Studies on Carbanilic Acid Esters of Cyclic Amino Alcohols. 4. Esters of Pyrrolidinols and Piperidinols as Local Anesthetics[1]

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A series of 46 substituted phenylcarbamic acid esters of *N*-alkyl-3-pyrrolidinols, *N*-alkyl-3-piperidinols, and *N*-alkyl-4-piperidinols have been prepared and tested as local anesthetics. Some of the compounds are considerably more potent than lidocaine when tested for nerve blocking activity on the frog sciatic nerve *in vitro* and in different types of block *in vivo*. The structure–activity relationship of the compounds has been studied. Two of the new compounds, *N*-*n*-butyl-3-piperidyl 2′,6′-dimethylcarbanilate (**29**) and *N*-*n*-butyl-3-piperidyl 2′-chloro-6′-methylcarbanilate (**35**), showed substantially greater potency in sciatic nerve blocking and peridural anesthesia than the reference compound.

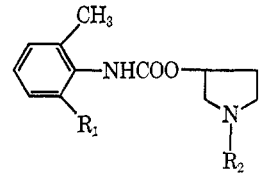
In the literature can be found numerous reports of carbanilates of amino alcohols with local anesthetic activity.[2] However, esters of cyclic amino alcohols other than *N*-hydroxyalkyl derivatives of cyclic amines have been studied very little in this respect. In 1914,[3] the cocaine-like phenylcarbamic acid ester of *l*-ecgonine methyl ester was prepared and tested. It was found to be more toxic than cocaine but possessed equal or superior surface anesthetic activity. Few related compounds have since been investigated in this respect.

Previous studies in these laboratories of the local anesthetic potencies of carbanilic acid esters of certain pyrrolidinyl and piperidyl carbinols revealed that some of the compounds have 3–4 times the activity of lidocaine when tested on the rabbit cornea and have approximately the same blocking activity as lidocaine when tested on the isolated frog sciatic nerve *in vitro*.[4] We therefore considered it worthwhile to extend the investigation to carbanilic acid esters of *N*-alkyl pyrrolidinols and piperidinols.

This paper reports the synthesis and anesthetic properties of a number of phenylcarbamic acid esters of *N*-alkyl-3-pyrrolidinols (Table I), *N*-alkyl-3-piperidinols (Table II), and *N*-alkyl-4-piperidinols (Table III), and the structure–activity relationships have been studied. Among these compounds we have now found local anesthetics of considerably greater potency than lidocaine. The pharmacological results are presented in Tables IV and V.

TABLE I

CARBANILIC ACID ESTERS OF *N*-ALKYL-3-PYRROLIDINOLS



Compd	R_1	R_2	Yield,[a] %	Mp, °C	Formula[b]
1	H	CH_3	64	66–68	$C_{13}H_{18}N_2O_2$
2	H	C_2H_5	75	112–114	$C_{14}H_{20}N_2O_2 \cdot C_2H_2O_4$[c]
3	CH_3	CH_3	64	84–85.5	$C_{14}H_{20}N_2O_2$
4	CH_3	C_2H_5	57	57–58.5	$C_{15}H_{22}N_2O_2$
5	CH_3	$(CH_2)_2CH_3$	75	77–79	$C_{16}H_{24}N_2O_2$
6	CH_3	$CH(CH_3)_2$	70	57–58.5	$C_{16}H_{24}N_2O_2$
7	CH_3	$C(CH_3)_3$	56	207–208	$C_{17}H_{26}N_2O_2 \cdot HCl$[d]
8	Cl	CH_3	40	76–78	$C_{13}H_{17}ClN_2O_2$
9	Cl	C_2H_5	57	54–56	$C_{14}H_{19}ClN_2O_2$
10	Cl	$(CH_2)_2CH_3$	65	71–72	$C_{15}H_{21}ClN_2O_2$
11	Cl	$CH(CH_3)_2$	71	80–82	$C_{15}H_{21}ClN_2O_2$
12	Cl	$C(CH_3)_3$	64	108–109	$C_{16}H_{23}ClN_2O_2$

[a] All esters were prepared by method A. [b] The compds were analyzed for C, H, and N. Analytical results are within ±0.4% of the theoretical value. [c] Oxalate. [d] Hydrochloride.

