with (I) m. p. 121–122°. From the dibromide (VI), 1.6 g. of a product, m. p. 92–94°, resulted; mixed with (II) m. p. 92–94°.

Dibromides and Various Basic Media.—(1) The dibromide (V) was refluxed with stirring, with potassium acetate in absolute alcohol or in 95% alcohol for nine hours. When the reaction mixtures were cooled at least 90% of the starting material (V) was recovered.

(2) When (V) was refluxed in an absolute alcohol solution of potassium hydroxide for fifteen hours, again much of the starting material was recovered.

(3) Ten grams of (V) was refluxed with 9.1 g. of piperidine in 200 ml. of methyl alcohol for five hours. The solution turned red and all of the dibromide dissolved. On cooling the solution, 0.5 g. of (V) precipitated. The methyl alcohol was evaporated and the residue washed with water and recrystallized several times from alcohol and water to give 4.0 g. of (I), m. p. 120–122°; mixed with (I) m. p. 121–122°.

Amines and Cinnamamides.—A solution of 4 g. of (I) and 1.7 g. of piperidine in 6 ml. of 95% alcohol was refluxed for fifteen minutes and allowed to stand at room temperature for twelve hours. From the cooled solution was obtained 3.8 g. of (I). In another experiment one pellet of potassium hydroxide was added to the reaction mixture but again all of the unchanged starting material was recovered.

Similar results were obtained with morpholine and (II).

Summary

1. Methods for preparing cinnamamides and their dibromides have been described.

2. The reactivity of these dibromides with secondary amines has been studied and several examples of a new type of basic amide have been obtained for pharmacological studies.

3. The conjugated unsaturated system present in cinnamamides has been found to differ in reactivity from that present in α,β-unsaturated ketones.

LINCOLN, NEBRASKA RECEIVED MARCH 5, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY, MONTEFIORE HOSPITAL AND COLUMBIA UNIVERSITY]

Synthetic Anticonvulsants. The Preparation and Properties of Some Benzoxazoles[1]

BY W. G. BYWATER, W. R. COLEMAN, OLIVER KAMM AND H. HOUSTON MERRITT

There is some evidence that in certain series of compounds having hypnotic activity, higher molecular weight members possess anticonvulsant activity without inducing a hypnotic effect, *i. e.*, the change from 5-phenyl-5-ethylhydantoin to dilantin (5,5-diphenylhydantoin) resulted in a greatly increased convulsive threshold and no hypnotic effect. This observation prompted us to investigate the benzoxazoles for three reasons. First, benzoxazolone (2-hydroxybenzoxazole) induces a sleeping state when administered hypodermically to mice but exerted no such action when given orally.[1a] Second, benzoxazolone is relatively non-toxic since it has been isolated as the hydrolytic product of an unknown substance obtained from the urine after feeding formanilide or acetanilide to dogs.[2] Third, 2-ethylbenzoxazole also possesses mild hypnotic activity. We have, therefore, synthesized eight higher homologs of 2-ethylbenzoxazole as well as four aryl substituted derivatives and tested them for anticonvulsant activity.

Two general methods have been applied to the synthesis of 2-alkyl- or 2-arylbenzoxazoles: (I) condensation of an acid, acid chloride, amide, nitrile or ester with *o*-aminophenol by heating the mixture at or near its boiling point for several hours and distilling the product[3]; and (II) reduction of *o*-nitro acyl or aroylphenols, ring closure usually occurring during the reduction.[4] Method (I) has been employed to prepare fourteen benzoxazoles, seven of which have not been previously described. Their physical properties are recorded in Table I.

Experimental

Benzoxazoles, General Method of Preparation.—Molecular equivalents of technical *o*-aminophenol and the appropriate acid, amide or nitrile were heated to boiling for several hours in a Claisen flask. The temperature was slowly increased, as water or ammonia distilled from the flask, until the refluxing temperature remained constant. The black reaction mixture was then distilled at atmospheric pressure. The crude product, if a liquid, was dissolved in petroleum ether and washed with 10% sodium hydroxide solution. This treatment destroyed the characteristic fluorescence noted in many of the crude benzoxazoles. The oil remaining after removal of the petroleum ether was purified by distillation. The liquids were usually straw colored. The solids were pulverized and washed with 10% alkali and water before recrystallizing them from dilute alcohol or acetone. All melting points recorded in Table I are corrected while all boiling points were determined with Anschütz precision thermometers.

