11 (5 g) in absolute EtOH (140 ml) was added. The theoretical amount of H_2 (332 ml) was taken up in 15 min. After the catalyst was removed by filtration, the solvent was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2, washed (H_2O), and dried. Crystallization from CH_2Cl_2–C_6H_{14} yielded 3.39 g (67%) of **12**: mp 178.5–181°; $[\alpha]D$ +74°; nmr, δ 1.05 (13-CH_3, 10-CH_3), 1.44 (16-CH_3), and 2.20 (20-CH_3) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

Preparation of 14 from 12.—A solution of **12** (1.022 g) in dioxane (15 ml) was stirred with concentrated HCl (5 ml) at 5° for 65 min. The reaction mixture was added to H_2O (500 ml), and the precipitate was filtered, dried, and chromatographed over Florisil (22 × 3 cm). Elution with C_6H_6–Et_2O (9:1) gave 410 mg of somewhat impure **15** (λ_{max} 309 mμ). Further elution with C_6H_6–Et_2O (2:1) gave a mixture of **13** and **14**. Several crystallizations from Me_2CO–C_6H_{14} yielded 252 mg (24.7%) of pure **14**: mp 181–184°; $[\alpha]D$ −72°; nmr, δ 0.79 (13-CH_3), 1.01 (10-CH_3), 2.21 (20-CH_3), 5.08, and 5.27 (16 =CH_2) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

16-Methyl-17α-hydroxy-5β,15-pregnene-3,20-dione (13).—A solution of **12** (301 mg) in THF (13 ml) was cooled to 5°, and 48% HI (2.4 ml) was added dropwise over 5 min. The dark solution was stirred at room temperature for 25 min. After dilution (H_2O, 15 ml) the solution was decolorized with 5% $NaHSO_3$ and poured into H_2O (200 ml). The precipitate was filtered and dried. Crystallization from Me_2CO–C_6H_{14} gave 181 mg (60%) of **13**: mp 188° (softening), 193–196°; $[\alpha]D$ −73°; nmr, δ 0.82 (13-CH_3), 1.06 (10-CH_3), 1.76 (16-CH_3, m), 2.22 (21-CH_3), and 5.82 (15-H, m) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H. The nmr spectrum of the mother liquor indicated the presence of **14**.

16β-Methyl-16,17α-oxido-5α-pregnane-3,20-dione (17).—A solution of **16** (1.05 g) in Me_2CO (75 ml) under N_2 was titrated with 8 *N* H_2CrO_4 to permanent yellow color. The color change was observed after the addition of 1.17 ml of the reagent. The reaction mixture was added to H_2O (300 ml), and the precipitate was collected by filtration and dried. Crystallization from CH_2Cl_2–C_6H_{14} gave 811 mg (78%) of **17**: mp 209–211.5°; $[\alpha]D$ +73°; nmr, δ 1.02 (13-CH_3, 10-CH_3), 1.42 (16-CH_3), and 2.20 (20-CH_3) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

16-Methyl-17α-hydroxy-5α-15-pregnene-3,20-dione (18).—A solution of **17** (1.72 g) in Me_2CO (160 ml) was stirred with concentrated HCl (6 ml) for 30 min. H_2O (80 ml) was added dropwise, and on concentration to 100 ml *in vacuo* crystallization occurred. The crude solid was filtered, dried, and recrystallized (Me_2CO), yielding 1.149 g (67%) of **18**: mp 236–239°; $[\alpha]D$ −64°; nmr, δ 0.87 (13-CH_3), 1.08 (10-CH_3), 1.78 (16-CH_3, m), 2.23 (20-CH_3), and 5.82 (15-H, m) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

Acknowledgments.—The authors wish to thank Mr. Elliot Shapiro and Dr. Georges Teutsch for helpful discussions, Mr. M. D. Yudis and Mrs. H. M. Marigliano for interpretation of the nmr spectra, and Dr. T. Traubel for the mass spectra.

Preparation and Antiinflammatory Properties of Some 1-Substituted 3-(5-Tetrazolylmethyl)indoles[1] and Homologs

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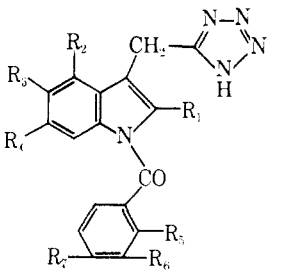
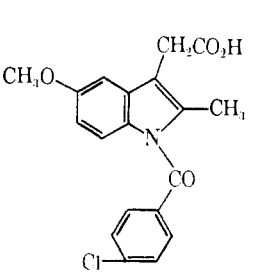
A series of 1-substituted 3-(5-tetrazolylmethyl)indoles and homologs were prepared as tetrazole analogs of indomethacin and other indole-3-acetic acid antiinflammatory agents. Some of the products show significant antiinflammatory activity when tested orally in rats. Structure–activity relationships in this series do not correspond to those for the carboxylic acid compounds. The most active compound is 1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole.

