brate has no significant effect on mouse serum cholesterol under these conditions. Although the mechanism of action of 1[19] has not been elucidated, it does not appear to have any significant effect on the incorporation of mevalonate into cholesterol.

(19) The generic name of 1, formerly designated DH 581, is probucol.

Acknowledgment.—We wish to thank Dr. E. P. Previc, Dr. E. G. Choby, and Mr. J. De Fazio for the preparation of many of the compounds screened in this program, and Mr. P. J. Shea for assisting in the biological evaluation.

Synthesis and Antiinflammatory Activity of Some Aryltetrazolylalkanoic Acids

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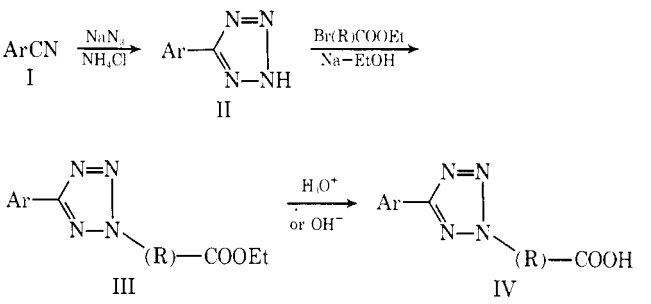
A number of aryltetrazolylalkanoic acids were prepared and screened for antiinflammatory activity by two acute and one chronic assay. Maximum activity was found in those members of the series having halogenated aromatic substituents in the *meta* positions and a propionic acid residue at position 2 of the tetrazole ring.

In the past few years, research on nonsteroidal antiinflammatory agents has, in large measure, focused on various types of arylalkanoic and arylcarboxylic acids. The numerous structural patterns that have been investigated have been discussed in varying degrees of detail in a number of recent reviews.[1] While the exact mechanism(s) of action of these drugs is still unclear, the introduction into therapy of indomethacin and mefenamic acid is indicative of the relative success of this approach. Our continuing efforts in the area of nonsteroidal antiinflammatory agents led us to an examination of the aryltetrazolylalkanoic acids.

Although relatively novel as an aromatic system, the tetrazole group is present in a number of biologically active molecules. Apart from serving as an allosteric replacement for the carboxyl function,[2] it appears in the CNS active 1-aryl-5-dialkylaminomethyl- and 1-(or 5-) alkyl-5-(or 1-)aminophenyltetrazoles.[3] A recent report has disclosed antihypertensive activity for some 5-[ω-(4-aryl-1-piperizinyl)alkyl]tetrazoles.[4] In addition, 5-amino-1-phenyltetrazole has been clinically investigated as an antiinflammatory agent.[5]

The most interesting of the title compounds are the 5-aryltetrazolyl-2-alkanoic acids, IV, prepared by the reaction sequence outlined in Scheme I. The starting nitriles, I, were either obtained commercially or prepared by known procedures. These were converted into the 5-aryltetrazoles, II, by reaction with NaN_3 and NH_4Cl in DMF in yields of about 90% and used without further purification. Alkylation of the 5-aryltetrazole Na salts (Method B) with the appropriate ethyl bromoalkanoate produced the esters, III. Such alkylations have consistently been reported to yield a

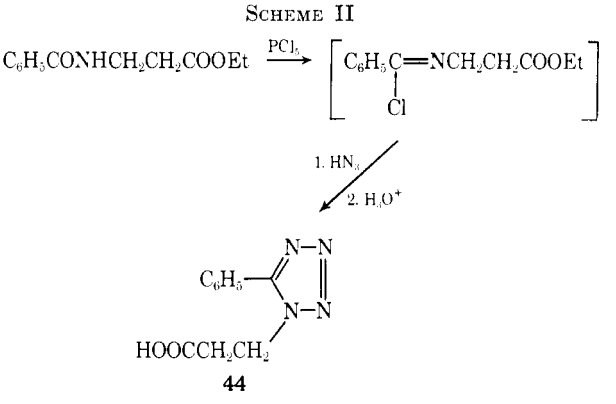
SCHEME I



mixture of both the 1 and 2 isomers with the 2 isomer predominating.[6] The procedure used here with refluxing ethanol as the solvent produced, in every case, only the 2 isomer in good yield. No attempt was made to detect any 1 isomer that might have formed.

