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.

(15) S. Wiedling, *Acta Pharmacol. Toxicol.*, **8**, 117 (1952).
(16) B. Åkerman, to be published.
(17) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(18) S. Wiedling, *Acta Pharmacol. Toxicol.*, **4**, 351 (1948).

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

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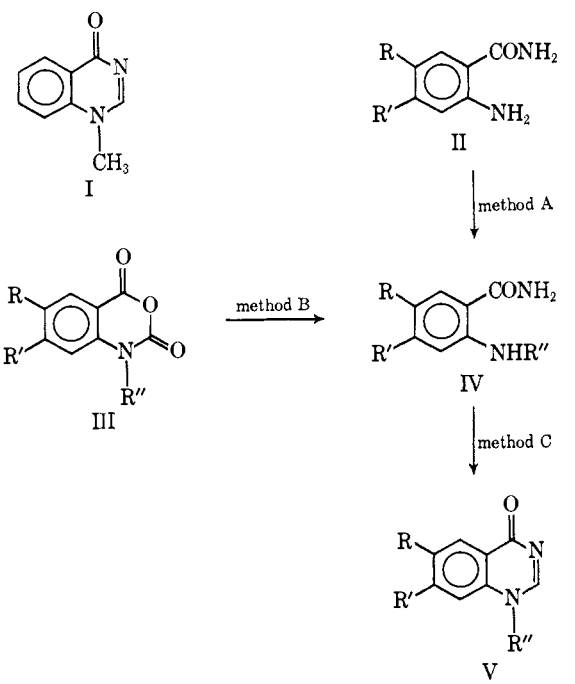
Nineteen 2-(alkenylamino)benzamides were ring closed to their corresponding 1-(alkenyl)-4(1*H*)-quinazolinones. The analgetic–antiinflammatory activities of both groups of compounds were investigated; 4 of the compounds were equal to or better than codeine in the analgetic assays. 1-Allyl-4(1*H*)-quinazolinone, 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.

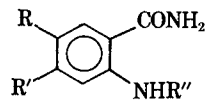
SCHEME I

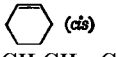


Analgetic activity was determined in the mouse by the hot plate technique.[4] Edema following the in-

(1) J. Maillard, M. Benard, M. Vincent, and R. Jolly, *Chim. Ther.*, 231 (1967).
(2) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).
(3) R. A. Petyunin and V. S. Shklyaev, *Zh. Prikl. Khim. (Leningrad)*, **33**, 1428 (1960); *Chem. Abstr.*, **54**, 22, 426*i* (1960).
(4) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exp. Ther.*, **80**, 300 (1944).