The replacement of the carboxyl group in biologically active compounds with the comparably acidic 5-tetrazolyl group (CN_4H) has not always resulted in the retention of activity.[2,3] The discovery,[2] however, that tetrazole analogs of a series of known N-phenylanthranilic acids showed antiinflammatory activity comparable to that of the corresponding acids has encouraged us to prepare tetrazole analogs of other carboxylic acid antiinflammatory agents. We now report the preparation, properties, and preliminary pharmacology of a series of 1-substituted 3-(5-tetrazolylmethyl)indoles and homologs suggested by indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] and related compounds.[4]

Chemistry.—The first aim was to prepare close analogs (I) of indomethacin (II). Two synthetic approaches



I



II

were made and these are outlined in Scheme I. Route A failed at the first step, probably because of the ability of III to react with NaH to form a carbanion at the CH_2 carbon which could react with the acylating agent.

An example of the first step of route B has already been reported by McManus and Herbst.[5] Using the general conditions of Finnegan, *et al.*,[6] we were able to convert the nitriles III to the tetrazoles V with NaN_3 and NH_4Cl in DMF in yields of 46–85%. The acidic 3-(5-tetrazolylmethyl)indoles (V) were converted to their disodium salts with NaH in DMF. Treatment of each salt with 1 molar equiv of a benzoyl chloride gave

(1) Bristol-Myers Co., South African Patent 66/3650 (1967).

(2) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, 11, 111 (1968).

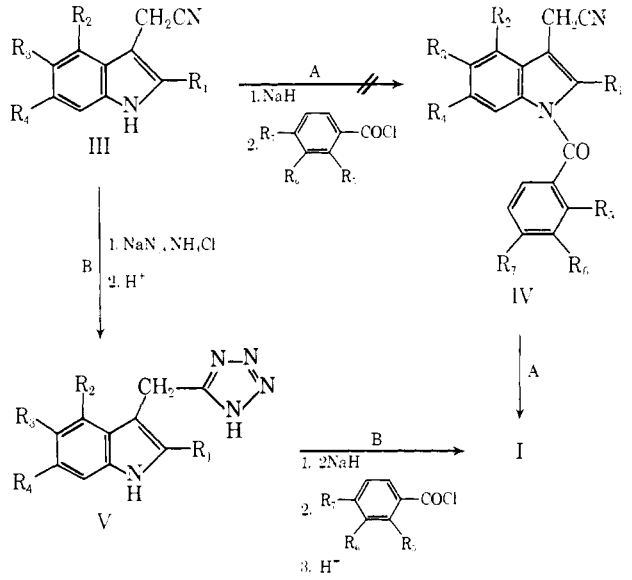
(3) F. R. Benson in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, Chapter 1.

(4) (a) T. Y. Shen, *et al.*, *J. Am. Chem. Soc.*, 85, 488 (1963); (b) T. Y. Shen, U. S. Patent 3,161,654 (1964); (c) T. Y. Shen, U. S. Patent 3,190,889 (1965); (d) T. Y. Shen, U. S. Patent 3,201,414 (1965); (e) L. H. Sarett and T. Y. Shen, U. S. Patent 3,242,162 (1966); (f) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exptl. Therap.*, 141, 369 (1963); (g) F. D. Hart and P. L. Boardman, *Brit. Med. J.*, 2, 965 (1963); (h) T. Y. Shen in "Nonsteroidal Antiinflammatory Drugs," S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1965, pp 13–20.

(5) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, 24, 1464 (1959).

(6) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, 80, 3908 (1958).

SCHEME I

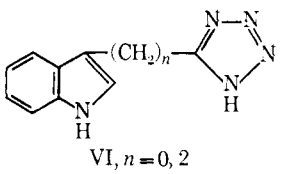


1-benzoyl-3-(5-tetrazolylmethyl)indoles (I) in 20–68% yields (**3–23**, **25**, **27–30**, Table I). 1-(4-Chlorobenzoyl)-5-hydroxy-3-(5-tetrazolylmethyl)indole (**24**) and 5-amino-1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)-indole (**26**) were obtained by hydrogenolysis of 5-benzyloxy-1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (**23**) and reduction of 1-(4-chlorobenzoyl)-5-nitro-3-(5-tetrazolylmethyl)indole (**25**), respectively.

The final products were characterized by the presence of typical, broad tetrazole NH stretching bands (2200–3500 cm^{-1}) and by the absence of sharp indole NH bands in their ir spectra. No evidence of any acylated tetrazole products was observed.

Most of the intermediate 3-indolylacetonitriles (III) were prepared from indoles unsubstituted in the 3 position using a Mannich procedure. The indoles were converted to gramines with CH_2O and Me_2NH and the quaternary salts of the gramines were then treated with NaCN or KCN to give the nitriles.

Homologs (**1**, **2**, and **31**, Table I) of I were prepared by acylation of the tetrazoles VI in a manner similar to that described for the conversion of V to I. The tetrazoles VI were obtained from the corresponding nitriles by the method of Finnegan, *et al.*[6] The nitriles were prepared by standard procedures.



