Journal of Medicinal and Pharmaceutical Chemistry
VOL. 4, No. 2 (1961)

N-Alkoxy-*N*-alkyl(aryloxy)acetamides and their Hypnotic Activity

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The compound *N*,*N*-diethyl(4-allyl-2-methoxyphenoxy)acetamide, $CH_2{=}CHCH_2(CH_3O)C_6H_3OCH_2CON(C_2H_5)_2$, is a hypnotic of considerable interest.[1a–g] In view of the similarities between the pharmacological activities of some derivatives of hydroxylamine and those of the corresponding amines[2] it was felt worthwhile to prepare *N*-ethoxy-*N*-ethyl(4-alkyl-2-methoxyphenoxy)-acetamide, $CH_2{=}CHCH_2(CH_3O)C_6H_3OCH_2CON(C_2H_5)OC_2H_5$, as well as some other *N*-alkoxy-*N*-alkyl(aryloxy)acetamides, $ArOCH_2CON(R)OR$. All these new compounds were colourless oils which were rather insoluble in water.

Each of the new compounds was synthesized from the corresponding aryloxyacetic acid through its acid chloride, which in turn was prepared by the action of thionyl chloride on the acid. The *N*-alkoxy-*N*-alkyl(aryloxy)acetamides were formed by the slow addition of a solution of a molar equivalent of the acid chloride in ether to a stirred solution of two molar equivalents of the appropriate *N*-alkoxy-*N*-alkylamine in ether. The crystalline or oily precipitate was removed by filtration. After the ethereal solution had been washed with water, dried and distilled, the amides were obtained. Purification was achieved by filtration of a benzene solution of the amide through an alumina column. The impurities were readily absorbed on the alumina. In this way *N*-alkoxy-*N*-alkyl(aryloxy)acetamides in which the *N*-alkoxy-*N*-alkyl groups were *N*-methoxy-*N*-methyl and *N*-ethoxy-*N*-ethyl were made. The aryloxy groups used were phenoxy, 5-methyl-2-isopropylphenoxy, 2-methyl-5-isopropylphenoxy, 4-allyl-2-methoxyphenoxy and 2-methoxy-4-*n*-propylphenoxy. For purposes of comparison, *N*,*N*-diethyl-(2-methoxy-4-*n*-propylphenoxy)acetamide was prepared by the above general procedure. Also,

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N,*N*-diethyl-(4-allyl-2-methoxyphenoxy)acetamide[1g] was prepared by published procedures.

In order to obtain a compound of this general type which would form a water-soluble salt, an effort was made to produce an *N*-alkoxy-*N*-alkyl(quinolyl-8-oxy)acetamide. This was unsuccessful, but in the course of this work quinolyl-8-oxyacetamide and quinolyl-8-oxyacethydrazide were synthesized. These were prepared by the action of ammonia or hydrazine hydrate respectively on the corresponding ester. Ethyl quinolyl-8-oxyacetate was prepared by the action of a mixture of absolute alcohol and concentrated sulphuric acid on the corresponding acid.[3] Attempts to prepare quinolyl-8-oxyacetyl chloride were unsuccessful; only black tars were obtained when efforts were made to purify the chloride.

Pharmacological activity. Dr S. S. McKinney and associates in the Merck Institute for Therapeutic Research, West Point, Pennsylvania, to whom we are much indebted, have kindly given us the information shown in Table I on the toxicity and hypnotic activity of these new compounds.

On the basis of potency and therapeutic index (lethal dose/hypnotic dose), compounds I, III and V in Table I would appear to have potential interest as intravenous short-acting anaesthetic agents, similar to the known anaesthetic agent, compound XII.[1a-g] The most promising compound on the list is compound I. However, the other two compounds mentioned above, namely III and V, have therapeutic indices similar to or greater than those obtained for barbiturates that are used as anaesthetics.

It is quite clear that at least some of the *N*-alkoxy-*N*-alkylamides in this series possess hypnotic activity equal to or greater than that of the corresponding *N*,*N*-dialkylamides.

Experimental

Aryloxyacetyl chlorides. A 30 per cent excess of thionyl chloride was refluxed with the appropriate aryloxyacetic acid for 30–60 min. After removal of excess thionyl chloride by distillation the oily acid chloride was distilled *in vacuo*.

