears possible to conclude that, as in the case of the antibacterial activity[9] of SA, high activity of these compounds as inhibitors of dihydropteroate synthase is related to the following electronic features: (a) high polarization of the S–O bonds (i.e., high negative charges on the oxygens) and (b) low conjugation within the common moiety p-$NH_2C_6H_4SO_2$, due to (c) low engagement of the p-NH_2 lone pair to the aromatic system.

Moreover, it appears that permeability factors, while highly effective in depressing the antibacterial activity (GII_{50} with respect to EII_{50}) of all the SA, do not contribute significantly to the activity variation in this class of compounds, which appears to be mainly determined by the electronic structure of the different forms of SA.

Acknowledgment. This work was carried out with financial support of the Consiglio Nazionale delle Ricerche, Roma.

(19) P. H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2905 (1942).

Synthesis and Pharmacological Properties of 1,2,3,4,5,6-Hexahydro-1,6-methano-2-benzazocines

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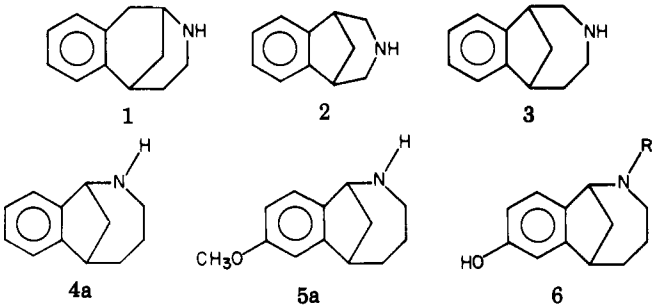
1,2,3,4,5,6-Hexahydro-1,6-methano-2-benzazocine, 2′-methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine, and *N*-alkyl derivatives of 2′-hydroxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine have been synthesized in order to evaluate their analgesic activities. These compounds show only slight antinociceptive activities in the mouse hot-plate assay.

Structural modifications of the benzomorphan ring system (1) have produced a number of interesting new



compounds; for example, *B*-norbenzomorphan (**2**) is a morphine-like analgesic with one-third the activity of codeine.[1] Benzazocine **3** is an active analgesic (ED_{50} = 4.9 mg/kg) which does not support morphine dependence in rats and monkeys.[2] As part of a long-term program to investigate the structure-activity relationships of potential analgesics structurally related to 6-7-benzomorphans, we have synthesized the related system 1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (**4a**), its methoxy analogue (**5a**), and appropriate *N*-alkyl derivatives of **4a**, **5a**, and the hydroxy analogue **6**.

(1) Mokotoff, M.; Jacobson, A. E. *J. Heterocycl. Chem.* **1970**, *7*, 733.
(2) Mazzocchi, P. H.; Harrison, A. M. *J. Med. Chem.* **1978**, *21*, 238.

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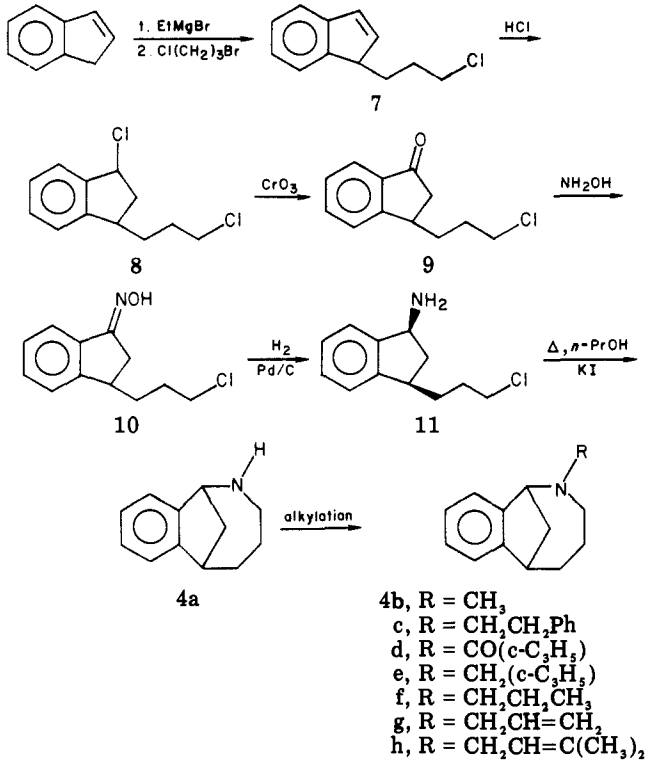
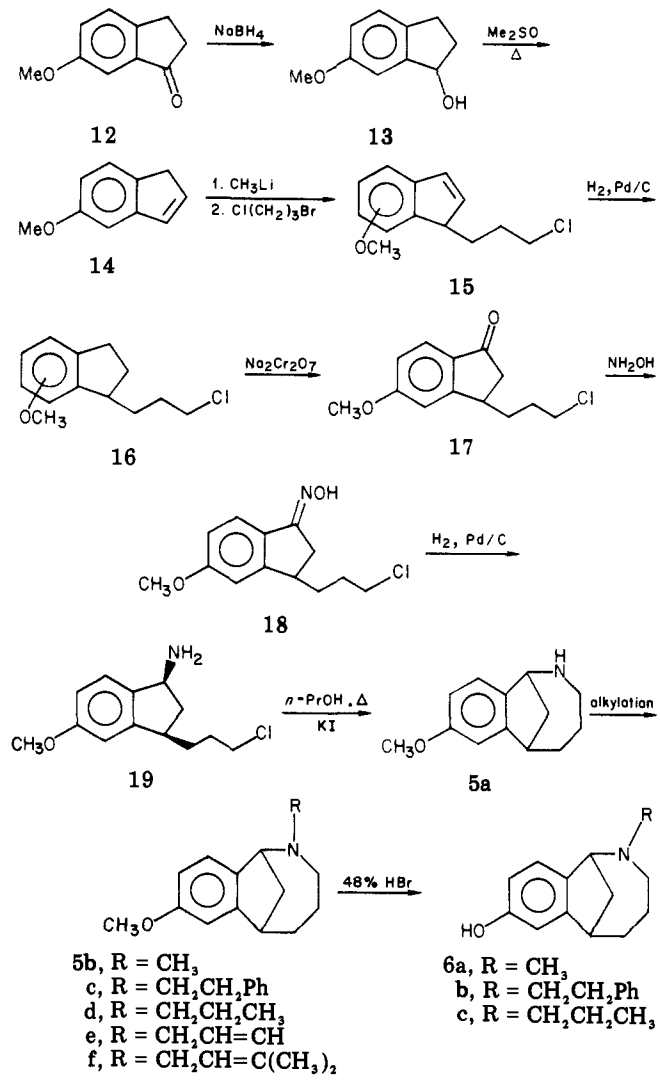
Scheme I