Chemistry.—The syntheses of the carbanilic acid esters were accomplished by 3 different procedures. Most of the esters were prepared by treating the appropriate amino alcohol with a mono- or disubstituted phenyl isocyanate in PhMe (method A). This pro-

(1) Previous paper in this series: J. L. G. Nilsson, R. Dahlbom, and B. Åkerman, *Acta Pharm. Suecica*, **7**, 239 (1970).

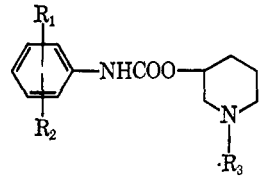
(2) For reviews see (a) K. Soehring and H.-D. Rautmann, *Arzneim.-Forsch.*, **2**, 551 (1952); (b) S. Wiedling and C. Tegnér, *Progr. Med. Chem.*, **3**, 332 (1963).

(3) (a) German Patent 272529; *Chem. Zentralbl.*, **1**, 1534 (1914); (b) K. Fromherz, *Arch. Exp. Pathol. Pharmacol.*, **76**, 257 (1914)

(4) J. L. G. Nilsson, H. Sievertsson, R. Dahlbom, and B. Åkerman, *Acta Pharm. Suecica*, **5**, 219 (1968).

TABLE II

CARBANILIC ACID ESTERS OF *N*-ALKYL-3-PIPERIDINOLS

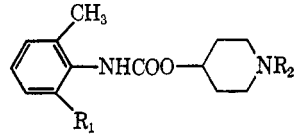


Compd	R_1	R_2	R_3	Method	Yield, %	Mp, °C	Formula[a]
13	H	2-CH_3	CH_3	A	75	245–246 dec	$C_{14}H_{20}N_2O_2 \cdot HCl$[b]
14	H	2-CH_3	C_2H_5	B	84	52–55	$C_{15}H_{22}N_2O_2$
15	H	3-CH_3	C_2H_5	A	48	56.5–58	$C_{15}H_{22}N_2O_2$
16	H	4-CH_3	C_2H_5	C	33	83–84	$C_{15}H_{22}N_2O_2$
17	H	2-Cl	C_2H_5	A	21	133–135	$C_{14}H_{19}ClN_2O_2 \cdot C_2H_2O_4$[c]
18	H	3-Cl	C_2H_5	A	50	73.5–74.5	$C_{14}H_{19}ClN_2O_2$
19	H	4-Cl	C_2H_5	C	33	91.5–93	$C_{14}H_{19}ClN_2O_2$
20	H	3-Br	C_2H_5	A	53	71.5–72.5	$C_{14}H_{19}BrN_2O_2$
21	H	4-Br	C_2H_5	C	30	96–97	$C_{14}H_{19}BrN_2O_2$
22	H	4-CN	C_2H_5	C	20	98.5–100	$C_{15}H_{19}N_3O_2$
23	H	4-OCH_3	C_2H_5	C	28	73–74	$C_{15}H_{22}N_2O_3$
24	H	4-$COCH_3$	C_2H_5	A	36	149–151.5	$C_{16}H_{22}N_2O_3$
25	2-CH_3	6-CH_3	CH_3	B	63	101–102	$C_{15}H_{22}N_2O_2$
26	2-CH_3	6-CH_3	C_2H_5	B	66	83–83.5	$C_{16}H_{24}N_2O_2$
27	2-CH_3	6-CH_3	$(CH_2)_2CH_3$	A	25	75–76	$C_{17}H_{26}N_2O_2$
28	2-CH_3	6-CH_3	$CH(CH_3)_2$	A	33	209–210	$C_{17}H_{26}N_2O_2 \cdot HCl$[b]
29	2-CH_3	6-CH_3	$(CH_2)_3CH_3$	A	40	122–124	$C_{18}H_{28}N_2O_2 \cdot HCl$[b]
30	2-CH_3	6-CH_3	$C(CH_3)_3$	A	70	110–111	$C_{18}H_{28}N_2O_2$
31	2-CH_3	6-Cl	CH_3	A	61	120–121	$C_{14}H_{19}ClN_2O_2$
				B	21		
32	2-CH_3	6-Cl	C_2H_5	A	64	83–84	$C_{15}H_{21}ClN_2O_2$
				B	14		
33	2-CH_3	6-Cl	$(CH_2)_2CH_3$	A	58	100–101	$C_{16}H_{23}ClN_2O_2$
34	2-CH_3	6-Cl	$CH(CH_3)_2$	A	69	207–208	$C_{16}H_{23}ClN_2O_2 \cdot HCl$[b]
35	2-CH_3	6-Cl	$(CH_2)_3CH_3$	A	43	76.5–77.5	$C_{17}H_{25}ClN_2O_2$
36	2-CH_3	6-Cl	$C(CH_3)_3$	A	73	219–220 dec	$C_{17}H_{25}ClN_2O_2 \cdot HCl$[b]

