leaeba and roots of *A. indica* supplied to us by the Ayurvedia Aushadi Bhandar, Bombay, India. The Wisconsin school has since kindly identified our samples as *A. indica*. Dean Heber W. Youngken, Jr., of the College of Pharmacy, University of Rhode Island, also has confirmed the identity of our samples as *A. indica* by comparison with an authentic sample of *A. indica* from the Harvard University Botanical Museum. Microscopic studies of the two samples reveal that both are from the same plant and tissues including starch granules and cellular components in both dried root samples seem to be identical. Dean Youngken has informed us that comparative pharmacognostic studies have not been concluded due to the non-availability of an authentic specimen of *Cocculus leaeba DC* and lack of sufficient information about it in the literature.

Acknowledgments.—We are indebted to Prof. S. Morris Kupchan, Dean Heber W. Youngken, Jr., and Prof. M. Pailer. We also thank Dr. Edward Pelican for pharmacological screening of aristolochic acid.

Some 2-Substituted 2H-1,4-Benzoxazin-3(4H)-ones

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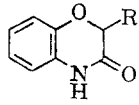
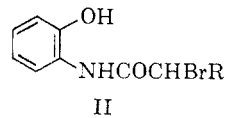
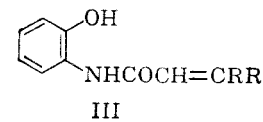
Although the heterocyclic system 2H-1,4-benzoxazin-3(4H)-one (I, R = H) has been known[1] since 1879, very few 2-substituted de-



I



II



III

rivatives of the ring system have been reported. The 2-methyl,[2] 2,2-dimethyl,[3] the 2-isopropyl and 2-isobutyl[4] and the 2-benzyl[5]

(1) P. Fritzche, *J. prakt. Chem.*, [2] **20**, 288 (1879).
(2) C. A. Bischoff, *Ber.*, **33**, 924 (1900).
(3) C. A. Bischoff, *ibid.*, **33**, 931 (1900).
(4) G. Sanna and A. Vacca, *Gazz. chim. ital.*, **62**, 555 (1932).
(5) J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 739 (1955).

compounds have been prepared. However, no report of any study of biological activity was found.

As part of our program on central nervous system agents, a number of compounds of type I have been prepared, where R is an alkyl group of one to six carbon atoms, benzyl or cyclohexyl. These were prepared by the known procedure[4,6] of cyclizing an α-halo-*o*-hydroxyalkanoylanilide by treatment with aqueous alkali. The compounds we have prepared and studied are characterized in Table I.

As intermediates we have used the α-bromo-*o*-hydroxyalkanoylanilides II (Table II), and these were prepared by the reaction of an α-bromo acid chloride with two molar equivalents of *o*-aminophenol in dioxane. Yields of crystalline product satisfactory for cyclization were very good, but in some cases it was difficult to obtain analytically pure bromo anilides, apparently because the tendency to cyclize during recrystallization resulted in contamination with the cyclized product. In the case of the condensation of α-bromohydrocinnamoyl chloride with *o*-aminophenol, the intermediate bromo anilide could not be isolated at all, but instead the cyclized product, 2-benzyl-2H-1,4-benzoxazin-3(4H)-one, was obtained in good yield. This compound has been prepared previously[5] by reduction of the 2-benzylidene compound and physical constants agree well with those reported.

The compounds α-bromo-α-ethyl-*o*-hydroxybutyranilide and α-bromo-α-ethyl-*o*-hydroxycaproanilide were also prepared. However, several attempts to cyclize these compounds to the 2,2-diethyl and 2-ethyl-2-butyl derivatives of I were entirely unsuccessful. Mild conditions resulted only in recovery of unchanged bromo anilides, while more drastic conditions gave only intractable tars.

