shaken under nitrogen for 1.5 hr. After removing the solvent and heating under nitrogen on a steam bath for 1 hr, the very dark residue was sublimed up to 188° (0.01 mm) giving about 5 g of crude solid. The sublimate was recrystallized from ethanol with the aid of Darco G-60, yielding 3.75 g of golden brown, silky needles mp 130–131.5°.

Ammonium Salt of 2-Oxo-3-phenyl-2H-1,4-benzoxazine-6-sulfonic Acid (22).—A solution of 14 g (0.05 mole) of technical (67.5%) *o*-aminophenol-*p*-sulfonic acid, 17.8 g (0.1 mole) of ethyl phenylglyoxylate, and 4 ml (0.06 mole) of aqueous NH_4OH in 25 ml of ethanol and 10 ml of water was boiled to dryness in an oil bath at 150° during 2 hr. The residue was boiled with 500 ml of ethanol, cooled, and filtered. The solid (7.3 g), mp 277–303°, appeared to be a mixture. The filtrate was concentrated and cooled giving 9 g (56%) of tan crystals, mp 292.5–294.5° dec. A sample recrystallized from ethanol with Darco G-60 treatment had the same melting point.

Methyl (4-Pyridyl)glyoxylate and Hydrate.—A mixture of 10.15 g (0.067 mole) of methyl 4-pyridylacetate, 10 ml of AcOH, 30 ml of benzene, and 7.44 (0.067 mole) of SeO_2 was stirred under reflux using a Dean–Stark trap. Approximately the theoretical amount of water was condensed in about 0.5 hr. The solvent was then removed *in vacuo* below 50° and the residue was distilled in a short-path apparatus. The product distilled below 150° (3 mm) giving 5.1 g of methyl 4-pyridylglyoxylate as a light yellow solid mixed with a little acetic acid. This was recrystallized from water from which the hydrate [methyl α,α-dihydroxy-α-(4-pyridyl)acetate] crystallized as light pink crystals, mp 114–118°, yield 2.33 g (19.0%). The structure of the hydrate was confirmed by infrared, ultraviolet, and nmr spectra and analysis.

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65; O, 34.94; H_2O, 9.84. Found: C, 52.50; H, 4.79; N, 7.92; O, 34.70; H_2O, 9.86 (Karl Fischer).

3-(4-Pyridyl)-2H-1,4-benzoxazin-2-one (29).—A solution of 4.66 g (0.0254 mole) of methyl 4-pyridylglyoxylate hydrate and 2.79 g (0.0254 mole) of *o*-aminophenol in 50 ml of methanol was heated at 40° for 5 hr and evaporated to dryness *in vacuo* below 50°, and the residual oil was heated on a steam bath for 20 min. The resulting solid was shaken with 2% aqueous NaOH to dissolve phenolic material (see below). The product was collected, washed with water, dried, and sublimed up to 162° (0.001 mm) giving 2.6 g of solid. This was recrystallized from ethanol with the aid of Darco G-60 yielding 2.13 g of silky needles, mp 168–169°.

2′-Hydroxy-4-pyridineglyoxylanilide.—The above aqueous solution was acidified with acetic acid (pH 6) giving a solid which was collected, washed with water, and dried; 1.2 g, mp 212–213° dec. This was recrystallized from ethanol with Darco G-60 treatment yielding 0.7 g (11.4%) of the phenolic amide, mp 221.5–222.5° dec. The structure was confirmed by infrared, ultraviolet, and nmr spectra.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 64.46; H, 4.16; N, 11.57; O, 19.82. Found: C, 64.62; H, 4.08; N, 11.61; O, 20.39.

2-Carbethoxy-2-phenylbenzothiazoline.—A mixture of 35.7 g (0.2 mole) of ethyl phenylglyoxylate and 25.1 g (0.2 mole) of *o*-aminobenzenethiol was heated under nitrogen in an oil bath at 135–150° for 1 hr. After cooling the orange-yellow liquid crystallized. This was well mixed with pentane and dilute HCl and filtered. The solid was washed with water and dried giving 30.8 g (54%) of waxy crystals, mp 77–97°. This was recrystallized from 150 ml of 95% ethanol yielding 20.1 g of light yellow crystals, mp 97.5–99.5°. Infrared and ultraviolet spectra and analysis are in agreement with the benzothiazoline structure.

Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.37; H, 5.37; N, 4.79; S, 11.67.

Acknowledgments.—The author wishes to thank the following people who contributed to this work: our Department of Physical and Analytical Chemistry for analytical and spectral data; Dr. Hugh H. Keasling, Dr. P. H. Seay, Dr. Margaret E. Greig, Dr. Gerald W. Caniener, and Dr. William L. Miller for the pharmacological data; and Dr. R. V. Heinzelman for guidance.

2-Amino-5-Substituted 1,3,4-Oxadiazoles and 5-Imino-2-Substituted Δ^2-1,3,4-Oxadiazolines. A Group of Novel Muscle Relaxants

HARRY L. YALE AND KATHRYN LOSEE

The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903

Received December 23, 1965

The synthesis of 2-amino-5-substituted 1,3,4-oxadiazoles by the reaction of a 1-acyl-3-thiosemicarbazide with Pb_3O_4 is described. One of the procedures, namely the use of Pb_3O_4 in N,N-dimethylformamide, has some advantages over the earlier literature methods. Several of the oxadiazoles are highly potent in producing a profound flaccid paralysis in laboratory animals. Structure–activity relationships in this series of compounds are discussed. Protonation of these 2-amino-1,3,4-oxadiazoles produces large hypsochromic shifts of the endocyclic >C=N- band seen in the infrared spectra of the bases, thus indicating preferential formation of an endocyclic cation. This phenomenon is not observed with the 2-amino-1,3,4-thiadiazoles, 2-aminooxazoles, 2-aminooxazolines, and 2-aminothiazoles; in these systems, protonation occurs at the exocyclic NH_2.

