

then heated briefly, diluted with water, and the precipitate was recrystallized from ethanol-hexane to give 4.5 g. (54%) of product, m.p. 201–202°.

**5-Aminodibenzo[a,d]cycloheptadiene-5-carboxamide.**—A mixture of 5-chlorodibenzo[a,d]cycloheptadiene-5-carbonyl chloride<sup>16</sup> (3.0 g., 0.01 moles) and liquid ammonia (25 ml.) was stirred overnight in a pressure bottle. The ammonia was evaporated and the residue was slurried with a little water. The chlorine-free, insoluble material was recrystallized from ethanol-hexane giving 0.7 g. (28%) of amide, m.p. 281–282° dec.

**5-Oximinodibenzo[a,d]cycloheptadiene.**—Dibenzo[a,d]cycloheptadiene-5-one (100 g., 0.48 mole) and hydroxylamine hydrochloride (84.5 g., 1.2 moles) were heated under reflux for 96 hr. with a 1:1 mixture of aqueous pyridine (610 ml.). The solution was evaporated *in vacuo* and the residue taken up in chloroform. The solution was washed with water, dried, and the solvent removed giving 89 g. (83%) of the oxime m.p. 161–167°. A purified sample had m.p. 167–170° (from ethanol).

**5-Acetamidodibenzo[a,d]cycloheptadiene.**—A solution of the preceding oxime (12.0 g., 0.054 mole) in ethanol (250 ml.) was saturated with ammonia and hydrogenated at 3.5 kg./cm. and ambient temperature in the presence of 10% palladium-on-charcoal. The theoretical quantity of hydrogen was consumed after 14 hr. The catalyst was filtered, the solution evaporated *in vacuo*, and the residue was warmed on the steam bath for 20 min. with acetic anhydride (100 ml.). Water (500 ml.) was added and the mixture was heated to boiling. The aqueous layer was decanted and the solid material was triturated with a little methanol and recrystallized once from dioxane to give 5.3 g. (39%), m.p. 280–282°.

**5-Dibenzo[a,d]cycloheptadienyl Isocyanate.**—Silver cyanate (22.5 g., 0.15 mole) was added to a solution of 5-chlorodibenzo[a,d]cycloheptadiene<sup>16</sup> (22.9 g., 0.10 mole) in anhydrous acetonitrile (140 ml.). The mixture was slowly heated to the boiling

point and then kept under reflux for 12 hr. in the dark. Filtration, followed by evaporation of the solvent, left a solid residue from which the product was isolated by trituration with hot hexane. Removal of the hexane left 17.4 g. (74%) of the isocyanate, m.p. 62–63°, unchanged on recrystallization from pentane.

*Anal.* Calcd. for  $C_{16}H_{13}NO$ : C, 81.68; H, 5.57; N, 5.95. Found: C, 81.49; H, 5.74; N, 5.82.

**5-Dibenzo[a,d]cycloheptadienylurea.**—A solution of the isocyanate (6.3 g., 0.027 mole) in dry acetone (40 ml.) was added dropwise while stirring to concentrated ammonium hydroxide (30 ml.). The reaction mixture was heated under reflux for 0.5 hr., cooled, diluted with water, and the precipitate was collected. Recrystallization from a 1:1 ethanol-ethylene dichloride mixture gave 3.8 g. (56%) of the urea as fine needles, m.p. 282–283° dec.

**1-(5-Dibenzo[a,d]cycloheptadienyl)-3-acetylurea.**—Acetyl chloride (12 ml.) was added dropwise to a stirred suspension of the preceding compound (2.8 g., 0.11 mole) in dry pyridine (65 ml.), the internal temperature being kept below 20° by means of external cooling. The mixture was then heated on the steam bath for 1 hr., cooled, and treated with ethanol (25 ml.) followed by water (300 ml.). The precipitate was collected, washed with water, and a little cold ethanol. Recrystallization from ethanol (charcoal) gave 1.4 g. (44%), m.p. 203–204°.

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## The Anticonvulsant Activity of 3-Acylindoles Compared with Phenobarbital

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The anticonvulsant activity of various 3-acylindoles was determined and the structure-activity relationship studied. The optimum compound tested was 3-isobutyryl-1-methylindole.