VI, $n = 0, 2$

Alternatives to the amide linkages of I were provided by treatment of the disodium salt of 3-(5-tetrazolylmethyl)indole (V, R_{1-4} = H) with a variety of reagents (Table II). Alkylation with benzyl chlorides gave **32** and **33**, treatment with *p*-chlorophenyl isocyanate gave the urea **34**, and treatment with *p*-chlorobenzenesulfonyl chloride gave the sulfonamide **35**.

A series of heterocyclic analogs (**36–41**, Table II) of I were prepared by the treatment of the disodium salt of 3-(5-tetrazolylmethyl)indole (V, R_{1-4} = H) with the appropriate heterocylic carbonyl chlorides. A 1-naphthoyl analog (**42**) was prepared in a similar manner.

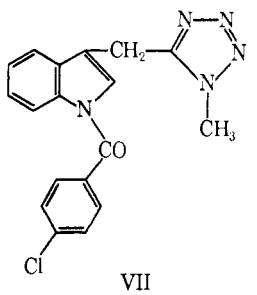
Two α-substituted products (**43** and **44**) were prepared (Table III). 1-(4-Chlorobenzoyl)-3-[1-(5-tetrazolyl)ethyl]indole was obtained from 2-(3-indolyl)-propionitrile by methods outlined in route B of Scheme I. However, 2-(3-indolyl)-2-methylpropionitrile failed to give an acceptable yield of 3-{2-[2-(5-tetrazolyl)]-propyl}indole when treated with NaN_3 and NH_4Cl in DMF. The tetrazole was eventually obtained in good yield using NaN_3 and $AlCl_3$ in THF.[7] Apparently, the latter conditions are more favorable for the formation of tetrazoles from more sterically hindered and unreactive nitriles. Benzoylation of the product proceeded normally.

Finally, 1-(4-chlorobenzoyl)indole-3-acetic acid, which was required for comparison with the 1-substituted 3-(5-tetrazolylmethyl)indoles with respect to antiinflammatory activity, was synthesized by procedures similar to those described by Shen for indomethacin and analogs.[4b]

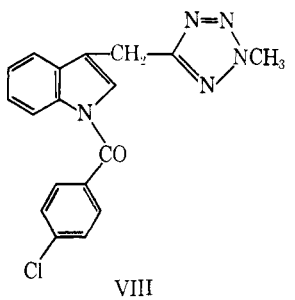
The final products which contain the simple amide linkage were found to be particularly susceptible to base-catalyzed hydrolysis. In order to obtain acceptable yields it was necessary to maintain the pH below 10 in work-up procedures.

The acidities of a number of the final products in 2-methoxyethanol–water (2:1) were determined,[8] and these indicate the products to be weak acids with pK_a's in the range of 5.7–6.2. For example, 1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (**5**) had a pK_a of 5.99. By comparison, indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] had a pK_a of 6.73.

Treatment of 1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (**5**) with diazomethane in ether gave both of the possible N-methyltetrazole derivatives (VII and VIII). On the basis of nmr spectra,[9] the product with



VII



VIII

a chemical shift of 2.94 ppm for the N-methyl protons was assigned structure VII. Structure VIII was assigned to the other isomer whose N-methyl protons had a chemical shift of 3.25 ppm.

Structure–Activity Relationships.—All of the final products were tested orally for antiinflammatory activity using the carrageenin-induced foot edema method in the rat.[10] The results, expressed as the percentage inhibition of edema, are recorded in Tables I–III. Compounds VII and VIII, not included in the

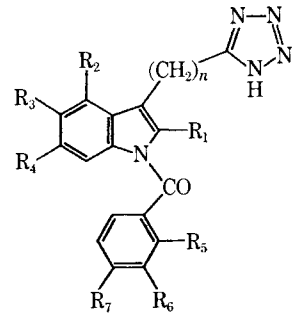
(7) E. Wiberg and H. Michaud, *Z. Naturforsch.*, **9b**, 496 (1954).

(8) Reproducibility of ±0.04.

(9) J. H. Markgraf, W. T. Bachmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965), reported that the signal from the N-methyl protons of 1,5-dimethyltetrazole appears upfield from the signal from the N-methyl protons of 2,5-dimethyltetrazole.