In order to demonstrate that our alkylation procedure was actually producing the 2 isomer, the 1 isomer, 3-(5-phenyl-1-tetrazolyl)propionic acid (**44**), was prepared by an unambiguous route. As shown in Scheme II, ethyl 3-benzamidopropionate was converted into

SCHEME II



the iminochloride with PCl_5. This, upon cyclization with hydrazoic acid and saponification, gave **44**, mp 146°. The 3-(5-phenyl-2-tetrazolyl)propionic acid produced by the alkylation of 5-phenyltetrazole with ethyl

(1) (a) K. J. Doebel, *et al.*, *Ann. Rep. Med. Chem.*, **1968**, 209 (1969); (b) T. Y. Shen, *ibid.*, **1967**, 219 (1968); (c) T. Y. Shen, "Topics in Medicinal Chemistry," Vol I, J. L. Rabinowitz and R. M. Myerson, Ed., Interscience, New York, N. Y., 1967, p 53; (d) S. S. Adams and R. Cobb, *Progr. Med. Chem.*, **5**, 59 (1967).

(2) (a) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968); (b) P. F. Juby and T W. Hudyma, *ibid.*, **12**, 396 (1969); (c) J. K. Elwood, R. M. Herbst, and G. L. Kilgour, *J. Biol. Chem.*, **240**, 2073 (1965).

(3) (a) E. G. Gross and R. M. Featherstone, *J. Pharmacol. Exp. Ther.*, **92**, 323 (1948); (b) E. G. Gross and R. M. Featherstone, *ibid.*, **92**, 330 (1948).

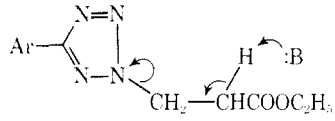
(4) S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, and R. Rodriguez, *J. Med. Chem.*, **10**, 400 (1967).

(5) G. R. Bobalik and J. W. Bastian, *Arch. Int. Pharmacodyn. Ther.*, **166**, 466 (1967).

(6) (a) R. A. Henry, *J. Amer. Chem. Soc.*, **73**, 4470 (1951); (b) R. Rapp and J. Howard, *Can. J. Chem.*, **47**, 813 (1969); (c) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).

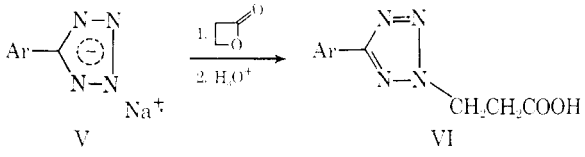
3-bromopropionate had mp 126° and the mixture melting point of this and **44** was depressed. Thus the alkylation product must be the 2 isomer **5**. While this work was in progress, the synthesis of both the 1 and 2 isomers of 5-phenyltetrazolylacetic acid was reported with melting points of 149–150° and 182–184°, respectively.[6b] The latter is identical with our 5-phenyl-2-tetrazolylacetic acid (**1**), mp 186°.

Once obtained, the esters were smoothly hydrolyzed using mineral acid (Hydrolysis Procedure **1**) for the propionates and strong alkali (Hydrolysis Procedure **2**) for the others. The former procedure was necessary due to the tendency of the propionates to undergo a



base-catalyzed reverse Michael type elimination of the 5-aryltetrazole moiety.

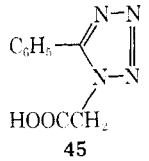
An alternate one-step procedure for the attachment of the side chain was utilized in the early stages of this work. This involved the condensation of the Na salts of the 5-aryltetrazoles V with propiolactone to give,



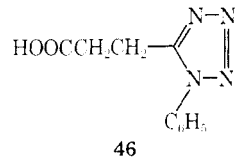
V VI

upon acidification, the 3-(5-aryl-2-tetrazolyl)propionic acids directly (method A). The yields by this method, however, were generally lower than the overall yields by the alkylation–saponification route.

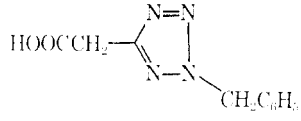
In addition to the 5-aryl-2-tetrazolylalkanoic acids, several miscellaneous analogs were synthesized to determine the effect on the activity of the positioning of the substituents on the tetrazole ring. These were



45



46



47

5-phenyl-1-tetrazolylacetic acid[7] (**45**), 3-(1-phenyl-5-tetrazolyl)propionic acid[8] (**46**), and 2-benzyl-5-tetrazolylacetic acid (**47**). This latter compound was prepared by the benzylation and saponification of ethyl 5-tetrazolylacetate.