It is conceivable that dehydrobromination of the compounds of type II might proceed by formation of an α,β- double bond to give the *o*-hydroxyalkenoylanilides of type III, isomeric with compounds of type I. Therefore, for comparison, most of the compounds of type III corresponding to those of type I also have been prepared from the appropriate unsaturated acid chloride with two molar equivalents of *o*-aminophenol in absolute ether. Moureu[7] prepared *o*-hydroxyacrylanilide from acrylyl chloride and *o*-aminophenol and Loudon and Ogg[5] obtained the same compound by the action of alkali on *o*-hydroxy-β-chloropropionanilide. Huisgen[8] and co-workers have prepared *o*-hydroxycrotonanilide from crotonyl chloride and *o*-amino-

(6) O. Aschan, *Ber.*, **20**, 1523 (1887).
(7) C. Moureu, *Ann. chim. et phys.*, [7] **2**, 186 (1894).
(8) R. Huisgen, H. Eder, L. Blazejewicz, and E. Mergenthaler, *Ann.*, **573**, 121 (1951).

TABLE I

2H-1,4-BENZOXAZIN-3(4H)-ONES (I)

R	Yield, %[a]	M.p., °C.	Mol. formula	Calcd., %			Found, %		
				C	H	N	C	H	N
CH_3[b]	84.5	142–143	$C_9H_9NO_2$	66.25	5.56	8.59	66.29	5.48	8.49
C_2H_5	82	103.5–104	$C_{10}H_{11}NO_2$	67.76	6.26	7.90	67.97	6.21	7.92
n-C_3H_7	90	85–85.5	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	69.11	6.90	7.44
i-C_3H_7[c]	54	118.5	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	69.15	6.96	7.28
n-C_4H_9	43	100.5–101.5	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	70.01	7.22	6.81
i-C_4H_9[d]	33	92	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	70.32	7.42	6.89
n-C_5H_{11}	30	81–82	$C_{13}H_{17}NO_2$	71.20	7.82	6.39	71.07	7.71	6.37
n-C_6H_{13}	20	85–86	$C_{14}H_{19}NO_2$	72.06	8.21	6.00	71.83	8.14	6.15
$C_6H_5CH_2$[e]	54	160–161	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	75.19	5.48	5.93
C_6H_{11}[f]	37	149.5–150.5	$C_{14}H_{17}NO_2$	72.70	7.41	6.05	72.64	7.43	6.07

[a] Yields of analytically pure material; yield of once-crystallized material usually 90% or better. [b] Lit.[3] m.p. 143–144°. [c] Lit.[4] m.p. 125°. [d] Lit.[4] m.p. 128°. [e] Lit.[5] m.p. 159°. [f] Cyclohexyl.

TABLE II

α-BROMO-*o*-HYDROXYALKANOYLANILIDES (II)

R	Yield, %[a]	M.p., °C.[b]	Mol. formula	Calcd., %			Found, %		
				C	H	N	C	H	N
CH_3	87	97.5–98	$C_9H_{10}BrNO_2$	44.29	4.13	5.74	44.53	4.20	6.00
C_2H_5	89	96.5–98	$C_{10}H_{12}BrNO_2$	46.52	4.69	5.43	46.93	4.80	5.83
n-C_3H_7	85	87.5–88.5	$C_{11}H_{14}BrNO_2$	48.54	5.18	5.15	49.15	5.50	5.05
i-C_3H_7[c]	71	110–110.5	$C_{11}H_{14}BrNO_2$	48.54	5.18		48.44	5.20	

n-C_4H_9[d]	82	66–68	$C_{12}H_{16}BrNO_2$	50.35	5.64	4.89	50.60	5.68	4.90
i-C_4H_9[e]	63	115–116	$C_{12}H_{16}BrNO_2$	50.35	5.64	4.89	50.74	5.77	5.10
n-C_5H_{11}	91	75–76	$C_{13}H_{18}BrNO_2$	52.01	6.04		54.01	6.37	
n-C_6H_{13}	81	57–59	$C_{14}H_{20}BrNO_2$	53.51	6.42		55.45	6.77	

[a] Yield is of once-recrystallized material suitable for cyclization, but not necessarily analytically pure. [b] Melting point is of the analytical sample. [c] Lit.[4] m.p. is 114°. [d] This reaction was run in ether; when carried out in dioxane an oil was obtained. [e] Lit.[4] m.p. is 115°.