[a] See footnote *b*, Table I. [b] Hydrochloride. [c] Oxalate.

TABLE III

CARBANILIC ACID ESTERS OF *N*-ALKYL-4-PIPERIDINOLS



Compd	R_1	R_2	Method	Yield, %	Mp, °C	Formula[a]
37	CH_3	CH_3	B	22	123–124	$C_{15}H_{22}N_2O_2$
38	CH_3	C_2H_5	A	82	135–136	$C_{16}H_{24}N_2O_2$
39	CH_3	$(CH_2)_2CH_3$	A	78	104–106	$C_{17}H_{26}N_2O_2$
40	CH_3	$CH(CH_3)_2$	A	48	102–103	$C_{17}H_{26}N_2O_2$
41	CH_3	$C(CH_3)_3$	A	43	145–147	$C_{18}H_{28}N_2O_2$
42	Cl	CH_3	B	52	161–162	$C_{14}H_{19}ClN_2O_2$
43	Cl	C_2H_5	A	89	138–139	$C_{15}H_{21}ClN_2O_2$
44	Cl	$(CH_2)_2CH_3$	A	81	141–143	$C_{16}H_{23}ClN_2O_2$
45	Cl	$CH(CH_3)_2$	A	67	115–116	$C_{16}H_{23}ClN_2O_2$
46	Cl	$C(CH_3)_3$	A	67	141–143	$C_{17}H_{25}ClN_2O_2$

[a] See footnote *b*, Table I.

cedure was used when the isocyanate could be obtained conveniently from the corresponding ethyl phenylcarbamate by distillation with P_2O_5.

As an alternative, transesterification of the ethyl phenylcarbamate with the amino alcohol could be used (method B). Some of the carbanilates were more easily obtained by the Curtius reaction of the appropriate aroyl azide and the amino alcohol in refluxing benzene (method C).

Pharmacological Results.—The results of the primary screening tests for local anesthetic activity and toxicity are summarized in Table IV. The effects of the compounds varied considerably and several of them were much more active than lidocaine in the different tests. A few substances were clearly less toxic when injected iv than the control, lidocaine, but were about as active in sciatic nerve and corneal blocks (*e.g.*, **14** and **18**). Despite this, none of them has

