# Anticonvulsant Properties of Some Mannich Bases of Conjugated Arylidene Ketones

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Received March 22, 1991, from the *College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada.* Accepted for publication July 13, 1991.

**Abstract** □ Thirty 1-aryl-5-dimethylamino-1-penten-3-one hydrohalides and related compounds were prepared as candidate anticonvulsants and evaluated in maximal electroshock seizure (MES), subcutaneous pentylenetetrazole threshold, and neurotoxicity screens. Following administration by the intraperitoneal route, many of the compounds were active in the MES screen, whereas only 10% of the Mannich bases afforded protection in the subcutaneous pentylenetetrazole test. Quantitation of half of the compounds prepared revealed that many had activity comparable with that of clinically useful drugs in the MES screen. The anticonvulsant properties of eight of the compounds following oral administration were reduced considerably or abolished compared with those following intraperitoneal administration. Various synthetic strategies for future development of potential anticonvulsants are outlined.

The general structure of some common monocyclic anticonvulsant drugs (1) shows that, in many cases, the presence of at least one aryl ring, a carbonyl group, and a nitrogen atom appears to be important in conferring anticonvulsant properties. However, the compounds in series 1 contain the dicarboximide function (—CONRCO—), which may contribute to unwanted side effects, such as sedation and toxicity.[1] Thus, to find new classes of drugs to treat epilepsy, a group of Mannich bases with the general structure 2 were screened as candidate anticonvulsants for the following reasons. First, in series 2, the aryl ring, carbonyl group, and nitrogen atom are separated by spacer groups containing two carbon atoms each. These spacer arms either confer rigidity between important functional groups, namely the aryl ring and carbonyl group, or permit flexibility such as is found with the dimethylene or substituted dimethylene chain between the carbonyl group and the nitrogen atom. Hence, if activity was demonstrated in series 2, subsequent studies could investigate the importance of these spacer groups (e.g., reduction of the olefinic double bond would permit increased flexibility between the aryl ring and carbonyl group). Second, the literature contains a few examples of anticonvulsant properties displayed by $\alpha,\beta$-unsaturated ketones[2,3] and Mannich bases.[4,5] Hence, the combination of both structural features in series 2 may lead to bioactive molecules. Third, the structural requirement for activity in the maximal electroshock (MES) screen, which is claimed to be a predictor of compounds that are active against grand mal seizures,[6] is two electron donor atoms close to a bulky hydrophobic group.[7] The molecular feature conferring activity in the subcutaneous pentylenetetrazole (scPTZ) test, which is believed to detect compounds useful in treating petit mal,[6] is two electron donors close to a smaller, less hydrophobic group than found in MES-active derivatives.[7] Two donor atoms, namely oxygen and nitrogen, are present in series 2, and selective activity in either the MES or scPTZ screens would indicate the importance of the size of the phenyl or styryl groups in the design of agents for treating grand mal or petit mal seizures, respectively.

Three series of compounds based on the general structure 2 were envisaged: substitution at the alkyl carbon atom adjacent to the carbonyl group (series 3), substitution in the aryl ring (series 4), and replacement of an olefinic proton and/or dimethylamino function by other groups (series 5). These compounds were thought to have sufficiently diverse electronic, steric, and hydrophobic characteristics to permit correlations between these physicochemical parameters and anticonvulsant properties.

## Experimental Section

**Chemistry**—Melting points (mp) and boiling points (bp) are uncorrected. Elemental analyses were undertaken by the late Mr. R. E. Teed and Mr. R. Thoms, Department of Chemistry, University of Saskatchewan. Compounds described previously were analyzed satisfactorily, and the following compounds gave combustion analyses within 0.4% of the calculated values with the exception of **5h** (calc.: H, 7.63%; found: H, 8.23%): C,H,N analyses on **4e**, **4f**, **4i–k**, **4m**, and **5a–c**, **5h** and C,H analyses on 1-(2,6-dichlorophenyl)-1-penten-3-one, 1-(2,4-difluorophenyl)-1-penten-3-one, and 1-(2,5-difluorophenyl)-1-penten-3-one. TLC plates were composed of silica gel. IR spectra were recorded on a Beckman Aculab 4 IR spectrophotometer, and NMR spectra were obtained with a Varian T-60 instrument.