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

TABLE I: 1-BENZOYL-3-(5-TETRAZOLYLMETHYL)INDOLES AND HOMOLOGS

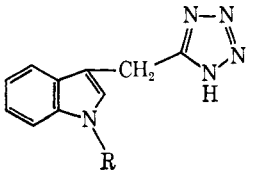


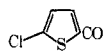
No.	n	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Mp, °C[a]	Crystn solvent[b]	Yield,[c] %	pK_a	Formula	Analyses	Dose, mg/kg	Anti-inflam act., % inhib of edema
1	0	H	H	H	H	H	H	Cl	230.5–232	A–B	53		$C_{16}H_{10}ClN_5O$	C, H, Cl, N	150	4
2	0	H	H	OCH_3	H	H	H	Cl	243–244	A	73		$C_{17}H_{12}ClN_5O_2$	C, H, Cl, N	150	21
3	1	H	H	H	H	H	H	H	124–126	C	51	6.03	$C_{17}H_{13}N_5O$	C, H, N	128	30
4	1	H	H	H	H	H	H	F	183.5–184.5	A	67		$C_{17}H_{12}FN_5O$	C, H, N	150	21
5	1	H	H	H	H	H	H	Cl	233–234	D[d]	50	5.99	$C_{17}H_{12}ClN_5O$	C, H, Cl, N	128	55
6	1	H	H	H	H	H	H	Br	238–239	A	42		$C_{17}H_{12}BrN_5O$	C, H, N	150	34
7	1	H	H	H	H	H	H	CH_3	200–201	A	26		$C_{18}H_{15}N_5O$	C, H, N	128	34
8	1	H	H	H	H	H	H	CF_3	251–253	A	42	5.95	$C_{18}H_{12}F_3N_5O$	C, H, N	128	18
9	1	H	H	H	H	H	H	OCH_3	182–183	A	68	6.06	$C_{18}H_{15}N_5O_2$	C, H, N	128	12
10	1	H	H	H	H	H	H	SCH_3	201.5–202.5	A	52		$C_{18}H_{15}N_5OS$	C, H, N, S	128	15
11	1	H	H	H	H	H	H	OCF_3	225–226	E	49		$C_{18}H_{12}F_3N_5O_2$	C, H, N	150	0
12	1	H	H	H	H	H	F	H	156–157	A–B	23		$C_{17}H_{12}FN_5O$	C, H, N	128	0
13	1	H	H	H	H	H	Cl	H	190–191	A	42	6.21	$C_{17}H_{12}ClN_5O$	C, H, Cl, N	128	32
14	1	H	H	H	H	H	CF_3	H	213–214.5	A	44	5.98	$C_{18}H_{12}F_3N_4O$	C, H, N	128	36
15	1	H	H	H	H	H	OCH_3	H	207–209	A	64		$C_{18}H_{15}N_5O_2$	C, H, N	128	2
16	1	H	H	H	H	Cl	H	H	*e*			6.16	$C_{17}H_{12}ClN_5O$	C, H, Cl	128	9
17	1	H	H	H	H	OCH_3	H	H	213–214	A	57		$C_{18}H_{15}N_5O_2$	C, H, N	128	0
18	1	H	H	H	H	H	Cl	Cl	241–242	A	33		$C_{17}H_{11}Cl_2N_5O$	C, H, Cl, N	128	16
19	1	H	H	H	H	Cl	H	Cl	228–229	E	68		$C_{17}H_{11}Cl_2N_5O$	C, H, Cl, N	128	13
20	1	H	H	H	OCH_3	H	H	Cl	204.5–206.5	A	46		$C_{18}H_{14}ClN_5O_2$	C, H, Cl, N	150	2
21	1	H	H	Br	H	H	H	Cl	239–240	F	50	6.00	$C_{17}H_{11}BrClN_5O$	C, H, N	150	6
22	1	H	H	OCH_3	H	H	H	Cl	208–209	A	51		$C_{18}H_{14}ClN_5O_2$	*f*	150	0
23	1	H	H	$OCH_2C_6H_5$	H	H	H	Cl	197–199	C	27		$C_{24}H_{18}ClN_5O_2$	C, H, Cl, N	128	15
24	1	H	H	OH	H	H	H	Cl	250–252	C	67		$C_{17}H_{12}ClN_5O_2$	C, H, Cl, N	128	9
25	1	H	H	NO_2	H	H	H	Cl	247–248	C	51	5.73	$C_{17}H_{11}ClN_6O_3$	C, H, Cl, N	150	9
26	1	H	H	NH_2	H	H	H	Cl	173–215	A	50		$C_{17}H_{13}ClN_6O$	C, H, N	150	10
27	1	H	CH_3	H	H	H	H	Cl	256–258	F	32		$C_{18}H_{14}ClN_5O$	C, H, Cl, N	128	18
28	1	CH_3	H	H	H	H	H	Cl	202–204	E	33	6.17	$C_{18}H_{14}ClN_5O$	C, H, Cl, N	128	0
29	1	CH_3	H	Cl	H	H	H	Cl	223–223.5	C–H	20		$C_{18}H_{13}Cl_2N_5O$	C, H, Cl, N	128	4
30	1	CH_3	H	OCH_3	H	H	H	Cl	225–226	F	24		$C_{19}H_{16}ClN_5O_2$	C, H, Cl, N	100	24
31	2	H	H	H	H	H	H	Cl	194–196	A	20		$C_{18}H_{14}ClN_5O$	C, H, Cl, N	150	29

[a] Most of the products melt with decomposition. [b] Final recrystallization: A = EtOAc, B = Skellysolve B (bp 60–80°), C = MeOH, D = $CHCl_3$, E = *i*-PrOH, F = EtOH, G = *n*-BuOH, H = H_2O, I = Me_2CO, J = CCl_4, K = C_6H_6, L = Et_2O. [c] After first crystallization. [d] After prior recrystallization from MeOH. *i*-PrOH was later found to be a more suitable solvent. [e] Noncrystalline product, purified by reprecipitation. [f] Product crystallized with 0.5 mole of EtOAc. *Anal.* ($C_{18}H_{14}ClN_5O_2 \cdot 0.5C_4H_8O_2$) H, Cl, N; C: calcd, 58.34; found, 58.79.