TABLE III

o-HYDROXYALKENOYLANILIDES (III)

					Calcd., %			Found, %		
R	R′	Yield, %	M.p., °C.	Mol. formula	C	H	N	H	H	N
H	H[a]	58	119–120	$C_9H_9NO_2$	66.25	5.56	8.59	65.93	5.61	9.09
H	CH_3[b]	41	130–131	$C_{10}H_{11}NO_2$	67.76	6.26	7.90	67.70	6.29	7.85
H	C_2H_5	66	107–108	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	68.99	6.90	7.58
CH_3	CH_3	72	150–151.5	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	68.92	6.86	7.65
H	n-C_3H_7	77	64–65	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	70.19	7.63	6.88
H	i-C_3H_7	72	83–85	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	69.82	7.44	7.08
H	n-C_4H_9	75	75–76	$C_{13}H_{17}NO_2$	71.20	7.82	6.39	71.21	7.84	7.02
H	n-C_5H_{11}	75	73–74	$C_{14}H_{19}NO_2$	72.06	8.21	6.00	71.93	8.20	5.95

[a] Lit.[5] m.p. is 122–123°; lit.[7] m.p. is 123–124°. [b] Lit.[8] m.p. is 138°.

phenol. They also prepared *o*-hydroxycinnamanilide, isomeric with 2-benzyl-2H-1,4-benzoxazin-3(4H)-one, and reported it to melt at 164°, whereas the 2-benzyl heterocycle melts at 160–161°.

The compounds of type III which were prepared are characterized in Table III. In all cases, they are different from the compounds prepared by alkaline treatment of type II compounds. Thus, it may be assumed that the latter reaction does indeed produce compounds of type I rather than of type III. Furthermore, those of type III do not give type I compounds on treatment with alkali under the conditions used for preparing type I from type II.

The compounds in Table I were screened for anticonvulsant and for hypnotic action in white rats. They were administered orally, as suspensions with 5% gum acacia, and at doses of 500 and 1000 mg./kg. varying degrees of depression were noted but none of the compounds showed any true hypnotic action. The method of Everett and Richards[9] was used to test for anticonvulsant action. Against 125 mg./kg. of pentylenetetrazole, none of the compounds, in doses as high as 2000 mg./kg., orally, showed a useful degree of anticonvulsant activity.

Experimental[10]

α-Bromo Acid Chlorides.—The known α-bromo acid chlorides were prepared by the action of thionyl chloride on the α-bromo acid if commercially available. Otherwise, the acid was converted to the acid chloride and brominated by bromine in the presence of red phosphorus.

α-Bromocyclohexaneacetyl Chloride.—This new compound was prepared by the bromination of 64 g. of cyclohexaneacetyl chloride with 64 g. of bromine and 0.5 g. of red phosphorus at 120–125° in 5.5 hr. The product was distilled twice to give 77 g. (80% yield) of material boiling at 130–135° (24 mm.). The product was not analyzed, but it gave the desired final product after condensation with *o*-aminophenol and subsequent cyclization.

α-Bromo-*o*-hydroxyalkanoylanilides (Table II).—To a stirred solution of 0.3 mole of *o*-aminophenol in 250–300 ml. of purified dioxane at about 30° was added 0.15 mole of the α-bromo acid chloride in about 5 min. The resulting exothermic reaction raised the internal temperature 15–30° in a few minutes, and *o*-aminophenol hydrochloride precipitated rapidly. The reaction was completed by a further period of 0.5–2 hr. on the steam bath. The cooled mixture was filtered, and the precipitate was washed with hot benzene, which was added to the filtrate. The collected *o*-aminophenol hydrochloride generally amounted to 95–100% of the calculated weight. The filtrate then was evaporated to dryness under vacuum, and the dark brown residue was extracted with hot benzene. From the chilled extract was obtained the crude anilide which usually melted only a few degrees below the analytical sample and was sufficiently pure for cyclization. Further recrystallizations from mixtures of petroleum ether (75–90°) and chloroform or benzene gave the analytically pure products, except in the case

(9) G. M. Everett and R. K. Richards, *J. Pharmacol. Exptl. Therap.*, **81**, 402 (1944).