Scheme II



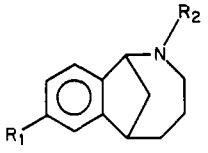
Chemistry. Benzazocine **4a** was synthesized from indene in an overall yield of 15% as outlined in Scheme I. Treatment of indene with ethylmagnesium bromide and then with 3-bromo-1-chloropropane provided **7**.[3] Addition of dry hydrogen chloride to **7**, followed by chromium trioxide oxidation[5] of the unstable dichloride **8**, afforded ketone **9**. Conversion of **9** to the oxime and subsequent reduction with hydrogen using a large amount of palladium on carbon gave, as a result of H_2 addition from the less hindered side, *cis*-3-(3-chloropropyl)-1-indanamine (**11**). Compound **11** closed to the parent benzazocine **4a** in refluxing 1-propanol. *N*-Alkyl derivatives were obtained by treating **4a** with the appropriate halide or by treatment with formic acid–formaldehyde in the case of **4b**.[2] The cyclopropylmethyl derivative **4e** was obtained by $LiAlH_4$ reduction of the cyclopropyl carbonyl derivative **4d**.

The methoxy (**5a–f**) and hydroxy (**6a–c**) analogues of benzazocine **4a** were synthesized as shown in Scheme II following the same synthetic approach as that used to generate **4a**. The preparation of 6-methoxyindanone (**12**) involved a series of known procedures.[6] Reduction of **12** with sodium borohydride and dehydration of the resulting alcohol (**13**) by heating in dimethyl sulfoxide[7] gave 6-methoxyindene (**14**). Treatment of **14** with methyllithium and then with 3-bromo-1-chloropropane afforded a mixture of 3-(3-chloropropyl)-5-methoxyindene and 3-(3-chloropropyl)-6-methoxyindene (**15**). In order to encourage formation of the appropriate alkylindene isomer, methyllithium was used in place of ethylmagnesium bromide for generation of the indenyl anion. During anion formation, the lithium cation presumably complexes both the anion and the methoxy oxygen, producing the 5-methoxy isomer (ca. 75%) in preference to the 6-methoxy isomer (ca. 25%). This type of complexation is well precedented.[8] In retrospect, the choice of methyllithium as a base was an excellent one, since subsequent attempts to alkylate methoxyindene using ethylmagnesium bromide proved unsuccessful.

Although the attempted addition of hydrogen chloride to **15** produced only polymeric material even at high dilution, indanone **17** could be obtained by direct sodium dichromate oxidation[9] of alkylindans **16**, which were prepared by hydrogenation of the isomeric mixture **15** using 5% palladium on carbon as catalyst. Since benzylic oxidations with chromium compounds are accelerated by para-substituted electron-donating substituents,[10] treatment of mixture **16** with sodium dichromate resulted in selective oxidation of the 3-methoxy isomer to give the

(3) The preparation of 3-(3-chloropropyl)-1-indene (**4**) has previously been reported by Anderson et. al.,[4] who did not fully characterize the compound. They suggested that it was actually a mixture of **4** and the corresponding bromo analogue.
(4) Anderson, A. G., Jr.; Masada, G. M.; Montana, A. F. *J. Org. Chem.* **1973**, *38*, 1439.
(5) "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. 2, p 336.
(6) (a) Johnson, W. S.; Shelberg, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 1853; (b) House, H. O.; Hudson, C. B. *J. Org. Chem.* **1970**, *35*, 647.
(7) Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377.
(8) Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, 191 and references cited therein.
(9) Shiotani, S.; Kametani, T. *J. Med. Chem.* **1975**, *18*, 1266.
(10) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: New York, 1972; p 288.