Pharmacology.—Three models of inflammation, two acute and one chronic, were used to define the anti-inflammatory activity of the compounds in this series. They are: the carrageenin-induced pleurisy, the carrageenin-induced abscess, and the adjuvant-induced arthritis.

TABLE I

ANTIINFLAMMATORY ACTIVITY OF SOME ARYLTETRAZOLYLALKANOIC ACIDS

	Pleural effusion		Carrageenin abscess	
Compd	AI[a]	Potency[b]	AI[c]	Potency[b]
1	3.1		6.0	
2	7.0			
3	6.2			
4	0.7			
5	8.2	0.9	10.5	
6	6.4	0.3	3.9	0.3
7[d]	11.2	2.2	13.3	2.1
8	5.9		8.0	
9[e]	11.2	3.2	10.7	2.4
10[f]	7.9	1.2	9.1	1.8
11	1.4			
12[g]	11.1	5.2	16.5	6.2
13[h]	9.2	1.5	10.9	2.3
14[i]	11.2	3.6	15.9	4.3
15	2.6	0.1	9.4	
16	8.4	0.6	8.1	0.5
17	3.7		0.8	0.0
18	5.7	0.7	9.7	
19	3.1		3.9	1.5
20[j]	7.9			
21	1.4			
22	5.0			
23	4.9		1.9	
24	3.2			
25	6.0			
26	1.1			
27	6.0			
28	0.3			
29	1.1		5.4	0.1
30	4.8		0.3	
31	5.2		1.3	
32	3.5		0.2	
33	3.0			
34	6.5		4.2	0.1
35	6.6	0.3	3.9	
36	4.6		5.9	0.6
37	0.8			
38	0.8		4.8	
39	4.4			
40	5.3		7.0	
41	6.2		0.1	
42	1.2			
43	0.3		1.9	
44	3.1			
45	6.2		4.1	
46	0.0		6.1	0.3
47	8.1		4.4	
Phenylbutazone	14.3			
Flufenamic acid	13.8	1.1	12.8	
Mefenamic acid	12.3	0.7		

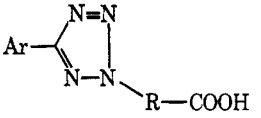
[a] Activity Index = 10 times the ratio of the mean pleural exudate volumes of the test compound at 1 mmol/kg over 1 mmol/kg of aspirin. [b] Phenylbutazone = 1.0. [c] Activity Index = 10 times the per cent reduction of abscess weight due to 16 mg of test compound divided by the per cent reduction due to 16 mg of phenylbutazone. [d] Potency = 0.8 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [e] Potency = 3.2 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [f] Potency = 1.2 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [g] Potency = 3.6 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [h] Potency = 1.6 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [i] Potency = 3.5 phenylbutazone in chronic adjuvant-induced rat arthritis screen. [j] Potency = 1.9 phenylbutazone in chronic adjuvant-induced rat arthritis screen.

(7) C. R. Jacobson, A. B. Kerr, Jr., and E. D. Amstutz, *J. Org. Chem.*, **19**, 1909 (1954).

(8) C. R. Jacobson and E. D. Amstutz, *ibid.*, **21**, 311 (1956).

