was obtained with Raney nickel catalyst.

Reduction of Vb to IVb.—A solution of 6 g. (0.02 mole) of Vb in 200 ml. of ethanol was reduced in the Parr hydrogenerator in the presence of 5 g. of 5% palladium-on-carbon at room temperature and an initial hydrogen pressure of 4.22 kg./cm.^{2} for 18 hr. The catalyst was removed and the filtrate was concentrated to a residue, which was dissolved in 400 ml. of absolute ether and acidified with an alcoholic solution of hydrogen chloride. The white crystalline product was filtered and recrystallized from a mixture of absolute ethanol and absolute ether; m.p. 183–185°.

Anal. Calcd. for $C_{20}H_{26}ClN$: C, 76.04; H, 8.30. Found: C, 76.47; H, 8.37.

The Anticonvulsant Activity of 1,2,4-Triazoles

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A series of 1- and 4-substituted 1,2,4-triazoles has been studied for convulsant and anticonvulsant activity by both the maximal electroshock seizure and subcutaneous pentylenetetrazole seizure tests in rats. 1,2,4-Triazole and 1- and 4-lower alkyl-1,2,4-triazoles are inactive at 200 mg./kg. 1-Aryl, 4-*m*- and *p*-substituted phenyl-1,2,4-triazoles are anticonvulsants. 4-*o*-Chlorophenyl-1,2,4-triazole and 4-*o*-tolyl-1,2,4-triazole are convulsants, whereas 4-*o*-methoxyphenyl-1,2,4-triazole is an anticonvulsant orally but a convulsant when administered by I.P. injection. Qualitatively opposite effects were noted for several isomeric compounds. 1-(1,2,4-Triazolyl-1)-4-(4,1,4-triazolyl-4)benzene (Compound A) showed weak anti-electroshock activity.

Recently, Gibson, Swanson, and Meyers[1] reported the pharmacology of the structurally isomeric compounds 1-phenyl-1,2,4-triazole and 4-phenyl-1,2,4-triazole. They substantiated the earlier report of Pellizzari[2] which stated that 4-phenyl-1,2,4-triazole was a

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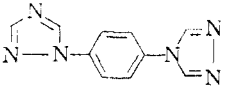
(1) W. R. Gibson, E. E. Swanson, and D. B. Myers, *J. Am. Pharm. Assoc.*, **47**, 778 (1958).

(2) G. Pellizzari and C. Massa, *Atti Real. Acad. Lincei*, **10**, 363 (1901); *J. Chem. Soc.*, **80**, I, 488 (1901).

convulsant. In contrast, they found 1-phenyl-1,2,4-triazole to be an anticonvulsant.

This paper reports the preparation and pharmacological evaluation of a series of 1 and 4-substituted 1,2,4-triazoles. In addition, Compound A was prepared. This molecule encompasses structural features of both 1 and 4-phenyl-1,2,4-triazoles.



A

Experimental

Preparation of 1-Substituted-1,2,4-triazoles. (a) **1-Alkyl and Aralkyl-1,2,4-triazoles.**—

General Procedure.—A mixture of 0.1 mole of 1,2,4-triazole,[3] 0.1 mole of sodium methoxide, 0.1 mole of alkyl bromide, and 50 ml. of ethanol was heated overnight under reflux. About 100 ml. of ether was added and the sodium chloride was removed by filtration. The filtrate was concentrated and the residue was distilled under reduced pressure. In this way 1-alkyl and 1-aralkyl-1,2,4-triazoles shown in Table I were prepared in about 50% yield.

(b) **1-Aryl-1,2,4-triazoles.**—Data given in Table I.

1-*p*-Nitrophenyl-1,2,4-triazole.—A mixture of 60 g. (0.33 mole) of 1-formyl-2-*p*-nitrophenylhydrazine[4] and 45 g. (1.0 mole) of formamide was heated under reflux for 4 hr. The solid that formed on cooling was recrystallized from ethanol and gave 21 g. (37%) of product.

1-*p*-Aminophenyl-1,2,4-triazole.—A mixture of 19 g. (0.1 mole) of 1-*p*-nitrophenyl-1,2,4-triazole, 500 ml. of 95% ethanol, 20 ml. of 85% hydrazine hydrate, and 0.5 g. of Raney nickel was heated on a steam bath under mild reflux for 1 hr.[5] About 2 g. of Raney nickel was added and the mixture was heated for an additional 0.5 hr. The nickel was removed by filtration and the filtrate was concentrated to approximately 100 ml. About 500 ml. of ice water was added and the solid that separated was recrystallized from water. (Some high melting material did not dissolve in the water.) The yield was 8 g. (50%).