**Synthesis of 3, 4a–d, 4g, 4h, 4l, and 5d–g**—The methods of preparation of the following compounds have been described previously: **3a**,[8] **3b**, **4a–d**, **4g**, **4h**, and **4l**,[9] **3c–e** and **3g**,[10] **3f**,[11] **3h**,[12] **3i**,[13] and **5d–g**.[14]

**Synthesis of 4e, 4f, 4i–k, and 4m**—The 1-aryl-1-penten-3-ones required for the synthesis of **4e**, **4f**, **4i–k**, and **4m** were prepared by a literature method[9] to give compounds with the following aryl substitution pattern, mp or bp, and yield: 2,6-$Cl_2$, 121–123 °C (0.05 mm Hg), 63%; 2-F, 120–123 °C (0.05 mm Hg), 58%; 2,4-$F_2$, 44.3 °C, 78%; 2,5-$F_2$, 38.6 °C, 68%; 2,6-$F_2$, 44.3 °C, 63%; 4-Br, 90.5 °C, 78%. The solids were recrystallized from petroleum ether (bp, 30–60 °C)–diethyl ether. All derivatives were pure as determined by TLC with an eluting solvent of petroleum ether (bp 30–60 °C): diethyl ether (1:1), and all had NMR ($CDCl_3$) spectra in accord with the proposed structures.

The Mannich bases **4e**, **4f**, **4i–k**, and **4m** were prepared by a published method,[9] and the products were purified in the following way. Compound **4e** was obtained by removal of the solvent under reduced pressure, the resultant residue was triturated with anhydrous diethyl ether, the ethereal extracts were discarded, and the product was recrystallized from diethyl ether–methanol. For **4f**, **4i–k**, and **4m**, the pure compounds deposited from the reaction mixtures and the mother liquors were evaporated to dryness to give residues that were recrystallized from diethyl ether–methanol. All compounds were pure as determined by TLC with a solvent system of chloroform:methanol (9:1), and the structures were confirmed by elemental analysis and NMR ($D_2O$) and IR (KBr) spectroscopy. The melting points and yields of compounds were as follows: **4e**, 168–170 °C and 63%; **4f**, 134–135 °C and 43%; **4i**, 152–153 °C and 63%; **4j**, 162–163 °C and 56%, **4k**, 163–165 °C and 68%; **4m**, 159–161 °C and 70%.

**Synthesis of 5a and 5c**—A mixture of 1-(4-methylphenyl)-1-buten-3-one (9.61 g, 0.060 mol), paraformaldehyde (1.86 g, 0.062 mol), dimethylamine hydrobromide (7.56 g, 0.060 mol), and acetonitrile (80 mL) was acidified with hydrogen bromide gas to pH 4 and heated under reflux for ~12 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure, and



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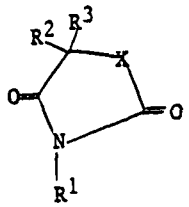
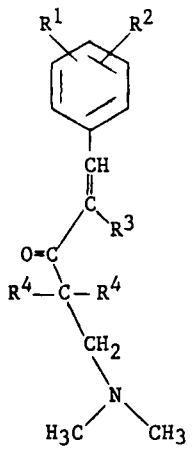


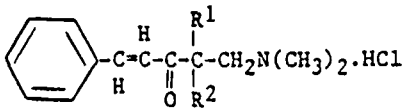
1

$R^1$ = H,alkyl
$R^2$ = phenyl,alkyl,H
$R^3$ = phenyl,alkyl
X = CONH,NH,$NH_2$,O,$CH_2$,$CH_2CH_2$