N-*Alkoxy*-N-*alkyl*-(*aryloxy*)-*4*-*acetamides.* To a vigorously stirred solution of 0·2 mole of *O*-*N*-dialkylhydroxylamine (where

Table I. Toxicity and hypnotic activity of *N*,*N*-disubstituted aryloxyacetamides

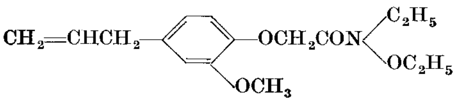
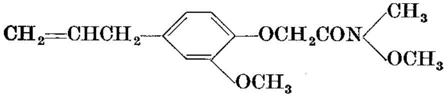
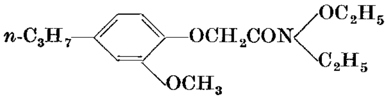
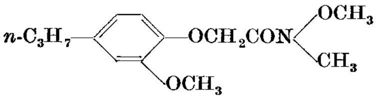
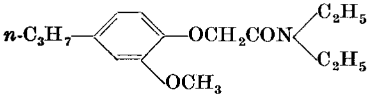
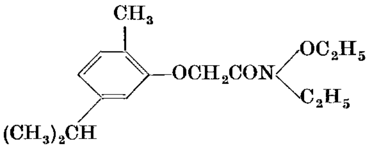
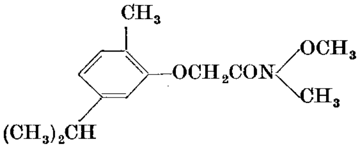
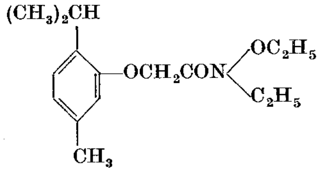
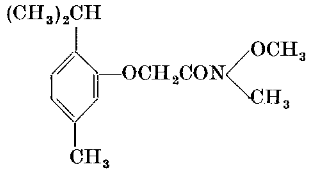
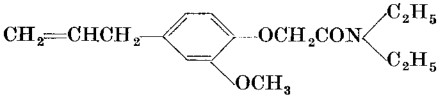
Compounds	Route[a] of admin.	Toxicity, mg/kg[b]			Hypnotic dose, mg/kg[c]			Ratio $\frac{LD_{50}}{HD_{50}}$	Av. dose of RR—at HD_{100} min
		LD_0	LD_{50}	LD_{100}	HD_0	HD_{50}	HD_{100}		
 I	i.v.		> 500	(2/10)	8·4	14·4	17·3	> 35	1·0
	i.p.		> 2000	(1–10)	173	244	360	> 8	9·0
	p.o.	1400	2100	2740	1000	2110	> 2740	1·0	
 II	i.v.	69	85	120	30	43	52	2·0	1·0
	i.p.	500	625	720	173	219	360	2·9	8·0
	p.o.	1090	1745	3000	1090	1806	3000	—	
 III	i.v.	120	166	1250	20	24	35	6·9	3·0
	i.p.	870	1123	1250	174	245	300	4·6	6·0
	p.o.		> 3000			—		—	None
 IV	i.v.	63	88	> 108	23	32	40	2·7	1·0
	i.p.	375	541	780	243	331	420	1·6	4·0
	p.o.	1400	1960	2750	1400	2318	> 2750	—	
 V	i.v.	52	75	> 90	14	18	24	4·2	2·0
	i.p.	300	452	> 518	58	84	101	5·4	12·5
	p.o.		ca 2100		572	980	1570	2·0	180 to O.N.