Table I. Analgetic Data



compd	R_1	R_2	ED_{50},[a] mg/kg	ED_{50}, μmol/kg	LD_{50},[a] mg/kg
4a·HCl	H	H	12 (8.4-16.1)	57	225
4a·$(COOH)_2$	H	H			225
4b·HBr	H	CH_3	45**	168	3/10 at 50 mg/kg*
4c·HCl	H	CH_2CH_2Ph	86**	246	225
4c·$(COOH)_2$	H	CH_2CH_2Ph			225
4e·HCl	H	$CH_2(c\text{-}C_3H_5)$	inactive		2/10 at 50 mg/kg*
4f·HCl	H	$CH_2CH_2CH_3$	28**	112	75
4f·$(COOH)_2$	H	$CH_2CH_2CH_3$			110
4g·HCl	H	$CH_2CH=CH_2$	28**	112	110
4g·$(COOH)_2$	H	$CH_2CH=CH_2$			150
4h·HCl	H	$CH_2CH=C(CH_3)_2$	48**	173	65
4h·$(COOH)_2$	H	$CH_2CH=C(CH_3)_2$			130
5a·$(COOH)_2$	OCH_3	H	64 (55.1-73.4)	218	
5b·$(COOH)_2$	OCH_3	CH_3	16 (11.7-22.4)	52	157
5c·$(COOH)_2$	OCH_3	CH_2CH_2Ph	inactive		
5f·$(COOH)_2$	OCH_3	$CH_2CH=C(CH_3)_2$	inactive		300
6a·HBr	OH	CH_3	inactive		3/10 at 50 mg/kg*
6b·HBr	OH	CH_2CH_2Ph	14 (9.7-20.0)	37	3/10 at 50 mg/kg*
6c·HBr	OH	$CH_2CH_2CH_3$	32 (20.5-48.2)	103	
morphine sulfate			1.0	2.6	
codeine phosphate			6.8	17	

[a] * = Insufficient material was available for toxicity testing. Value given indicates the number of mice that died out of ten mice treated with a 50 mg/kg dose. ** = Complete activity not obtainable without toxicity. Approximate value cited, these materials are essentially inactive.

desired ketone **17**. The aromatic portion of the proton NMR spectrum of **17** clearly shows the presence of only the 3-(3-chloropropyl)-5-methoxy-1-indanone isomer.

Conversion of **17** to the oxime and subsequent reduction with hydrogen and palladium on carbon afforded *cis*-3-(3-chloropropyl)-5-methoxy-1-indanamine (**19**), which closed in refluxing 1-propanol to give the parent methoxybenzazocine **5a**. The yield of **5a** from 6-methoxyindene was 20%. Derivatives **5a–f** were obtained by treatment of **5a** with the appropriate alkyl halide or formic acid–formaldehyde[2] in the case of **5b**. O-Demethylation to give the hydroxy analogues **6a–c** was accomplished by heating the oxalate salts of the corresponding methoxy compounds in 48% aqueous hydrogen bromide.

Pharmacology and Conclusions

Analgesic potencies were determined by the Eddy hot-plate method on mice[11] using aqueous solutions of the hydrochloride, hydrobromide, or oxalate salts. Tests results and toxicities are listed in Table I. It has been suggested by a referee that the use of an oxalate salt might contribute to the toxicity of the compound tested. In order to obtain information on this point, we have obtained toxicity data for both the hydrochloride and oxalate salts of several compounds (**4a**, **4c**, and **4f–h**) and have found that, if anything, the oxalates are slightly less toxic than the corresponding hydrochloride salts.

It is apparent from the data in the table that the 1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine system exhibits only marginal antinociceptive activity, with the parent compound (**4a**) half as active as codeine in the same analysis but similar to that of the parent benzomorphan (**1**).[12] Clearly, the change in the position of the nitrogen atom in going from **3** to **4** has resulted in a significant change in activity.

Experimental Section

Melting points were taken in capillary tubes and are uncorrected. Elemental analyses (indicated by C, H, and N when within ±0.4% of calculated values) were performed by Dr. Franz Kasler of the University of Maryland. IR (Beckmann IR-8 or Perkin-Elmer 281) and NMR (Varian XL-100, EM-390, or HR-220) spectra are consistent with assigned structures.

3-(3-Chloropropyl)-1-indene (7). To the Grignard reagent prepared from 18 g (0.74 mol) of Mg and 72 g (0.66 mol) of bromoethane in THF was added freshly distilled indene (45 g, 45 mL, 0.39 mol) in one portion, and the solution was heated at 100 °C for 2 h. The reaction mixture was cooled to 0–5 °C with an ice–water bath, and 174.6 g (118.8 mL, 1.11 mol) of 3-bromo-1-chloropropane was added as quickly as the reaction would allow. The resulting solution was heated at 100 °C for 30 min, cooled, hydrolyzed with 225 mL of saturated NH_4Cl, and 300 mL of water was added. The organic layer was removed, dried ($MgSO_4$), evaporated, and fractionally distilled to give 29.3 g (39%) of colorless **7**: bp 90–92 °C (0.2 mm); IR (thin film) 3060, 2940, 2860, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 4 H, aromatic), 6.8 and 6.5 (AB system, 2 H, olefinic), 3.4 (m, 3 H, benzylic and CH_2Cl), 1.5–2.2 (m, 4 H, methylenes). Anal. ($C_{12}H_{13}Cl$) C, H.