TABLE IV

PHARMACOLOGICAL SCREENING RESULTS

Compd	Excitation block activity relative to lidocaine: Sciatic nerve block, *In vitro*[a]	Sciatic nerve block, *In vivo*[b]	Corneal anesthesia[c]	Toxicity,[d] LD_{50}, mg/kg, base iv	base sc	Local irritation[e]
Lidocaine	1.0	1.0	1.0	23	265	0–1+
1	0.2		0	59		
2	0.7	0.9	0	63	158	0–1+
3	0.8		0	31		
4	1.3		3.1	23		
5	1.5–2.0		3.6	17		
6	1.5–2.0		2.8	22		
7	1.5		5.5	12		
8	1.0		0.9	23		
9	1.0–1.5	1.2	4.1	21	74	1+
10	1.5–2.0		4.5	14		
11	1.5–2.0		4.0	14		
12	1.5–2.0		4.9	10		
13	0.5	0.7	0.8	25		
14	0.7	1.0[f]	1.0	34	277	1+
15	0.4	0.6	0.5	25		
16	0.2	0.8	0.6	37		
17	1.0–1.5	1.2	1.0	24		
18	0.6	1.9	1.2	57		3+
19	0.4	0.6	0.8	56		
20	0.4	0.8	1.4	48		
21	0.3	1.9	0.4	48		
22	0.7	0.5	0	72		
23	0.3	0.7	0	48		
24	0.4	0.2	0	66		
25	1.0–1.5	1.3[f]	3.0	15	84	1+
26	1.5–2.0	1.9[f]	2.8	14	60	0–1+
27	1.5–2.0		3.2	9		
28	1.5–2.0	1.4	3.2	13	54	2+
29	2.5–3.5	2.5	2.9	10	59	1+
30	2.5–3.5	2.0	5.1	7	48	
31	3.0–4.0	1.3	4.0	14	66	0–1+
32	3.0–4.0	1.5	6.7	14	69	0–1+
33	3.0–4.0		4.8	12		
34	3.0–4.0		4.8	11		
35	3.0–4.0	2.8	4.7	13	58	1+
36	2.5–3.5		6.0	5		
37	0.5	0.7	2.2	39	93	0–1+
38	1.0	*g*				
39	1.0–1.5	1.7	1.5	18		
40	1.0		1.7	19		
41		*g*				
42	0.7	0.9	1.8	14	63	0–1+
43	0.7		1.0	21		
44	1.0–1.5		2.0	21		
45	1.0		1.6	23		
46		*g*				

[a] Frog, 5 m*M*, 5-min blocking time. [b] Guinea pig or rat, 1.0%, 0.2 ml injected at the hip. [c] Rabbit, 2.0%, 0.25 ml applied for 0.5 min. [d] Mice (male albino). [e] Rabbit, 2.0% + epinephrine 1:80 000, 0.1 ml injected between dermal layers of ear; 1 + denotes weak, 2 + moderate, and 3 + strong irritation. [f] Rat. [g] Not sol.

been submitted for further trials, mainly because of the relatively high scores for local irritancy. A second group of agents (**4–6**, **9**, **17**, **44**, and **45**) showed a better anesthetic index than lidocaine. A third group embracing a large number of compounds were definitely more active than the control (**10–12**, and **25–36**), and although they were fairly toxic, satisfactory local anesthesia was obtained with small doses of the compounds.

In order to exemplify this further the effects of compounds **29**, **35**, and lidocaine in sciatic nerve block and peridural anesthesia are shown in Table V. Apparently 0.5% solns of the new agents were longer acting than 2.0% lidocaine. The effect of the solns was improved by addition of epinephrine. The incidence of block was excellent with rapid onset of the block. The solns did not produce local irritation on the rabbit ear.

Structure–Activity Relationships.—The effect of variation of the aromatic substitution, the size of the heterocyclic ring, and the size of the substituent at the amino N have been studied. Comparison is also made between derivatives of 3- and 4-piperidinols.

A number of carbanilates of *N*-ethyl-3-piperidinol with one aromatic substituent have been studied (**14–24**). The results show that esters with the aromatic substituent in the ortho or meta position to the carbamoyl N generally have better effect than compounds

TABLE V

LOCAL ANESTHETIC EFFECT[a] OF 29 AND 35 IN SCIATIC NERVE BLOCK AND PERIDURAL ANESTHESIA

	Sciatic nerve block[b]			Peridural anesthesia[c]		
Compd	Concn, %	Plain soln	+ Epinephrine 1:200,000	Concn, %	Plain soln	+ Epinephrine 1:200,000
Lidocaine	2.0	66 ± 7	108 ± 5	2.0	25 ± 1	36 ± 4
29	0.5	139 ± 9	216 ± 11	0.5	54 ± 3	68 ± 6
	1.0	178 ± 9		1.0	70 ± 4	118 ± 7
35	0.5	163 ± 13	228 ± 18	0.5	51 ± 4	75 ± 4
	1.0	219 ± 12		1.0	82 ± 4	112 ± 6