(10) Melting and boiling points are uncorrected. Analyses are by Huffman Microanalytical Laboratories and Micro-Tech Laboratories.

of the amyl and hexyl derivatives, which could not be obtained entirely pure after 6 and 4 recrystallizations, respectively.

α-Bromo-α-ethyl-*o*-hydroxybutyranilide.—This was prepared in the usual manner from *o*-aminophenol and α-bromo-α-ethylbutyryl chloride, a yield of 71.5% of red product, m.p. 100.5–101.5°, being obtained. The analytical sample was recrystallized twice more from petroleum ether (75–90°) with charcoal decolorization to give light cream-colored crystals, m.p. 101.5–102°.

Anal. Calcd. for $C_{12}H_{16}BrNO_2$: C, 50.35; H, 5.64; Br, 27.92. Found: C, 50.43; H, 5.45; Br, 27.63.

α-Bromo-α-ethyl-*o*-hydroxycaproanilide.—This compound was obtained in 82% yield from *o*-aminophenol and α-bromo-α-ethylcaproyl chloride. The once-crystallized product melted at 93–95°. Three crystallizations from mixtures of petroleum ether and chloroform gave nearly-white, fine needles, m.p. 95–95.5°.

Anal. Calcd. for $C_{14}H_{20}BrNO_2$: C, 53.51; H, 6.42; N, 4.46. Found: C, 53.50; H, 6.20; N, 4.28.

α-Bromo-*o*-hydroxycyclohexaneacetanilide.—This compound was isolated as a dark red viscous oil which resisted all efforts at crystallization. However, it gave the desired cyclohexyl compound (I, R = cyclohexyl) upon cyclization.

2H-1,4-Benzoxazin-3(4H)-ones (Table I).—One-tenth mole of finely-powdered α-bromo-*o*-hydroxyalkanoylanilide was added rapidly to about 200 ml. of a stirred 1 *N* sodium hydroxide solution at 40–50°. The phenol dissolved readily and a precipitate began to appear within a few minutes. The mixture was heated by steam for 30 min., then was allowed to stand at room temperature for several hr. The chilled mixture was filtered, and the collected brown solid was washed with cold water. Recrystallization of the crude products from petroleum ether with charcoal decolorization gave the pure products as white, nicely crystalline solids, insoluble in water and soluble in the usual organic solvents. Yields generally decreased with increasing size of the alkyl group in the 2-position.

α,β-Unsaturated Acid Chlorides.—These were prepared in the usual way by the action of thionyl chloride on the unsaturated acid. **2-Octenoyl chloride** appears not to have been described previously. It was obtained in 80% yield by the action of 1.5 moles of purified thionyl chloride per mole of 2-octenoic acid in anhydrous benzene, allowed to react spontaneously for 2 hr., then heated to reflux for 45 min. longer. Distillation gave the product as a colorless liquid, boiling at 93–95° (15 mm.), $n^{25}D$ 1.4630.

Anal. Calcd. for $C_8H_{13}ClO$: C, 59.81; H, 8.16. Found: C, 59.28; H, 8.09.

***o*-Hydroxyalkenoylanilides (Table III).**—To a stirred suspension of 0.2 mole of finely ground *o*-aminophenol in 200 ml. of anhydrous ether was added a solution of the unsaturated acid chloride in 50 ml. anhydrous ether, keeping the temperature below 30° by tap-water cooling. After the addition of the acid chloride was complete, the suspension was stirred for an additional 2 hr. Water was added to dissolve the *o*-aminophenol hydrochloride. The ether layer was separated, washed, dried and evaporated. The residue was recrystallized from mixtures of petroleum ether and chloroform to give the pure products as white, nicely crystalline materials, insoluble in water and soluble in the usual organic solvents and in sodium hydroxide solution.

Acknowledgment.—We are indebted to the Pharmacology Department of The Wm. S. Merrell Co. Division of Richardson-Merrell Inc. for the pharmacological results.