3-(3-Chloropropyl)-1-indanone (9). A stream of dry HCl was bubbled through 29.3 g (0.153 mol) of **7** for 5 h. The resulting crude chloride **8** was added dropwise to a solution of 23.9 g (0.239 mol) of CrO_3 in 24 mL of water and 24 mL of glacial acetic acid, keeping the temperature of the solution between 35 and 45 °C. After the addition, the reaction mixture was stirred at room temperature for 15 min, diluted with 70 mL of water, neutralized carefully with saturated Na_2CO_3, and extracted several times with ether. The combined ether extracts were dried, evaporated, and fractionally distilled to give 24.3 g (76%) of colorless **9**: bp 130–135 °C (0.2 mm); IR (thin film) 3080, 2950, 2860, 1720, 1600, 1460, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5 (m, 4 H, aromatic), 1.5–3.8 (m,

(11) (a) Eddy, N. B.; Leimbach, D. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385; (b) Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1965**, *8*, 563.

(12) Kanematsu, K.; Takeda, M.; Jacobson, A. E.; May, E. L. *J. Med. Chem.* **1969**, *12*, 405.

9 H, aliphatic). Anal. ($C_{12}H_{13}ClO$) C, H.

3-(3-Chloropropyl)-1-indanone Oxime (10). A solution of 24.3 g (0.117 mol) of ketone **9** in 200 mL of ethanol was treated with a solution of 27.7 g (0.337 mol) of sodium acetate and 23.5 g (0.337 mol) of $NH_2OH·HCl$ in 170 mL of water. The mixture was heated to reflux for 1 h, concentrated in vacuo to remove the ethanol, and extracted several times with $CHCl_3$. The combined organic layers were washed with water, dried ($MgSO_4$), evaporated, and recrystallized from petroleum ether (bp 60–110 °C) to give 17.9 g (68%) of **10**: mp 89–89.5 °C; IR ($CHCl_3$) 2900–3500, 2920, 2860, 1700, 1460, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.0–10.5 (br s, 1 H, NOH), 7.1–7.9 (m, 4 H, aromatic), 2.2–3.8 (m, 5 H, benzylic, CH_2Cl, and $CH_2C{=}NOH$), 1.1–2.2 (m, 4 H, methylenes). Anal. ($C_{12}H_{14}ClNO$) C, H, N.

***cis*-3-(3-Chloropropyl)-1-indanamine (11) Hydrochloride.** A solution of 5.0 g (22 mmol) of oxime **10**, 100 mL of absolute ethanol, and 1.5 mL of concentrated HCl was hydrogenated in a Parr apparatus for 24 h at 50 psi using 5.0 g of 5% palladium on carbon as catalyst. The reaction mixture was filtered through Celite and evaporated to give 5.0 g (91%) of white, solid **11**·HCl. An analytical sample was obtained by recrystallization from methanol–ether to give shiny needles of **11**·HCl: mp 228–229 °C; IR (KBr) 2500–3500, 1605, 1520, 1380 cm^{-1}. Anal. ($C_{12}H_{17}Cl_2N$) C, H, N.

An aqueous solution of **11**·HCl was made basic with 5% NaOH and extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give the free amine **11**, which was used without further purification. An analytical sample was obtained by bulb to bulb distillation (120 °C bath, 0.2 mm) to give colorless **11**: ^1H NMR ($CDCl_3$) δ 7.2 (s, 4 H, aromatic), 4.2 (m, 1 H, $CHNH_2$), 3.6 (t, 2 H, CH_2Cl), 1.0–3.2 (m, 9 H, aliphatic and amino).

1,2,3,4,5,6-Hexahydro-1,6-methano-2-benzazocine (4a). A well-stirred mixture of 4.0 g (19 mmol) of free amine **11**, 150 mL of 1-propanol, and 1.5 g of finely ground KI was heated at reflux for 24 h. The reaction mixture was concentrated in vacuo and partitioned between ether and 5% NaOH. The aqueous layer was separated and extracted several times with ether. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled to give 2.7 g (80%) of colorless **4a**: bp 70–72 °C (0.1 mm); IR (thin film) 3100–3500, 3010, 2910, 2840, 1470, 1450, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2 (s, 4 H, aromatic), 4.4 (d, 1 H, CHN), 3.4 (m, 1 H, benzylic), 1.0–2.9 (m, 9 H, aliphatic and amino).

A sample of free amine **4a** was treated with ethereal oxalic acid to give **4a** oxalate: mp 159–160 °C. Anal. ($C_{14}H_{17}NO_4$) C, H, N.

2-Methyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4b) Hydrochloride. Free amine **4a** (0.50 g, 2.9 mmol) was treated with 0.6 mL of formic acid and 0.6 mL of 40% formaldehyde. The mixture was heated at 95–105 °C for 3 h, cooled, treated with 9 mL of 15% NaOH, and extracted with four 10-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and bulb to bulb distilled (110 °C bath, 0.05 mm) to give 0.52 g (96%) of colorless **4b**. Dry HCl was bubbled through an ethereal solution of **4b**, and the resulting precipitate was collected and recrystallized from ethyl acetate–ether to give **4b**·HCl: ^1H NMR ($CDCl_3$) δ 7.4 (m, 4 H, aromatic), 4.7 (d, 1 H, CHN), 3.5 (m, 1 H, benzylic), 2.9 (s, 3 H, methyl), 1.6–3.2 (m, 8 H, aliphatic).