1-*p*-Acetamidophenyl-1,2,4-triazole.—A solution of 3.2 g. (0.02 mole) of 1-*p*-aminophenyl-1,2,4-triazole and 10 ml. of acetic anhydride was heated on a steam-bath for 0.5 hr. About 100 ml. of 1 *N* sodium hydroxide was added, and the mix-

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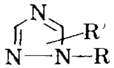
(3) C. Ainsworth, *Organic Syntheses*, **40**, 99 (1960).

(4) E. Hyde, *Ber.*, **32**, 1810 (1899).

(5) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

TABLE I

1-SUBSTITUTED-1,2,4-TRIAZOLES,



No.	R	R'	M.p. or B.p.		Nitrogen, %		ED$_{50}$ + S.E. (mg./kg.)		Duration of action M.E.S. (hours)
			°C.	Mm.	Calcd.	Found	Maximal electroshock seizure	Pentylene-tetrazole seizure	
1	n-C_3H_7	H	85	10[a]	37.80	37.87	>200	>200	
2	iso-C_3H_7	H	81	10[b]	37.80	37.64	>200	>200	
3	n-C_4H_9	H	88	10[c]	33.57	33.60	>200	>200	
4	$CH(CH_3)C_2H_5$	H	84	10[d]	33.57	33.21	200	>200	
5	iso-C_4H_9	H	81	10[e]	33.57	33.81	[f]		
6[g]	C_6H_5	H					24 ± 2	52 ± 8	2–6
7	p-$NO_2C_6H_4$	H	190		29.47	29.41	50 ± 2	>100	6
8	p-$NH_2C_6H_4$	H	140		34.98	35.23	34 ± 6	>100	6
9	p-$CH_3CONHC_6H_4$	H	198–200		[h]		>100	>100	
10	p-ClC_6H_4	H	138–139		23.40	23.17	16 ± 2	>100	4–6
11[i]	C_6H_5	3-CH_3					34 ± 2	54 ± 8	2–6
12[i]	C_6H_5	5-CH_3					70 ± 7	132 ± 12	2–6
13[j]	$C_6H_5CH_2$	H					21 ± 5	41 ± 8	1–7
14	p-$ClC_6H_4CH_2$	H	63–65		21.70	21.63	22 ± 1	44 ± 8	2–7
15	$C_{11}H_9$[k]	H	65		20.08	19.79	16 ± 2	85 ± 18	1–5
16	$C_6H_5CH_2CH_2$	H	[l]				53 ± 4	80 ± 14	2–5

[a] n_D^{25} 1.4600; [b] n_D^{25} 1.4570; [c] n_D^{25} 1.4580; [d] n_D^{25} 1.4560; [e] n_D^{25} 1.4570. [f] Convulsant at 50 mg./kg. [g] Reported ref. 2. [h] *Anal.* Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98. Found: C, 59.95; H, 5.11. [i] Reported by G. Pellizzari, *Gazz. Chim. Ital.*, **41,** II, 20 (1911). [j] R. G. Jones and C. Ainsworth, *J. Am. Chem. Soc.*, **77,** 1538 (1955). [k] $C_{11}H_9$ is α-naphthylmethyl. [l] Obtained as the hydrochloride, m.p. 163–166°; *Anal.* Calcd. for $C_{10}H_{11}N_3{\cdot}HCl$: C, 57.28; H, 5.77; N, 20.04. Found: C, 57.44; H, 5.76; N, 19.81.

ture was concentrated to near dryness by heating under reduced pressure. The insoluble product that separated was recrystallized from water. The yield was almost quantitative.

1-*p*-Chlorophenyl-1,2,4-triazole.—A mixture of 5.7 g. (0.033 mole) of 2-*p*-chlorophenyl-1-formylhydrazine (m.p. 190°) and 50 ml. of formamide was heated under reflux for 3 hr. The solid that formed on cooling was recrystallized from water and gave 3 g. (50%) of product.

Preparation of 4-Substituted 1,2,4-Triazoles. General Procedure.[6]—A mixture of 0.1 mole of N,N'-diformylhydrazine[7] and 0.1 mole of the substituted aniline was heated at 180–200° (depending on the temperature at which water was evolved) for 1 hr. The material was distilled under reduced pressure, and the product was either recrystallized from ethanol–water mixture or was converted to the hydrochloride salt by treating an ethanol solution with ethereal hydrogen chloride. In this way the 4-substituted 1,2,4-triazoles shown in Table II were prepared in about 20–50% yield. The formyl derivative of the starting amine was also usually formed.