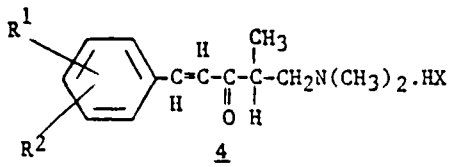
2

$R^1$=$R^2$=H,Cl,etc.
$R^3$=H,$CH_3$,$COOC_2H_5$,$C_6H_5$
$R^4$=H,alkyl



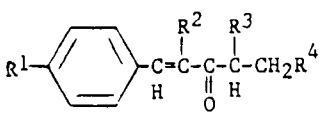
3

a: $R^1$=$R^2$=H
b: $R^1$=$CH_3$;$R^2$=H
c: $R^1$=$(CH_2)_3CH_3$;$R^2$H
d: $R^1$=$CH_2CH(CH_3)_2$;$R^2$=H
e: $R^1$=$C(CH_3)_3$;$R^2$=H
f: $R^1$=$(CH_2)_4CH_3$;$R^2$=H
g: $R^1$=$(CH_2)_6CH_3$;$R^2$=H
h: $R^1$=$R^2$=$CH_3$
i: $R^1$=$(CH_2)_3CH_3$;$R^2$=$CH_3$



4

a: $R^1$=4-Cl;$R^2$=H;X=Br
b: $R^1$=3-Cl;$R^2$=4-Cl;X=Cl
c: $R^1$=4-$CH_3$;$R^2$=H;X=Br
d: $R^1$=4-$OCH_3$;$R^2$=H;X=Cl
e: $R^1$=2-Cl;$R^2$=6-Cl;X=Cl
f: $R^1$=2-F;$R^2$=H;X=Cl
g: $R^1$=3-F;$R^2$=H;X=Cl
h: $R^1$=4-F;$R^2$=H;X=Cl
i: $R^1$=2-F;$R^2$=4-F;X=Cl
j: $R^1$=2-F;$R^2$=5-F;X=Cl
k: $R^1$=2-F;$R^2$=6-F;X=Cl
l: $R^1$=3-F;$R^2$=4-F;X=Cl
m: $R^1$=4-Br;$R^2$=H;X=Cl



5

a: $R^1$=$CH_3$;$R^2$=$R^3$=H;$R^4$=$N(CH_3)_2$.HBr
b: $R^1$=$R^2$=$R^3$=H;$R^4$=$N(C_2H_5)_2$.HBr
c: $R^1$=$CH_3$;$R^2$=$R^3$=H;$R^4$=$N(C_2H_5)_2$.HBr
d: $R^1$=$R^2$=$R^3$=H;$R^4$=$N(CH_2)_4O$.HCl
e: $R^1$=$R^3$=H;$R^2$=$CH_3$;$R^4$=$N(CH_2)_4O$.HCl
f: $R^1$=$R^3$=H;$R^2$=$COOC_2H_5$;$R^4$=$N(CH_2)_4O$.HCl
g: $R^1$=$R^3$=H;$R^2$=$C_6H_5$;$R^4$=$N(CH_2)_4O$.HCl
h: $R^1$=$R^2$=H;$R^3$=$(CH_2)_4CH_3$;$R^4$=$N(CH_2)_4O$.HBr

the resultant product was triturated with diethyl ether and then recrystallized from diethyl ether–methanol to give **5a** (mp, 156–157 °C) in 35% yield.

Compound **5c** was prepared from diethylamine hydrobromide with the same protocol to give the desired compound (mp, 141–142 °C) in 20% yield. Both NMR ($CDCl_3$) and IR (KBr) spectra supported the structures assigned to **5a** and **5c**.

**Synthesis of 5b and 5h**—A mixture of 4-phenyl-3-buten-2-one (14.6 g, 0.1 mol), paraformaldehyde (4.5 g, 0.15 mol), diethylamine hydrochloride (12.05 g, 0.11 mol), hydrochloric acid (0.3 mL), and ethanol (30 mL) was heated under reflux for 24 h. The ethanol was removed under reduced pressure, and the resultant residue was treated with ether (4 × 10 mL) and then dissolved in water (30 mL). The pH of the solution was adjusted to 10–11 with aqueous NaOH solution (10%, w/v), and the liberated free base was extracted with ether (4 × 20 mL). The combined ether extracts were washed with water (3 × 10 mL) and dried (anhydrous magnesium sulfate). Removal of ether and some diethylamine gave a viscous oil, which was dissolved in anhydrous ether (50 mL) and treated with dry hydrogen bromide gas. The colorless solid that precipitated was

removed, washed with dry ether, dried, and recrystallized from ethyl acetate to give **5b** (8.78 g; 56%; mp, 124–125 °C).