Due to the hygroscopic nature of the hydrochloride salt, a sample of **4b**·HBr was prepared by treating **4b** with hydrogen bromide and recrystallizing the resulting salt from ethyl acetate–ether: mp 125–127 °C. Anal. ($C_{13}H_{18}BrN$) C, H, N.

2-(2-Phenylethyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4c) Hydrochloride. Free amine **4a** (0.40 g, 2.3 mmol) was dissolved in 14 mL of dry DMF and treated with 0.79 g (5.6 mmol) of K_2CO_3 and 0.43 g (2.4 mmol) of 2-phenylethyl bromide. The mixture was heated at 100 °C for 24 h, filtered, concentrated in vacuo, and bulb to bulb distilled (190 °C bath, 0.1 mm) to give 0.60 g (94%) of crude **4c**, which was treated with hydrogen chloride to provide **4c**·HCl: mp 152.5–154 °C (ethyl acetate–hexane); ^1H NMR ($CDCl_3$) δ 7.4 (m, 9 H, aromatic), 4.9 (m, 1 H, CHN), 1.6–3.6 (m, 13 H, aliphatic). Anal. ($C_{20}H_{26}ClNO·H_2O$) C, H, N.

2-(Cyclopropylcarbonyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4d). To 1.1 g (6.3 mmol) of free amine **4a** in 20 mL of methanol were added 3.0 mL of water and 2.0 g (14 mmol) of K_2CO_3. The mixture was stirred vigorously and cooled in an ice–water bath while 1.6 g (15 mmol) of freshly distilled cyclopropanecarbonyl chloride was added dropwise. Stirring was continued for 3 h at room temperature. The reaction mixture was concentrated in vacuo, and the resulting residue treated with 42 mL of water, 28 mL of benzene, and 14 mL of 1-butanol. The organic layer was separated and the aqueous phase was washed twice with ether. The combined ether extracts were washed with two 40-mL portions of 3 N HCl and two 40-mL portions of water, dried ($MgSO_4$), evaporated, and bulb to bulb distilled (200 °C bath, 0.3 mm) to give 1.01 g (67%) of white solid **4d**: IR ($CDCl_3$) 3010, 2915, 2860, 1620, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.5 (m, 4 H, aromatic), 5.6 and 5.9 (d, 1 H, CHN), 3.0–4.2 (m, 3 H, benzylic and CH_2N), 0.5–2.6 (m, 11 H, aliphatic). Anal. ($C_{16}H_{19}NO$) C, H, N.

2-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4e) Hydrochloride. A solution of 0.89 g (3.7 mmol) of amide **4d** in 10 mL of dry THF was added dropwise to a slurry of 0.44 g (12 mmol) of $LiAlH_4$ in 17 mL of dry THF. The mixture was heated to reflux for 3 h, cooled, hydrolyzed with 0.9 mL of water in 16 mL of THF, filtered, diluted with benzene, concentrated in vacuo, and bulb to bulb distilled (140 °C bath, 0.05 mm) to provide **4e**, which was treated with dry HCl to afford **4e**·HCl (0.70 g, 73%): mp 169.5–170.5 °C (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.3 (m, 4 H, aromatic), 5.0 (d, 1 H, CHN), 1.4–3.5 (m, 12 H, aliphatic and cyclopropyl), 0.3–1.0 (m, 4 H, cyclopropyl). Anal. ($C_{16}H_{22}ClN$) C, H, N.

2-Propyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4f) Hydrochloride. A solution of free amine **4a** (0.60 g, 3.5 mmol) in 10 mL of dry DMF was treated with 1.2 g (8.8 mmol) of K_2CO_3 and 0.46 g (3.6 mmol) of 1-bromopropane. The mixture was heated to reflux for 2 h, cooled, filtered, concentrated in vacuo, and bulb to bulb distilled (120 °C bath, 0.01 mm) to give 0.67 g (90%) of colorless **4f**, which was treated with dry HCl to provide **4f**·HCl: mp 176.5–178 °C (ethyl acetate–hexane); ^1H NMR ($CDCl_3$) δ 7.4 (m, 4 H, aromatic), 5.9 (d, 1 H, CHN), 3.5 (m, 1 H, benzylic), 2.7–3.4 (m, 4 H, CH_2N), 1.5–2.7 (m, 8 H, aliphatic), 1.1 (t, 3 H, methyl). Anal. ($C_{15}H_{22}ClN$) C, H, N.

2-Allyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4g) Hydrochloride. A solution of 0.40 g (2.3 mmol) of **4a** in 15 mL of absolute ethanol was treated with 0.74 g (8.8 mmol) of $NaHCO_3$ and 0.37 g (3.1 mmol) of 3-bromopropene. The mixture was heated to reflux for 24 h, filtered, concentrated in vacuo, and bulb to bulb distilled (140 °C bath, 0.1 mm) to give 0.33 g (67%) of **4g**, which was treated with dry HCl to provide **4g**·HCl: mp 156–157 °C (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.5 (m, 4 H, aromatic), 6.5 (m, 1 H, olefinic), 5.5 (m, 2 H, olefinic), 4.9 (d, 1 H, CHN), 3.3–4.0 (m, 3 H, benzylic and allylic), 1.5–3.3 (m, 8 H, aliphatic). Anal. ($C_{15}H_{20}ClN$) C, H, N.

