# Triazolines XIII: $\Delta^2$-1,2,3-Triazolines, a New Class of Anticonvulsants

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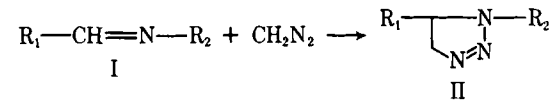
**Abstract** □ A series of 1,5-diaryl-$\Delta^2$-1,2,3-triazolines has been synthesized and evaluated for the first time as potential anticonvulsant agents using the standard subcutaneous pentylenetetrazol seizure threshold and maximal electroshock seizure tests. Out of the 31 triazolines that were screened, 11 exhibited moderate anticonvulsant activity; 9 of the compounds afforded protection against pentylenetetrazol-induced seizures, while two antagonized electrically induced convulsions.

**Keyphrases** □ 1,5-Diaryl-$\Delta^2$-1,2,3-triazolines—synthesis, anticonvulsant activity in mice □ Anticonvulsants—potential, 1,5-diaryl-$\Delta^2$-1,2,3-triazolines, synthesis, screening in mice

Although several five-membered heterocyclic ring systems containing up to four nitrogen atoms have been synthesized and screened for anticonvulsant activity (1, 2), no studies have appeared describing the $\Delta^2$-1,2,3-triazolines(4,5-dihydro-1*H*-1,2,3-triazoles; II). Since better anticonvulsants are needed in the treatment of epilepsy (2, 3) and since the triazolines are a new class of heterocyclic compounds (4), we decided to investigate these compounds as potential anticonvulsants.

Although triazolines are formed when Schiff bases (I) react with diazomethane (5, 6) (Scheme I), earlier synthetic procedures have either failed to give a triazoline adduct or have yielded insignificant amounts of the products (5).



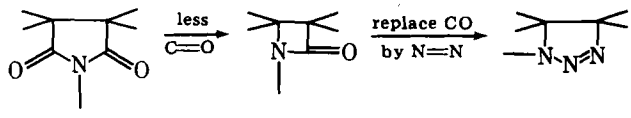
I II

Studies in our laboratories on the role of protic and dipolar aprotic solvents in 1,3-cycloaddition reactions (7–10) have led to a versatile method for the synthesis of the rarely encountered triazolines (11). By utilizing the accelerating effect of protic solvents, such as water, on the addition of diazomethane to Schiff bases, a variety of previously unknown triazolines bearing aryl (11) or heteroaryl (12) substituent groups has become readily available in sufficient quantities to permit, for the first time, a detailed screening of these compounds for biological activity. Two earlier papers reported the results of screening for herbicidal activity (13) and pesticidal properties (14). The present paper investigates the potential of the triazoline heterocycles as anticonvulsant compounds.

## RESULTS AND DISCUSSION

The triazoline ring system is different from those of the conventional anticonvulsant drugs, the majority of which have a dicarboximide (ureylene) —CO—NH—CO—, function as in barbiturates, hydantoins, succinimides, and oxazolidinediones or a closely related structure as in primidones. The absence of the dicarboximide function, which contributes to the inherent hypnotic and sedative activity of the barbiturates and related compounds, may be expected to reduce the toxic side effects in potential triazoline anticonvulsants.

The triazolines may be considered to be derived from the succinimides (III) by the loss of one C=O moiety (IV) and the replacement of the other by an N=N group (II). Several azetidinones have been reported to have varying degrees of anticonvulsant activity (15) as well as some 2-azetidinthiones (16).




III IV II

**Pharmacology**—The compounds were evaluated for anticonvulsant activity in two seizure models in the mouse, the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazol seizure threshold (scMet) test. These two methods of seizure provocation are known to reliably elicit well-characterized seizure phenomena (17) and are the standard screens of choice for identification of anticonvulsant activity in a compound (18). CNS toxicity is determined in the rotorod ataxia test (19). This test has a clear end-point, is quantifiable, and correlates well with the clinical assessment of minimal toxicity. Testing is done in the dose range of 30–600 mg/kg (with a few exceptions) at both 30-min and 4-h intervals. This provides a profile of the anticonvulsant activity, toxicity, potency, and pharmacokinetics of each compound and minimizes the likelihood of failing to identify slowly absorbed compounds or those with possible anticonvulsant activity in a metabolite.