1-Phenyl-1-nonen-3-one, required in the synthesis of **5h**, was prepared by a literature method.[15] Compound **5h** (mp, 166–168 °C) was prepared in a similar manner to **5b** in 46% yield and was purified by recrystallization from ethyl acetate.

**Evaluation of Series 3–5 for Anticonvulsant Activity**—The compounds were assessed for anticonvulsant properties by the National Institute of Neurological Disorders and Stroke, National Institutes of Health, with their protocols.[16] In the phase II screen [quantitation of the effect after intraperitoneal (ip) injection in mice], **4a** had an $ED_{50}$ (dose that is effective in 50% of animals) value of 80.22 mg/kg [95% confidence internal (CI), 55.26–152.70 mg/kg] in the scPTZ screen 1 h after injection. The following compounds (dose in mg/kg) also afforded some protection in this test: **3b** (25, 50), **3h** (225, 300), **4e** (64), and **4m** (200). However, at these doses, death (**3b**, **3h**, **4m**) and/or continuous seizure activity (**4e**, **4m**) occurred. The remaining 10 compounds listed in Table I were inactive in the scPTZ screen. In the oral MES screen, the $ED_{50}$ value of **3e** was 461.42 mg/kg (95% CI, 366.05–627.53 mg/kg) after 0.25 h. Compounds administered orally to rats were inactive in the MES screen, with the exception of **4j** at a dose of 50 mg/kg, which protected 25% of the animals 1 h after administration of the compound.

## Results

The compounds were prepared by methods that have been used previously in these laboratories.[8–15] Initially, a Claisen–Schmidt condensation between the appropriate aryl aldehydes and requisite ketones afforded the corresponding conjugated styryl ketones. These enones were converted by the Mannich reaction into the compounds in series **3–5**.

The initial (phase I) evaluation of the compounds in series **3–5** as candidate anticonvulsants was by MES, scPTZ, and neurotoxicity screens in mice. In phase I screening, each compound was administered ip at doses of 30, 100, and 300 mg/kg, and observations were made 0.5 and 4 h after the injections. The Mannich bases **4a**, **4c**, **5d**, and **5h** were tolerated at a dose of 300 mg/kg. At this dose, all of the other compounds caused death by respiratory depression in some or all of the animals within 0.5 h, the only exception being **5f**, which caused fatalities between 0.5 and 4 h (during this time, the animals were not observed, and the cause of death by **5f** was not recorded). At a dose of 100 mg/kg, these derivatives were nonlethal, with the exception of **3f** and **5b**, which caused some mortalities within 0.5 h. Thus, in most cases, the phase I screening results should be viewed in light of responses to the test compounds at doses of 30 and 100 mg/kg.

In series **3**, with the exception of **3a**, all the compounds were active in the MES screen at a dose of 100 mg/kg, either at the end of 0.5 h but not at 4 h (**3b–3e**, **3h**, **3i**) or at both time intervals (**3f**, **3g**). No activity was observed in the scPTZ screen, except for **3f** at a dose of 100 mg/kg, which gave protection at the end of 4 h. In series **4**, at the end of 0.5 h, all of the compounds were active in the MES screen at a dose of 100 mg/kg, except for **4c** and **4d** (active at a dose of 300 mg/kg) and **4h**, **4k**, and **4l** (inactive). Compound **4a** (300 mg/kg) is the only compound in series **4** that gave protection in the MES screen at the end of 4 h. Compound **4c** displayed anticonvulsant properties in the scPTZ test at a dose of 300 mg/kg at the end of 4 h but not after 0.5 h. Evaluation of series **5** in the MES screen showed that **5d** and **5e** were active at the end of 0.5 h but not after 4 h, at doses of 300 and 100 mg/kg, respectively, and **5g** was active at 4 h only at a dose of 300 mg/kg. The remaining five compounds were inactive in the MES screen. No activity was noted in the scPTZ test, except for **5f**, which afforded protection at the end of 0.5 and 4 h at doses of 300 and 100 mg/kg, respectively. Neurotoxicity was noted after 0.5 h for **3g**, **4a**, **4c**, **5d**, **5f**, and **5g** at a dose of 300 mg/kg, and for **3d–3f**, **4e**, **4f**, **4m**, **5a**, and **5b** at a dose of 100 mg/kg. At the end of 4 h, neurotoxicity was observed for **4c**, **5d**, and **5g** at a dose of 300 mg/kg and for **3g**, **4e**, and **5f** a dose of 100 mg/kg.