During the pharmacological evaluation of a number of heterocycles, the observation was made that 2-acetamido-5-phenyl-1,3,4-oxadiazole (**28**) produced a profound flaccid paralysis in rats.[1] Subsequent investigation showed that this activity was shared by the parent base, 2-amino-5-phenyl-1,3,4-oxadiazole (**20**), and its hydrochloride (**22**)[2] and a number of other 2-amino-5-aryl-1,3,4-oxadiazoles. These compounds, their physical properties, and analytical data are shown in Table II. This paper will discuss their structure and synthesis and will present a structure–activity relationship in this and related heterocyclic systems.

Structure.—The 2-amino-1,3,4-oxadiazoles, when visualized as cyclic amidines, would be expected to show spectrophotometric differences upon protonation.[3] The infrared spectral data[4] now being reported show that protonation invariably produced a large hypsochromic

(1) This observation was first made by Dr. J. J. Piala of these laboratories.

(2) The detailed pharmacologic and toxicologic studies made with this compound were reported by G. L. Hassert, Jr., J. W. Poutsiaka, D. Papandrianos, J. C. Burke, and B. N. Craver, *Toxicol. Appl. Pharmacol.*, **3**, 726 (1961).

(3) This phenomenon has been discussed by B. Witkop, *Experientia*, **10**, 420 (1954), insofar as it is concerned with the aminopyridines, α-aminoindolenine, and a number of alkaloids.

(4) The insolubility of these compounds has necessitated determining the infrared spectra on mineral oil mulls. This lack of solubility has also led to inconclusive deuterium exchange studies and has made impossible nmr spectral studies except with a few of the compounds prepared.

TABLE I

1-ACYL-3-THIOSEMICARBAZIDES

RCONHNHCSNH$_2$

R	Method[a]	Formula	Mp, °C	Yield, %	Recrystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
o-ClC$_6$H$_4$	B (a)	C$_8$H$_8$ClN$_3$OS	160–161	57	*b*	...	...	...[c]	...	...	...
m-ClC$_6$H$_4$	A (b)	C$_8$H$_8$ClN$_3$OS	196–197	40	*d*	41.83	3.51	...	41.92	3.29	...
(C$_6$H$_5$)$_2$CH	B (a)	C$_{15}$H$_{15}$N$_3$OS	196–198 dec	44	*b*	...	...	14.73	...	...	14.07
C$_6$H$_5$CH(C$_2$H$_5$)	B (a)	C$_{11}$H$_{15}$N$_3$OS	166–168	6	*b*	...	...	17.71	...	...	17.65
1-Ethylpropyl	B (a)	C$_7$H$_{15}$N$_3$OS	192–194	54	*b*	...	...	22.21	...	...	21.81
p-FC$_6$H$_4$	B (a)	C$_8$H$_8$FN$_3$OS	192–194	55	*d*	45.06	3.92	...	44.94	4.11	...
o-CH$_3$OC$_6$H$_4$	A (b)	C$_9$H$_{11}$N$_3$O$_2$S·2H$_2$O	202–203	56	*e*	...	...	16.08[f]	...	...	15.64
m-CH$_3$OC$_6$H$_4$	A (b)	C$_9$H$_{11}$N$_3$O$_2$S	205–207	35	*e*	...	...	18.65[g]	...	...	18.37
1-Methylpiperidyl	A (b)	C$_8$H$_{17}$ClN$_4$OS[h]	237–238 dec	10	*i*	...	...	22.15[j]	...	...	21.89
o-CH$_3$C$_6$H$_4$	A (b)	C$_9$H$_{11}$N$_3$OS	188–190	41	*k*	56.22	4.74	21.98	56.47	4.56	22.04
o-CF$_3$C$_6$H$_4$	B (a)	C$_9$H$_7$F$_3$N$_3$OS	205–206	70	*b*	...	...	15.96	...	...	15.69
m-CF$_3$C$_6$H$_4$	B (a)	C$_9$H$_7$F$_3$N$_3$OS	210–212	80	*e*	41.22	2.68	...	41.34	3.00	...
3,4,5-(CH$_3$O)$_3$C$_6$H$_2$	B (a)	C$_{11}$H$_{15}$N$_3$O$_4$S	248–250 dec	38	*l*	46.30	5.31	14.73	46.52	5.07	14.67

[a] See Experimental Section for details. [b] Aqueous ethanol. [c] *Anal.* Calcd: Cl, 15.43. Found: Cl, 15.81. [d] Water. [e] 95% Ethanol. [f] *Anal.* Calcd: S, 12.28. Found: S, 12.48. [g] *Anal.* Calcd: S, 14.23. Found: S, 14.01. [h] Hydrochloride salt. [i] Aqueous acetic acid. [j] *Anal.* Calcd: S, 12.68. Found: S, 12.78. [k] Propanol. [l] Propanol–DMF (75:25).

shift of the >C=N– band seen in the bases and hence clearly established these compounds as cyclic amidines. In addition, these data have shown that the salts of 2-amino-1,3,4-oxadiazoles are uniquely different in their spectral behavior from the salts of 2-amino-1,3,4-thiadiazoles,[5] the 2-aminooxazoles,[6] the 2-aminooxazolines,[7] and the 2-aminothiazoles, none of which showed these shifts to lower wavelengths. In this respect, the latter group of bases resembled such aromatic amines as aniline. These data have, finally, indicated that the protonated 2-amino-1,3,4-oxadiazoles should be more correctly designated as 5-imino-Δ^2-1,3,4-oxadiazolines.[7]

In the infrared, 2-amino-5-phenyl-1,3,4-oxadiazole (**20**) absorbed strongly at 3.05, 3.20, 6.05, and 6.25 μ; the 3.05- and 3.20-μ bands are associated with the asymmetric and symmetric stretch of the unassociated NH_2 group, the band at 6.25 μ is assigned to the NH_2 deformation, and the 6.05-μ band to the endocyclic >C=N– stretch.[8] The hydrochloride (**22**) showed residual weak absorption at 2.98, 3.20, and 6.20 μ, and none at 6.05 μ, but an intense absorption at 5.85 μ, attributable to the formation of the endocyclic cation. This hypsochromic shift of *ca.* 0.2 μ was also seen in the spectrum of 2-phenyl-1,3,4-oxadiazole, where the single strong band at 6.20 μ was eliminated upon protonation and replaced by a strong absorption at 6.0 μ. Another compound of interest was 2-diethylamino-5-phenyl-1,3,4-oxadiazole (**35**), where the band at 6.17 μ seen in the base was eliminated upon protonation and replaced by a strong band at 5.84 μ; this represented a shift of *ca.* 0.33 μ.[9] In contrast, 2-amino-5-phenyl-1,3,4-thiadiazole, with strong absorption at 3.08, 3.27, 6.12, and 6.63 μ, upon protonation, showed medium to weak absorption at 3.08, 3.27, and 6.53 μ but retained the strong band at 6.15 μ.