[a] Duration of hind-limb paralysis (min ± SE) in guinea pig. [b] Vol injected, 0.2 ml at the hip; $N = 8$. [c] Vol injected, 0.1 ml, $N = 16$.

with the same substituent in the para position. If the group in the para position is strongly polar, like CN, OCH_3, or $COCH_3$, the compounds are only weakly active, probably because of decreased lipid solubility When the esters have 2 aromatic substituents ortho to the carbamoyl N, better effects are obtained with compounds that have the 2-Cl-6-Me rather than the 2,6-Me_2 substitution. However, compounds of the former type are also slightly more toxic when tested iv in mice.

Comparing compounds that are structurally equal in all respects, except size of the heterocyclic ring, those with a piperidine ring are generally more potent than those with a pyrrolidine ring. This may be due to greater lipid solubility of piperidine derivatives.

A great difference in activity was found between esters of 3- and 4-piperidinols, the latter type being less potent (*cf.* **25–29** with **37–41** and **31–35** with **42–46**).

In agreement with the results of previous[2] structure–activity studies of local anesthetics, we found that both activity and toxicity are increased with the size of the substituent at the amino group.

On the basis of the preliminary tests presented above it appears that some of the carbanilic acid esters of pyrrolidinols and piperidinols described here should be studied in more detail. An extended evaluation of the local anesthetic potency as well as of other pharmacological and toxicological properties has therefore been started with the purpose of eventual submission for clinical trials.

Experimental Section

Melting points were determined in an electrically heated metal block, using calibrated Anschütz thermometers. Microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. Before analysis, the compounds were dried at 50° (0.05 mm). Ir spectra were run on a Perkin-Elmer 237 spectrophotometer with grating monochromator.

Materials.—*N*-Methyl-, *N*-ethyl-, *N*-*n*-propyl-, *N*-isopropyl-, and *N*-*tert*-butyl-3-hydroxypyrrolidine were all prepd according to Lunsford, *et al.*[5] *N*-Methyl- and *N*-ethyl-3-hydroxypiperidine and *N*-methyl-4-hydroxypiperidine were commercially available. *N*-*n*-Propyl-3-hydroxypiperidine was prepd as previously described.[6]

***N*-Isopropyl-3-hydroxypiperidine** was prepd by a method described by Biel, *et al.*,[7] for the *N*-Et compd. Hydrogenation of furfural and *i*-$PrNH_2$ in EtOH (Raney Ni) afforded *N*-isopropyltetrahydrofurfurylamine in 67% yield: bp 66–68° (14 mm). Treatment of this intermediate with HBr in glacial AcOH yielded the amino alcohol (78%): bp 72–74° (2.5 mm); $n^{24}D$ 1.4705. *Anal.* ($C_8H_{17}NO$) C, H, N.

N-*n*-**Butyl-3-hydroxypiperidine.**—Reductive aminolysis of furfural by the same method yielded *N*-*n*-butyltetrahydrofurfurylamine as an oil (52%): bp 55–57° (0.4 mm); $n^{22}D$ 1.4425. *Anal.* ($C_9H_{19}NO$) C, H, N. The furfurylamine was then converted to the piperidinol as described above, affording an oil (51%): bp 62–65° (0.5 mm); $n^{24}D$ 1.4645. *Anal.* ($C_9H_{19}NO$) C, H, N.

N-*tert*-**Butyl-3-hydroxypiperidine.**—The intermediate *N*-*tert*-butyltetrahydrofurfurylamine was obtained in 80% yield: bp 69–70° (11 mm); $n^{22}D$ 1.4426. *Anal.* ($C_9H_{19}NO$) C, H, N. The amino alcohol was obtained in 80% yield: bp 88–90° (11 mm); $n^{25}D$ 1.4658. The compd was analyzed as its hydrochloride, mp 232–233° (from Et_2O–EtOH). *Anal.* ($C_9H_{19}NO \cdot HCl$) C, H, N.