Phase II screening consisted of quantifying both the activities in the MES screen and the neurotoxicities for 15 of the Mannich bases. The data are presented in Table I. A representative compound, **4j**, had an $ED_{50}$ value of ~100 mg/kg in protecting seizures induced by picrotoxin, but it had no anticonvulsant activity in the bicuculline or strychnine screens.[16] This Mannich base (**4j**) did not displace radiolabeled flunitrazepam,[17] γ-aminobutyric acid,[18,19] or adenosine[20] from mouse brain synaptic membranes and synaptosomes at concentrations of 3–100, 0.005–10, and 0.3–100 μM, respectively.

Some compounds were examined for oral activity in mice (phase IV screening) and rats (phase VI tests). In the phase IV MES screen, **3e** had an $ED_{50}$ value of 461 mg/kg, whereas a dose range of up to and including 1000 mg/kg revealed that **3d** was inactive. Some protection to mice was afforded by **3i** (1/2 and 2/2 animals were protected at doses of 500 and 1000 mg/kg, respectively) and **4e** (2/8 animals were protected at a dose of 750 mg/kg). Compounds **3d**, **3e**, **3i**, and **4k** were inactive in the MES screen when administered orally to rats at doses up to 100 mg/kg. In this screen, **3i**, **4e**, **4i**, and **5e** at a dose of 50 mg/kg were inactive, whereas **4j** displayed marginal activity.

**Table I—Quantitation of MES Activity and Neurotoxicity of Compounds in Series 3–5 after ip Injection in Mice**

| Compound | MES Screen | | | | | Neurotoxicity Screen | | | | | PI |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Time, h[a] | $ED_{50}$, mg/kg | 95% CI | Slope | SE[b] | Time, h[a] | $TD_{50}$, mg/kg | 95% CI | Slope | SE[b] | |
| **3b** | 0.25 | 87.87 | 81.87–92.07 | 35.11 | 12.94 | 0.50 | 106.32 | 88.85–122.91 | 9.16 | 2.72 | 1.21 |
| **3c** | 0.25 | 53.86 | 49.97–61.66 | 16.30 | 5.77 | 0.25 | 100.39 | 66.04–106.96 | 24.63 | 11.06 | 1.86 |
| **3d** | 0.25 | 36.24 | 32.63–41.45 | 18.30 | 6.33 | 0.25 | 98.42 | 89.31–111.07 | 23.93 | 9.36 | 2.72 |
| **3e** | 0.25 | 29.68 | 21.37–37.63 | 5.69 | 1.73 | 0.25 | 77.57 | 53.92–94.13 | 8.14 | 2.72 | 2.61 |
| **3h** | 0.50 | 73.07 | 59.45–87.23 | 6.90 | 1.82 | 0.50 | 133.93 | 70.06–100.05 | 7.78 | 3.02 | 1.83 |
| **3l** | 0.25 | 60.65 | 46.13–72.42 | 9.15 | 3.02 | 0.25 | 121.31 | 92.26–144.85 | 9.15 | 3.02 | 2.00 |
| **4a** | 1.00 | 119.55 | 92.92–142.61 | 7.30 | 2.12 | 0.25 | 143.50 | 116.19–183.74 | 5.96 | 1.83 | 1.20 |
| **4e** | 1.00 | 33.16 | 27.93–44.02 | 7.05 | 2.22 | 0.25 | 60.80 | 48.50–75.24 | 6.68 | 1.88 | 1.83 |
| **4f** | 0.50 | 58.41 | 48.63–69.42 | 11.33 | 3.39 | 0.25 | 152.45 | 89.44–168.75 | 9.55 | 3.94 | 2.61 |
| **4g** | 0.25 | 63.11 | 45.81–78.49 | 6.58 | 2.16 | 0.25 | 147.31 | 129.03–172.97 | 10.62 | 3.12 | 2.33 |
| **4l** | 0.25 | 60.21 | 54.25–67.27 | 13.20 | 4.10 | 0.50 | 136.67 | 87.24–167.73 | 10.89 | 5.00 | 2.27 |
| **4j** | 0.25 | 32.29 | 28.14–36.95 | 11.82 | 3.69 | 0.25 | 95.19 | 80.18–111.38 | 7.55 | 1.96 | 2.95 |
| **4k** | 0.25 | 50.24 | 41.81–57.47 | 9.78 | 2.84 | 0.25 | 117.86 | 97.99–141.15 | 9.00 | 2.43 | 2.35 |
| **4m** | 0.50 | 67.79 | 58.34–81.91 | 7.58 | 2.35 | 0.25 | 90.28 | 66.15–132.43 | 4.36 | 1.33 | 1.33 |
| **5e** | 0.25 | 82.52 | 69.68–88.75 | 15.73 | 5.41 | 0.25 | 165.84 | 157.07–175.69 | 29.44 | 9.50 | 2.01 |