TABLE II

5-ARYLTETRAZOLYL-2-ALKANOIC ACIDS



No.	Ar	R	Mp, °C	Formula	% yield[a]	Method	Recryst Solvent	Analysis
1	C_6H_5	CH_2	186[b]	$C_9H_8N_4O_2$	82	B	MeOH–H_2O	N, n e[c]
2	4-ClC_6H_4	CH_2	218	$C_9H_7ClN_4O_2$	67	B	MeOH–H_2O	C,H,N
3	3,4-$Cl_2C_6H_3$	CH_2	212	$C_9H_6Cl_2N_4O_2$	79	B	MeOH–H_2O	C,H,N
4	3,5-$Br_2C_6H_3$	CH_2	204	$C_9H_6Br_2N_4O_2$	77	B	AcOH–H_2O	n e[d]
5	C_6H_5	$(CH_2)_2$	128	$C_{10}H_{10}N_4O_2$	13	A	MeOH–H_2O	C,H,N
6	4-FC_6H_4	$(CH_2)_2$	141	$C_{10}H_9FN_4O_2$	65	B	MeOH–H_2O	C,H,N
7	3-FC_6H_4	$(CH_2)_2$	124	$C_{10}H_9FN_4O_2$	29	B	C_6H_6–heptane	C,H,N
8	4-ClC_6H_4	$(CH_2)_2$	152	$C_{10}H_9ClN_4O_2$	22	A	Me_2CO–H_2O	C,H,N
9	3-ClC_6H_4	$(CH_2)_2$	116	$C_{10}H_9ClN_4O_2$	34	B	C_6H_6–heptane	C,H
10	3,4-$Cl_2C_6H_3$	$(CH_2)_2$	148	$C_{10}H_8Cl_2N_4O_2$	79	B	MeOH–Et_2O	N
11	2,6-$Cl_2C_6H_3$	$(CH_2)_2$	137	$C_{10}H_8Cl_2N_4O_2$	92	B	C_6H_6	C,H,N
12	3,5-$Cl_2C_6H_3$	$(CH_2)_2$	166	$C_{10}H_8Cl_2N_4O_2$	92	B	MeOH–H_2O	C,H,N
13	4-BrC_6H_4	$(CH_2)_2$	161	$C_{10}H_9BrN_4O_2$	92	B	*i*-PrOH	C,H,N
14	3-BrC_6H_4	$(CH_2)_2$	128	$C_{10}H_9BrN_4O_2$	74	B	EtOH–H_2O	C,H,N
15	3,5-$Br_2C_6H_3$	$(CH_2)_2$	197	$C_{10}H_8Br_2N_4O_2$	82	B	DMF–EtOAc	C,H[e]
16	3-IC_6H_4	$(CH_2)_2$	146	$C_{10}H_9IN_4O_2$	52	B	EtOH–H_2O	C,H
17	4-$CF_3C_6H_4$	$(CH_2)_2$	222	$C_{11}H_9F_3N_4O_2$	74	B	MeOH–H_2O	C,H,N
18	3-$CF_3C_6H_4$	$(CH_2)_2$	96	$C_{11}H_9F_3N_4O_2$	74	B	C_6H_6–pentane	C,H,N
19	4-$CH_3C_6H_4$	$(CH_2)_2$	156	$C_{11}H_{12}N_4O_2$	39	B	EtOH	C,H
20	3-$CH_3C_6H_4$	$(CH_2)_2$	91	$C_{11}H_{12}N_4O_2$	31	B	C_6H_6–pentane	C,H,N
21	2-HOC_6H_4	$(CH_2)_2$	113	$C_{10}H_{10}N_4O_3$	18	B	C_6H_6	H,N; C[f]
22	4-HOC_6H_4	$(CH_2)_2$	199	$C_{10}H_{10}N_4O_3$	32	B	C_6H_6	C,H,N
23	4-$CH_3OC_6H_4$	$(CH_2)_2$	153	$C_{11}H_{12}N_4O_3$	27	B	EtOH–H_2O	C,H,N
24	4-$CH_3COC_6H_4$	$(CH_2)_2$	183	$C_{12}H_{12}N_4O_3$	46	B	MeOH	C,H,N
25	3-$NO_2C_6H_4$	$(CH_2)_2$	123	$C_{10}H_9N_5O_4$	43	B	AcOH–H_2O	C,H,N
26	4-$NO_2C_6H_4$	$(CH_2)_2$	160	$C_{10}H_9N_5O_4$	90	B	AcOH–H_2O	C,H,N
27	3,5-$(NO_2)_2C_6H_3$	$(CH_2)_2$	170	$C_{10}H_8N_6O_6$	57	B	AcOH–H_2O	C,H,N
28	3-$NH_2C_6H_4$	$(CH_2)_2$	134	$C_{10}H_{11}N_5O_2$	98	B	EtOAc–*i*-PrOH	C,H
29	3-$CH_3CONHC_6H_4$	$(CH_2)_2$	207	$C_{12}H_{13}N_5O_3$	71	B	EtOH	C,H
30	3-$C_6H_5N{=}NC_6H_4$	$(CH_2)_2$	155	$C_{16}H_{14}N_6O_2$	52	B	EtOAc	C,H
31	4-$SO_2NH_2C_6H_4$	$(CH_2)_2$	210	$C_{10}H_{11}N_5O_4S$	80	B	AcOH–H_2O	C,H,N
32	3,4-$(CH_3O)_2C_6H_3$	$(CH_2)_2$	147	$C_{12}H_{14}N_4O_4$	27	A	EtOH–H_2O	N
33	C_6H_5	$(CH_2)_3$	81	$C_{11}H_{12}N_4O_2$	47	B	MeOH–H_2O	N
34	C_6H_5	$(CH_2)_4$	93	$C_{12}H_{14}N_4O_2$	80	B	Me_2CO–pentane	C,H,N
35	C_6H_5	$CH(CH_3)$	146 dec	$C_{10}H_9N_4O_2Na$[g]	70	B	*i*-PrOH–H_2O	N
36	C_6H_5	$CH(C_6H_5)$	173	$C_{15}H_{12}N_4O_2$	56	B	MeOH–H_2O	N
37	2-Pyridyl	$(CH_2)_2$	182	$C_9H_9N_5O_2$	13	B	H_2O	H,N; C[h]
38	3-Pyridyl	$(CH_2)_2$	210	$C_9H_9N_5O_2$	13	B	MeOH	N
39	2-Thienyl	$(CH_2)_2$	130	$C_8H_8N_4O_2S$	39	A	MeOH–H_2O	N
40	4-$ClC_6H_4CH_2$	CH_2	260 (dec)	$C_{10}H_9ClN_4O_2K$[i]	26	B	EtOH–H_2O	N
41	4-$ClC_6H_4CH_2$	$(CH_2)_2$	213 (dec)	$C_{11}H_{10}ClN_4O_2Na$[g]	11	A	*i*-PrOH–H_2O	N,n e[j]
42	$C_6H_5CH_2CH_2$	$(CH_2)_2$	169 (dec)	$C_{12}H_{13}N_4O_2Na$	61	B	*i*-PrOH–MeOH	N, n e[k]
43	$(C_6H_5)_2CH$	$(CH_2)_2$	171	$C_{17}H_{16}N_4O_2$	9	B	$CHCl_3$–pentane	H,N,C[l]