The reaction of **20** with acetic anhydride led to the formation of a mixture of mono- and diacetylated derivatives. That the former was the 2-acetyl- and not the 3-acetyl derivative followed from its spectra. Thus, in the infrared, it showed absorption at 3.10, 5.80, and 6.10 μ; this slight shift of only *ca.* 0.05 μ indicated an intact endocyclic >C=N–. Its nmr spectrum in dimethyl-d_6 sulfoxide showed a single 3-proton signal at τ 7.77; 2-acetamido-5-phenyl-1,3,4-thiadiazole, whose structure has been confirmed,[10] showed a similar 3-proton signal at τ 7.77. The nmr spectrum of the diacetylated derivative established its structure as 4-acetyl-5-acetylimino-2-phenyl-Δ^2-1,3,4-oxadiazoline; this spectrum showed two dissimilar 3-proton signals at τ 7.57 and 7.79; in contrast, the spectrum of N,N-diacetyl-α-naphthylamine, in the same solvent, showed a single 6-proton signal at τ 7.73.

The several criteria for structure assignment outlined above were used to establish the structures of the remaining compounds described in this paper.

Synthesis.—The majority of the 2-amino-5-substituted 1,3,4-oxadiazoles were prepared by the reaction of a 1-acyl-3-thiosemicarbazide with Pb_3O_4. When 1-benzoyl-3-thiosemicarbazide and acetic anhydride were heated under reflux, hydrogen sulfide was evolved, and the product obtained was 2-acetamido-5-phenyl-1,3,4-oxadiazole.[11] As mentioned above, the same compound could also be obtained from **20** and acetic anhydride, but in addition there was isolated a small amount of 4-acetyl-5-acetylimino-2-phenyl-Δ^2-1,3,4-oxadiazoline. 5-Imino-2-(*p*-aminophenyl)-Δ^2-1,3,4-oxadiazoline dihydrochloride (**3**) was prepared *via* the iron–acetic acid reduction of 2-amino-5-(*p*-nitrophenyl)-1,3,4-oxadiazole (**19**). The Δ^2-1,3,4-oxadiazolin-5-ones

(5) E. Testa, G. G. Gallo, F. Fava, and G. Weber, *Gazz. Chim. Ital.*, **88**, 812 (1958), have studied the spectral behavior of the 2-amino-1,3,4-thiadiazoles and have inferred that the 2-amino-1,3,4-oxadiazoles would behave similarly. They did not, however, give data to support this generalization. We are unaware of any other literature directed to spectrophotometric observations with the latter class of compounds.

(6) The authors are grateful to Dr. G. I. Poos of the McNeil Laboratories who was kind enough to make available these unpublished data; he and his associates have recently reported on spectral studies with 2-aminooxazolines: J. R. Carson, G. I. Poos, and H. R. Almond, Jr., *J. Org. Chem.*, **30**, 2225 (1965).

(7) The latest index citation to **22** [J. J. Piala and H. L. Yale (to Olin Mathieson Chemical Corp.), U. S. Patent 3,141,022 (July 14, 1964); *Chem. Abstr.*, **61**, 8317*c* (1964)] refers to it as 2-amino-5-phenyl-1,3,4-oxadiazole hydrochloride.

(8) The difficulty in making an absolute assignment to the >C=N– stretching absorption in heterocyclic compounds has been discussed by L. J. Bellamy ("The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1959, pp 267–271) and by Witkop.[3] As pointed out by Witkop, such an assignment is possible, however, when the spectra of the base and its salt are compared.

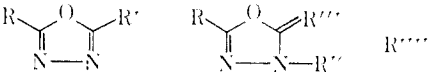
(9) While hyposochromic shifts of *ca.* 0.2 μ are not unusual, *e.g.*, the >C=N– band at 6.17 μ in 2-aminopyridine is shifted to 5.98 μ in the hydrochloride,[3] the shift of *ca.* 0.33 μ in **35**, is, to our knowledge, without precedent.

(10) E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.*, **88**, 1272 (1958).

(11) This is not a general reaction, since under the same conditions, 1-acetyl-3-thiosemicarbazide gave 2-acetamido-5-methyl-1,3,4-thiadiazole.