Ethyl α-ethyloenanthylate when heated with *o*-aminophenol did not give 1-(α-ethyl-*n*-heptyl)-benzoxazole as expected. It is the only case in which an ester was used.

We have found it convenient to prepare benzoxazolone by fusing urea with technical *o*-aminophenol at 200° (bath temperature) until ammonia is no longer evolved[5] rather than heating N-(*o*-hydroxyphenyl)-urethan.[6] The product is distilled at atmospheric pressure and recrystallized from dilute acetone (1:1 by volume). While the yield is only 35%, the reactants are inexpensive and the process is

(1) Presented in part at the meeting of the Division of Medicinal Chemistry, Detroit, Michigan, September 9–13, 1940.

(1a) Gruhzit, unpublished report.

(2) Jaffe and Hilbert, *Z. physiol. Chem.*, **12**, 229 (1887) [Beilstein, Prager, Jacobson, 4th edition, Springer, Berlin, Vol. 27, 177]; *see also* Kleine, *Z. physiol. Chem.*, **22**, 327 (1897).

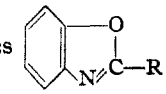
(3) (a) Ladenberg, *Ber.*, **9**, 1524 (1876); (b) Skraup, *Ann.*, **419**, 1 (1919); (c) Skraup and Moser, *Ber.*, **55**, 1080 (1922).

(4) Hubner, *Ann.*, **210**, 384 (1882).

(5) Sandmeyer, *Ber.*, **19**, 2656 (1886), prepared benzoxazolone by fusing urea and *o*-aminophenol hydrochloride.

(6) (a) Bender, *Ber.*, **19**, 2269 (1886); (b) see also Desai, *et al.*, *J. Chem. Soc.*, 1187 (1934).

TABLE I

SUBSTITUTED BENZOXAZOLES 

R	Prepared from o-aminophenol and	Boiling points, °C.		M. p., °C.	Yield, %	Nitrogen, %[i] Calcd.	Found	
Ethyl[a]	Propionitrile	216–218		.....	50			
n-Amyl*	Caproic acid	264–266	125 (2 mm.)	.....	67.2	7.40	7.25	7.28
α-Ethylpropyl*	Diethylacetic acid	250–252	110 (1 mm.)	.....	44.3	7.40	7.37	7.32
n-Hexyl[b]	Heptamide	281–283		.....	71.4			
n-Heptyl*	Caprylic acid	294–298	174–175 (4 mm.)	.....	61.5	6.45	6.28	6.38
Undecyl*	Lauramide	347–353	179–184 (1 mm.)	32 – 33	30	5.12	5.08	5.10
Pentadecyl[c]	Palmitamide	340–344		50.5– 51.5	26	4.44	4.50	4.57
Heptadecyl[c]	Stearamide	355–357		56 – 57	27.7	3.92	4.10	4.03
Δ[8]-Heptadecenyl*	Oleic acid	248–249	(2 mm.)	.....	38.6	3.94	4.00	3.96
Phenyl[d]	Benzamide	311–312		104.5–105.5	33.3			
Benzyl[e]	Phenylacetic acid	163–165	(3 mm.)	.....	82.4			
	Benzyl cyanide	321–322			40.6			
p-Chlorophenyl[f]	*p*-Chlorobenzonitrile	345–347		152.3	30.5			
Diphenylmethyl*	Diphenylacetic acid	.....		69.5– 70.5	55.1	4.91	4.97	4.82
Ethylene bis-*	Succinic acid	.....		194.5–195.5	44.5	10.60	10.35	10.39
Hydroxy[g]	Urea	335–357		142 –143	35			
Styryl[h]	Cinnamic acid	.....		83 – 84	4	6.33	6.41	6.60