2-(3-Methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (4h) Hydrochloride. To 0.54 g (3.1 mmol) of **4a** were added 25 mL of dry DMF, 0.47 g (3.1 mmol) of 1-bromo-3-methyl-2-butene, and 0.40 g (4.7 mmol) of $NaHCO_3$. The mixture was heated at reflux for 3 h, cooled, filtered, concentrated in vacuo, and bulb to bulb distilled (130 °C bath, 0.05 mm) to give 0.64 g (84%) of **4h**, which was treated with dry HCl to provide **4h**·HCl: mp 163–163.5 °C (CCl_4); ^1H NMR ($CDCl_3$) δ 7.4 (m, 4 H, aromatic), 5.8 (m, 1 H, olefinic), 4.8 (d, 1 H, CHN), 3.3–3.8 (m, 3 H, benzylic and allylic methylene), 2.7–3.3 (m, 2 H, CH_2N), 1.4–2.6 (m, 6 H, aliphatic), 1.9 and 1.7 (s, total 6 H, methyls). Anal. ($C_{17}H_{24}ClN$) C, H, N.

3-(3-Chloropropyl)-5- and -6-methoxy-1-indene (15). A solution of 12.0 g (82 mmol) of methoxyindene **14** in 130 mL of anhydrous ether was treated slowly with 46 mL (82 mmol) of 1.8 M CH_3Li (in ether). The mixture was stirred at room temperature for 15 min, cooled in ice–water bath, and treated with 25.6 g (17.5 mL, 164 mmol) of 3-bromo-1-chloropropane in 47 mL of anhydrous ether. After stirring at room temperature for 1 h, the reaction mixture was hydrolyzed with 35.5 mL of saturated ammonium chloride and 35.5 mL of water. The aqueous phase was removed and washed with three 60-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and fractionally distilled to give 0.63 g (5.3%) of unreacted starting material (bp 60–65 °C, 0.15 mm) and 15.5 g (85%) of **15**: bp 125–130 °C (0.15 mm); IR (thin film) 3060, 2950, 2850, 1610, 1475,

1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.2–7.3 (m, 5 H, aromatic and olefinic), 3.8 (s, 3 H, methyl), 3.6 (m, 3 H, benzylic and CH_2Cl), 1.5–2.1 (m, 4 H, methylenes). Anal. ($C_{13}H_{15}ClO$) C, H.

1-(3-Chloropropyl)-6- and -5-methoxyindan (16). A solution of 2.36 g (10.6 mmol) of indenes **15** in 200 mL of absolute ethanol was hydrogenated with 0.2 g of 5% palladium on carbon 24 h in a Parr apparatus at 50 psi. The mixture was filtered through Celite, concentrated in vacuo, and distilled to give 2.31 g (97%) of **16**: bp 95–98 °C (0.05 mm); IR (thin film) 2940, 2850, 1605, 1490, 1450, 1250, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.6–7.2 (m, 3 H, aromatic), 3.8 (s, 3 H, methyl), 3.6 (m, 3 H, benzylic and CH_2Cl), 1.4–3.2 (m, 8 H, methylenes). Anal. ($C_{13}H_{17}ClO$) C, H.

3-(3-Chloropropyl)-5-methoxy-1-indanone (17). To a stirred solution of 12 g (55 mmol) of indans **16** and 25 g (95 mmol) of $Na_2Cr_2O_7$ in 400 mL of 1 N H_2SO_4 and 624 mL of glacial acetic acid was added dropwise 803 mL of 10 N H_2SO_4. The reaction mixture was stirred at room temperature for 24 h, poured into 1500 mL of water, and extracted several times with CH_2Cl_2. The combined organic layers were washed wth water and saturated $NaHCO_3$, dried ($MgSO_4$), concentrated in vacuo, and bulb to bulb distilled (180 °C bath, 0.1 mm) to give 7.3 g (59%) of oily **17**, which was used without further purification. An analytical sample was obtained by crystallization of the oil from CH_2Cl_2–hexane to provide colorless crystals of **17**: mp 61.5–62.6 °C; IR ($CHCl_3$) 3005, 2960, 1700, 1600, 1250, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.8–7.8 (m, 3 H, aromatic), 3.9 (s, 3 H, methyl), 3.6 (m, 3 H, benzylic and CH_2Cl), 1.6–3.5 (m, 6 H, methylenes). Anal. ($C_{13}H_{15}ClO_2$) C, H.

3-(3-Chloropropyl)-5-methoxy-1-indanone Oxime (18). A solution of 29.3 g (0.122 mol) of ketone **17** in 200 mL of ethanol was treated with a solution of 34.4 g (0.420 mol) of sodium acetate and 26.3 g (0.378 mol) of NH_2OH·HCl in 180 mL of water. The mixture was heated at reflux for 1 h, cooled, and extracted several times with 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$), concentrated in vacuo, and recrystallized from ethanol–water to give 25.0 g (81%) of **18**: mp 100.5–102 °C; IR ($CDCl_3$) 3580, 3100–3500, 3000, 2950, 1605, 1255, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.9–9.5 (br s, 1 H, NOH), 6.7–7.6 (m, 3 H, aromatic), 3.8 (s, 3 H, methyl), 1.6–3.7 (m, 9 H, aliphatic). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

***cis*-3-(3-Chloropropyl)-5-methoxy-1-indanamine (19).** A solution of 3.0 g (12 mmol) of oxime **18** and 0.9 mL of concentrated HCl in 150 mL of absolute ethanol was hydrogenated for 24 h in a Parr apparatus at 50 psi using 3.0 g of 5% palladium on carbon as catalyst. The mixture was filtered through Celite, concentrated in vacuo, and recrystallized from methanol–ether to give 2.1 g (64%) of **19**·HCl: mp 199–200 °C.