TABLE II

1,3,4-OXADIAZOLES AND Δ^2-1,3,4-OXADIAZOLINES



No.	R	R′	R″	R‴	R⁗	Method[a]
1	H	NH_2	...	...	...	J
2	H	...	H	NH	HCl	K
3	p-$H_2NC_6H_4$	...	H	...	2HCl	D, J
4	o-ClC_6H_4	...	H	NH	HCl·H_2O	H
5	m-ClC_6H_4	NH_2	...	...	...	D
6	p-ClC_6H_4	...	H	NH	HCl	D, H
7	$(C_6H_5)_2CH$	NH_2	...	...	...	D
8	$(C_6H_5)_2CH$	...	H	O[c]	...	C
9	$C_6H_5CH(C_2H_5)$	NH_2	...	...	...	D
10	$C_6H_5CH(C_2H_5)$	...	H	NH	HCl	L
11	1-Ethylpropyl	NH_2	...	...	...	D
12	1-Ethylpropyl	...	H	NH	HCl	K
13	p-FC_6H_4	NH_2	...	...	...	D
14	2-Furyl	NH_2	...	...	...	D
15	o-$CH_3OC_6H_4$	NH_2	...	...	...	D
16	m-$CH_3OC_6H_4$	NH_2	...	...	...	D
17	p-$CH_3OC_6H_4$	NH_2	...	...	...	D
18	1-Methyl-4-piperidyl	NH_2	...	...	...	A (e)
19	p-$O_2NC_6H_4$	NH_2	...	...	...	A (e)
20	C_6H_5	NH_2	...	...	...	A (e)
21	C_6H_5	...	H	O[c]	...	C
22	C_6H_5	...	H	NH	HCl	I
23	C_6H_5	...	H	NH	HNO_3	I
24	C_6H_5	...	H	NH	$0.5H_2SO_4$	I
25	C_6H_5	...	H	NH	$0.5C_4H_4O_4$	N
26	C_6H_5	...	H	NH	$0.5C_6H_8O_7$	O
27	C_6H_5	...	H	NH	H_3PO_4	I
28	C_6H_5	$NHCOCH_3$	...	...	...	G
29	C_6H_5	...	H	$NCOCH_3$	HCl	K
30	C_6H_5	$NHCOCH_2CH(CH_3)_2$	...	...	...	H
31	C_6H_5	$NHCONHC_2H_5$	...	...	...	M
32	C_6H_5	$NHCOCH_2CH_2CO_2H$	...	...	...	E
33	C_6H_5	$NHCOCH_2Cl$	...	...	...	H
34	C_6H_5	$N(CH_2)_3N(CH_3)_2$	...	NH	2HCl	F
35	C_6H_5	$N(C_2H_5)_2$	...	...	...	B (a)
36	C_6H_5	$N(C_2H_5)_2$	(Hydrochloride)	...	...	K
37	2-C_5H_4N	NH_2	...	...	...	D
38	3-C_5H_4N	NH_2	...	...	...	D
39	4-C_5H_4N	NH_2	...	...	...	D
40	o-$CH_3C_6H_4$	NH_2	...	...	...	A (e)
41	o-$CH_3C_6H_4$	...	H	NH	HCl	I
42	o-$CF_3C_6H_4$	NH_2	...	...	...	B (b)
43	o-$CF_3C_6H_4$	...	H	NH	HCl	K
44	m-$CF_3C_6H_4$	NH_2	...	...	...	B (b)
45	m-$CF_3C_6H_4$	...	H	NH	HCl	K
46	3,4,5-$(CH_3O)_3C_6H_2$	NH_2	...	...	...	A (e)

[a] See Experimental Section for details. [b] Ataxic dose. [c] Paralytic dose. [d] The procedure of K. Stolle and K. Fehrenbach, *J. Prakt. Chem.*, **122**, 289 (1929), was followed; they reported mp 156°. [e] Ethyl acetate–absolute ethanol. [f] A mixture melting point with 1 was 129–131°. [g] Loses HCl during attempted recrystallization. [h] *Anal.* Calcd: Cl, 29.17. Found: Cl, 28.90. [i] Absolute ethanol anhydrous ether. [j] *Anal.* Calcd: Cl, 28.47. Found: Cl, 28.62. [k] 2% Aqueous HCl. [l] *Anal.* Calcd: Cl, 28.35. Found: Cl, 28.46. [m] 95% Ethanol. [n] No suitable recrystallization solvent could be found. [o] Aqueous ethanol. [p] Compounds **8** and **21** exist as the Δ^2-1,3,4-oxadiazolin-5-ones. [q] Acetonitrile. [r] *Anal.* Calcd: Cl, 14.73. Found: Cl, 14.44. [s] *Anal.* Calcd: Cl, 18.50. Found: Cl, 18.35. [t] Water. [u] H. Gehlen and K. Moeckel, *Ann.*, **651**, 128 (1962), reported mp 178°. [v] Lit.[r] mp 249°. [w] Propanol. [x] Lit.[r]

(**8** and **21**) were synthesized by the reaction of the acid hydrazide with phosgene.[12]

Several unsuccessful attempts were made to treat **22** with potassium isocyanate; however, **20** and ethyl isocyanate readily gave 1-ethyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)urea (**31**); **20** and succinic anhydride gave a mixture of 5-phenyl-2-succinimido-1,3,4-oxadiazole and N-(5-phenyl-1,3,4-oxadiazol-2-yl)succinamic acid (**32**); and, finally, **28** and 3-dimethylaminopropyl chloride in the presence of sodamide gave the 2-(3-dimethylaminopropyl) derivative (**34**).[13]

(12) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).

(13) The mechanism of this reaction is of interest; presumably, it might involve direct displacement of the acetyl group, since as described in U. S. Patent 2,997,468 (Aug. 22, 1961), 10-acetyl-2-(trifluoromethyl)phenothiazine, 3-dimethylaminopropyl chloride, and sodamide under very similar conditions gave 10-(3-dimethylaminopropyl)-2-trifluoromethylphenothiazine.