N-Ethyl-, *N*-*n*-propyl-, *N*-isopropyl-, and *N*-*tert*-butyl-4-hydroxypiperidine were all prepd by the procedure used by Frankhauser, *et al.*,[8] in the prepn of *N*-*tert*-butyl-4-hydroxypiperidine. The physical constants were in good agreement with lit. values.

Ethyl 2,6-dimethylphenylcarbamate[9] and ethyl 2-chloro-6-methylphenylcarbamate[10] were prepd as previously described. The isocyanates used have been previously described and were prepd by the method described for 2-chloro-6-methylphenyl isocyanate.[11] The benzoyl azides used have also been previously described and were prepd by the method described by Hayao, *et al.*[12]

Carbamates. Method A.—Equimolar amts (0.01 mole) of the appropriate amino alcohol and isocyanate in 50 ml of dry PhMe were refluxed for 2 hr under exclusion of atmospheric moisture. The soln was then cooled and extd twice with 25 ml of 2 *M* HCl. The aq ext was made alk and extd three times with 25 ml of $CHCl_3$, then the extract was dried (Na_2SO_4) and evapd *in vacuo*. The residue usually crystd on standing and was recrystd from PhMe. Oily products were converted to HCl or oxalate salts and recrystd from EtOH–Et_2O.

Method B.—The ethyl arylcarbamate (0.06 mole) and the appropriate *N*-alkylhydroxypiperidine (0.09 mole) were dissolved in dry xylene (100 ml) and a piece of Na (0.2 g) was added. The mixt was heated under N_2 until a clear soln was obtd, after which the EtOH formed in the reaction was slowly distd off (8 hr). The reaction mixt was then washed with H_2O, and the amino ester was isolated and purified as described for method A.

Method C.—A soln made up of the appropriate aroyl azide (0.02 mole) and the amino alcohol (0.03 mole) in dry C_6H_6 (20 ml) was refluxed for 2 hr. The soln was then washed with H_2O (2 × 25 ml) to remove unreacted amino alcohol, and the product was isolated and purified as described for method A.

Pharmacological Methods.—Excitation block *in vitro* was tested on isolated frog sciatic nerves as described by Truant and Wiedling[13] and Åström and Persson.[14] A sciatic nerve including the tibial branch was mounted on a set of electrodes and placed in an incubation chamber contg Tasaki–Ringer soln (pH 7.4). The blocking effect of a drug was tested by immersing a portion of the nerve in a 4-ml bath contg the anesthetic dissolved in the Tasaki–Ringer soln at 20°. Stimuli (0.05 msec monophasic pulses, frequency 30/sec, and about 2.5 V) were applied at the proximal end, and recordings were made at the distal end. The reduction in the amplitude of the action potential (A-spike)

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was followed during 5 min of exposure time. The recovery from block was followed after washing the nerve free of the local anesthetic with the buffer soln; 5 m*M* solutions were used in the present study. Test and control substance (lidocaine) were compared on the same nerve. Between each trial the nerve was allowed to rest for at least 30 min.

Guinea pigs or rats were used in the sciatic nerve block test *in vivo*. The test soln (0.2 ml) was injected at hip level into groups of 4 animals. The latency period and duration of block were recorded. After recovery, the effect of the control was tested on injection into the contralateral leg.

The method of Wiedling[15] was followed for testing the topical anesthetic effect on the rabbit cornea. The test and control solns (0.25 ml, 2%) were applied to the conjunctival sac for 30 sec. The 2 solns were tested on the same animals but on different eyes. A graphite point was used as stimulator and the onset time and duration of block were recorded.

Peridural anesthesia in the guinea pig was induced by delivering 0.1 ml of the solns in the lumbar region *via* a flexible catheter permanently placed in the peridural space. The details of the technique will be reported elsewhere.[16] The onset time and duration of hind-limb paralysis were readily observed and recorded.

