N-**Benzyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)propionamide Hydrochloride (7).** Compd **6** (10 g, 0.034 mole) was dissolved in 150 ml of C_6H_6. To the resulting soln was added $(EtCO)_2O$ (4.5 g, 0.035 mole), and an initial rise in temp of 5° was noted. The soln was heated to reflux for 2 hr, then cooled, and extd 3 times with aq Na_2CO_3. The C_6H_6 layer was dried ($MgSO_4$) and filtered. The filtrate was concd *in vacuo* to a syrup (13.0 g), ir ($CHCl_3$) 1630 cm^{-1} (NHC=O). The hydrochloride was formed by dissol of the syrup in Et_2O followed by bubbling through gaseous HCl. The white solid which formed was removed by filtration and was recrystd from anhyd EtOH–EtOAc to yield 5.7 g, mp 194–196°.

All the other propionamides and acetamides were prepd similarly and are recorded in Table I.

N-**Phenyl-*N*-(1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-yl)benzamide Monohydrochloride Monomethanolate (29).** BzCl (7 ml, 0.06 mole) was added dropwise to a stirred, refluxing soln of 2-anilino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (13.9 g, 0.05 mole), 100 ml of dry THF, and 25 ml of dry pyridine. The resulting soln was heated to reflux for 12 hr and then poured over ice. A white solid formed, and 20% NaOH was added to decomp any excess BzCl. The mixt was extd with Et_2O and the combined Et_2O exts were dried ($MgSO_4$) and filtered. The filtrate was concd *in vacuo*. The residue was recrystd from a mixt of C_6H_6 and Skelly C to yield 11.1 g of white solid, mp 113–115°. The product was dissolved in warm MeOH and 11 ml of 2.7 *N* HCl in *i*-PrOH was added. A ppt formed which was filtered and recrystd from MeOH–EtOAc to give 10.3 g of white solid melting at 175–176.5°.

Compd **30** was similarly prepd.

2-Methylamino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Dihydrochloride (8). 1,3,4,6,7,11b-Hexahydro-2*H*-benzo-[*a*]quinolizin-2-one (40.2 g, 0.20 mole) and a catalytic amt of *p*-TsOH was dissolved in 300 ml of anhyd EtOH. Anhyd $MeNH_2$ was bubbled through the soln until it was satd. The soln was then heated at 65° at a pressure of 3.5 kg/cm^2 for 8 hr. The soln was concd to a syrup *in vacuo*, ir ($CHCl_3$) 1670 cm^{-1} (C=N). The syrup was then dissolved in 300 ml of MeOH and cooled in an ice bath. $NaBH_4$ (16.0 g, 0.42 mole) was added in small portions with stirring. After the bubbling had ceased the soln was heated to reflux for 1.5 hr. The solvent was removed *in vacuo* to yield a syrup. The syrup was shaken with 1:1 H_2O–Et_2O (400 ml). The resulting 2 phases were sepd and the aq phase was extd with Et_2O. The combined Et_2O exts were dried ($MgSO_4$) and then filtered. The filtrate was concd *in vacuo* to a syrup, yield 46.2 g. A 20-g sample of the syrup was dissolved in anhyd Et_2O (1000 ml) and gaseous HCl was bubbled through the stirred soln. The white ppt which formed was removed by filtration and recrystd from anhyd EtOH–EtOAc to yield 6.0 g, mp 305–310°.

1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one Oxime. A mixt of 1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizin-2-one (20.1 g, 0.10 mole), $NH_2OH \cdot HCl$ (20.1 g, 0.289 mole), 100 ml of pyridine, and 100 ml of anhyd EtOH was heated to reflux on a steam bath for 2.5 hr. The solvent was removed *in vacuo*, and the residue was triturated with 100 ml of cold H_2O and then filtered to yield 31 g, mp 254°. The product was dissolved in 1500 ml of hot H_2O, and the soln was cooled in an ice bath. The cold soln was made alk with $NaHCO_3$ and the resulting ppt was recrystd from C_6H_6–Skelly C to yield 16.2 g, mp 160–165°, lit.[1] mp 182–183°.

2-Amino-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Dimaleate (22). A soln of 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizin-2-one oxime (15.0 g, 0.069 mole) in 275 ml of dry THF was added dropwise with stirring to a suspension of LAH (7.8 g, 0.21 mole) in 300 ml of dry THF. The reaction mixt was heated to reflux for 25 hr. The redn complex and excess LAH were decompd by the successive dropwise addn of 7.8 ml of H_2O in 78 ml of THF, 5.85 ml of 20% NaOH, and 27.3 ml of H_2O to the stirred cold reaction mixt. The resulting mixt was stirred in an ice bath for 2 hr, then filtered, and washed with THF. The filtrate was concd *in vacuo* to an oil which was dissolved in $CHCl_3$, dried ($MgSO_4$), and then filtered. The filtrate was concd *in vacuo* to a yellow oil. Sufficient anhyd EtOH was added to the yellow oil to effect dissolution at room temp. To the resulting soln was added maleic acid (15.4 g, 0.14 mole) in anhyd EtOH. The ppt which formed upon cooling was removed by filtration and washed with cold anhyd EtOH. Recrystn from EtOH gave 12.0 g, mp 164–166°.