Numerous workers have implicated serotonin<sup>1a</sup> as having some important role in central nervous system function. For a summary of the uncertain state of affairs regarding the possible function of this amine in the CNS one should consult the concluding remarks of Erspamer's review.<sup>1b</sup>

Bonnycastle<sup>2</sup> has shown in the rat that elevation of brain serotonin is a consequence of the administration of various central nervous system depressants. On the other hand, many simple indole derivatives show predominately excitatory actions.<sup>3</sup> During the course of routine screening, it was noted that a considerable number of 3-acylindoles had anticonvulsant action. The present report describes the study of a series of 3-acylindoles as anticonvulsants and the correlations between structure and activity are noted.

**Pharmacological Methods.**—All compounds were injected intraperitoneally in freshly prepared solutions or suspensions using 0.25% aqueous methyl cellulose. Injection volume was

0.01 ml./g. body weight. A Hans Tech electroshock apparatus delivering current of variable intensity for 0.2 sec. through ear clip electrodes was utilized.

**Mice.**—Groups of 15 Carworth Farms male mice weighing 18–22 g. were injected with test compound at 100 mg./kg. Similar groups were injected with phenobarbital sodium (10 and 20 mg./kg.) and vehicle in each experiment. Thirty min. after administration (separate experiments at 30, 60, and 90 min. after administration had shown that peak effect occurred in representative compounds at 30 min.) the animals were subjected to electroshock. Current strength in milliamperes was varied in 0.05 log units. The "up-down" procedure described by Kimball<sup>4</sup> was utilized to estimate the log of the current strength causing tonic extensor seizures in 50% of the animals and its 95% confidence interval.

**Rats.**—The procedure described for mice was utilized with the following changes: (1) rats (Upjohn-Sprague-Dawley ancestry) weighing 80 to 150 g. were utilized (within an experiment the weight range was  $\pm 10$  g. of the mean); (2) phenobarbital sodium controls received 9 and 18 mg./kg.; (3) test compounds were injected at 25 mg./kg. Test compounds were evaluated relative to the control groups in each experiment. Compounds were reported as active if the current strength 50 (test compound) was greater than the upper 95% confidence interval of untreated controls. The activity of test compound relative to phenobarbital was based upon the effect of test compound relative to

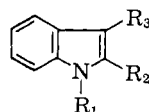
(1) (a) For a recent review on serotonin see V. Erspamer in "Progress in Drug Research," Vol. 3, E. Jucker, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 151; (b) p. 329.

(2) D. D. Bonnycastle, M. F. Bonnycastle, and E. G. Anderson, *J. Pharmacol. Exptl. Therap.*, **135**, 17 (1962).

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TABLE I  
STRUCTURES AND ANTIELECTROSHOCK ACTIVITIES (RELATIVE TO PHENOBARBITAL) OF VARIOUS 3-ACYLINDOLES



No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Activity <sup>a</sup>		Reference to source or method of synthesis
				Mice <sup>b</sup>	Rats <sup>c</sup>	
1	H	H	CHO	0		d
2	H	H	COCH <sub>3</sub>	<10		d
3	CH <sub>3</sub>	H	COCH <sub>3</sub>	<10		e
4	H	CH <sub>3</sub>	COCH <sub>3</sub>	<10		d
5	CH <sub>3</sub>	CH <sub>3</sub>	COCH <sub>3</sub>	<10		f
6	COCH <sub>3</sub>	H	COCH <sub>3</sub>	<10		g
7	H	H	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	<10		h
8	H	H	CH <sub>2</sub> COCH <sub>3</sub>	<10		i
9	H	H	CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>2</sub> OH	0	0	h
10	H	H	COC <sub>2</sub> H <sub>5</sub>	>10	<9	e
11	CH <sub>3</sub>	H	COC <sub>2</sub> H <sub>5</sub>	>10	0	e
12	H	H	COCH=CH <sub>2</sub>	0		e
13	CH <sub>3</sub>	H	COCH(CH <sub>3</sub> ) <sub>2</sub>	>20	=9	f
14	C <sub>2</sub> H <sub>5</sub>	H	COCH(CH <sub>3</sub> ) <sub>2</sub>	<10		f
15	H	H	COCH(CH <sub>3</sub> ) <sub>2</sub>	=10	<9	h
16	H	H	COC(CH <sub>3</sub> ) <sub>2</sub> OH	<10 <sup>j</sup>	<9	h
17	CH <sub>3</sub>	H	CHOHC(CH <sub>3</sub> ) <sub>2</sub> OH	<10		h
18	C <sub>2</sub> H <sub>5</sub>	H	COC(CH <sub>3</sub> ) <sub>2</sub> OH	<10	<9	f
19	H	H	CHOHC(CH <sub>3</sub> ) <sub>2</sub> OH	>10	0	h
20	H	H	C(=NOH)C(CH <sub>3</sub> ) <sub>2</sub> OH	0	<9	h
21	CH <sub>3</sub>	H	COC(CH <sub>3</sub> ) <sub>2</sub> OH	>10 <sup>j</sup>	<9	h
22	C <sub>2</sub> H <sub>5</sub>	H	COC(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> OH	<10	=9	f
23	CH <sub>3</sub>	H	COC(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> OH	>10	<9	f
24	H	H	COC(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> OH	<10 <sup>j</sup>		f
25	H	H	COC <sub>2</sub> H <sub>7-n</sub>	<10		f
26	H	H	CH <sub>2</sub> COC <sub>2</sub> H <sub>5</sub>	<10		f
27	H	CH <sub>3</sub>	COCH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	<10		k
28	H	CH <sub>3</sub>	COCH(CH <sub>3</sub> )C <sub>2</sub> H <sub>5</sub>	<10		k
29	H	H	CH <sub>2</sub> CH <sub>2</sub> COCH <sub>3</sub>	<10		l
30	H	H	COC <sub>6</sub> H <sub>5</sub>	0		m
31	CH <sub>3</sub>	H	COC <sub>6</sub> H <sub>5</sub>	0		m
32	H	CH <sub>3</sub>	COC <sub>6</sub> H <sub>5</sub>	0		m
33	CH <sub>3</sub>	CH <sub>3</sub>	COC <sub>6</sub> H <sub>5</sub>	<10		m
34	H	H	COCH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	0		n
35	CH <sub>3</sub>	H	COCH(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	<10		n
36	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	COC <sub>6</sub> H <sub>5</sub>	0		n
37	H	H	COC(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> OH	<10		n
38	CH <sub>3</sub>	H	COC(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> OH	0		n