Table I—*continued*

Compounds	Route[a] of admin.	Toxicity, mg/kg[b]			Hypnotic dose, mg/kg[c]			Ratio $\frac{LD_{50}}{HD_{50}}$	Av. dose of RR— at HD_{100} min
		LD_0	LD_{50}	LD_{100}	HD_0	HD_{50}	HD_{100}		
 VI	i.v.	not detrm. (poor susp.)				—		—	—
	i.p.	870	1278	2160	No loss of RR			—	—
	p.o.		> 3000			—		—	—
 VII	i.v.	58	82	144	43	53	75	1·5	2·0
	i.p.	600	733	1037	416	552	864	1·3	
	p.o.	1120	1678	> 2200	1570	1919	> 2200	—	
 VIII	i.v.	145	218	250	145	213	250	1·0	
	i.p.	1000	1245	1730	1000	1440	1730	—	
	p.o.		> 3000		No loss of RR at 3000			—	—

 IX	i.v.	not detrm. CMC suspension							
	i.p.	480	643	830	480	643	830	1·0	
	p.o.	1090	1530	3000	No loss of RR at 3000			—	—
 $C_6H_5OCH_2CON\genfrac{}{}{0pt}{}{C_2H_5}{OC_2H_5}$ X	i.v.	144	183	250	75	110	130	1·7	2·0
	i.p.	720	1272	1790	292	337	420	3·8	3·0
	p.o.		> 3000		No loss of RR at 3000			—	—
 $C_6H_5OCH_2CON\genfrac{}{}{0pt}{}{OCH_3}{CH_3}$ XI	i.v.	232	361	480	150	207	259	1·7	1·0
	i.p.	723	1065	1500	300	375	518	2·9	4·0
	p.o.	1530	2370	3000	1090	1690	2140	1·4	18·0
 (G29505) XII	i.v.	96	129	> 200	15	19·3	26	6·7	1·5
	i.p.	375	475	> 540	55	71	95	6·7	12·0
	p.o.	600	840	1175	428	733	1175	1·1	—

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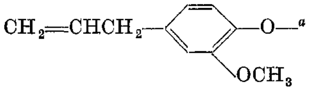
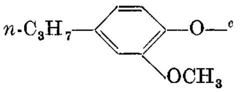
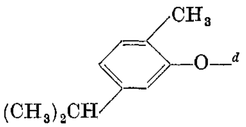
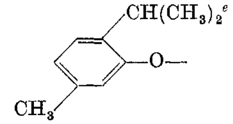
[a] Intravenously as a water emulsion. Intraperitoneally and orally as a suspension in 1·0 per cent aqueous carboxymethylcellulose.

[b] Ten mice used at each dose level. A minimum of forty mice were used for each calculated value, utilizing the method of Weil.[4]

[c] Recovery from loss of the righting reflex was determined by the ability of the animal to right itself following a pressure stimulus to the tail.

the alkyl group was either methyl[11] or ethyl[11]) in 50 to 200 ml of absolute ether was added 0·1 mole of the appropriate acid chloride in 100 to 200 ml of absolute ether, slowly over a period of about 20 min. During the procedure, a crystalline or oily precipitate formed and the reaction mixture warmed slightly. After the acid chloride had all been added the mixture was refluxed for 30 min or allowed to remain at room temperature overnight.

Table II. Aryloxyacetyl chlorides

Aryloxy group of acid	Yield of chloride, %	b.p. of chloride, °C/mm
	—	—[b]
	83·4	133–139/1·4–1·8
	49·5	150/14
	65·0	148/14 m.p. 57–69° (from pet. ether)
C_6H_5O—[f]	91·0	117/14[g]

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[a] Prepared by the method of Clauser.[5]

[b] Prepared by the method of Shigematsu and Kobayashi.[1g]

[c] Prepared by refluxing a solution of 2-methoxy-4-*n*-propylphenol and sodium chloracetate in water for 10 h. When poured into dilute acid an oil precipitated which crystallized as needles, recrystallized from alcohol, m.p. 78°. Fujita, Watanabe and Matsuura give m.p. 71–72°.[6]

[d] Prepared by the method of Spica.[7]

[e] Prepared by the method of Mameli.[8]

[f] Prepared by the method of Hantzsch.[9]

[g] Prepared by the method of Rosemund and Zetzsche.[10]

The precipitate was then removed by filtration or decantation. The ether solution was repeatedly washed with water and then dried with sodium sulphate. Evaporation of the ether left almost colourless or slightly yellow oils, which decomposed rather readily on distillation. They were dissolved in benzene and filtered through an alumina column. Most of the impurities were adsorbed while the *N*-alkoxy-*N*-alkylamide passed through the column. Evaporation of the benzene and vacuum distillation of the residue gave analytically pure compounds as shown in Table III.