The acute iv and sc toxicities in mice were determined on animals (male albino, 18–22 g) of the same strain. The solns used were of 0.2 and 2.0% strength, respectively, and pH 6.0. The method of Litchfield and Wilcoxon[17] was used for detn of the LD_{50} values.

The tissue toxicity was studied on the ear of the rabbit, as described by Wiedling.[18] Test compd and control (0.1 ml of 2.0% solns) were injected between the dermal layers. The solns contd epinephrine (1:80,000). Different ears of the same animals were used for test and control, and the reactions were recorded for 1 week.

All solns were prepared on the day of the experiment. The solns for the *in vivo* experiments were prepd in 0.85% saline. The pH was adjusted to 6.5–7.0 with the exception noted above and in the case of the experiments with solns contg epinephrine when the pH was 3.8–4.5.

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2-(Alkenylamino)benzamides and Related 1-(Alkenyl)-4(1*H*)-quinazolinones as Analgetics and Antiinflammatories

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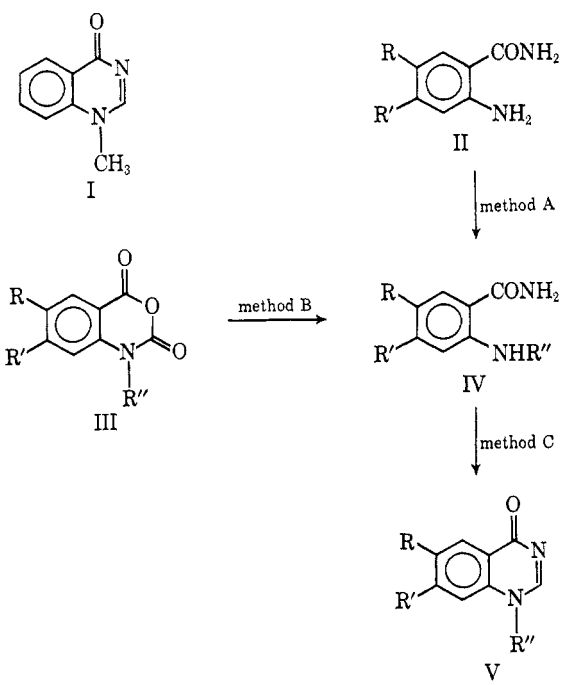
Nineteen 2-(alkenylamino)benzamides were ring closed to their corresponding 1-(alkenyl)-4(1*H*)-quinazolinones. The analgetic–antiinflammatory activities of both groups of compounds were investigated; 4 of the compounds were equal to or better than codeine in the analgetic assays. 1-Allyl-4(1*H*)-quinazolinone, showing a good biological antinociceptive effect, was selected for clinical trials.

A consistent antiinflammatory activity was observed among some simple 1-alkyl homologs of glycorine I.[1] Searching for more active compounds, we have synthetized 19 1-(alkenyl)-4(1*H*)-quinazolinones (V) *via* ring closure of the corresponding 2-(alkenylamino)-benzamides (IV) with ethyl orthoformate (method C).[1] The compounds IV required for the ring-closure step were prepared in 2 ways, either through the reaction of 2-aminobenzamides (II) with the appropriate alkenyl bromide and Na_2CO_3 in DMF (method A),[2] or through ammonolysis of the appropriate *N*-alkenyl isatoic anhydrides III (method B).[3] Scheme I illustrates these 3 methods of preparation. The new products are listed in Tables I and II.

The intermediates II and III were commercially available or were synthesized by known procedures. Purity was determined by potentiometric titration either with $HClO_4$ in AcOH for amides II, or with $Bu_3NH^+OH^-$ in pyridin–*i*-PrOH for anhydrides III.

Biological Activity.—Both series of compounds [benzamides and (1*H*)-quinazolinones] were submitted to a pharmacological screening program to assess their potential activities. The analgetic and antiinflammatory properties were studied, and in some cases, the antitussive activity was also determined.

SCHEME I



Analgetic activity was determined in the mouse by the hot plate technique.[4] Edema following the in-

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