[a] Yield calcd from starting tetrazole. [b] R. Rapp and J. Howard [*Can. J. Chem.*, **47**, 813 (1969)] report mp 182–184°. [c] Neutralization equivalent, calcd, 226; found, 224. [d] Neutralization equivalent, calcd, 362; found, 363. [e] C: Calcd, 31.93; found, 32.55. H: Calcd, 2.14; found, 2.56. [f] C: Calcd, 51.28; found, 51.72. [g] Isolated as the Na salt. [h] C: Calcd, 49.31; found, 49.85. [i] Isolated as the K salt. [j] Neutralization equivalent, calcd, 288; found, 284. [k] Neutralization equivalent, calcd, 268; found, 273. [l] C: calcd, 66.23; found, 65.30.

The aryltetrazolylalkanoic acids were first screened in rats in the pleurisy model as described by Sancilio[9] (see Table I). Initial evaluations were made at 1 mmol/kg, orally, with acetylsalicylic acid as the reference compound. The results were expressed as an activity index (AI), a value equal to 10 times the ratio of the mean pleural exudate volume (ml) of the 6 animals treated with the test compound divided by the mean pleural exudate volume from the reference drug group. Compounds with an AI value of less than 10 were considered to be inactive. Most compounds with AI values of greater than 6.0 in this screen were then assayed in parallel with phenylbutazone to determine the relative potency.

Most compounds were also screened in the carrageenin-induced abscess model[10] in 60-g weanling rats. Each drug was administered as 0.05 ml of a 0.316% solution mixed with irritant, with phenylbutazone as the reference compound. Again a number of compounds which displayed a range of activity were assayed in parallel with phenylbutazone and their relative potencies determined. In two separate experiments, one

(9) L. F. Sancilio, *Proc. Soc. Exp. Biol. Med.*, **127**, 597 (1968).

(10) K. F. Benitz and L. M. Hall, *ibid.*, **102**, 442 (1959).

of the more active compounds in this series, the 3,4-dichlorophenyl analog **10** was administered both separately at a remote site and mixed with the irritant and was found to be equally effective by either route. This strongly suggests that the acute antiinflammatory activity of these compounds is not due to counter-irritant action.