**Structure–Activity Relationships**—The results of screening 31 1,5-diaryl-substituted $\Delta^2$-1,2,3-triazolines are reported in Table I. Eleven compounds exhibited moderate anticonvulsant activity; while nine of these afforded protection against scMet-induced seizures, only two (IX and XVI) were active in the MES test. The parent compound (V) is the most potent and is active at the 100-mg/kg dose level. Six other compounds (XVI, XX, XXI, XXIV, XXIX, and XXXIV) afforded protection in the scMet test at 300 mg/kg and three more (VI, VII, and XIX) at the 600-mg/kg dose level. Compounds IX and XXI show delayed activity after 4 h: IX in the MES test at 600 mg/kg and XXI in the scMet test at 300 mg/kg. Compound XVI, in addition to its activity in the scMet test, shows activity in the MES test at the 600-mg/kg level at both 0.5 and 4 h. With the exception of XVI and XXIV, the triazoline compounds are relatively nontoxic.

Certain structure–activity relationships have emerged from the varying substitution patterns on the phenyl rings of the parent compound. Introduction of a 2-chloro substituent on the 5-phenyl ring gives VI, which affords 75% protection at 0.5 h and 50% at 4 h with no symptoms of neurological deficit. When the chloro group is in the 4-position of either phenyl ring, activity disappears in the scMet test, although the 5-(4-chlorophenyl) compound, IX, evinces delayed activity in the MES test.

Compounds XV–XXIII illustrate the effect of different substituents on the 1-phenyl of VI. A 3-$CF_3$ group increases activity as well as toxicity, while a 4-$CF_3$ or 4-$C_2H_5$ affords protection at the same dose level without signs of neurotoxicity. The almost parallel activities of VI and XIX are interesting, since the 4-F analogue XIX provides minimal change in $\pi$ and $\sigma$ effects (20) compared with the unsubstituted VI. The presence of 4-Cl, 4-Br, 4-$OCH_3$, or 3,4-$Cl_2$ yields inactive compounds XVIII, XVII, XXII, and XXIII, respectively. However, with the introduction of a second chloro group in the 6-position of the 5-phenyl ring of XVII, activity reappears, as in XXXIV; similar substitution in XIX leads to a loss of activity in XXXV. A more meaningful analysis of the structure–activity pattern to obtain information on parameter dependency using the Topliss manual approach (20) to Hansch analysis in this compound group, XV–XXIII, has not been possible, since the activity spread between the members is not large enough (20). However, the structure–activity relationships do indicate the anticonvulsant potential of appropriately substituted 1,2,3-triazolines.

Finally, the effect of a nitro substituent is noteworthy. While a 4-$NO_2$ on either phenyl ring does not contribute to activity, a 3-$NO_2$ by itself, as in VII, or in combination with 2,4-$Cl_2$, as in XXIX, yields an active compound.

## EXPERIMENTAL

**Chemistry**—The 1,5-diaryl-$\Delta^2$-1,2,3-triazolines were prepared as described previously (7–12). All compounds except XIII–XVI, XVIII–XXII, XXIV, XXVIII, XXX, and XXXII–XXXV have been reported previously (11). Data on the newly synthesized compounds are presented in Table II.



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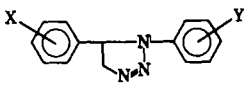
**Table I—Results of Screening 1,5-Diaryl-$\Delta^2$-1,2,3-triazolines for Anticonvulsant Activity in the Mouse after Intraperitoneal Administration**