4-Benzyl-1,2,4-triazole Hydrochloride.—Benzylamine and diformylhydrazine treated according to the general procedure above failed to form 4-benzyl-1,2,4-triazole but gave *N*-benzylformamide. The 4-benzyl-1,2,4-triazole was prepared in a manner analogous to that reported by Freund[8] for the preparation of 4-ethyl-1,2,4-triazole. It was converted to the hydrochloride salt, m.p. 201–202° dec. (capillary).

Anal. Calcd. for $C_9H_9N_3 \cdot HCl$: C, 55.24; H, 5.15; N, 21.47. Found: C, 55.02; H, 5.16; N, 21.21.

1-(1,2,4-Triazolyl-1)-4-(4,1,2-triazolyl-4)-benzene (Compound A).—A mixture of 6.4 g. (0.04 mole) of 1-*p*-aminophenyl-1,2,4-triazole and 3.5 g. (0.04 mole) of N,N'-diformylhydrazine[7] was heated at 190° for 2 hr. The residue was extracted with 100 ml. of boiling ethanol. The insoluble fraction was recrystallized from water and gave 2 g. (23% yield) of Compound A, m.p. 300°.

Anal. Calcd. for $C_{10}H_8N_6$: C, 56.59; H, 3.80; N, 39.61. Found: C, 56.83; H, 3.43; N, 39.76.

Pharmacological Testing Methods

The compounds were given orally as 5% gum acacia suspensions to Wistar–Strain rats of both sexes weighing 160 to 220 g. The anticonvulsant activity was evaluated at a predetermined time of peak activity by the maximal electroshock seizure test (M.E.S.) of Toman, *et al.*,[9] and by the subcutaneous pentylenetetrazole seizure test described by Goodman, *et al.*[10] At least three dosage groups of

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(6) Based on the method of Pellizzari, ref. 2.

(7) C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.*, **77**, 621 (1955).

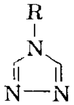
(8) M. Freund and H. P. Schwarz, *Ber.*, **29**, 2483 (1896).

(9) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

(10) L. S. Goodman, J. E. P. Toman, and E. A. Swinyard, *Am. J. Med.*, **1**, 213 (1946).

TABLE II

4-SUBSTITUTED-1,2,4-TRIAZOLES,



No.	R	M.p., °C.	Nitrogen, %		ED$_{50}$ ± S.E. (mg./kg.)		Duration of action M.E.S. (hours)
			Calcd.	Found	Maximal electroshock seizure	Pentylene-tetrazole seizure	
17	o-$CH_3C_6H_4$	[a]			[b]		
18	m-$CH_3C_6H_4$	104–106	26.39	26.64	62 ± 5	>100	1–5
19[a]	p-$CH_3C_6H_4$				>100	>100	
20	o-$CH_3OC_6H_4$	87–89	23.98	23.73	>100	>100	
21	m-$CH_3OC_6H_4$	97–98	23.98	24.14	80 ± 7	>100	1–4
22	p-$CH_3OC_6H_4$	100–102	23.98	24.08	>100	>100	
23	o-ClC_6H_4	77–79	23.40	23.69	[b]		
24	m-ClC_6H_4	[c]			72 ± 9	>100	1–6
25	p-ClC_6H_4	176–178	23.40	23.32	42 ± 4	>100	2–6
26	p-BrC_6H_4	177–179	18.76	19.13	36 ± 2	>100	2–6
27	p-$NO_2C_6H_4$	290	29.47	29.00	>100	>100	
28	2,4-$Cl_2C_6H_3$	199–201	19.63	19.88	37 ± 4	>100	2–6
29	$C_6H_5CH_2$	[d]			>100	>100	

[a] G. Pellizzari and M. Bruzzo, *Atti Real. Acad. Lincei*, **10**, 414 (1901); *J. Chem. Soc.*, **80**, I, 570 (1901). Compound 17 was isolated as the hydrochloride salt, m.p. 75° (resolidified and remelted at 140°); *Anal.* Calcd. for $C_9H_9N_3 \cdot HCl$: N, 21.47. Found: N, 21.46. [b] Convulsant at 400 mg./kg. [c] Obtained as the hydrochloride salt, m.p. 203–204°; *Anal.* Calcd. for $C_8H_6ClN_3 \cdot HCl$: N, 19.45. Found: N, 19.33. [d] See Experimental section.