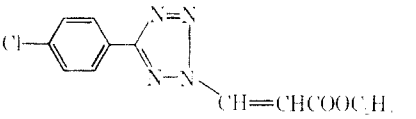
Those members of the series found to be active in the acute screens were examined in the chronic adjuvant-induced rat arthritis assay. The parameters of weight change, foot volume change,[11] secondary lesion score,[12] and plasma inflammation units[13] were weighted and pooled.[14] The activities so obtained were expressed as potencies relative to phenylbutazone.

A representative number of compounds in this series were also subjected to other screens. They were found to be virtually devoid of hypothermic and analgetic activities. In general, no CNS effects were observed. Some gastrointestinal irritation was seen at high oral doses in the rat with some of the more active members, particularly the chlorinated derivatives **10** and **12**.

Three types of structural variation were examined in the aryltetrazolylalkanoic acid series. They are: the nature of the aryl substitution pattern, the length and degree of branching of the carboxyl-bearing side chain, and the relative placement of each on the tetrazole nucleus.

The direct attachment of the aromatic group to the tetrazole ring was found to be necessary in every case for maximum activity. The insertion of CH_2 groups between the two as in **40**, **41**, **42**, and **43** resulted in decreased activity when compared with **2**, **5**, and **8**. In addition, there appears to be some requirement for coplanarity between the two aromatic rings. This stems from the observation that the 3,4-dichlorophenyl (**10**) and 3,5-dichlorophenyl (**12**) analogs were quite active while the 2,6-dichlorophenyl (**11**) was not. Analogous biphenyl systems[15] predict a considerable loss in coplanarity for the latter. The lessened activity of the 2-hydroxyphenyl **21** compared with the 4-hydroxyphenyl **22** may also be due to this. Maximum activity is associated with the halogenated aromatic systems with the exception of 3,5-dibromophenyl **15** and the previously mentioned **11**. The most active compounds of the entire series are the 3-fluorophenyl **7**, the 3-chlorophenyl **9**, the 3,5-dichlorophenyl **12**, and the 3-bromophenyl **14**. Heterocyclic aromatic groups such as 2-pyridyl **37**, 3-pyridyl **38**, and 2-thienyl **39** are only slightly active.

The length of the carboxyl-bearing side chain also has a critical bearing on activity. The 5-aryltetrazolyl-2-acetic acids **1**, **2**, **3**, and **4** are all less active than the corresponding propionic acids **5**, **8**, **10**, and **15**. Branching of the acetic acid side chain as in **35** and **36** offers no improvement in activity. Extending the side chain to 4–5 carbons as in **33** and **34** produces a decrease in activity over **5**. An attempt was made to prepare some 3-(5-aryl-2-tetrazolyl)acrylic acids to see what effect an unsaturated side chain would have on activity. A poor yield of ethyl 3-[5-(4-chlorophenyl)-2-tetrazolyl]acrylate (**48**) was obtained by the base-



48

catalyzed addition of 5-(4-chlorophenyl)tetrazole to ethyl propiolate. Unfortunately, attempts to saponify this ester merely regenerated the starting tetrazole.

The positions of attachment of the aryl group and the propionic acid side chain are also critical to the antiinflammatory activity. Of the 4 possible phenyltetrazolylpropionic acids, 3 were prepared. Of these, 3-(5-phenyl-1-tetrazolyl)propionic acid (**44**) is nearly 3 times less active than 3-(5-phenyl-2-tetrazolyl)propionic acid (**5**) while 3-(1-phenyl-5-tetrazolyl)propionic acid (**46**) is completely inactive. The fourth isomer, 3-(2-phenyl-5-tetrazolyl)propionic acid, was inaccessible but a related compound, 2-benzyl-5-tetrazolylacetic acid (**47**), had moderate activity. Clearly then, the optimum structure requires the aromatic group to be attached at position 5 and the propionic acid residue at position 2 of the tetrazole ring.

Experimental Section[16]

Preparation of the 5-Aryltetrazoles II.—These were prepared by refluxing the appropriate nitrile for 16 hr with 1.1 equiv each of NH_4Cl and NaN_3 in DMF (250 ml/0.1 mol of nitrile). After reprecipitation from base, the tetrazoles were used directly.