An aqueous solution of **19**·HCl was made basic with 5% sodium hydroxide and extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give the free amine **19**: IR (thin film) 3300, 2950, 2840, 1610, 1490, 1250, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.8–7.3 (m, 3 H, aromatic), 4.2 (m, 1 H, C*H*NH_2), 3.9 (s, 3 H, methyl), 3.6 (m, 3 H, benzylic and CH_2Cl), 1.0–3.3 (m, 8 H, methylenes and amino). Anal. ($C_{13}H_{19}Cl_2NO$) C, H, N.

2′-Methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5a) Oxalate. A solution of 7.7 g (0.032 mol) of free amine **19** in 500 mL of 1-propanol was treated with 3.0 g of finely ground KI and heated at reflux for 24 h. The cooled reaction mixture was filtered, concentrated in vacuo, and partitioned between CH_2Cl_2 and 5% NaOH. The aqueous phase was removed and extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), evaporated, and distilled to give 5.6 g (85%) of **5a**: bp 112–114 °C (0.5 mm); IR (thin film) 3300, 2910, 2820, 1605, 1480, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.6–7.2 (m, 3 H, aromatic), 4.4 (d, 1 H, CHN), 3.8 (s, 3 H, methyl), 3.3 (m, 1 H, benzylic), 1.3–2.9 (m, 9 H aliphatic and amino). Anal. ($C_{13}H_{17}NO$) C, H, N.

Amine **5a** was dissolved in ether and treated with an ethereal solution of oxalic acid. The resulting salt was removed by filtration and recrystallized from methanol–ether to give **5a** oxalate: mp 142–143 °C.

2′-Methoxy-2-methyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5b) Oxalate. Free amine **5a** (0.50 g, 2.5 mmol) was treated with 0.5 mL of formic acid and 0.5 mL of 40% formaldehyde. The mixture was heated at 95–105 °C for 3 h, cooled, treated with 7.7 mL of 15% NaOH, and extracted with four 10-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and bulb to bulb distilled (130 °C bath, 0.25 mm) to give 0.49 g (93%) of **5b**: ^{1}H NMR ($CDCl_3$) δ 6.6–7.2 (m, 3 H, aromatic), 4.1 (m, 1 H, CHN), 3.8 (s, 3 H, O-methyl), 3.2 (m, 1 H, benzylic), 2.4 (s, 3 H, *N*-methyl), 1.2–2.4 (m, 8 H, methylenes).

Treatment of **5b** with ethereal oxalic acid provided **5a** oxalate: mp 149–151 °C (methanol–ether). Anal. ($C_{16}H_{21}NO_5$) C, H, N.

2′-Methoxy-2-(2-phenylethyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5c) Oxalate. A solution of 0.20 g (0.98 mmol) of **5a** in 7 mL of dry DMF was treated with 0.34 g (2.5 mmol) of K_2CO_3 and 0.19 g (140 μL, 1.0 mmol) of 2-phenylethyl bromide. The mixture was heated at 100 °C for 24 h, filtered, concentrated in vacuo, and bulb to bulb distilled (200 °C bath, 1 mm) to give 0.23 g (76%) of **5c**. Treatment of **5c** with ethereal oxalic acid provided **5c** oxalate: mp 181–182 °C (methanol–ether); ^{1}H NMR (D_2O) δ 7.1–7.7 (m, 8 H, aromatic), 4.9 (m, 1 H, CHN), 3.8 (s, 3 H, methyl), 1.5–3.7 (m, 13 H, aliphatic). Anal. ($C_{23}H_{27}NO_5$) C, H, N.

2′-Methoxy-2-propyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5d) Oxalate. A solution of 1.0 g (4.2 mmol) of **5a** in 14 mL of dry DMF was treated with 1.7 g (12 mmol) of K_2CO_3 and 0.65 g (5.1 mmol) of 1-bromopropane. The mixture was heated at reflux for 2 h, cooled, filtered, concentrated in vacuo, and bulb to bulb distilled (180 °C bath, 1 mm) to yield 1.0 g (86%) of **5d**: ^{1}H NMR ($CDCl_3$) δ 6.6–7.3 (m, 3 H, aromatic), 4.2 (m, 1 H, CHN), 3.8 (s, 3 H, *O*-methyl), 3.2 (m, 1 H, benzylic), 1.0–2.9 (m, 12 H, methylenes), 0.9 (t, 3 H, methyl). Treatment of **5d** with ethereal oxalic acid provided **5d** oxalate: mp 157–158 °C (methanol–ether). Anal. ($C_{18}H_{25}NO_5$) C, H, N.

