After 20 min, an addnl 1.0 ml of the 0.26 *M* methyl chloroformate soln was added, and the mixt was stirred 40 min longer. The red ppt was collected, washed with water, triturated with ether, and dried *in vacuo* to yield 0.72 g (69%), mp 149–154°, $[\alpha]^{23}D + 251°$ (*c* 0.1, $CHCl_3$), R_f 0.7 (60:10:1), nmr δ 3.54 s (NCOOMe). *Anal.* ($C_{29}H_{31}NO_{12}\cdot 0.5H_2O$) C, H; N: calcd, 2.36; found, 2.71.

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New Compounds

Mannich Bases of 2,3-Dihydro-4(1*H*)-carbazolones as Potential Psychotropic Agents

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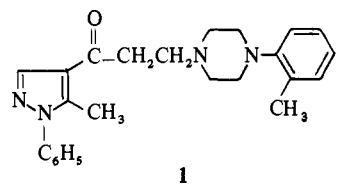
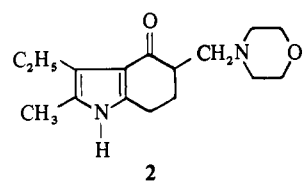
The potential utility of Mannich bases as pharmaceutical agents has been investigated frequently, and compounds **1** and **2** represent recent examples. The pharmacological profile of the former substance is similar to that of reserpine,[1] whereas the latter material is reported to be a potent antipsychotic agent in man.[2] Despite the availability of 2,3-dihydro-4(1*H*)-carbazolone (**3**)[3] and its 9-methyl derivative **4**,[4] the preparation of Mannich bases derived from these heterocycles has not been reported. Inasmuch as clinical studies with **2** suggest that it possesses utility in humans,[5] the preparation of similar compounds from **3** and **4** was undertaken. The synthesis of the Mannich bases **5** and **6** was accomplished by conventional procedures, the details of which may be found in the Experimental Section.

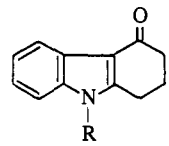
Pharmacology. Mannich bases **5** and **6** were tested for



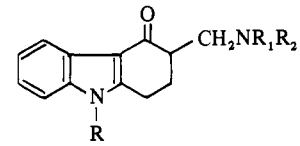
1



2



3, R = H
4, R = CH_3



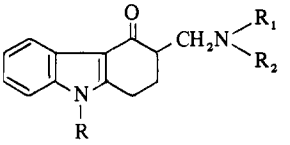
5, R = H
6, R = CH_3

Table I. Biological Activities of Representative 3-(Substituted aminomethyl)-2,3-dihydro-4(1*H*)-carbazolones

Compound	Median effective dose, mg/kg ip				
	Ataxia[a]	Motor act. decrease[a]	Antielectro-shock[b]	Antistrych[c]	Lethality
1-(5-Methyl-1-phenyl-4-pyrazolyl)-3-(4-*o*-tolyl-1-piperazinyl)-1-propanone hydrochloride (1)	27	3			110
3-(1-Pyrrolidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		30			300
3-(4-Morpholinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		4			40
3-(1-Piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	50	7			68
9-Methyl-3-(4-morpholinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		30	29		300
9-Methyl-3-(1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		16			160
3-(3-Methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone		8			80
9-Methyl-3-(3-methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	78	18	40		180
9-Methyl-3-(4-methyl-1-piperidinomethyl)-2,3-dihydro-4(1*H*)-carbazolone	32	10			128

[a]Determined as described by Wright, *et al.*,[6] the absence of a figure signifies no effect at 100 mg/kg. [b]Determined as described by Swinyard, *et al.*;[7] the lack of a figure indicates no effect at 50 mg/kg. [c]Determined by a modification of the method of Hanson and Stone;[8] the compounds were without effect at 50 mg/kg.