Preparation of the 3-(5-Aryl-2-tetrazolyl)propionic Acids (VI). Method A.—The 5-aryltetrazoles (0.1 mol) were added to a solution of Na (0.1 g-atom) in 150 ml of abs EtOH. The solution was stirred at room temp and β-propiolactone (0.1 mol) was added dropwise over a 15-min period. Stirring was continued for 16 hr during which time a solid formed. The solvent was removed under reduced pressure and the residue taken up in H_2O and acidified. Recrystallization was usually from MeOH.

Preparation of 5-Aryl-2-tetrazolylalkanoic Acids (IV).—Method B.—The 5-aryltetrazoles (0.1 mol) were added to a solution of Na (0.1 g-atom) in 350 ml of abs EtOH. The solution was stirred at reflux and the appropriate bromo ester (0.1 mol) was added. After 16 hr, the reaction mixture was filtered and concd *in vacuo*. The oily residue was taken up in 500 ml of Et_2O and extracted with 250 ml of 5% aq $NaHCO_3$ to remove any unreacted starting tetrazole. The Et_2O solution was usually dried and evapd. The esters so obtained were often oils and were used without further purification. Two procedures were followed for the hydrolyses. See Table II for melting points and yields.

Hydrolysis Procedure 1.—The ethyl 5-aryl-2-tetrazolylpropionates were refluxed under N_2 for 16 hr in a 1:1 v/v mixture of concd HCl and glacial AcOH (20 ml/g of ester). After cooling, the solutions were diluted with H_2O and the acids were collected and dried.

Hydrolysis Procedure 2.—The ethyl 5-aryl-2-tetrazolylpropionates, butyrates, and valerates were refluxed for 4 hr in a 1:1 v/v mixture of abs EtOH and 20% aq NaOH (10 ml/g of ester). After cooling and diluting with H_2O, the free acids were liberated with dil HCl.

3-[5-(3-Aminophenyl)-2-tetrazolyl]propionic Acid (28).—A solution of 21 g (0.079 mol) of 3-[5-(3-nitrophenyl)-2-tetrazolyl]propionic acid in 400 ml of MeOH was hydrogenated at room temp and 3 atm pressure over 0.4 g of 10% Pd–C. Recrystallization from EtOH gave 18 g (98%) of white needles, mp 135°.

(11) C. A. Winter and G. W. Nuss, *Arthritis Rheum.*, **9**, 394 (1966).
(12) B. B. Newbould, *Brit. J. Pharmacol.*, **21**, 127 (1963).
(13) E. M. Glenn, *Amer. J. Vet. Res.*, **26**, 1195 (1965).
(14) Details of the ranking procedure will be given in a forthcoming publication.
(15) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 156.

(16) All melting points are uncorrected and were determined with a Büchi capillary melting point apparatus (W. Büchi, Glasapparatefabrik, Flawil, Switzerland). Ir spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. Titrations were carried out with NaOH in EtOH on a Sargent Model D recording titrator. Where analyses are indicated by symbols, the elements or functions were within ± 0.4% of the calculated values.

3-[5-(3-Acetamidophenyl)-2-tetrazolyl]propionic Acid (29).—3-[5-(3-aminophenyl)-2-tetrazolyl]propionic acid (7 g, 0.03 mol) was stirred for 12 hr at room temp in 100 ml of an equivolume mixture of Ac_2O–AcOH. The pale yellow ppt was reprecipitated from $NaHCO_3$ and recrystd from EtOH to give 5 g (61%) of pale yellow crystals, mp 207°.

3-[5-(3-Phenylazophenyl)-2-tetrazolyl]propionic Acid (30).—To a solution of 7 g (0.03 mol) of 3-[5-(3-aminophenyl)-2-tetrazolyl]propionic acid in 75 ml of glacial AcOH was added 3.25 g (0.03 mol) of nitrosobenzene. After stirring at room temp for 16 hrs the ppt was collected and dried. Two recrystallizations from aq MeOH gave 5 g (52%) of red crystals, mp 155°.

3-(5-Phenyl-1-tetrazolyl)propionic Acid (44).—PCl_5 (51 g, 0.245 mol) was added portionwise to a solution of ethyl 3-benzamidopropionate (50 g, 0.232 mol) in 300 ml of dry C_6H_6. The solution was refluxed until the evolution of HCl ceased. After cooling, 100 g of a 13.4% solution of HN_3 in C_6H_6[17] was added. After stirring for 1 hr at 0° and 16 hr at reflux, HCl gas ceased to evolve. The solvent was removed under recuced pressure and the residue was hydrolyzed according to procedure 1. Two recrystallizations from H_2O gave 10.5 g (21%) of white plates, mp 146°. *Anal.* ($C_{10}H_{10}N_4O_2$) N.