[a] Skraup and Moser, ref. 3c, report b. p. 210°. [b] Skraup, ref. 3b, reports b. p. 282–5°, and m. p. 19°. [c] Fierz-David and Küster, *Helv. Chim. Acta*, **22**, 82 (1939), [*C. A.*, **33**, 6289 (1939)], report m. p. for the pentadecyl as 45.5° and for the heptadecyl as 55°. [d] Desai, *et al.*, ref. 6b, from benzaldehyde and *o*-aminophenol, m. p. 103°. [e] Skraup, ref. 3b, b. p. 325°. [f] Skraup, ref. 3b, m. p. 150°. [g] Sandmeyer, ref. 5, m. p. 137°; Desai, *et al.*, m. p. 142°. [h] Skraup, ref. 3b, reports this compound to be an oil, b. p. 325–335°; Dent, Thesis Presented to the Graduate Faculty of the University of Cincinnati, 1942, p. 50, found the b. p. 193–194° (2 mm.) and m. p. 79–80°. Our product boils 220–221° (14 mm.) before recrystallization from ligroin. A second product, b. p. 87–89° (14 mm.), which has not been identified, was also obtained from our reaction. This compound with alcoholic hydrogen chloride readily forms a hydrochloride, which when recrystallized from absolute alcohol, melts 154–155° (with sublimation) [*Anal.* Found: C, 56.65; H, 5.11; N, 8.2; Cl, 20.38]. [i] Micro-analyses by the Micro-analytical Section of Parke, Davis and Company. * New compound.

not time-consuming. Butyl urea and *o*-aminophenol also react to give a 10.2% yield of benzoxazolone. When equal molecular equivalents of urethan and *o*-aminophenol are fused together, the yield of benzoxazolone was 53%.

Pharmacology.—Preliminary anticonvulsant tests in the cat with selected members of this series (Table II) using the method previously described[7] demonstrated definite activity of the series of compounds when given in large doses. The methyl, ethyl, hexyl and benzyl benzoxazoles

TABLE II

ANTICONVULSANT ACTIVITY

Benzoxazole	Activity		Toxicity[h] (LD_{50}), g./kg.
2-Hydroxy	–	0.25[a]	0.94
2-Methyl[b]	++++	0.5	1.10
2-Ethyl[c]	+++	0.37	1.0
2-*n*-Amyl	+++	0.15	1.3
2-α-Ethylpropyl	+++	0.25	1.3
2-*n*-Hexyl	+++	1.0	2.75
2-*n*-Heptyl	++++	0.38	2.3
2-Pentadecyl	+++	0.41	5.0+
2-Heptadecyl	–	0.66	10.5+
2-(8-Heptadecenyl)	–	0.9	....
2-Phenyl	–	0.3	
	–	1.40[a]	5.0+
2-Benzyl	++++	0.3	1.75
2-*p*-Chlorophenyl	±	.75[a]	6.0
2-Diphenylmethyl	–	.23[a]	0.05[g]
2-Methylbenzothiazole[b]	±	.1[d]	....
	–	.4[d]	....
2-Aminobenzimidazole[b]	–	.43	
	–	.476[d]	0.60
	–	.083[e]	
Benzimidazole[b]	–	.138	....
	–	.147[d]	....
	–	.242	....
	++++	.47	....
N-Benzoylbenzimidazole[f]	±	.5	....
Dilantin sodium	++++	.05	0.5

[a] Solid, administered in capsules orally. [b] Eastman Kodak Company preparation. [c] Possesses hypnotic activity; MED = 0.75 g./kg. [d] Lethal within twenty-four hours. [e] Administered as the hydrochloride. [f] M. p. 91.5–93°. [g] MLD for white mice intraperitoneally; administered as a solution in 50% alcohol. We are indebted to Mr. L. W. Rowe for these data. [h] For white mice orally.

have been reported as active synthetic drugs[8] and are included in the present table for comparative purposes. A ++++ rating was given if the convulsive threshold is elevated to more than 50 ma., +++ if raised to 50 ma., ++ if increased by 20 to 30 ma., and + if raised by 5 to 15 ma., two hours after treatment. The minus sign indicates no activity. The figure following the rating in the activity column is the dose in g./kg. at which the rating was established. All the compounds were given orally by intubation unless

(7) Putnam and Merritt, *Science*, **85**, 525 (1937).

(8) Putnam and Merritt, *Arch. Neurol. Psychiat.*, **45**, 505 (1941).

otherwise noted in the table. The toxic dose for white mice was determined by Dr. O. M. Gruhzit by oral administration of the drug suspended in acacia and is the amount at which 60% of the animals survived, expressed as g./kg. These values are to be regarded as approximate since some of the compounds were so non-toxic the LD-50 was not determined; however, they served as a guide in choosing doses for the cat test.

Eight of the benzoxazoles exhibited definite anticonvulsant activity at the dose levels tested. The relative activity of the compounds in this series was not determined in these preliminary tests Benzyl benzoxazole was chosen for further study because it was apparently the most active, least soporific and most readily available compound of this series. The results of the tests with 2-methylbenzothiazole were invalidated since the animals died within twenty-four hours. Benzimidazole was active at a relatively high dose level; however, benzoylation of it destroyed its anticonvulsant properties. Neither 2-aminobenzimidazole nor benzoxazolone was active.