Ethyl quinolyl-8-oxyacetate. A solution of quinolyl-8-oxyacetic acid[3] (30 g) in a mixture of absolute alcohol (300 ml) and concentrated sulphuric acid (33 ml) was refluxed for 5 h, concentrated *in vacuo* and made alkaline with sodium carbonate. It was then extracted repeatedly with chloroform and dried, and the chloroform was evaporated. Distillation *in vacuo* gave 22 g of a colourless, viscous oil, b.p. 160°/0·03 mm. In the infrared it exhibited absorption bands at 5·7 μ and at 8·9 μ.

Picrate. The ester formed a picrate, m.p. 167° (d.).

Anal. Calcd. for $C_{19}H_{16}N_4O_{10}$: C, 49·57; H, 3·50. Found: C, 49·29; H, 3·48.

Quinolyl-8-oxyacetamide. Ethyl alcohol was added to a mixture of ethyl quinolyl-8-oxyacetate and an excess of concentrated ammonium hydroxide until solution took place. After the solution had stood overnight, long colourless needles had formed, which were recrystallized twice from alcohol, m.p. 170°. The infrared spectrum showed bands at 6·15 μ and 9·0 μ.

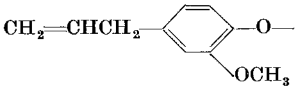
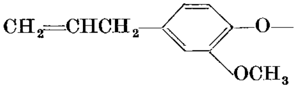
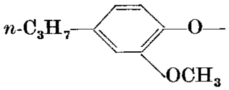
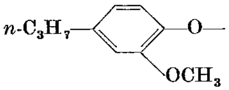
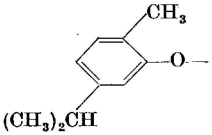
Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65·33; H, 4·99. Found: C, 65·43; H, 4·83.

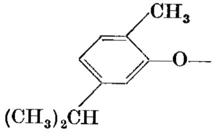
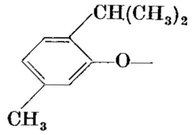
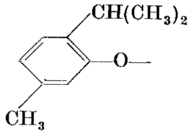
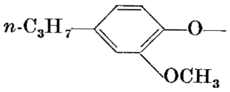
Quinolyl-8-oxyacethydrazide. A solution of ethyl quinolyl-8-oxyacetate (6 g) and hydrazine hydrate (1·5 g) in absolute alcohol (50 ml) was refluxed for 2·5 h. After the solution had stood at room temperature overnight colourless needles had precipitated. These were recrystallized from absolute alcohol; m.p. 140°; yield 80 per cent.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C,60·81; H, 5·10. Found: C, 60·77; H, 5·12.

Summary. A series of *N*-alkoxy-*N*-alkyl(aryloxy)acetamides was prepared. Several of these compounds showed some hypnotic activity in the mouse. The most active was *N*-ethoxy-*N*-ethyl-(4-alkyl-2-methoxyphenoxy)acetamide. In order to obtain an analogous compound which

Table III. *N*-Alkoxy-*N*-alkyl-(aryloxy)-acetamide

Aryloxy group	Alkoxy or alkyl group	Alkyl group	b.p., °C/mm	Mol. formula	Yield, %	Analysis, % Calcd. C	Analysis, % Calcd. H	Analysis, % Calcd. N	Analysis, % Found C	Analysis, % Found H	Analysis, % Found N
	C_2H_5O—	C_2H_5—	161/0·08	$C_{16}H_{23}NO_4$	94	65·50	7·90	4·78	64·99	7·79	—
	CH_3O—	CH_3—	170/0·005	$C_{14}H_{19}NO_4$	99	63·38	7·22	5·28	63·05	7·16	5·42
	C_2H_5O—	C_2H_5—	165/0·03	$C_{16}H_{25}NO_4$	71	65·06	8·53	4·74	65·27	8·88	4·96
	CH_3O—	CH_3—	174–180/0·2	$C_{14}H_{21}NO_4$	83	62·90	7·92	5·24	62·27	8·02	5·25
	C_2H_5O—	C_2H_5—	144/0·1	$C_{16}H_{25}NO_3$	84	68·78	9·02	5·01	68·31	8·92	5·20