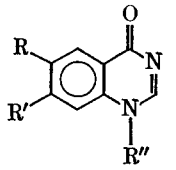
TABLE I

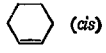


Compd	R	R′	R″	Mp, °C	Solvent	Method	Formula[a]	Intermediates amides II, mp, °C	Intermediates isatoics III, mp, °C	Dose, mg/kg, po	Antiinflam act. (rat), % edema inhibition 3 hr after carageenin injection
1	H	H	$CH_2CH{=}CH_2$	145–146	Cyclohexane–EtOAc	B	$C_{10}H_{12}N_2O$		110–112[b]	100	11.8
										150	44.1
										200	55.9
2	Cl	H	$CH_2CH{=}CH_2$	114–116	Cyclohexane	A	$C_{10}H_{11}ClN_2O$	172–174[c]		100	29.4
										200	38.6
3	H	H	$CH_2C{\equiv}CH$	180–183	EtOAc	B	$C_{10}H_{10}N_2O$		140–143[d]	75	20.3
										150	39.3
4	H	H	$CH_2CH_2CH{=}CH_2$	117–119	EtOAc	B	$C_{11}H_{14}N_2O$		68–70[d]	150	17.8
5	H	H	$CH_2CH{=}CHCH_3$ (*trans*)	132–134	C_6H_6	B	$C_{11}H_{14}N_2O$		100–102[d]	200	20.1
6	H	H	 (*cis*)	73.5–74.5	*e*	A	$C_{13}H_{16}N_2O$	109–110		200	3.6
7	H	Cl	$CH_2CH{=}CH_2$	137–137.5	C_6H_6	B	$C_{10}H_{11}ClN_2O$		104–106[f]	75	25.0
										150	45.0
8	H	H	$CH_2CH{=}CHC_6H_5$ (*trans*)	135–136.5	C_6H_6	A	$C_{16}H_{16}N_2O$	109–110		200	4.9
9	H	H	$CH_2CH{=}C(CH_3)_2$	122–123	C_6H_6	B	$C_{12}H_{16}N_2O$		118–120[d]	150	14.5
10	CH_3O	H	$CH_2CH{=}CH_2$	101–102	C_6H_6	B	$C_{11}H_{14}N_2O_2$		110–111[f]	80	44.3
11	H	C_6H_5	$CH_2CH{=}CH_2$	182–183	MeOH	A	$C_{16}H_{16}N_2O$	219–220[g]		75	13.7
										150	30.2
12	OCH_2O		$CH_2CH{=}CH_2$	191–193	EtOAc	B	$C_{11}H_{12}N_2O_3$		183–183.5[h]	150	36.5
13	H	CH_3O	$CH_2CH{=}CH_2$	155–157	C_6H_6	B	$C_{11}H_{14}N_2O_2$		155–157[f]	80	5.9
14	CH_3	H	$CH_2CH{=}CH_2$	150–151	C_6H_6–EtOAc	B	$C_{11}H_{14}N_2O$		102–104[f]	150	48.2
15	H	H	$CH_2CH{=}CHCl$ (*trans*)	164–166	C_6H_6	B	$C_{10}H_{11}ClN_2O$		137–138[d]	150	18.9
16	H	CF_3	$CH_2CH{=}CH_2$	160–160.5	H_2O–EtOH	B	$C_{11}H_{11}F_3N_2O$		94–96[h]	80	20.0
17	F	H	$CH_2CH{=}CH_2$	136–137	H_2O then C_6H_6	A	$C_{10}H_{11}FN_2O$	146–148[c]		*j*	*j*
18	H	H		155–157	C_6H_6	B	$C_{10}H_{12}N_2O$		180–183	*j*	*j*
19	H	H	CH_2–	129–130	Cyclohexane–C_6H_6	A	$C_{11}H_{14}N_2O$	109–110		*j*	*j*
	Phenylbutazone									40	43.1
										80	62.0

[a] Analytical results obtained were within ±0.4% of the theoretical value. [b] Abbott Lab, Australian Patent 64,080 (1965); *Derwent Farmdoc*, 27,268 (1967). [c] R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24,** 1214 (1959); R. Dorsh, *J. Prakt. Chem.*, **33,** 50 (1886); *Beilstein*, **14,** 365 (1931). [d] Nippon Shinyaku Co., Japanese Patent, 17,326 (1963); *Derwent Farmdoc*, 9,170 (1963). [e] See Experimental Section. [f] R. A. Petyunin and V. S. Shklyaev, *Zh. Prikl. Khim. (Leningrad)*, **33,** 1428 (1960); Aziende Chimiche Riunite Angelini Francesco, British Patent 1,057,667 (1967); *Chem. Abstr.*, **68,** 21, 717*h* (1968). [g] J. E. Jones, *J. Org. Chem.*, **10,** 537 (1965). [h] See first ref footnote *f* and A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29,** 2717 (1964). [i] Houben Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag Stuttgart, 1957, p 65. [j] Insufficient data to state potency.