TABLE II

1-SUBSTITUTED 3-(5-TETRAZOLYLMETHYL)INDOLES

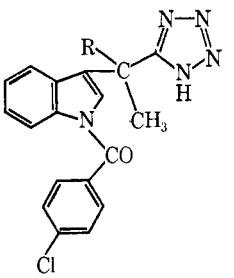


No.	R	Mp, °C[a]	Crystn solvent[b]	Yield,[c] %	Formula	Analyses	Dose, mg/kg	Anti-inflam act., % inhib of edema
32	4-$ClC_6H_4CH_2$	204.5–205.5	A	55	$C_{17}H_{14}ClN_5$	C, H, Cl, N	150	4
33	4-$FC_6H_4CH_2$	194.5–195.5	A	45	$C_{17}H_{14}FN_5$	C, H, N	128	2
34	4-ClC_6H_4NHCO	244–245	C	81	$C_{17}H_{13}ClN_6O$	C, H, Cl, N	128	24
35	4-$ClC_6H_4SO_2$	244–245	F	29	$C_{16}H_{12}ClN_5O_2S$	C, H, Cl, N	150	9
36		175.5–176.5	I-B	29	$C_{15}H_{11}N_5O_2$	C, H, N	150	0
37		158.5–159.5	A	26	$C_{15}H_{11}N_5OS$	C, H, N, S	150	20
38		189–190	A	25	$C_{15}H_{10}ClN_5OS$	C, H, N	150	0
39		213.5–214.5	C	46	$C_{14}H_{10}N_6OS$	C, H, N, S	150	0
40		232–234	G	46	$C_{16}H_{12}N_6O$	C, H, N	150	6
41		247–248	G	26	$C_{15}H_{11}N_7O$	C, H, N	150	0
42		205.5–207	A	57	$C_{21}H_{15}N_5O$	C, H, N	150	16

[a–c] See corresponding footnotes in Table I.

TABLE III

α-SUBSTITUTED 1-BENZOYL-3-(5-TETRAZOLYLMETHYL)INDOLES



No.	R	Mp, °C[a]	Crystn solvent[b]	Yield,[c] %	Formula	Analyses	Dose, mg/kg	Antiinflam act., % inhib of edema
43	H	200–202	A–B	52	$C_{18}H_{14}ClN_5O$	C, H, Cl, N	150	0
44	CH_3	238–239	A	56	$C_{19}H_{16}ClN_5O$	C, H, Cl, N	128	22

[a–c] See corresponding footnotes in Table I.

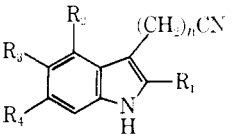
tables, showed 7 and 15% inhibition of edema, respectively, at doses of 128 mg/kg. An inhibition of more than 30% is greater than three times the standard deviation from controls and is considered to indicate significant activity.

Several general observations may be made on the structure–activity relationships of the tetrazole products. A carboxamide linkage at the indole nitrogen appears to be essential for significant antiinflammatory activity. This contrasts with the carboxylic acid analogs where urea linkages[4c] and benzyl group substitution[4e] have been reported to give compounds with good activity. For optimum activity in those compounds with a carboxamide linkage, a benzene ring, preferably substituted in the *meta* or *para* position, is attached to the carbonyl group. Substitution on the benzene ring of the indole nucleus with both electron-withdrawing and -releasing groups results in reduced activity. Limited substitution in the 2 position of the indole nucleus gives compounds of low activity. One unsubstituted CH_2 between the indole and tetrazole rings is required for optimum activity. A free hydrogen atom on the tetrazole ring is necessary for significant activity.

The most active compound in the tetrazole series is

Table IV

Intermediate Nitriles



No.	n	R_1	R_2	R_3	R_4	Mp or bp (mm), °C	Cryst solvent[a]	Yield, %	Formula	Analyses
45	0	H	H	H	H	180–182[b]	F–H	65	$C_9H_8N_2$	
46	0	H	H	H	OCH_3	155–156.5	F–H	49	$C_{10}H_8N_2O$	C, H, N
47	1	H	H	H	OCH_3	110–112.5[c]	C	97	$C_{11}H_{10}N_2O$	
48	1	H	H	Br	H	102.5–104[d]	J	43	$C_{10}H_7BrN_2$	
49	1	H	H	NO_2	H	[e]			$C_{10}H_7N_3O_2$	
50	1	H	H	OCH_3	H	175–177 (0.01)[f]		89	$C_{11}H_{10}N_2O$	
51	1	H	H	$OCH_2C_6H_5$	H	[g]		82	$C_{17}H_{14}N_2O$	
52	1	H	CH_3	H	H	92–103[h]		97	$C_{11}H_{10}N_2$	
53	1	CH_3	H	H	H	81–83[i]	K B	95	$C_{11}H_{10}N_2$	
54	1	CH_3	H	Cl	H	142–144	F–H	90	$C_9H_9ClN_2$	C, H, Cl, N
55	1	CH_3	H	OCH_3	H	115–116	I	89	$C_{12}H_{12}N_2O$	C, H, N