[a] The time when maximal activity or neurotoxicity was demonstrated. [b] Standard error of the slope.

## Discussion

The results of phase I screening indicate that 70% of the 30 Mannich bases described in this report were active in the MES test, whereas only 10% of the compounds afforded protection in the scPTZ screen. Thus, these compounds display a propensity towards MES selectivity at doses tolerated by the host. Therefore, the Mannich bases indicated by the general formula 2 possibly do fulfill the criterion for MES activity: an aryl ring in close proximity to two electron donor atoms,[7] which in this case are oxygen and nitrogen atoms. Activity in the MES test was found with greater frequency among the Mannich bases in series 3 and 4 than in 5; hence, the following discussion will focus on series 3 and 4 compounds. The compounds generally displayed activity at the first time of observation (0.5 h) and not at the end of 4 h. Thus, they are rapidly acting anticonvulsants of sufficient interest to us that we proceeded to quantitate the effects of representative compounds, compare their bioactivities with clinically useful drugs, and investigate whether activity is retained when the compounds are administered orally.

Most of the 21 compounds that were active in the phase I MES test were evaluated quantitatively in the MES and neurotoxicity screens, and the data are summarized in Table I (**3b**, in addition to being part of series **3**, is also an unsubstituted member of series 4; hence, in discussing the data in Table I, series 4 refers to **4a**, **4e–g**, **4i–k**, **4m**, plus **3b**). The average $ED_{50}$ (56.9 and 63.6 mg/kg, respectively) and $TD_{50}$ (dose that is toxic to 50% of animals; 106 and 117 mg/kg, respectively) values of the compounds in series 3 and 4 were similar. The protection indices (PI; i.e., $TD_{50}/ED_{50}$) were also similar: 1.83 for the six compounds in 3 and 1.87 for series 4 compounds. In the MES screen, the times of peak effects (TPE) were generally recorded as 0.25 h, which was the first time of observation after administration of the Mannich bases. This phenomenon corroborates the phase I screening results that the compounds are rapidly acting anticonvulsants, and is in contrast to the effect of certain drugs such as mephobarbital, which has a TPE of 4 h.[6] The quantitative data generated were compared with those obtained for drugs with similar TPE values in the MES screen.[6] The $ED_{50}$ and $TD_{50}$ values of mephenytoin are 60.5 and 154 mg/kg, respectively (PI = 2.55) and those for phenobarbital are 21.8 and 69.0 mg/kg, respectively (PI = 3.17). Thus, at the 95% CI, **3d**, **3e**, **4e**, and **4i** are more potent than mephenytoin, and **3c**, **4f**, **4i**, and **4h** are as potent as mephenytoin. Four compounds (**3d**, **3e**, **4f**, and **4j**) have higher PI values than that of mephenytoin. The values for phenobarbital fall within the 95% CI for **3e**, a fact indicating that **3e** and phenobarbital are approximately equipotent.