TABLE II



Compd	R	R′	R″	Mp, °C	Solvent	Formula[a]	Analgetic act. (mouse), hot plate test: Route	Dose, mg/kg	Av % increase in reaction time[b]	Antiinflam act. (rat): Dose, mg/kg, po	% edema inhibition[c]
20	H	H	$CH_2CH{=}CH_2$	136–137	Cyclohexane–C_6H_6	$C_{11}H_{10}N_2O$	Ip	50	233.9	80	27.3
							Po	25	135.4	160	29.1
								50	169.8		
21	Cl	H	$CH_2CH{=}CH_2$	126–128	Ethyl orthoformate–Et_2O	$C_{11}H_9ClN_2O$	Po	50	13.3	150	46.5
								100	43.2		
22	H	H	$CH_2C{\equiv}CH$	225–226	*i*-PrOH–H_2O	$C_{11}H_8N_2O$	Po	50	155.7	40	21.8
										120	27.1
23	H	H	$CH_2CH_2CH{=}CH_2$	100–101	C_6H_6	$C_{12}H_{12}N_2O$	*d*	*d*	*d*	80	20.0
24	H	H	$CH_2CH{=}CHCH_3$ (*trans*)	83–84	H_2O	$C_{12}H_{12}N_2O$	Ip	25	11.4	160	12.0
								50	9.6		
							Po	50	23.1		
25	H	H	 (*cis*)	127–128	Cyclohexane	$C_{14}H_{14}N_2O$	Po	50	46.1	200	33.5
26	H	Cl	$CH_2CH{=}CH_2$	127–130	C_6H_6	$C_{11}H_9ClN_2O$	Po	50	20.0	20	25.6
								100	131.1	40	46.1
										80	43.7
27	H	H	$CH_2CH{=}CHC_6H_5$ (*trans*)	183–184	EtOH	$C_{17}H_{14}N_2O$	Po	100	19.8	160	6.7
28	H	H	$CH_2CH{=}C(CH_3)_2$	133–134	C_6H_6	$C_{13}H_{14}N_2O$	Po	50	7.0	160	4.6
29	CH_3O	H	$CH_2CH{=}CH_2$	127–129	C_6H_6	$C_{12}H_{12}N_2O_2$	Ip	50	30.1	80	27.8
								100	76.1		
							Po	50	50.5		
30	H	C_6H_5	$CH_2CH{=}CH_2$	177–178	EtOH	$C_{17}H_{14}N_2O$	Po	50	10.0	40	6.5
										80	7.1
31	OCH_2O		$CH_2CH{=}CH_2$	198–200	H_2O	$C_{12}H_{10}N_2O_3$	Po	50	3.0	80	3.9
32	H	CH_3O	$CH_2CH{=}CH_2$	122–125	C_6H_6	$C_{12}H_{12}N_2O_2$	Po	50	34.6	40	23.1
										80	36.8
33	CH_3	H	$CH_2CH{=}CH_2$	135–137	C_6H_6	$C_{12}H_{12}N_2O$	Po	50	11.3	80	10.7
34	H	H	$CH_2CH{=}CHCl$ (*trans*)	121–122	EtOAc	$C_{11}H_9ClN_2O$	Po	50	72.1	80	15.0
35	H	CF_3	$CH_2CH{=}CH_2$	141–142	EtOH–H_2O	$C_{12}H_9F_3N_2O$	Po	25	44.3	40	14.5
										80	39.9
36	F	H	$CH_2CH{=}CH_2$	104–105	Cyclohexane–C_6H_6	$C_{11}H_9FN_2O$	Po	50	59.0	*d*	
37	H	H		126–128	EtOAc–C_6H_6	$C_{11}H_{10}N_2O$	Po	50	41.4	80	27.1
38	H	H		135–136	Cyclohexane–C_6H_6	$C_{12}H_{12}N_2O$	Ip	50	169.0	80	1.2
								75	237.0		
	Codeine phosphate						Ip	50	156.0		
							Po	25	39.8		
								50	64.1		

[a] See footnote *a*, Table I. [b] Average of reaction time detd at 30 mn after administration of compds. [c] Per cent edema inhibition detd at 3 hr after carrageenin injection. [d] Insufficient data to state potency.

jection of carrageenin into the hind paw of the rat was employed to measure the antiinflammatory potency of these substances.[5] A citric acid spray in the guinea pig was used to test the possible antitussive activity.[6]

Tables I and II state the results of biological studies. Substances of the benzamides series were only tested as potential antiinflammatory compounds, with phenylbutazone as a standard. Substances of the (1*H*)-quinazolinones series were tested as analgetic and antiinflammatory agents. Codeine phosphate was employed for comparison in the hot plate test. Among the compounds studied, none was equal to phenylbutazone. Only compounds **20**, **22**, **34**, and **38** were equal to or better than codeine phosphate as analgetic agents.