2-Allyl-2′-methoxy-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5e) Oxalate. A solution of 1.0 g (4.9 mmol) of **5a** in 30 mL of absolute ethanol was treated with 1.6 g (19 mmol) of $NaHCO_3$ and 0.78 g (6.4 mmol) of 3-bromopropene. The mixture was heated at reflux for 24 h, filtered, concentrated in vacuo, and bulb to bulb distilled (180 °C bath, 1 mm) to give 1.0 g (84%) of **5e**: ^{1}H NMR ($CDCl_3$) δ 6.6–7.4 (m, 3 H, aromatic), 5.9 (m, 1 H, olefinic), 5.5 (m, 2 H, olefinic), 4.2 (m, 1 H, CHN), 3.8 (s, 3 H, methyl), 1.1–3.4 (m, 11 H, aliphatic).

Treatment of **5e** with ethereal oxalic acid provided **5e** oxalate: mp 163–165 °C (methanol–ether). Anal. ($C_{18}H_{23}NO_5$) C, H, N.

2′-Methoxy-2-(3-methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (5f) Oxalate. A solution of 1.0 g (4.9 mmol) of **5a** in 34 mL of dry DMF was treated with 0.75 g (5.0 mmol) of 1-bromo-3-methyl-2-butene and 0.64 g (7.6 mmol) of $NaHCO_3$. The mixture was heated to reflux for 3 h, filtered, concentrated in vacuo, and bulb to bulb distilled (180 °C bath, 1 mm) to give 0.96 g (72%) of **5f**: ^{1}H NMR ($CDCl_3$) δ 6.7–7.3 (m, 3 H, aromatic), 5.3 (m, 1 H, olefinic), 4.2 (m, 1 H, CHN), 3.8 (s, 3 H, methyl), 1.1–3.4 (m, 17 H, aliphatic).

Treatment of **5f** with ethereal oxalic acid provided **5f** oxalate: mp 142–143.5 °C (methanol–ether). Anal. ($C_{20}H_{27}NO_5$) C, H, N.

2′-Hydroxy-2-methyl-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (6a) Hydrobromide. A solution of 0.46 g (1.5 mmol) of **5a** oxalate in 7 mL of 48% aqueous HBr was heated at 100 °C for 2 h, evaporated to dryness, and recrystallized from methanol–ether to give 0.24 g (56%) of **6a**·HBr: mp 112–114 °C; ^{1}H NMR (D_2O) δ 6.8–7.5 (m, 3 H, aromatic), 4.6 (m, 1 H, CHN), 1.2–3.7 (m, 9 H, aliphatic), 2.9 (s, 3 H, methyl).

A solution of crude **6a**·HBr in 5% hydrochloric acid was adjusted to pH 9 with ammonium hydroxide and extracted several times with ether. The combined ether layers were dried ($MgSO_4$) and treated with an ethereal solution of oxalic acid. The resulting oil was crystallized from methanol–ether to give **6a** oxalate: mp 113–115 °C; IR (KBr) 3200–3600, 2940, 1715, 1615, 1460, 1240, 815 cm^{-1}. Anal. ($C_{15}H_{19}NO_5$) C, H, N.

2′-Hydroxy-2-(2-phenylethyl)-1,2,3,4,5,6-hexahydro-1,6-methano-2-benzazocine (6b) Hydrobromide. A solution of 0.43 g (1.1 mmol) of **5c** oxalate in 7 mL of 48% aqueous HBr was heated at 100 °C for 2 h and evaporated to dryness. The residue was dissolved in methanol, treated with decolorizing carbon, filtered, concentrated in vacuo, and recrystallized from methanol–ether to give 0.19 g (55%) of **6b**·HBr: mp 161.5–162.5 °C; ^{1}H NMR (D_2O) δ 6.8–7.5 (m, 8 H, aromatic), 4.9 (m, 1 H, CHN), 1.4–3.7 (m, 13 H, aliphatic). Anal. ($C_{20}H_{24}BrNO$) C, H, N.

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.

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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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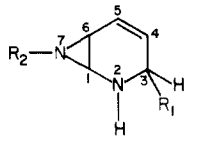
The 1,3-dipolar cycloaddition reaction of 1,4-dihydropyridines, **2**, with organic azides, **3**, afford 2,7-diazabicyclo[4.1.0]hept-3-enes, **4**, which exhibit significant analgesic and antiprotozoal activities. The most active analgesics, **4a** and **4c**, were more potent than aspirin or dextropropoxyphene. 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 analgesic,[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**.

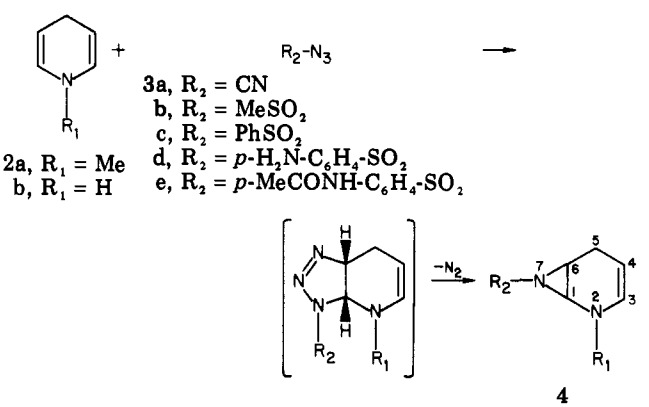


1, R_1 = *n*-Bu, Ph; R_2 = CN, MeOCO, $MeSO_2$, $PhSO_2$, *p*-H_2N-C_6H_4-SO_2, *p*-MeCONH-C_6H_4-SO_2

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

Scheme I



4

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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