Formula	Mp, °C	Yield, %	Recrystn solvent	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	AD_{50} (mouse), mg/kg *po*[b]	PD_{50} (mouse), mg/kg *po*[c]	LD_{50} (mouse), mg/kg *po*
$C_2H_3N_3O$	152–154[d]	10	*e*	28.23	3.55	...[h]	28.00	3.42	...	>1200	...	>2400
$C_2H_4ClN_3O$	152–154 dec[f]	62	*g*	...	...	...	...	...	...	...	...	...
$C_8H_{10}Cl_2N_4O$	>300	20	*i*	...	...	22.49[j]	...	...	22.59	*pp*	...	140
$C_8H_9Cl_2N_3O_2$	184–186 dec	58	*k*	...	...	16.80[l]	...	...	16.41	120	350	680
$C_8H_6ClN_3O$	245–246	35	*m*	49.12	3.09	21.48	49.41	3.14	21.44	980	>2400	3400
$C_8H_7Cl_2N_3O$	214–216 dec	22	*n*	41.39	3.04	...	41.14	3.11	...	1200	>2400	>2400
$C_{15}H_{13}N_3O$	220–222 dec	18	*o*	71.70	5.21	16.72	71.69	5.21	16.71	500	...	3500
$C_{15}H_{12}N_2O_2$	141–143	28	*o*	71.41	4.80	11.11	71.64	4.76	10.94	Stimulant	...	...
$C_{11}H_{13}N_3O$	195–196	82	*q*	...	...	20.68	...	...	21.17	...	...	...
$C_{11}H_{14}ClN_3O$	135–136	58	*q*	...	...	17.46[r]	...	...	17.59	220	1400	>2400
$C_7H_{13}N_3O$	189–190	70	*o*	...	...	27.08	...	...	27.38	...	...	...
$C_7H_{14}ClN_3O$	155–156	75	*o*	...	...	21.95[s]	...	...	22.31	200	...	740
$C_8H_6FN_3O$	251–253 dec	14	*t*	53.63	3.25	23.45	53.77	3.37	23.79	230	...	...
$C_6H_5N_3O_2$	225–226	47	*q*	47.69	3.34	27.81	47.90	3.58	27.50	315	550	850
$C_9H_9N_3O_2$	176–177[v]	59	*t*	56.53	4.72	21.98	56.58	4.84	21.86	50	120	550
$C_9H_9N_3O_2$	190–191	35	*o*	56.53	4.72	21.98	56.29	4.79	22.12	450	...	>1200
$C_9H_9N_3O_2$	247–248[v]	47	*m*	56.53	4.72	...	56.35	4.55	...	2100	...	...
$C_8H_{14}N_4O$	228–230	44	*q*	52.72	7.74	30.75	52.91	7.55	30.48	...	...	>1500
$C_8H_6N_4O_3$	264–265 dec	90	*w*	46.59	2.93	...	46.82	3.00	...	...	...	...
$C_8H_7N_3O$	243–245 dec[z]	68	*w*	...	...	26.07	...	...	26.14	65	...	300
$C_8H_6N_2O_2$	137–138[y]	52	*z*	...	...	17.28	...	...	17.21	280	500	1520
$C_8H_8ClN_3O$	186–188 dec[aa]	82	*bb*	48.62	4.08	21.27	48.14	3.89	21.21	40	360	440
$C_8H_8N_4O_4$	166–167 dec	74	*q*	...	...	25.00	...	...	25.12	...	...	...
$C_{16}H_{20}N_6O_6S$[cc]	182–184 dec	82	*q*	...	...	19.99[dd]	...	...	19.99	...	...	...
$C_{20}H_{20}N_6O_6$[cc]	158–160 dec	63	*q*	...	...	19.18	...	...	19.38	...	...	...
$C_{22}H_{22}N_6O_9$[cc]	180–182 dec	71	*q*	...	...	16.34[ee]	...	...	16.43	...	...	...
$C_8H_{10}N_3O_5P$	172–174	49	*q*	...	...	16.22	...	...	15.97	...	...	...
$C_{10}H_9N_3O_2$	219–221[ff]	38	*gg*	59.10	4.46	20.68[hh]	58.84	4.27	20.96	120	370	520
$C_{10}H_{10}ClN_3O_2$	207–210 dec	68	*g*	...	...	17.49	...	...	17.72	...	...	...
$C_{13}H_{15}N_3O_2$	161–163	24	*ii*	63.64	6.16	17.13	62.88	5.86	17.39	150	...	800
$C_{11}H_{12}N_4O_2$	217–218	18	*gg*	56.88	5.21	24.12	57.08	4.97	24.05	650	>1200	...
$C_{12}H_{11}N_3O_4$	173–175	49	*gg*	55.16[jj]	4.25	16.09	55.30	4.28	16.07	>1200	...	...
$C_{10}H_8ClN_3O_2$	216–218 dec	83	*u*	...	...	17.69[kk]	...	...	17.31	300	...	730
$C_{13}H_{20}Cl_2NO_4$	228–230	9	*w*	48.91	6.31	17.55	48.95	6.20	17.51	...	...	>1500
$C_{12}H_{15}N_3O$	148 (0.06 mm)[ll]	46	..	66.64	7.00	6.48	66.53	7.04	6.52	...	...	...
$C_{12}H_{16}ClN_3O$	176–184 dec[mm]	80	*gg*	56.81	6.37	16.59[nn]	56.87	6.49	16.80	180	380	550
$C_7H_6N_4O$	260–262	35	*m*	51.85	3.73	34.56	51.97	3.98	34.82	500	>2400	3400
$C_7H_6N_4O$	231–233	16	*t*	51.85	3.73	...	51.62	3.91	...	425	>1200	1290
$C_7H_6N_4O$	252–253	8	*j*	51.85	3.73	34.56	52.11	4.96	34.52	>580	>580	580
$C_9H_9N_3O$	152–154	77	*n*	61.70	5.18	23.98	61.84	5.43	24.17	46	86	375
$C_9H_{10}ClN_3O$	217–218 dec	85	..	...	...	19.85	...	...	19.56	...	...	...
$C_9H_6F_3N_3O$	186–187	71	*p*	47.16	2.64	18.33	47.34	2.77	18.49	...	...	...
$C_9H_7ClF_3N_3O$	177–179	77	*p*	...	...	15.83[hh]	...	...	15.66	26	...	...
$C_9H_6F_3N_3O$	218–219	37	*m*	47.16	2.64	18.33	46.81	2.44	18.27	57	150	190
$C_9H_7ClF_3N_3O$	194–195	75	*g*	...	...	15.83	...	...	15.53	30	...	...
$C_{11}H_{13}N_3O_4$	214–215	85	*m*	52.57	5.22	16.73	52.80	5.28	16.69	150	2400	1000[oo]

mp 245° dec. [y] A. Dornow and K. Brunchen, *Chem. Ber.*, **82**, 121 (1940), reported mp 138°. [z] Benzene. [aa] Lit.[a] mp 177° dec. [bb] 10% Aqueous HCl–DMF. [cc] Neutral salt. [dd] *Anal.* Calcd: S, 7.63. Found: S, 7.57. [ee] *Anal.* Calcd: neut equiv, 257. Found: neut equiv, 255. [ff] Lit.[a] mp 223°. [gg] 2-Propanol. [hh] *Anal.* Calcd: S, 0.0. Found: S, 0.0. [ii] Skellysolve E. [jj] *Anal.* Calcd: neut equiv, 261. Found: neut equiv, 266. [kk] *Anal.* Calcd: Cl, 14.92. Found: Cl, 14.15. [ll] The product is a colorless oil. [mm] *Anal.* Calcd: neut equiv, 216. Found: neut equiv, 215. [nn] *Anal.* Calcd: Cl, 13.98; neut equiv, 257. Found: Cl, 14.34; neut equiv, 254. [oo] Delayed deaths. [pp] No CNS depression to lethal dose.