The most interesting compound was **20**, which is twice as active as codeine phosphate after parenteral or oral administration in analgetic and antitussive screening assays. The LD_{50} for this substance administered intragastrically to mice is 438 mg/kg (400–476).[7] Neither respiratory failure nor ataractic effect were observed in laboratory animals after the administration of effective analgetic doses of the compound, which was selected for preliminary clinical trials.

(5) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(6) .R. Gösswald, *Arzneim.-Forsch.*, **8**, 550 (1958).

(7) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Experimental Section

2-(Alkenylamino)benzamides (IV). Table I. Method A.—Adapted from ref 2. To a stirred soln of the amide II (2 moles) in DMF contg anhyd Na_2CO_3 (2 moles) and maintained at 30° by external cooling, was added the alkenyl bromide (2 moles) over a period of 0.75 hr. Stirring was contd for 24 hr, the mixt was poured into cracked ice (2.5 kg) and the ppt formed was filtered, washed (H_2O) to neutrality, air-dried, and crystd from the appropriate solvent.

Method B.—Adapted from ref 3. To stirred, concd NH_4OH (2 moles of NH_3 in 135 ml) was added portionwise the isatoic anhydride III (0.25 mole) over a period of 0.25 hr. The thick suspension was dild with H_2O (50–100 ml) so that it could be stirred easily and stirring was contd for 15 hr. The ppt was suctioned off, washed (H_2O) to neutrality, dried under vacuum (10 mm) at 50°, and crystd from an appropriate solvent.

1-(Alkenyl)-4-(1*H*)-quinazolinones (V). Table II. Method C.—Adapted from ref 1. A soln of the amide IV (2 moles) in ethyl *o*-formate (2 l) was kept boiling for 35 hr while distg off the EtOH formed. The mixt was then stirred for 15 hr at room temp. The ppt formed was suctioned off, washed with ethyl *o*-formate (20–50 ml), then with pentane (100–200 ml), dried, and cryst. When the product did not cryst from ethyl *o*-formate, the excess of solvent was distd off (water bath, 10 mm), and the residue was crystd from an appropriate solvent.

***cis*-2-(2-Cyclohexenylamino)benzamide (6).**—Prepd by method A, the product crystd from DMF–H_2O as a solvate contg 1 mole of DMF per mole of amide. It also gave a solvate with C_6H_6 and had to be purified by pptg the HCl salt from Et_2O, decompg the salt with the calcd amt of NaOH in H_2O, filtration, and drying.

Conformational Studies of Amphetamine and Medicinally Important Derivatives by Nuclear Magnetic Resonance Spectroscopy†

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Conformational analysis of amphetamine free base (I), amphetamine·HCl (II), methamphetamine·HCl (III), *o*-methoxymethamphetamine·HCl (IV), and benzphetamine·HCl (V) by high-resolution nmr spectroscopy has demonstrated a high preference for the *trans*-phenylamino rotamers (Ia, IIIa, IVa, Va) in aq solution. Since the same trans conformational preference was recently established for norepinephrine (NE), the prototype for α-adrenergic catecholamines, this structural evidence is compatible with the increasingly popular view that amphetamines may exert their pharmacological activity as α-adrenergic agonists. Evidence has been obtained for the first time that intramolecular H bonding occurs in methoxyphenamine·HCl (IV) between an ammonium proton and the O of the *o*-OMe substituent. Amphetamine·HCl (II) was found to give a "deceptively simple" ABC spectrum in H_2O.

In recent years, various ring-substituted amphetamine derivatives have been studied in humans by Shulgin[1] and in animals by Smythies, *et al.*,[2,3] to derive structure–activity relationships. From human dose–response relationships for psychotomimetic phenethylamines, Shulgin, *et al.*,[4] have concluded that optimum activity is conferred by an isopropylamine side chain and triple MeO substitution. A correlation between hallucinogenic activity of drugs and their electronic

† Issued as NRCC No. 11971.

(1) A. T. Shulgin, *Experientia*, **20**, 366 (1964); *Nature (London)*, **201**, 1120 (1964).

(2) J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **216**, 128 (1967).

(3) J. M. Beaton, J. R. Smythies, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **220**, 800 (1968).

(4) A. T. Shulgin, T. Sargent, and C. Naranjo, *ibid.*, **221**, 537 (1969).