| Compound | X | Y | Anticonvulsant Activity (scMet) Effective Dose, mg/kg | Animals Protected, % 0.5 h | 4 h | Neurotoxicity Animals Toxic at 0.5 h, % |
|---|---|---|---|---|---|---|
| V | H | H | 100 | 25 | 0 | 0 |
| VI | 2-Cl | H | 600 | 75 | 50 | 0 |
| VII | 3-$NO_2$ | H | 600 | 75 | 0 | 0 |
| VIII | 4-$NO_2$ | H | 600 | 0 | 0 | 0 |
| IX | 4-Cl | H | 600[a,b,c] | 0 | 0 | 0 |
| X | H | 4-$NO_2$ | 600 | 0 | 0 | 0 |
| XI | H | 4-Cl | 600 | 0 | 0 | 0 |
| XII | H | 4-$CH_3$ | 600 | 0 | 0 | 0 |
| XIII | 4-Cl | 4-Br | 600 | 0 | 0 | 0 |
| XIV | 3-Cl | 4-Br | 600 | 0 | 0 | 0 |
| XV | 2-Cl | 3-Cl | 600 | 0 | 0 | 0 |
| XVI | 2-Cl | 3-$CF_3$ | 300[c,d] | 100[c] | 0 | 100 |
| XVII | 2-Cl | 4-Br | 600 | 0 | 0 | 0 |
| XVIII | 2-Cl | 4-Cl | 600 | 0 | 0 | 0 |
| XIX | 2-Cl | 4-F | 600 | 100 | 0 | 25 |
| XX | 2-Cl | 4-$CF_3$ | 300 | 25 | 0 | 0 |
| XXI | 2-Cl | 4-$C_2H_5$ | 300 | 0 | 100[b,c] | 0 |
| XXII | 2-Cl | 4-$OCH_3$ | 600 | 0 | 0 | 0 |
| XXIII | 2-Cl | 3,4-$Cl_2$ | 600 | 0 | 0 | 0 |
| XXIV | 2-$NO_2$ | 3-Cl | 300 | 25 | 0 | 25 |
| XXV | 2-$NO_2$ | 3-$NO_2$ | 300 | 0 | 0 | 0 |
| XXVI | 2,4-$Cl_2$ | H | 300 | 0 | 0 | 0 |
| XXVII | 2,4-$Cl_2$ | 3-Cl | 600 | 0 | 0 | 0 |
| XXVIII | 2,4-$Cl_2$ | 3-$CF_3$ | 600 | 0 | 0 | 0 |
| XXIX | 2,4-$Cl_2$ | 3-$NO_2$ | 300 | 100[c] | 0 | 0 |
| XXX | 2,4-$Cl_2$ | 4-Cl | 600 | 0 | 0 | 0 |
| XXXI | 2,4-$Cl_2$ | 4-COOEt | 600 | 0 | 0 | 0 |
| XXXII | 2,6-$Cl_2$ | H | 300 | 0 | 0 | 0 |
| XXXIII | 2,6-$Cl_2$ | 3-Cl | 600 | 0 | 0 | 0 |
| XXXIV | 2,6-$Cl_2$ | 4-Br | 300 | 25 | 0 | 0 |
| XXXV | 2,6-$Cl_2$ | 4-F | 600 | 0 | 0 | 0 |

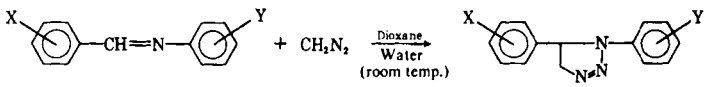
[a] At the same dose level, the compound afforded 100% protection in the MES test after 4 h. [b] The delayed effect could be because it is slowly absorbed or it has anticonvulsant activity in a metabolite. [c] Only one animal was tested. [d] At 600 mg/kg, this compound protected 100% animals in the MES test at 0.5 and 4 h, but it also showed 100% toxicity at both time periods.

**Pharmacology**—The 31 triazolines were screened by the Anticonvulsant Screening Project (ASP) under the Antiepileptic Drug Development (ADD) program of the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The compounds were solubilized in 30% polyethylene glycol 400. The solvent was tested for anticonvulsant and toxic effects and was found to introduce no significant bias into the testing of anticonvulsant activity. The compounds were administered intraperitoneally in a volume of 0.01 mL/g to male Carworth Farms #1 mice weighing ~20 g (21). Testing was done at dose levels of 30, 100, 300, and 600 mg/kg, and a total of 16 animals were used, four for each dose. After 30 min, each animal was examined for toxicity in the rotorod test (19). Immediately thereafter, anticonvulsant activity was evaluated by subjecting one mouse to the MES test and another to the scMet test. The same tests were repeated 4 h later on the two remaining mice at each dose level. When compounds were found to afford protection, the test was repeated at that dose level and time using four animals, and the results were expressed as number of animals protected/number of animals tested or as percent of animals protected (Table I).