<sup>a</sup> Activity when tested is indicated by the following symbols: 0, tested but not different from control; <9, etc., significant threshold increase but less than phenobarbital at the indicated dose; =10 not significantly different from phenobarbital at the indicated dose; >10 more active than phenobarbital at the stated dose. <sup>b</sup> 100 mg./kg. intraperitoneally 30 min. before electroshock. <sup>c</sup> 25 mg./kg. intraperitoneally 30 min. before electroshock. <sup>d</sup> Available from Aldrich Chemical Co., Milwaukee, Wis. <sup>e</sup> J. Szmuszkowicz, *J. Am. Chem. Soc.*, **82**, 1180 (1960). <sup>f</sup> See Experimental for details of synthesis. <sup>g</sup> J. E. Saxton, *J. Chem. Soc.*, 3592 (1952). <sup>h</sup> See footnote 7. <sup>i</sup> J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952). <sup>j</sup> In separate tests in mice at 30, 60, and 90 min. after administration it was found that 30 min. was peak effect time. <sup>k</sup> See footnote 8. <sup>l</sup> J. Szmuszkowicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957). <sup>m</sup> See footnote 6. <sup>n</sup> J. Szmuszkowicz, *J. Org. Chem.*, **27**, 1582 (1962).

the current strength 50 and 95% confidence intervals of the standard.

**Chemistry.**—The structures of the various indole derivatives tested are listed in the Table. References are given to compounds described in the literature. New compounds and old compounds prepared by new methods are described in Experimental.

## Discussion

### Structure vs. Anticonvulsant Activity Relationship.

**Effect of Substitution on the Indole Nitrogen.**—Examination of Table I shows that methylation of the indole nitrogen decreased activity in two cases (compare 19 and 17; 37 and 38), had no effect in four cases (4 and

5; 2 and 3; 10 and 11; 30 and 31) and increased activity in five cases (34 and 35; 32 and 33; 15 and 13; 16 and 21, 24 and 23). Replacement of methyl by ethyl decreased activity in all three cases (13 and 14; 21 and 18; 23 and 22). Replacement of hydrogen by acetyl was without effect (6 and 2).

**Effect of Substitution on the 2-Position of the Indole Ring.**—Methylation of the 2-position was without effect in three cases (2 and 4; 30 and 32; 3 and 5) and increased activity in one case (31 and 33). Replacement of methyl by phenyl decreased activity (33 and 36).