The new acylthiosemicarbazides are listed in Table I, along with their physical properties and analyses. Typical preparative procedures for these, as well as the 1,3,4-oxadiazoles and 1,3,4-oxadiazolines are described in the Experimental Section.

Structure–Activity Relationships.—The ataxic, paralytic, and lethal doses for the 1,3,4-oxadiazoles and 1,3,4-oxadiazolines are listed in Table II. The discussion of the structure–activity relationships for these compounds will be based on their ataxic dose. The procedures employed in evaluating these compounds have been described.[2] The compound receiving the major pharmacological and toxicological work-up was 5-imino-2-phenyl-Δ^2-1,3,4-oxadiazoline hydrochloride (**22**); the base (**20**) and the 2-acetamido derivative (**28**) were somewhat less potent. The 5-phenyl group in **20** was essential for activity since 2-amino-1,3,4-oxadiazole (**1**) was inactive. Replacement of the 2-amino group in

20 by hydrogen had a less profound effect, since that compound, 2-phenyl-1,3,4-oxadiazole, had AD_{50} = 110 mg/kg and was consequently about half as potent as **20**. Again, a 2-diethylamino group in place of the 2-amino group of **1** decreased the potency of **35** to about one-third of that seen with **20**. In the first two of the three series of isomeric aryl-substituted phenyl compounds studied (**4–6**, **15–17**, and **42–45**) the *ortho*-substituted derivatives were highly active, while the *meta* and *para* isomers were less active; in the third series, however, the *m*-trifluoromethyl compound retained essentially all of the activity of the *ortho* isomer. In **3**, the insertion of an amino group in the *para* position of **22** deprived the latter of all activity. The three isomeric pyridyl derivatives (**37–39**) were far less potent than the phenyl compound (**20**). It was also noteworthy that while (a) 2-amino-5-diphenylmethyl-1,3,4-oxadiazole (**7**) was a weak muscle relaxant, the related 1,3,4-oxadiazolinone (**8**) was a CNS stimulant, and (b) that **21**, the 1,3,4-oxadiazolinone related to **20**, was far less potent than the latter.[14] Finally, 2-amino-5-phenyl-1,3,4-thiadiazole[15] with AD_{50} = 80, PD_{50} = 250, and LD_{50} = 410 mg/kg and 2-amino-5-(*o*-methoxyphenyl)-1,3,4-thiadiazole with an AD_{50} = 240, PD_{50} = 280, and LD_{50} = 440 mg/kg were less potent than the corresponding 1,3,4-oxadiazole derivatives, **20** and **15**, respectively.

Experimental Section

All melting points are uncorrected.

2-Amino-5-*o*-tolyl-1,3,4-oxadiazole (41). Method A. (**a**) A mixture of 100.0 g (0.67 mole) of methyl *o*-toluate, 100 ml of 95% ethanol, and 50 g of 100% hydrazine hydrate was refluxed for 4 hr and concentrated to dryness to give 87.0 g (87%) of *o*-toluic acid hydrazide, mp 125–127°. An analytical sample, from toluene, melted unchanged at 125–127°.

Anal. Calcd for $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.63.

(**b**) The product from A (86.5 g, 0.57 mole), 500 ml of water, 69 ml of concentrated HCl, and 44 g of ammonium thiocyanate were heated 0.5 hr on the steam bath and cooled to give 49 g (41%) of 1-(*o*-tolyl)-3-thiosemicarbazide. An analytical sample was recrystallized from propanol.

(**c**) A mixture of 34 g (0.16 mole) of the product from (b), 28 g (0.04 mole) of Pb_3O_4, and 250 ml of N,N-dimethylformamide (DMF) was refluxed for 1 hr and filtered, the filtrate was concentrated to dryness, and the residue was treated with 100 ml of water. The precipitated solid was filtered and recrystallized from water to give 21.4 g of **41**.

2-Amino-5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxadiazole (44). Method B. (**a**) To 29.1 g (0.32 mole) of thiosemicarbazide, 25.6 g (0.32 mole) of pyridine, and 350 ml of DMF was added dropwise 66.0 g (0.32 mole) of *m*-trifluoromethylbenzoyl chloride at room temperature; subsequently, the clear solution was heated for 2 hr at 80–85°, about 200 ml of solvent was distilled *in vacuo*, and the residue poured into 1 l. of water. The precipitate was filtered, washed with water, and air dried to give 86.0 g of crude 1-[*m*-trifluoromethylbenzoyl]-3-thiosemicarbazide, mp 195–197° dec. An analytical sample was recrystallized from 95% ethanol; the recovery was 80%.

(**b**) A mixture of 84.0 g (0.32 mole) of crude **A**, 56.0 g (0.08 mole) of Pb_3O_4, and 2 l. of *n*-amyl alcohol was stirred and refluxed for 2 hr and filtered hot with the aid of Hyflo, and the filtrate was cooled. The product which separated was filtered and air dried to give 33.0 g of product, mp 215–217°. Concentration of the filtrate to about 250 ml gave an additional 7.0 g of product, mp 215–217°.

2-Diphenylmethyl-Δ²-1,3,4-oxadiazolin-5-one (8). Method C.—To 22.6 g (0.1 mole) of **diphenylacetic acid hydrazide** in 300 ml of dry chloroform was added, at −5°, 11.5 g (0.12 mole) of $COCl_2$ in 100 ml of dry toluene. The mixture was stirred for 2 hr as it warmed spontaneously to room temperature and filtered to give 13.0 g of diphenylacetic acid hydrazide hydrochloride, mp 285–287° dec. The chloroform filtrate was concentrated to dryness to give 9.0 g of **8**.