The maximal electroshock seizure test (MES) was performed according to the method of Swinyard *et al.* (22), and abolition of the hind limb tonic extension component of the seizure was defined as protection. In the subcutaneous pentylenetetrazol seizure threshold test (scMet), 85 mg/kg of pen-

**Table II—Newly Synthesized 1,5-Diaryl-$\Delta^2$-1,2,3-triazolines**




| Compound | Substituent X | Substituent Y | Schiff base mp, °C[a] | Schiff base Yield, % | Schiff base Formula[b] | Triazoline Reaction time, h | Triazoline mp, °C[a] | Triazoline Yield, % | Triazoline Formula[b] |
|---|---|---|---|---|---|---|---|---|---|
| XIII | 4-Cl | 4-Br | 118-121 | 72 | $C_{13}H_9BrClN$ | 240 | 147-149 | 88 | $C_{14}H_{11}BrClN_3$ |
| XIV | 3-Cl | 4-Br | 60-61 | 77 | $C_{13}H_9BrClN$ | 120 | 134-135 | 90 | $C_{14}H_{11}BrClN_3$ |
| XV | 2-Cl | 3-Cl | 41-43 | 81 | $C_{13}H_9Cl_2N$ | 96 | 72-74 | 69 | $C_{14}H_{11}Cl_2N_3$ |
| XVI | 2-Cl | 3-$CF_3$ | Oil | Q[c] | $C_{14}H_9ClF_3N$ | 144 | 49-51 | 77 | $C_{15}H_{11}ClF_3N_3$ |
| XVIII | 2-Cl | 4-Cl | 68-70 | 75 | $C_{13}H_9Cl_2N$ | 88 | 126-127 | 92 | $C_{14}H_{11}Cl_2N_3$ |
| XIX | 2-Cl | 4-F | 56-58 | 74 | $C_{13}H_9ClFN$ | 113 | 71-72 | 78 | $C_{14}H_{11}ClFN_3$ |
| XX | 2-Cl | 4-$CF_3$ | 48-50 | 40 | $C_{14}H_9ClF_3N$ | 96 | 83-86 | 80 | $C_{15}H_{11}ClF_3N_3$ |
| XXI | 2-Cl | 4-$C_2H_5$ | 33-34 | 93 | $C_{15}H_{14}ClN$ | 336 | 44-46 | 48 | $C_{16}H_{16}ClN_3$ |
| XXII | 2-Cl | 4-$OCH_3$ | 63 | Q[c] | $C_{14}H_{12}ClNO$ | 144 | 95-97 | 61 | $C_{15}H_{14}ClN_3O$ |
| XXIV | 2-$NO_2$ | 3-Cl | 76-78 | 89 | $C_{13}H_9ClN_2O_2$ | 120 | 90-92 | 60 | $C_{14}H_{11}ClN_4O_2$ |
| XXVIII | 2,4-$Cl_2$ | 3-$CF_3$ | 78-80 | 85 | $C_{14}H_8Cl_2F_3N$ | 96 | 68-69 | 82 | $C_{15}H_{10}Cl_2F_3N_3$ |
| XXX | 2,4-$Cl_2$ | 4-Cl | 129-130 | 96 | $C_{13}H_8Cl_3N$ | 192 | 106-108 | 90 | $C_{14}H_{10}Cl_3N_3$ |
| XXXII | 2,6-$Cl_2$ | H | 62-63 | 82 | $C_{13}H_9Cl_2N$ | 116 | 182-184 | 70 | $C_{14}H_{11}Cl_2N_3$ |
| XXXIII | 2,6-$Cl_2$ | 3-Cl | 114-115 | 90 | $C_{13}H_8Cl_3N$ | 48 | 148-148.5 | 88 | $C_{14}H_{10}Cl_3N_3$ |
| XXXIV | 2,6-$Cl_2$ | 4-Br | 80-81 | 81 | $C_{13}H_8BrCl_2N$ | 51 | 156-157 | 75 | $C_{14}H_{10}BrCl_2N_3$ |
| XXXV | 2,6-$Cl_2$ | 4-F | 128-130 | 93 | $C_{13}H_8Cl_2FN$ | 70 | 132-133 | 70 | $C_{14}H_{10}Cl_2FN_3$ |

[a] Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. [b] The elemental analyses (C, H, and N) for all new compounds were within ±0.4% of the theoretical values. [c] Quantitative.

tylenetetrazol was administered as a 0.5% solution subcutaneously in the posterior midline, and failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5-s duration) was defined as protection (22).

Neurotoxicity was evaluated by the rotorod ataxia test (19). The animal was placed on a wooden rod of 2.8-cm diameter rotating at 6 rpm. Normal mice can remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min and was expressed as number of animals exhibiting toxicity/number of animals tested or as percent of animals showing toxicity.

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