Examination of the 95% CI values of the slopes[21] for the compounds in series 3 and 4, generated in the MES screen, revealed no significant differences. Therefore, the mechanism(s) of action of the compounds could be similar; however, the lack of variability in the slopes may have been due to the large standard errors rather than the Mannich bases having identical modes of action. An attempt was made to discern the mode(s) of action of a representative compound. Because **4j** had the highest PI (Table I), it was examined for anticonvulsant activity against certain chemically induced seizures in mice. Bicuculline, picrotoxin, and strychnine cause convulsions by acting on γ-aminobutyric acid receptors, chloride channels, and glycine receptors, respectively.[22] The Mannich base **4j** protected against convulsions in mice induced by picrotoxin ($ED_{50}$, 100 mg/kg) to an extent comparable with that of mephenytoin ($ED_{50}$, 101 mg/kg) in the subcutaneous picrotoxin test.[16] No protection was afforded by **4j** in the γ-aminobutyric acid and strychnine screens. The ability of **4j** to displace radiolabeled flunitrazepam, γ-aminobutryic acid, and adenosine from receptors in mouse brain synaptic membranes and synaptosomes was evaluated. In the concentration range studied, no displacement of these bound ligands occurred. These in vivo and in vitro test results suggest that the mode of antiepileptic action of **4j** and related Mannich bases may be by reacting with chloride channels or by preventing seizures induced by naturally occurring convulsants on the chloride channels.

Correlations were sought between various physicochemical constants of the $R^1$ and $R^2$ groups obtained from the literature[23,24] and both anticonvulsant activity ($ED_{50}$) and neurotoxicity ($TD_{50}$) for those members of series 3 and 4 for which quantitative data are provided (Table I). The constants for the $R^1$ and $R^2$ groups in series 3 and 4 reflect the steric ($E_s$), electronic ($\sigma$ and/or $\sigma^*$), and hydrophobic ($f$) properties of these functions. The correlation coefficients for these 12 plots were calculated, and the data were evaluated with the test for zero correlation ($p < 0.1$).[25] The $\sigma$ and $\sigma^*$ values of the $R^1$ and $R^2$ substituents in series 4 were significantly correlated with the $ED_{50}$ values in the MES screen (i.e., potency increased as the magnitutude of the $\sigma$ and $\sigma^*$ values increased; $r = 0.748$). In addition, in series 4, an increase in the $TD_{50}$ values was directly related to increasing $E_s$ values ($r = 0.607$) and decreasing $f^{\Theta}$ constants ($r = 0.653$). Two additional molecular features associated with antiepileptic properties were noted. First, as shown in Table I, **3d** and **3e** were the most active compounds in series 3, and these derivatives have branching of the alkyl chain. Second, the five compounds with the lowest $ED_{50}$ values in series 4 contain *ortho* substituents, whereas the three compounds with the lowest activity either have atoms in the *para* position (**4a** and **4m**) or are unsubstituted (**3b**). The presence of *ortho* substituents causes loss of coplanarity of the aryl ring with the adjacent enone group.[26] These observations could serve as aids in the subsequent design of new anticonvulsants.

Four of the Mannich bases were examined for protection in the MES screen following oral administration to mice [up to 1000 mg/kg (**3d**, **3i**), up to 500 mg/kg (**3e**), and 750 mg/kg (**4e**)]. In the case of **3d** at the maximum dose of 1000 mg/kg, no activity was noted after 4 h. (At a dose of 2000 mg/kg, 1/8 animals was protected by **3d**, and 7/8 animals died before the test.) Compound **3e** had an $ED_{50}$ value of 461 mg/kg, whereas **3i** and **4e** gave protection at doses of 1000 and 750 mg/kg, respectively. Thus, the anticonvulsant properties of the bioactive Mannich bases in series 3–5 are probably retained when the bases are given orally, although potency is reduced compared with that following administration by the ip route. This conclusion is supported by the results of studies in which **3d**, **3e**, and **3i** were inactive in protecting against convulsions in rats in the MES screen following oral doses of 100 mg/kg, but were active following ip injection of the same dosage.