References

(1) D. Beke and C. Szantay, *Chem. Ber.*, **95**, 2132 (1962).
(2) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *Chem. Ber.*, **91**, 2157 (1958); E. Wenkert and D. F. Roychaudhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956); W. E. Rosen, *Tetrahedron Lett.*, 481 (1961).
(3) M. Uskokovic, H. Bruderer, C. Von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).
(4) J. Gootjes, A. M. De Roos, and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, **85**, 491 (1966).
(5) W. G. Dauben, G. J. Fauken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).
(6) E. G. Pardo and H. Vidrio, *J. Pharmacol. Exp. Ther.*, **144**, 124 (1964).

Notes

N-Carbalkoxy-*O*-alkylalkanamidoximes. A New Series of Insecticides

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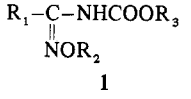
Aryl N-substituted carbamates are useful in the control of a variety of pests. Simple alkyl carbamates showing insecticidal activity have not been described, however. Of the commercially useful aryl carbamates those bearing an *N*-Me substituent show a broader spectrum of activity than the corresponding *N,N*-Me_2 derivatives.[1]

A new series of carbamate derivatives, *N*-carbalkoxy-*O*-alkylalkanamidoximes, 1, show activity though they are alkyl rather than aryl carbamates and bear a large substituent on N.



1

The new compounds were prepared from 2-alkoxyiminocarboxamides by a modification of the Hofmann hypobromite reaction[2] (Table I). The 2-alkoxyiminoamides were prepared by established procedures.[3] With the exception of 2-ethoxyiminobutanamide and 2-ethoxyiminopropanamide the amides have been reported previously.[3]

Biological Data. Test organisms used in the insecticidal screen are the blowfly [*Calliphora vicina* Robineau-Descoidy], the fruit fly [*Drosophila melanogaster* Meigen], German cockroach [*Blattella germanica* (L.)], yellow mealworm [*Tenebrio molitor* (L.)], saw-toothed grain beetle [*Oryzaephilus surinamensis* (L.)], and the varied carpet beetle [*Anthrenus verbasci* (L.)].

In the test, circles of filter paper (9-cm diam) were sprayed with 2.5 ml of a 5% Et_2O soln of the test compd. The filter paper was air-dried for 1 hr, placed in a covered petri dish

†M. S. Thesis, University of Illinois at the Medical Center, 1966.

Table I. Insecticidal *N*-Carbalkoxy-*O*-alkylalkanamidoximes, $R_1C(=NOR_2)NHCO_2R_3$

Compd No.	R_1	R_2	R_3	Bp (mm), °C	Refractive index, n^tD (*t*)	% yield	Composition[d]
1	Et	Et	Et	50–52 (0.025)	1.4560 (20)	43	$C_8H_{16}N_2O_3$
2	Et	Et	Me	61–62 (0.02)	1.4525 (22)	31	$C_7H_{14}N_2O_3$
3	Me	$PhCH_2$	Me	106.5–107.5 (0.03)	1.5283 (23)	57	$C_{11}H_{14}N_2O_3$[a]
4	Me	Et	Me	44–45 (0.04)	1.4550 (23)	39	$C_6H_{12}N_2O_3$
5	Et	$PhCH_2$	Et	118–120 (0.06)	1.5189 (22)	45	$C_{13}H_{18}N_2O_3$[b]
6	Et	$PhCH_2$	Me	114–115 (0.05)	1.5248 (23)	36	$C_{12}H_{16}N_2O_3$[c]
7	Me	Me	Me	31.5–32.5 (0.03)	1.4557 (24)	16	$C_5H_{10}N_2O_3$

[a] H: calcd, 6.30; found, 5.79. [b] N: calcd, 11.20; found, 11.60. [c] C: calcd, 61.01; found, 62.44. [d] *Anal.* C, H, N. In cases where elemental analyses were poor, the nmr spectra were consistent with those expected for the compds.

Table II. Insecticidal Activity of *N*-Carbalkoxy-*O*-alkylalkanamidoximes

Compd No.	Insects killed/total tested					
	C. vicina	*D. melanogaster*	*A. verbasci*	*O. surinamenis*	*T. molitor*	*B. germania*
1	17/20	6/8	0/5	5/15	0/5	0/5
2	13/20	6/7	2/5	0/11	0/5	0/5
3	9/16	8/9	3/6	4/11	0/5	0/5
4	7/14	5/5	2/6	1/6	0/5	0/5
5	3/23	0/5	0/5	1/6	0/5	0/5
6	0/25	0/6	3/5	0/5	1/5	0/5
7	7/12	0/4	0/5	0/5	0/5	0/5

(10 cm diam) and 3–5 insects were introduced and observed for 1 hr. After 1 hr of contact the organisms were transferred to clean petri dishes or in the case of blowflies to 250-ml erlenmeyer flasks which contd food and H_2O. Controls were run with filter paper that had been sprayed with Et_2O and air-dried.