[a] See footnote *b* in Table I. [b] See ref 19. [c] N. N. Suvorov, M. V. Fedotova, E. G. Balasheva, O. B. Ogareva, and A. I. Tishchenko, USSR Patent 134,263 (1960); *Chem. Abstr.*, **55**, 15510*a* (1961). [d] W. T. Colwell, J. K. Horner, and W. A. Skinner, "Synthesis of N-Containing Heterocyclic Compounds Possessing Physiological Activity," U. S. Department of Commerce, Office Technical Service AD 435,889, 1964; *Chem. Abstr.*, **62**, 11763*a* (1965). [e] Noncrystalline, crude product; S. P. Hiremath and S. Siddappa, *J. Med. Chem.*, 8, 142 (1965). [f] D. Desaty and D. Keglevic, *Croat. Chem. Acta*, **37**, 25 (1965); *Chem. Abstr.*, **63**, 8294*d* (1965). [g] Noncrystalline product; A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta*, **38**, 1452 (1955). [h] Product was not recrystallized; J. H. Gaddum, K. A. Hameed, D. E. Hathway, and F. F. Stephens, *Quart. J. Expl. Physiol.*, **40**, 49 (1955). [i] See reference in footnote *h*.

1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole[11] (**5**), whereas 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-(5-tetrazolylmethyl)indole (**30**), the direct tetrazole analog of indomethacin, shows only weak activity. 1-(4-Chlorobenzoyl)indole-3-acetic acid, the carboxyl analog of **5**, gave 32% inhibition of edema at a dose of 128 mg/kg. Compound **5** had a minimal effective dose of 16 mg/kg (30% inhibition of edema) and an oral LD_{50} of 1200 mg/kg in rats. By comparison indomethacin had a minimal effective dose of 1 mg/kg, with an LD_{50} of 28 mg/kg.

The substitution of the tetrazole ring for the carboxyl group in a series of carboxylic acid antiinflammatory agents has once again provided active compounds. However, for optimum activity in this tetrazole series other structural changes have also had to be made.

Experimental Section[12]

Amides.—2-(3-Indolyl)-2-methylpropionamide was prepared from 2-(3-indolyl)-2-methylpropionic acid[13] using the general method of Crosby, *et al.*[14] The crude product (75%) was recrystallized twice from $CHCl_3$ (Norit), mp 178.5–180°. *Anal.* ($C_{12}H_{14}N_2O$) C, H, N.

Similarly, 2-(3-indolyl)propionamide was prepared from 2-(3-indolyl)propionic acid.[15] The crude amide (99%) failed to crystallize and was used without purification.

Nitriles. Method A.—Compounds **47–54** (Table IV) were prepared *via* a Mannich procedure[16] from indoles unsubstituted in the 3 position.

Method B.—2-(3-Indolyl)propionitrile,[17] 2-(3-indolyl)-2-methylpropionitrile, and 5-methoxy-2-methyl-3-indolylacetonitrile (**55**) were prepared from the corresponding amides as illustrated for **55**. A solution of 5-methoxy-2-methyl-3-indolylacetamide[18] (30.0 g, 0.138 mole) and Et_3N (30.0 g, 0.297 mole) in $POCl_3$ (290 ml) was heated under reflux for 0.5 hr. The excess $POCl_3$ was removed under reduced pressure and a $CHCl_3$ solution of the residue was washed with aqueous Na_2CO_3 until the aqueous washings remained basic. The $CHCl_3$ solution was dried (Na_2SO_4), filtered, and reduced to dryness to leave a brown solid. This residue was exhaustively extracted with Et_2O and the combined Et_2O extracts were reduced in volume. Skellysolve B was added and the solution was further reduced in volume until **55** (24.5 g) crystallized, mp 113–115°.

2-(3-Indolyl)-2-methylpropionitrile (88%) had bp 143–160° (0.5 mm). *Anal.* ($C_{12}H_{12}N_2$) C, H, N.

Method C.—3-Cyanoindole[19] (**45**) and 3-cyano-5-methoxyindole (**46**) were prepared from the corresponding aldoximes by dehydration with formic acid.[19]

5-Methoxy-3-indolylaldoxime was prepared from the aldehyde[20] by the method of Shaw, *et al.*[21] The crude product was recrystallized twice from aqueous EtOH to give colorless needles, mp 129–140°. *Anal.* ($C_{10}H_{10}N_2O_2$) C, H, N.

3-Indolylacetonitrile and 3-indolylpropionitrile were obtained from commercial sources.

Intermediate Tetrazoles. Method A.—Compounds **56–68** (Table V) were prepared from the corresponding nitriles by a method[6] similar to that described for 3-[1-(5-tetrazolyl)ethyl]-indole, as follows. A mixture of 2-(3-indolyl)propionitrile (1.0 g, 0.00588 mole), NaN_3 (0.478 g, 0.00735 mole), and NH_4Cl (0.393 g, 0.00735 mole) in DMF (7 ml) was heated, with stirring, at 118° for 24 hr. The DMF was removed under reduced pressure and the residue was treated with H_2O (30 ml) followed by 5% NaOH until the mixture was strongly basic. The mixture was washed (Et_2O), and the resulting solution was treated with charcoal and filtered. The cooled filtrate (ice–water) was acidified to pH 2 with 10% HCl. The precipitated solid (0.657 g, 51.5%) was recrystallized twice from aqueous EtOH to give 3-[1-(5-tetrazolyl)ethyl]indole as colorless crystals, mp 164–165.5°. *Anal.* ($C_{11}H_{11}N_5$) C, H, N.