**Effect of Substitution on the 3-Position of the Indole Ring.**—Although in the 4-carbon unbranched alkyl

compounds the location of the carbonyl in relation to the indole ring did not seem to influence activity (compare **25**, **26**, **29**), in the 3-carbon chain  $\alpha$ -carbonyl was superior (**10** and **8**). The  $\alpha$ -carbonyl was also superior in branched compounds (compare **15**, **9**, **7** and **16**, **20**). Three carbons appeared the optimum in the unbranched  $\alpha$ -carbonyl sidechain (compare **1**, **2**, **10**, **25**). However, if the chain was branched an additional carbon increased activity (**10**, **15**). Hydroxyl on the  $\beta$  carbon (of a 4-carbon branched side chain) increased activity in mice only if the  $\alpha$  carbonyl was reduced to hydroxyl (**19**, **16**, **15**). However, in rats, the second hydroxyl reduced activity (**15**, **19**, **16**, and **13**, **21**). Increasing the substituents on the  $\beta$  carbon to ethyl (**16**, **24**), or phenyl (**15**, **34** or **16**, **37**) decreased activity when the indole nitrogen was unsubstituted. With methyl on the indole nitrogen  $\beta$ -dimethyl and  $\beta$ -diethyl compounds were equivalent (**21**, **23**), while  $\beta$ -diphenyl was much less active than the corresponding  $\beta$ -dimethyl (**35**, **13** or **21**, **38**).

The optimum structure tested was 3-isobutyryl-1-methylindole (**13**). This compound was 0.36 as active as phenobarbital in rats and 0.28 as active in mice.

### Experimental<sup>5</sup>

**1,2-Dimethyl-3-acetylindole (5).**—This compound was prepared in 72% yield from 2-methyl-3-acetylindole as described previously in the case of 2-methyl-3-benzoylindole.<sup>6</sup> The analytical sample melted at 113–114° (from benzene-ether). Ultraviolet spectrum showed  $\lambda_{\max}$  217 ( $\epsilon$  27,000), 245 (13,500), 266 (8450), and 305  $m\mu$  (11,700). Infrared spectrum showed C=O, 1642; C=C, 1612, 1595, 1570, 1515, and 1485 (sh); C-N; 1217, 1105, and 1050; ring, 762, 755, 735, and 670  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ : C, 76.97; H, 7.00; N, 7.48. Found: C, 77.00; H, 6.79; N, 7.46.

**3-Isobutyryl-1-methylindole (13).**—This compound was prepared in 87% yield from 3-isobutyryl indole<sup>7</sup> by the method described above and melted at 77–78° (from ether-petroleum ether 30–60°). Ultraviolet spectrum showed  $\lambda_{\max}$  244 ( $\epsilon$  14,500), 248 (sh), and 301  $m\mu$  (14,550). Infrared spectrum showed C=O, 1640; C=C, 1570, and 1522; C-N; 1216, 1120, 1075, and 1039; ring, 765, and 750  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}$ : C, 77.58; H, 7.51; N, 6.96. Found: C, 77.32; H, 7.23; N, 6.90.

**1-Ethyl-3-isobutyrylindole (14).**—Compound 14 was prepared in 86% yield as described above but using diethyl sulfate and melted at 79–80° (from ether-petroleum ether 30–60°). Ultraviolet spectrum showed  $\lambda_{\max}$  212 ( $\epsilon$  26,000), 245 (13,550), 250 (sh) (12,850), 302  $m\mu$  (14,750). Infrared spectrum showed C=O, 1630; C=C, 1610, 1573, 1520, and 1485; C-N, 1210, 1126, 1077, and 1048; ring, 772, 760, and 734  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}$ : C, 78.10; H, 7.96; N, 6.51. Found: C, 78.17; H, 7.91; N, 6.68.

**1-(1-Ethylindol-3-yl)-2-hydroxy-2-methyl-1-propanone (18)** was prepared in 88% yield by alkylation of acyloin 18<sup>7</sup> with diethyl sulfate and melted at 80–81° (from benzene-Skellysolve B). Ultraviolet spectrum showed  $\lambda_{\max}$  211 ( $\epsilon$  25,500), 247 (12,500), 306  $m\mu$  (14,100). Infrared spectrum showed OH, 3445; =CH, 3120, and 3055; C=O, 1603; C=C, 1575, and 1512; C-O, 1224, 1175, 1128, 1102, 1082, and 1050; ring, 798, 775, 760, and 750  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_2$ : C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.14; N, 6.18.