	CH_3O—	CH_3—	139–145/0·3	$C_{14}H_{21}NO_3$	85	66·90	8·42	5·57	66·61	8·52	5·72
	C_2H_5O—	C_2H_5—	154–156/0·6	$C_{16}H_{25}NO_3$	80	68·79	9·02	5·01	68·62	8·89	5·30
	CH_3O—	CH_3—	156/0·08	$C_{14}H_{21}NO_3$	46	66·90	8·42	5·57	66·59	8·16	5·74
C_6H_5O—	C_2H_5O—	C_2H_5—	138/0·05	$C_{12}H_{17}NO_3$	88	64·55	7·68	6·27	64·22	7·63	6·15
C_6H_5O—	CH_3O—	CH_3—	125/0·1	$C_{10}H_{13}NO_3$	93	61·52	6·71	7·18	61·18	6·77	7·14
	C_2H_5—	C_2H_5—	171/0·25 (m.p. 47°)	$C_{16}H_{25}NO_3$	83	68·79	9·02	5·01	68·46	9·16	5·19

would form soluble salts in water an effort was made to prepare *N*-alkoxy-*N*-alkyl(8-quinolyloxy)-acetamide. This was unsuccessful. However, quinolyl-8-oxyacetamide and quinolyl-8-oxyacethydrazide were prepared.

Acknowledgements. The authors are indebted to Merck and Company, Inc. for a grant in support of this research project. Microanalyses were done by Geller Laboratories, Bardonia, New York and by Mrs. Margaret Logan of this Laboratory, to whom we are indebted.

(*Received 14 December, 1960*)

References

[1] (a) Thuillier, M. J. and Domenjoz, C. *Der Anesthesist,* **6,** 163 (1957)
(b) Pulver, R. *Der Anesthesist,* **6,** 167 (1957)
(c) Frey, R. and Herrmann, K. J. *Der Anesthesist,* **6,** 170 (1957)
(d) Henschel, W. F. and Just, O. *Der Anesthesist,* **6,** 174 (1957)
(e) Feurstein, V. *Der Anesthesist,* **6,** 177 (1957)
(f) Thuiller, J. and Domenjoz, R. *Anésth. Analg.,* **15,** 853 (1958)
(g) Shigematsu, N. and Kobayashi, H. *Tanabe Seijaku, Kenkyû Nempo,* **3,** 33 (1958); *Chem. Abstr.,* **53,** 10095 (1959)

[2] Jones, L. W. and Major, R. T. *J. Amer. chem. Soc.,* **49,** 1527 (1927); Major, R. T. and Hess, H.-J. *J. med. pharm. Chem.,* **2,** 461 (1960)

[3] Nagel, O. *Mh. Chem.,* **18,** 31 (1897); *J. chem. Soc., Abstr.,* **72,** 1, 372 (1897)

[4] Weil, C. S. *Biometrics,* **8,** 249 (1952)

[5] Saarbach, L. *J. pr./2/* **21,** 158 (1880); Clauser, R. *Mh. Chem.,* **22,** 123; Cent. 1901$^{\text{I}}$, 1049.

[6] Fujita, K., Watanabe, Y., and Matsuura, T. *J. Sci. Hiroshima Univ., Ser. A,* **15,** 155 (1951); *Chem. Abstr.,* **48,** 1988 (1954)

[7] Spica, P. *Gazz. chim. ital.,* **10,** 340 (1880); *Ber. dtsch. chem. Ges.,* **13,** 1992 (1880)

[8] Mameli, E. *Gazz. chim. ital.,* **52,** I, 331 (1922); Beil. *Handbuch d. Org. Chem.,* 4th edn., 2nd supplement. Vol. VI, p. 499. 1944. Berlin; Springer-Verlag

[9] Hantzsch, A. *Ber. dtsch. chem. Ges.,* **19,** 1296 (1886)

[10] Rosenmund, K. W. and Zetzsche, F. *Ber. dtsch. chem. Ges.,* **56,** 1483 (1923)

[11] Major, R. T. and Fleck, E. E. *J. Amer. chem. Soc.,* **50,** 1479 (1928)