(11) A more detailed account of the pharmacology of this compound (BL-R743) will be reported elsewhere.

(12) Melting points were determined in a Mel-Temp apparatus and are uncorrected. Nmr spectra ($CDCl_3$) were obtained using a Varian Associates Model A-60 spectrometer. Chemical shifts (δ) were measured downfield from TMS. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(13) H. Erdtmann and Å. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954).

(14) D. G. Crosby, J. B. Boyd, and H. E. Johnson, *J. Org. Chem.*, **25**, 1826 (1960).

(15) H. E. Johnson and D. G. Crosby, *ibid.*, **28**, 1246 (1963).

(16) E. Walton, C. H. Stammer, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Med. Chem.*, **8**, 204 (1965).

(17) K. Eiter and O. Svierak, *Monatsh. Chem.*, **83**, 1453 (1952).

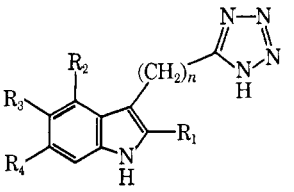
(18) E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955).

(19) S. Swaminathan, S. Ranganathan, and S. Sulochana, *J. Org. Chem.*, **23**, 707 (1958).

(20) K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 296 (1924).

(21) K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, **23**, 1171 (1958).

TABLE V
INTERMEDIATE TETRAZOLES



No.	n	R_1	R_2	R_3	R_4	Mp, °C[a]	Crystn solvent[b]	Yield,[c] %	Formula	Analyses
56	0	H	H	H	H	233–233.2	F–H	77	$C_9H_7N_5$	C, H, N
57	0	H	H	OCH_3	H	245.5–247	F–H	40	$C_{10}H_9N_5O$	C, H, N
58	1	H	H	H	H	182–183[d]	H	85	$C_{10}H_9N_5$	
59	1	H	H	H	OCH_3	203–204	F–H	68	$C_{11}H_{11}N_5O$	C, H, N
60	1	H	H	Br	H	207–208	A	76	$C_{10}H_8BrN_5$	C, H, Br, N
61	1	H	H	NO_2	H	227–228	F–H	46	$C_{10}H_8N_6O_2$	C, H, N
62	1	H	H	OCH_3	H	188–189	H	48	$C_{11}H_{11}N_5O$	C, H, N
63	1	H	H	$OCH_2C_6H_5$	H	173–175	F–H	64	$C_{17}H_{15}N_5O$	C, H, N
64	1	H	CH_3	H	H	224–224.5	F–H	51	$C_{11}H_{11}N_5$	C, H, N
65	1	CH_3	H	H	H	180–182	A	77	$C_{11}H_{11}N_5$	C, H, N
66	1	CH_3	H	Cl	H	201.5–203.5	F–H	77	$C_{11}H_{10}ClN_5$	C, H, Cl, N
67	1	CH_3	H	OCH_3	H	194–195	H	53	$C_{12}H_{13}N_5O$	C, H, N
68	2	H	H	H	H	125–126	H	63	$C_{11}H_{11}N_5$	C, H, N

[a–c] See corresponding footnotes in Table I. [d] See ref 5.

Method B.—A mixture of NaN_3 (35.1 g, 0.54 mole) and $AlCl_3$ (24.0 g, 0.18 mole) in THF (225 ml) was heated under reflux with stirring for 0.5 hr. To the cooled mixture was added a solution of 2-(3-indolyl)-2-methylpropionitrile (29.0 g, 0.157 mole) in THF (75 ml). The mixture was then heated under reflux with stirring for 5 days.[7] It was cooled, diluted (H_2O), and evaporated to dryness. The residue was triturated with dilute HCl and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 10% aqueous NaOH. The aqueous solution was treated with charcoal and filtered. The filtrate was acidified to pH 2 with concentrated HCl. The precipitated solid (30.0 g, 84%) was recrystallized twice from EtOAc–petroleum ether (bp 30–60°) to give 3-{2-[2-(5-tetrazolyl)]propyl}indole as off-white crystals, mp 206–207°. *Anal.* ($C_{12}H_{13}N_5$) C, H, N.

Acylation Reactions.—Compounds **1–23**, **25**, **27–31**, and **36–44** (Tables I–III) were prepared by treatment of the 3-(5-tetrazolylmethyl)indoles and homologs with benzoyl or heteroaroyl chlorides using procedures similar to the one described for **9**, as follows. A solution of 3-(5-tetrazolylmethyl)indole (5.0 g, 0.0251 mole) in dry DMF (25 ml) was added dropwise to a cooled (ice–water bath), stirred suspension of NaH (2.1 g, of a 58.6% NaH dispersion in mineral oil, 0.0513 mole of NaH) in DMF (25 ml). The mixture was then stirred at room temperature for 20 min. The resulting solution was cooled (ice–water bath), when a solution of 4-methoxybenzoyl chloride (4.3 g, 0.0252 mole) in DMF (25 ml) was added dropwise with stirring over a period of 25 min. Stirring was then continued at room temperature for 2 hr.