**2-Ethyl-2-hydroxy-1-indol-3-yl-1-butanone (24).**—Compound 24 was prepared in 40% yield from ethyl 3-indoleglyoxylate and ethylmagnesium bromide according to the procedure described previously in the case of methylmagnesium iodide<sup>7</sup> and melted at 161–161.5° (from benzene). Ultraviolet spectrum showed  $\lambda_{\max}$  243 (11,550), 258 (8100), 301  $m\mu$  (11,500). Infrared spectrum showed NH OH, 3320, and 3220; =CH; 3060; C-O, 1620; C=C, 1585, 1525, and 1495; C-N/C-O; 1248, 1160, 1140, 1125, 1095, 1040, and 1012  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_2$ : C, 72.70; H, 7.41; N, 6.06. Found: C, 72.19; H, 7.21; N, 6.04.

**2-Ethyl-2-hydroxy-1-(1-methylindol-3-yl)-1-butanone (23).**—This compound was prepared in 75% yield by alkylation of the above acyloin with dimethyl sulfate<sup>7</sup> and melted at 114–115° (from acetone-water). Ultraviolet spectrum showed  $\lambda_{\max}$  210 ( $\epsilon$  27,750), 246 (13,900), 306  $m\mu$  (14,550). Infrared spectrum showed OH, 3445; =CH, 3120; C=O, 1603; C=C, 1575, 1512; C-O/C-N; 1224, 1175, 1128, 1102, 1082, and 1050  $\text{cm}^{-1}$ ; ring, 798, 775, 760, and 750  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{19}\text{NO}_2$ : C, 73.44; H, 7.81; N, 5.71. Found: C, 73.69; H, 7.77; N, 5.66.

**2-Ethyl-1-(1-ethylindol-3-yl)-2-hydroxy-1-butanone (22).**—Compound 22 was prepared in 87% yield by alkylation of the above acyloin with diethyl sulfate<sup>7</sup> and melted at 87–88° (from ethanol-water). Ultraviolet spectrum showed  $\lambda_{\max}$  212.5 ( $\epsilon$  26,050), 246 (13,300), 306  $m\mu$  (14,900). Infrared spectrum showed OH, 3425, 3140; =CH, 3060; C=O, 1605; C=C, 1575, 1525, and 1485; C-N/C-O, 1226, 1164, 1150, 1130, 1104, 1089, and 1060; ring, 800, 785, 765, and 746  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{21}\text{NO}_2$ : C, 74.10; H, 8.16; N, 5.40. Found: C, 74.41; H, 8.55; N, 5.08.

**3-Butyrylindole (25).**—This compound was prepared in 67% yield from indole, N,N-dimethylbutyramide, and phosphorus oxychloride by a procedure described previously<sup>8</sup> and melted at 177–178.5° (from methanol), lit.<sup>9</sup> m.p. 169°. Ultraviolet spectrum showed  $\lambda_{\max}$  241 ( $\epsilon$  12,850), f 256 (9100), 296 (12,700), in base 241 (11,950), 260 (9600), 296 (11,800), f 332  $m\mu$  (2650). Infrared spectrum showed NH, 3120; C=O, 1655 (sh), 1633 (sh), and 1620; C-O, 1580, 1525, 1498; ring, 887, 875, 758, and 740  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ : C, 76.97; H, 7.00; N, 7.48. Found: C, 76.95; H, 7.03; N, 7.44.

**1-(3-Indolyl)-2-butanone (28).**—This compound was prepared<sup>10</sup> in 24% yield by reduction of 3-(2-acetylbutylidene)-3H-pseudoindole<sup>11</sup> with iron and hydrochloric acid according to the procedure of Myers, *et al.*,<sup>12</sup> and melted at 45–46.5° (from ether-Skellysolve B). Ultraviolet spectrum showed  $\lambda_{\max}$  220 ( $\epsilon$  33,000), 275 (6000), 281 (6350), 289  $m\mu$  (5300). Infrared spectrum showed NH, 3370; =CH, 3120, 3080, 3060; C-O, 1715; C=C, 1630; C-N, 1245, 1230, 1180, 1105, 1095, 1030, and 1010; ring, 820, 765, and 745  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ : C, 76.97; H, 7.00; N, 7.48. Found: C, 77.05; H, 6.99; N, 7.39.

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(5) Melting points were taken in a capillary tube and are corrected, ultraviolet spectra (recorded in  $m\mu$ ) were determined in 95% ethanol using a Cary Model 14 spectrophotometer. Infrared spectra (recorded in  $\text{cm}^{-1}$ ) were determined in Nujol using a Perkin-Elmer Model 21 recording infrared spectrophotometer. Skellysolve B is a commercial hexane, b.p. 60–70°, made by Skelly Oil Co., Kansas City, Mo.

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