There are two possible reasons for the observed reduced anticonvulsant activity of these compounds after oral administration compared with that following ip injection. First, the $pK_a$ of 1-phenyl-5-diethylamino-4,4-dimethyl-1-penten-3-one hydrobromide, which is structurally related to many of the compounds in this study, is 7.19.[27] Because the pH of the microsurface of the intestine is 5.3,[28] the compounds in series 3–5 containing strongly basic groups, such as the dimethylamino and diethylamino functions, will be almost entirely in the ionized form, and hence, absorption is likely to be poor. In contrast, after ip injection, passage to the blood supply (pH 7.4) is likely to be more rapid and complete. Thus, future synthetic strategies should be devoted, at least in part, to preparing compounds in which the basic center has a low $pK_a$. Second, the time from absorption from the gut to arrival to the site of action is probably longer following oral administration than ip injection of the compounds. Mannich bases with a proton on the saturated carbon atom adjacent to the carbonyl

group can undergo deamination.[29] In addition, a *retro*-Mannich reaction may occur.[30] Hence, a second reason for reduced potency when the compounds are given orally may be that the compounds undergo substantial decomposition before reaching the central nervous system. Future synthetic chemical endeavors to overcome this problem should include the replacement of protons at the saturated carbon atom adjacent to the carbonyl group by other functional groups.

One of the reasons for screening the compounds in series 5 was to discern the effect of changing the basic center in the β-aminoketones. Compounds **5a–5c**, like **3a** in that they contain dimethylamino or the diethylamino groups, were inactive in the MES and scPTZ tests. However, incorporation of the morpholino function resulted in **5d**, which was active in the MES screen. Substitution on the olefinic group *alpha* to the carbonyl function produced **5e–5g**, which were active in either the MES or scPTZ screens. Replacement of a proton of the methylene group adjacent to the carbonyl function gave **5h**, which, in contrast to both **5d** and **3f**, was inactive. In general, therefore, the morpholino group is useful in conferring activity and may be preferable to the dimethylamino group as the basic function in subsequent anticonvulsant-drug design.

## Conclusions

The results of this study reveal, first, that the design of anticonvulsant compounds based on structure **2** is valid (i.e., the use of two-carbon spacer groups between both the aryl ring and carbonyl function and also between the nitrogen atom and the carbonyl group gives rise to compounds with anticonvulsant properties). Second, the Mannich bases **3–5** almost invariably have greater activity in the MES screen than in the scPTZ test. Third, following administration of the compounds by the ip route, maximum activity occurs rapidly and some of the derivatives have potencies comparable with those of established drugs. Fourth, because the slopes obtained for the 15 compounds in Table I were similar, the compounds may act by a similar biochemical mechanism that may be associated with chloride channels. Fifth, some molecular features are important in the synthesis of Mannich bases designed as candidate antiepileptics. For example, in series **4**, anticonvulsant activity is correlated with the magnititude of the electronic constants, and neurotoxicity decreases as the size of the aryl substituents increases and hydrophobicity falls. Other important features are (1) insertion of branched alkyl groups in the position *alpha* to the carbonyl function, (2) substitution in the *ortho* positions of the aryl ring, (3) use of morpholine as the basic center, and (4) molecular modification to improve bioavailability when the compounds are given by the oral route.

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## Acknowledgments


We thank the Antiepileptic Drug Development Screening Project, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, MD, for undertaking the bioevaluation of the compounds described in this report. In particular, the extraordinary helpfulness of Mr. J. P. Stables is gratefully acknowledged. The Aegen University, Turkey, allowed Dr. Erciyas to spend time in Canada to work on this and other projects.