It can be seen (Table II) that the blowfly and fruit fly are most sensitive to the test compds. The blowflies became agitated on contact (within 5 min) with all of the test compounds. After 15 or 20 min they showed convulsions alternating with paralysis. When death occurred it was during the first hour while the insects were still in contact with the test compd. Those that survived the hour of contact always recovered. Aside from the fact that they showed decreased activity when in contact with the test compds, fruit flys showed no unusual behavior. Cockroaches and mealworms appeared to be completely unaffected.

The fact that insects recovered if not killed during contact indicates that the test compds have typical carbamate activity since carbamate activity (cholinesterase inhibition) is rapidly reversed when the insecticide is withheld due to dissociation of the enzyme-substrate complex.‡ Further, the selectivity demonstrated by the test compds is also characteristic of carbamates,[4] and as expected the heavily sclerotized *Coleoptera* and *Orthoptera* were not affected.‡ The LD_{50} of the most active compd **1**, was determined in mice by injecting 5% solns in tragacanth ip. At 750 mg/kg and 1000 mg/kg 2 out of 5 mice died.

Experimental Section

The prepn of the most active compd in the series of *N*-carbethoxy-*O*-ethylpropanamidoxime, **1** ($R_1 = R_2 = R_3 = Et$), illustrates the general method. 2-Ethoxyiminobutyramide (14.4 g, 0.1 mole) was dissolved in 90 ml of commercial abs EtOH, and 2 equiv of NaOEt in commercial abs EtOH was added. The addn of 1 equiv of Br_2 with stirring caused a white ppt (NaBr) to form. After 10 min of heating on the steam bath the mixt was cooled and neutralized with AcOH. The NaBr was sepd by filtration, and the EtOH was distd from the filtrate. The residual oil was taken up in Et_2O, washed (H_2O), and dried ($MgSO_4$). Distn of Et_2O and fractionation of the residue (60-mm Vigreaux column) produced a 43% yield of material which boiled at 50–52° (0.025 torr): $n^{20}D$ 1.4560; ir (film) 1648 (C=N) and 1725 cm^{-1} (monosubstituted urethane); nmr (in ppm, internal TMS) ($CDCl_3$) 1.18 (3 overlapping triplets, 9 H, CH_3CH_2), 2.64 (q, 2 H, $N{=}CCH_2$), 4.09 (m, 4 H, OCH_2CH_3), 7.74 (s, 1 H, NH, exchangeable with D_2O). *Anal.* ($C_8H_{16}N_2O_3$) N, calcd, 14.89. Found, 14.32. In spite of the poor N anal. the nmr was consistent with that expected for the compd.

2-Ethoxyiminobutyramide is a new compd prepd by an established procedure[5] in 77% yield: mp 44–45°. *Anal.* ($C_6H_{12}N_2O_2$) C; H: calcd, 8.33. Found, 7.66.

2-Ethoxyiminopropanamide was prepd by an established procedure[5] in 72% yield: mp 64–65°. *Anal.* ($C_5H_{10}N_2O_2$) C; H: calcd, 7.61. Found, 8.14.

References

(1) M. H. J. Weiden and H. M. Moorefield, *World Rev. Pest Cont.*, **3**, 102 (1964).
(2) E. Jeffreys, *Ber.*, **30**, 898 (1897).
(3) D. A. Coviello, *J. Med. Chem.*, **7**, 121 (1964).
(4) J. E. Casida, *Annu. Rev. Entomol.*, **8**, 39 (1963).
(5) D. W. Woolley, J. W. Hershey, and H. A. Jodlowsky, *J. Org. Chem.*, **28**, 2012 (1963).

Inhibition Studies on Antibody to Poly(L-tyrosyl-L-glutamyl-L-alanylglycyl)glycine-*1*-^{14}C Ethyl Ester. Synthesis and Immunochemical Properties of Poly(L-alanyl-L-glutamyl-L-alanylglycyl)glycine-*1*-^{14}C Ethyl Ester

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A recent investigation of the immunochemical properties of poly(L-tyrosyl-L-glutamyl-L-alanylglycyl)glycine-*1*-^{14}C ethyl ester[1,2] has shown that the polypeptide is antigenic in rabbits.[3] It has been shown that the tyrosyl residue is an important moiety in enhancing antibody formation. To investigate this point further, it was considered that the substitution of the tyrosyl residue with the nonaromatic alanyl residue may affect the immunochemical properties of the molecule. To this end we wish to report the immunochemical properties of poly(L-alanyl-L-glutamyl-L-alanylglycyl)-glycine-*1*-^{14}C.

Chemistry. The polymerizing unit Ala-γ-*tert*-Bu-Glu-Ala-Gly pentachlorophenyl ester hydrochloride (**5**) and the necessary intermediates for its preparation were synthesized as detailed in the Experimental Section. The polymerization was performed at a reagent concn of 100 mmoles/l. in the

‡A. W. A. Brown, University of Western Ontario, private communication.

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