2-Amino-5-(*p*-fluorophenyl)-1,3,4-oxadiazole (13). Method D.—A mixture of 47.0 g (0.22 mole) of **1-(*p*-fluorobenzoyl)-3-thiosemicarbazide**, 270.0 g (0.39 mole) of Pb_3O_4, and 1 l. of 95% ethanol was stirred and refluxed for 32 hr and filtered hot. The solid separating from the filtrate on cooling was filtered to give 5.0 g of **13**, mp 248–250°; the filtrate was partially concentrated to give an additional 1.2 g of product, mp 248–250°.

5-Phenyl-2-succinimido-1,3,4-oxadiazole and N-(5-phenyl-1,3,4-oxadiazol-2-yl)succiniamic Acid (32). Method E.—A finely ground, blended mixture of 10.0 g (0.062 mole) of **20** and 20.0 g (0.20 mole) of succinic anhydride in a large test tube was placed in an oil bath preheated to 165° and kept in the bath for 0.5 hr after a clear melt had formed. The solid obtained on cooling was powdered and stirred with a solution of 20.0 g (0.24 mole) of $NaHCO_3$ in 500 ml of water. The insoluble material was filtered to give 10.5 g of material, mp 197–199°. Recrystallization from 2-propanol gave 9.0 g (60%) of 5-phenyl-2-succinimido-1,3,4-oxadiazole, mp 199–200°.

Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28; neut equiv, 243. Found: C, 58.98; H, 3.98; N, 17.00; neut equiv ($KOCH_3$), 233.

The aqueous $NaHCO_3$ filtrate from the above product was made strongly acidic with concentrated HCl and kept at room temperature. The solid which separated after several days was filtered to give 0.29 g of material, mp 168–170°; recrystallization from 2-propanol gave 0.20 g (1%) of **32**.

A mixture of 2.43 g (0.01 mole) of 5-phenyl-2-succinimido-1,3,4-oxadiazole, 20 ml of methanol, and 10 ml of 1 *N* aqueous NaOH was heated under reflux for 0.25 hr and concentrated to dryness, the residue was taken up in 25 ml of water, and the solution acidified gave 2.50 g of **32**, mp 166–168°. Recrystallization from 2-propanol gave 2.12 g of **32**; the melting point and mixture melting point with the material obtained above was 168–170°.

5-[3-(Dimethylamino)propylimino]-2-phenyl-Δ²-1,3,4-oxadiazoline Dihydrochloride (34). Method F.—To 21.8 g (0.11 mole) of **28**, 5.3 g (0.13 mole) of solamide, and 400 ml of diglyme, under N_2 and at 60°, was added dropwise and with stirring, 59 ml of a 2.29 *M* solution (0.13 mole) of 3-dimethylaminopropyl chloride in dry xylene. Subsequently, the mixture was stirred and heated for 6 hr at 100–110°, filtered hot, and the filtrate was concentrated to dryness *in vacuo*. The residual oil, in 250 ml of anhydrous ether at 0°, was treated with ethereal HCl until no further precipitation occurred. This was filtered to give 3.17 g of **34** as a crystalline hygroscopic product.

2-Acetamido-5-phenyl-1,3,4-oxadiazole (28). Method G.—A mixture of 25.0 g (0.13 mole) of **1-benzoyl-3-thiosemicarbazide** and 75 g (0.74 mole) of acetic anhydride was heated under reflux for 1 hr; a gas (H_2S) was evolved during the entire heating period. The cooled reaction mixture deposited a solid; this was filtered and air dried to give 10.0 g of crude **28**, mp 215–217°.

4-Acetyl-5-(acetylimino)-2-phenyl-Δ²-1,3,4-oxadiazoline. Method H.—A mixture of 60.0 g (0.37 mole) of **20** and 300 ml of acetic anhydride was heated under reflux for 1 hr and cooled, and the precipitated solid was filtered to give 24 g (32%) of **28**. Concentration of the filtrate to about 100 ml followed by cooling caused no additional material to separate; concentration to dryness gave a viscous mass which partially crystallized; this was stirred with ice–water until a granular solid separated. The solid was filtered and recrystallized from methanol to give 3.0 g (3%) of product, mp 141–143°.

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 59.08; H, 4.26; N, 16.95.

5-Imino-2-phenyl-Δ²-1,3,4-oxadiazoline Hydrochloride (22). Method I.—A solution of 5.0 g (0.031 mole) of **20** in 50 ml of boiling DMF was cooled to 40° and 100 ml of 10% aqueous HCl was added rapidly. A clear solution formed and when this was cooled further, a solid crystallized. This was filtered and dried to give 5.0 g (82%) of **22** as the monohydrate, mp 186–188°.

Anal. Calcd for $C_8H_7N_3O \cdot HCl \cdot H_2O$: H_2O, 8.37. Found: H_2O, 8.35 (Karl Fischer).

The anhydrous compound was obtained by drying for 24 hr at 75° (0.3 mm).

(14) This was not observed with 2-amino-5-chlorobenzoxazole and 5-chloro-2-benzoxazolol; the latter was a significantly better muscle relaxant. *Cf.* A. H. Conney, N. Trousof, and J. J. Burns, *J. Pharmacol. Exptl. Therap.*, **128**, 333 (1960).

(15) G. Maff and E. Soncin, *Brit. J. Pharmacol.*, **13**, 357 (1958), have reported on the pharmacology of this compound.

5-Imino-2-(*p*-aminophenyl)-Δ^2-1,3,4-oxadiazoline Dihydrochloride (3). Method J.—To 10 g (0.05 mole) of **19** in 250 ml of glacial acetic acid heated initially to the boiling point and with the source of heat removed, was added portionwise a total of 10 g of Fe powder; the mixture was stirred an additional 0.5 hr, heated under reflux for 2 hr, and filtered hot. The filtrate was concentrated to dryness *in vacuo*, the residue was shaken with 250 ml of 10% aqueous NH_3, filtered, dried, and extracted with 500 ml of boiling 1-butanol. The butanol extract was concentrated to dryness *in vacuo* and the residue was dissolved in 10% aqueous HCl. The HCl solution was concentrated to dryness *in vacuo* to give **3**. An attempt at catalytic reduction of **19** with Pd–C in glacial acetic acid under 3.5 kg/cm^2 of hydrogen was unsuccessful.