Table II. 3-Disubstituted-2,3-dihydro-4(1*H*)-carbazolones



R	NR_1R_2	Reaction solvent	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
H	$N(CH_3)_2$	THF	27	Acetone-hexane	194-196	$C_{15}H_{18}N_2O$	C, H, N
H	Δ^3-Pyrrolino	THF	11	Acetone-hexane	180-183	$C_{17}H_{18}N_2O$	H, N; C[a]
H	Pyrrolidino	THF	9	Acetone-hexane	198-200	$C_{17}H_{20}N_2O$	C, H, N
H	Morpholino	EtOH	23	MeOH	227-229	$C_{17}H_{20}N_2O_2$	C, H, N
H	$N(C_2H_5)_2$	THF	13	Acetone-hexane	143-145	$C_{17}H_{22}N_2O$	C, H, N
H	Piperidino	THF	36	Acetone-hexane	182-184	$C_{18}H_{22}N_2O$	C, H, N
CH_3	Morpholino	EtOH	33	Acetone-hexane	171-174	$C_{18}H_{22}N_2O_2$	C, H, N
CH_3	Piperidino	EtOH	40	Acetone-hexane	136-137	$C_{19}H_{24}N_2O$	C, H, N
H	3-Methylpiperidino	EtOH	16	Acetone-hexane	173-176	$C_{19}H_{24}N_2O$	C, H, N
H	4-Methylpiperidino	EtOH	46	Acetone-hexane	178-181	$C_{19}H_{24}N_2O$	C, H, N
CH_3	4-Methyl-1-piperazinyl	EtOH	35	Acetone–hexane	128-130	$C_{19}H_{25}N_3O$	C, H, N
CH_3	3-Methylpiperidino	EtOH	13	Acetone-hexane	118-121	$C_{20}H_{26}N_2O$	C, H, N
CH_3	4-Methylpiperidino	EtOH	49	Acetone-hexane	146-148	$C_{20}H_{26}N_2O$	C, H, N

[a] C: calcd, 76.66; found, 76.17.

their ability to induce ataxia, to decrease locomotor activity, and to afford protection against electroshock- and strychnine-induced convulsions in mice. In general, the compounds described herein failed to afford protection at an acceptable dose (≤50 mg/kg) against convulsions induced by either method. However, many compounds induced ataxia, as judged by impairment of ability to traverse a suspended rod, and decreased motor activity. The data for the more interesting compounds are summarized in Table I; comparable data for Mannich base **1** are included.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. All products upon which yields are based were homogeneous as judged by tlc using Eastman Chromatogram No. 6060 sheets (silica gel with fluorescent indicator) developed by $CHCl_3$–hexane–EtOH (1:1:1) or acetone–HOAc–MeOH–benzene (5:5:20:100). Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the calculated values.

Mannich Reactions. The following preparation of 3-(dimethylaminomethyl)-2,3-dihydro-4(1*H*)-carbazolone illustrates the general procedure. A soln of 1.00 g (5.5 mmoles) of 2,3-dihydro-4(1*H*)-carbazolone (**3**), 500 mg (6.0 mmoles) of dimethylamine hydrochloride, and 210 mg (6.3 mmoles) of paraformaldehyde in 60 ml of tetrahydrofuran† containing 3 ml of 10% ethanolic HCl was heated at reflux temperature for 16 hr. The solvents were removed under reduced pressure, and the residue was treated with 20% HOAc. Extraction with EtOAc removed the starting ketone. The acid layer was rendered alkaline with NH_4OH to give 350 mg of crystals, mp 195-197° dec. The characterization of this substance and those prepared in a similar manner is given in Table II.

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†Alternatively, EtOH was used in certain preparations, as indicated in Table II.

Synthesis of Some Spin-Labeled Analogs of Drug Molecules

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Spin labels are stable free radicals that can be used as reporter groups to study the interaction of drugs and other ligands with biologically important macromolecules such as enzymes, nucleic acids, and membranes.[1-3] The most commonly employed spin label is the nitroxide free radical, since this group is very stable in aqueous systems at physiological pH values. Furthermore, the electron spin resonance of the nitroxide group is exquisitely sensitive to changes in its microenvironment.[1-3] Spin-labeled drugs have recently become important in studies of drug mechanisms at a molecular level. For example, drug analogs containing the nitroxide moiety have been used to study the topography of specific binding sites in receptor macromolecules.[4,5] Spin-labeled drugs have also been used, in conjunction with immunoassay techniques, to detect and assay low concentrations of drugs and their metabolites in biological fluids such as urine, plasma, and saliva.[6,7]

In this report, we describe the synthesis of spin-labeled analogs of three classes of drugs, the sulfonamides, the barbiturates, and the choline esters. The spin-labeled sulfon-