Summary

1. A series of 2-alkylbenzoxazoles have been prepared and tested for anticonvulsant activity.

2. Eight of the thirteen derivatives tested possessed anticonvulsant activity when administered in large doses.

DETROIT, MICH.
NEW YORK, N. Y. RECEIVED FEBRUARY 1, 1945

[CONTRIBUTION FROM THE STERLING CHEMICAL LABORATORY OF YALE UNIVERSITY]

American Musk. IV. On the Biological Origin of Animal Musk. Two More Large Ring Ketones from the Muskrat

BY PHILIP G. STEVENS

In the first paper[1] of this series it was shown that the musk of the muskrat, unlike that of the musk-deer and civet cat, consists mainly of a *pair* of odd-numbered macro-cyclic ketones, normuscone and dihydrocivetone. This suggested that these ketones[2] constitute a regular series analogous to that of the naturally occurring fatty acids. At that time, because of insufficient material, it was not possible to show the presence of the expected lower and higher macro-cyclic compounds. Now, however, examination of the low and high boiling fractions of the ketone mixture[3] resulting from the oxidation of the crude carbinols obtained from many thousands of glands, has indeed revealed the presence of two more macrocyclic ketones: cyclotridecanone and cyclononadecanone. Furthermore, the relative amounts of these ketones parallel closely the amounts of the corresponding fatty acids with one more carbon atom, found in total rodent fat[4] (Table I). Thus it is clear that these large ring ketones constitute a regular series like the fatty acids.

TABLE I

% Fatty acids[a] Total rodent fat[4,c]		% Macro-cyclic ketones[b]	
C_{10}	0.3	C_9	..
C_{12}	0.7	C_{11}	..
C_{14}	8.1	C_{13}	1.0[d]
C_{16}	29.9	C_{15}	40.0
C_{18}	59.3	C_{17}	58.0
C_{20}	1.5	C_{19}	0.7
C_{22}	0.2	C_{21}	?
Above C_{22}	..	C_{23}	..

[a] Since the unsaturated acids could yield the saturated ketones upon subsequent hydrogenation, these values include both saturated and unsaturated acids. [b] Approximate only. [c] Professor J. L. E. Erickson of Louisiana State University has kindly informed me that a preliminary analysis of the fat of the muskrat scent glands indicates the presence of C_{14}, C_{16}, C_{18} and C_{20} acids, and also a high percentage of acids above C_{22}, a finding in harmony with the results of Simmons and Hills, *Analyst*, **58**, 154 (1935). [d] This value may seem low, considering the percentage of myristic acid, but it must be remembered that the C_{13} ring is still in that size range where rings are hard to form, as evidenced by the relatively low yields obtained by Ziegler and Aurnhammer (*Ann.*, **513**, 43 (1934)) of the C_{13} ketone compared to that of the C_{15} and larger ketones.

The structures of these two ketones, which are the first cyclic compounds yet found in nature with 13 or 19 atoms in the ring, were conclusively proven as shown in Table II.

The establishment of this series of macro-cyclic ketones from one animal is the first positive evidence[5] that there is an intimate biological association of these ketones with the corresponding fatty acids. Ruzicka[6] made this suggestion in 1926, pointing out a similarity between the structures of muscone and civetone with palmitic and oleic acids, respectively. The chemistry of this relationship, while still uncertain, most probably involves the change: C_{2n} fatty acid $\rightarrow$ C_{2n-1} ring ketone, a change which could be valid for all ketones except muscone with its β methyl

(1) Stevens and Erickson, THIS JOURNAL, **64**, 144 (1942).

(2) And of course the corresponding carbinols.

(3) Many thanks are due to Givaudan-Delawanna, Inc., of New York, now in commercial production of this musk—"Musk Zibata"—(U. S. Patent 2,364,041), who so generously made this material available.

(4) Longenecker and Hilditch, *Biochem. J.*, **32**, 784 (1938).

(5) Evidence of a negative character comes from the fact that the anatomically similar beaver scent glands contain no large ring compounds, and little or no fatty acid; Stevens, THIS JOURNAL, **65**, 2471 (1943).

(6) Ruzicka, *Helv. Chim. Acta*, **9**, 230, 1008 (1926).