5-Imino-2-(1-ethylpropyl)-Δ^2-1,3,4-oxadiazoline Hydrochloride (12). Method K.—Compound **11** (9.0 g, 0.058 mole) was dissolved in 1:10 absolute ethanol–ether, and the solution was treated with ethereal HCl until acidic to congo red. The precipitate was filtered and air dried to give 9.0 g of **12**.

5-Imino-2-(α-ethylbenzyl)-Δ^2-1,3,4-oxadiazoline Hydrochloride (10). Method L.—To 4.0 g (0.02 mole) of **9** in anhydrous acetone was added 0.02 mole of HCl in absolute ethanol; anhydrous ether was added to turbidity and the whole was cooled to give **10**.

1-Ethyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)urea (32). Method M.—A solution of 4.5 g (0.028 mole) of **20** in 50 ml of ethyl isocyanate was heated under reflux for 4 hr and then partially concentrated *in vacuo* to give **32**.

5-Imino-2-phenyl-Δ^2-1,3,4-oxadiazoline Maleate (25). Method N.—A mixture of 1.61 g (0.01 mole) of **20**, 1.16 g (0.01 mole) of maleic acid, and 100 ml of propanol was heated to boiling and then cooled to give 2.4 g of **25**.

5-Imino-2-phenyl-Δ^2-1,3,4-oxadiazoline Citrate (26). Method O.—Method N was followed except that 100 ml of acetonitrile was the solvent.

Acknowledgment.—The authors are indebted to Dr. J. Bernstein for discussions helpful in resolving several of the problems during this investigation and to Miss B. Keeler for her assistance in the determination and interpretation of the infrared spectra. Dr. A. Cohen determined the nmr spectra. Several of the compounds were synthesized by Mr. E. J. Pribyl and Mr. C. F. Turk.

Compounds Acting on the Central Nervous System. IV. 4-Substituted 2,3-Polymethylenequinolines

G. K. PATNAIK, M. M. VOHRA,

Division of Pharmacology

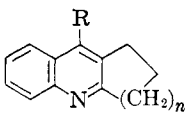
JASJIT S. BINDRA, C. P. GARG, AND NITYA ANAND

Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow, India

Received December 20, 1965

A number of 4-N-substituted amino- and carbamoyl-2,3-polymethylenequinolines have been synthesized and have been found to exhibit a wide spectrum of pharmacological properties, which include analgetic, local anesthetic, analeptic, and respiratory stimulant activities. In particular 4-(4-morpholinyl)-2,3-pentamethylenequinoline has shown significant and promising analeptic and respiratory stimulant activity.

5-Amino-1,2,3,4-tetrahydroacridine (4-amino-2,3-tetramethylenequinoline), although originally synthesized for antibacterial studies,[1] has been shown to possess a wide spectrum of pharmacologial actions, which include anticholinesterase,[2] antagonism to psychotomimetics,[3] morphine antagonist,[4] analeptic,[4c] and decurarizing[5] actions. This molecule seems to offer a good lead for further exploration. Except for an old report of analeptic action of 3,4-dihydro-1,2-benzacridine-5-carboxylic acid[6] (Tetrophan), local anesthetic activity for N,N-diethyl-1,2,3,4-tetrahydroacridine-5-carboxamide[7] and a report published during the course of this work on the analeptic activity of aminocycloheptaquinoline,[8] not much is known about the pharmacology of these compounds. Brian and Souther[9] have recently reported the synthesis of a few more substituted 5-amino-1,2,3,4-tetrahydroacridines but gave no data about their biological activity. The synthesis of a number of 4-N-substituted amino-2,3-polymethylenequinolines (I) and 4-N-substituted carbamoyl-2,3-polymethylenequinolines (II) has now been carried out and their pharmacological actions studied.



I, R = –N< n = 1-3
II, R = –CON<

The 4-chloro-2,3-polymethylenequinolines were prepared from the corresponding hydroxy compounds by treatment with phosphorus oxychloride,[10] which on condensation with the appropriate amines in phenol at

(1) A. Albert and W. Gledhill, *J. Soc. Chem. Ind.* (London), **64**, 169 (1945).

(2) (a) F. H. Shaw and G. A. Bentley, *Australian J. Exptl. Biol. Med. Sci.*, **31**, 573 (1953); (b) I. S. De La Lande and G. A. Bentley, *ibid.*, **33**, 555 (1955); (c) E. Heilbronn, *Acta Chem. Scand.*, **15**, 1386 (1961).

(3) S. Gershon, *Nature*, **186**, 1072 (1960).

(4) (a) F. H. Shaw and G. A. Bentley, *Med. J. Australia*, **2**, 868 (1949); (b) *Nature*, **169**, 712 (1952); (c) F. H. Shaw and G. A. Bentley, *Australian J. Exptl. Biol. Med. Sci.*, **33**, 143 (1955); (d) F. H. Shaw, S. Gershon, and G. A. Bentley, *J. Pharm. Pharmacol.*, **9**, 666 (1957).

(5) S. Gershon and F. H. Shaw, *ibid.*, **10**, 638 (1958).

(6) (a) E. Hesse, *Arch. Exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's*, **111**, 68 (1926); (b) J. Pohl and E. Hesse, *Klin. Wochschr.*, **4**, 344 (1926); *Chem. Abstr.*, **20**, 2204 (1926).

(7) O. Yu Magidson and A. I. Travin, *J. Gen. Chem. USSR*, **7**, 842 (1937).

(8) N. Plotnikoff, J. Keith, M. Heimann, W. Keith, and C. Perry, *Arch. Intern. Pharmacodyn.*, **146**, 406 (1963).

(9) W. P. Brian and B. L. Souther, *J. Med. Chem.*, **8**, 143 (1965).

(10) (a) B. K. Blount and S. G. P. Plant, *J. Chem. Soc.*, 376 (1937); (b) L. J. Sargent and L. Small, *J. Org. Chem.*, **11**, 359 (1946).