The reaction mixture was reduced to dryness in a rotary evaporator. A solution of the residue in H_2O (350 ml) was acidified to pH 2 with concentrated HCl. The precipitated solid was washed (cold H_2O) and dried. The dried material was washed with Skellysolve B (to remove any mineral oil) followed by a small volume of cold MeOH. The product was crystallized from MeOH to give **9** (5.7 g) as off-white crystals, mp 93–95°, resolidifying and remelting at 182–183°.

Compounds **37**, **38**, and **41** required column chromatography on silicic acid with C_6H_6–Me_2CO before they could be crystallized.

1-(4-Chlorobenzyl)-3-(5-tetrazolylmethyl)indole (32), **1-(4-fluorobenzyl)-3-(5-tetrazolylmethyl)indole (33)**, **1-(4-chlorophenylcarbamoyl)-3-(5-tetrazolylmethyl)indole (34)**, **and 1-(4-chlorobenzenesulfonyl)-3-(5-tetrazolylmethyl)indole (35)** were obtained from the treatment of the disodium salt of 3-(5-tetrazolylmethyl)indole (**58**) with 4-chlorobenzyl chloride, 4-fluorobenzyl chloride, 4-chlorophenyl isocyanate, and 4-chlorobenzenesulfonyl chloride, respectively, in a manner analogous to that described for the Acylation Reactions.

1-(4-Chlorobenzoyl)-5-hydroxy-3-(5-tetrazolylmethyl)indole (24).—A suspension of 5-benzyloxy-1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (**23**) (3.52 g) and 10% Pd–C (2.0 g) in EtOAc (300 ml) was shaken with H_2 at room temperature and 2.5–3.5 kg/cm² until absorption of H_2 had ceased (7 hr). The mixture was filtered and the filtrate was reduced in volume to give crystalline **24** (1.87 g), mp 244–247° dec.

5-Amino-1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (26).—A suspension of **1**-(4-chlorobenzoyl)-5-nitro-3-(5-tetrazolylmethyl)indole (**25**) (7.0 g) and 10% Pd–C (3.0 g) in MeOH (300 ml) was shaken with H_2 at room temperature and 1.4–3.5 kg/cm² until the uptake of H_2 had ceased (2.5 hr). The mixture was filtered and the collected solid was extracted with boiling EtOH. The EtOH extract and the MeOH filtrate were combined and concentrated. The solid residue was recrystallized from EtOH (Norit) to give **26** as light brown crystals (3.2 g), mp 160–190° dec.

1-(4-Chlorobenzoyl)-3-[5-(1-methyltetrazolyl)methyl]indole (VII) and 1-(4-Chlorobenzoyl)-3-[5-(2-methyltetrazolyl)methyl]-indole (VIII).—A suspension of 1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole (**5**) (4.5 g) in Et_2O (50 ml) was treated with ethereal CH_2N_2. The reaction mixture was filtered and the collected solid and filtrate were worked up separately. The solid was recrystallized from EtOH to give pale yellow crystals of VII (1.75 g, 37%), mp 178–179°. Recrystallization from EtOH gave off-white crystals, mp 180–181°, nmr peak ($CDCl_3$) at δ 2.94 (3 H singlet, $CH_3N<$). *Anal.* ($C_{18}H_{14}ClN_5O$) C, H, Cl, N.

The filtrate was reduced to dryness to give VIII (2.0 g, 43%) as pale yellow crystals, mp 111–113°. Two recrystallizations from EtOH gave colorless crystals, mp 111–112°, nmr peak ($CDCl_3$) at δ 3.25 (3 H singlet, $CH_3N<$). *Anal.* ($C_{18}H_{14}ClN_5O$) C, H, Cl, N.

1-(4-Chlorobenzoyl)indole-3-acetic Acid.—*t*-Butyl 1-(4-chlorobenzoyl)indole-3-acetate was prepared from *t*-butyl indole-3-acetate and 4-chlorobenzoyl chloride by a method similar to that described for *t*-butyl 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate.[4b] The crude N-acylated indole was partially purified by chromatography over silicic acid with C_6H_6 as the eluent. A solution of the chromatographed material (2.45 g) in CF_3CO_2H (48 ml) was allowed to stand at 25° for 17 hr. The solution was evaporated to dryness and the residue partitioned between aqueous $NaHCO_3$ and Et_2O. The Et_2O layer was reextracted with fresh aqueous $NaHCO_3$. The combined aqueous solutions were acidified with concentrated HCl to pH 2 to precipitate the product (1.28 g), mp 175–178°. The product was recrystallized twice from aqueous EtOH to give pale yellow needles, mp 178–180°. *Anal.* ($C_{17}H_{12}ClNO_3$) C, H, Cl, N.

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