8 animals each were used to compute the median effective doses (ED_{50}) with standard errors by the method of Bliss.[11]

Results.—The compounds noted were devoid of activity, either convulsant or anticonvulsant at 200 mg./kg.: 1,2,4-triazole, 1-methyl-1,2,4-triazole,[12] 1-ethyl-1,2,4-triazole,[13] compounds 1-3 of Table I, 1-acetyl-1,2,4-triazole,[12] 1,2,4-triazole-1-acetamide,[7] and 1-β-aminoethyl-1,2,4-triazole.[7] Only two of the 1-alkyl-1,2,4-trizoles were active and these were the butyl isomers 4 and 5 (Table I).

Table I shows the anticonvulsant activity of 1-phenyl-1,2,4-triazole (Compound 6) and related compounds. Of the *p*-substituted phenyl compounds (7–10), 1-*p*-chlorophenyl-1,2,4-triazole is the most active compound against electroshock seizure but has weak activity against pentylenetetrazole.

Addition of a methyl group to either carbon atom of the nucleus (Compounds 11 and 12) decreased anticonvulsant action compared with Compound 6. The 1-aralkyl-1,2,4-triazoles in which one methylene group separates the aryl group from the triazole nucleus (Compounds 13–15) are similar or slightly improved in antielectroshock activity compared with the reference compound. However, the activity is decreased when the aryl ring is two carbon atoms removed (Compound 16).

Table II shows the effect of substitution at the 4-position of the 1,2,4-triazole ring.[14] It is recalled from the work of Gibson[1] that 4-phenyl-1,2,4-triazole is a convulsant. Substitution on the phenyl ring in the *meta* or *para* position reversed the activity (Compounds 18, 19, 21, 22, 24–28). The *ortho*-substituted phenyl compounds had particularly interesting activity. *o*-Tolyl (Compound 17) and *o*-chlorophenyl (Compound 23) were convulsants and *o*-methoxyphenyl (Compound 20) was an anticonvulsant even at high dose levels (900 mg./kg.). Compound 20 was a convulsant, however, when administered by intraperitoneal injection at 800 mg./kg. 4-Benzyl-1,2,4-triazole (Compound 29) showed weak antielectroshock activity orally and also was a convulsant when given by intraperitoneal injection. Compounds 21 and 22 did not reverse activity when

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(11) C. I. Bliss, *Quart. J. Pharm. and Pharmacol.*, **11**, 192 (1938).

(12) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954).

(13) G. Pellizzari and A. Soldi, *Gazz. Chim. Ital.*, **35**, 373 (1905).

(14) A short note by G. R. Breese, J. W. Martin, and D. B. Meyers concerning 4-halophenyl-1,2,4-triazoles appeared in Abstracts, Scientific Section, American Pharmaceutical Association, Chicago Meeting, April 23–28, 1961.

given by injection. 4-Ethyl-1,2,4-triazole, as a representative of the 4-alkyl-1,2,4-triazole series, was inactive.

1-(1,2,4-Triazolyl-1)-4-(4,1,2-triazolyl-4)-benzene (Compound A) showed weak anti-electroshock activity at 100 mg./kg.

Acknowledgment.—The authors wish to thank J. K. Henderson and W. C. Wood for technical assistance.

Derivatives of 8-Hydroxy-2-quinolineacrylic Acid. II[1,2]

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A series of halogenated derivatives of 8-hydroxy-2-quinolineacrylic acid and related compounds has been prepared as a part of a study of the structure-activity relationship of quinoline compounds having potential anti-infective properties.

As a part of a study of the structure activity relationships of anti-infective agents containing a quinoline nucleus a series of 2-quinolineacrylic acids with a hydroxyl or an alkoxyl group in the 8-position has been described.[2] This paper will report a series of halogenated derivatives of these compounds.

It was demonstrated by earlier workers that substitution of halogen atoms at the 5- and 7-positions of 8-quinolinol[5,6] and of 2-methyl-8-

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[1] Presented before the Medical Chemistry Division of the American Chemical Society at the 140th Meeting at Chicago, Illinois, September 3–8, 1961.

[2] M. G. Vaidya and J. G. Cannon, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 10 (1959), should be considered as paper I of the series.

[3] Wisconsin Alumni Research Foundation Fellow 1957–1961. Abstracted from a thesis submitted by M. G. Vaidya in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Wisconsin, 1961.

[4] To whom all correspondence should be addressed.

[5] K. A. Oster and M. J. Golden, *J. Am. Pharm. Assoc.*, **37**, 429 (1948).

[6] E. Schraufstätter, *Z. Naturforsch.*, **5b**, 190 (1950).