2-Benzyl-5-tetrazolylacetic Acid (47).—Ethyl 5-tetrazolylacetate (36.5 g, 0.234 mol) was dissolved in 300 ml of abs EtOH containing 5.4 g (0.234 g-atom) of Na. To this was added, over a 15-min period, 29.6 g (0.234 mol) of $PhCH_2Cl$ in 50 ml of abs EtOH. After refluxing for 16 hr, the reaction mixture was filtered and concd *in vacuo* to give a yellow oil. Hydrolysis according to procedure **1** gave a waxy solid. Recrystallization from aq MeOH gave 14.4 g (28%) of pale yellow crystals, mp 154° dec. *Anal.* ($C_{10}H_{10}N_4O_2$) N; neut equiv, calcd 218; found 220.

Ethyl 3-[5-(4-chlorophenyl)-2-tetrazolyl]acrylate (48).—To a solution of 2 g (0.087 g-atom) of Na in 200 ml of abs EtOH was added 26 g (0.1 mol) of 5-(4-chlorophenyl)tetrazole and 11 g (0.11 mol) of ethyl propiolate. After refluxing 1 day under N_2, the solvent was removed under reduced pressure. The oily residue was stirred for 1 hr with 1 l. of 2% aq $NaHCO_3$. The undissolved yellow solid was recrystd first from EtOH and then from pentane to give 3 g (16%) of white needles, mp 121°, ir ($CHCl_3$) 1620 cm^{-1} (C=C), 1725 cm^{-1} (C=O). *Anal.* ($C_{12}H_{11}ClN_4O_2$) C, H, N.

(17) J. von Braun, *Justus Liebigs Ann. Chem.*, **490**, 100 (1931).

Synthesis and Screening for Antidepressant Activity of Some Aminoindanooxazolines, Aminoindanooxazines, and Aminoacenaphthoxazolines

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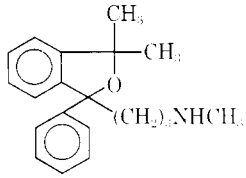
Some aminoindanooxazolines, aminoindanooxazines, and aminoacenaphthoxazolines having spatial orientations similar to those of the tricyclic drugs were synthesized and tested for potential antidepressant activity. None of the compounds were able to prevent reserpine-ptosis. Some of the compounds potentiated *d*-amphetamine toxicity and prolonged hexobarbital sleep time in mice.

Basically substituted phenylpththalanes, indans, indenes, isochromanes, tetralines, isoindolines, indolines, tetrahydroisoquinolines, phthalimidines, oxindoles, dihydrobenzofurans, and dihydrobenzoxazines have been synthesized and screened for antidepressant activity.[1] Of these, the dihydrobenzofuran, indane, and indene derivatives (I, II, and III) have shown the most promise as potential antidepressant agents.[1,2]



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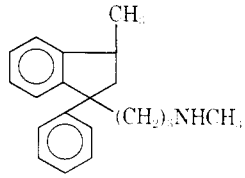
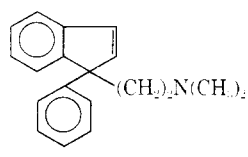


II



III

This paper reports the synthesis and testing as potential antidepressants of phenyl aminoindano-oxazines and oxazolines and aminoacenaphthoxazolines. These structures have the basic moiety fused onto either the indan nucleus (IV and V) or the acenaphthene nucleus (VI).

An examination of stereomodels showed that the angle between the two benzene rings in I, II, III, V, and imipramine is practically identical (110°) and that this results in the benzenoid-containing portion of these molecules being superimposable. Because indan is planar and rigid the C–C bond attaching the basic side chain to the ring is fixed at an angle of 55° to the ring. Because of N inversion, in imipramine the C–N bond attaching the basic side chain to the ring is either pseudoaxial or pseudoequatorial. In the former conformation the angle is similar to the phenylindans (~55°) and in the latter it is nearly in the same plane as one of the benzene rings. However, due to the flexibility of the propyl side chain the amino group of the phenylindans and imipramine can be made superimposable regardless of the configuration of the ring N in imipramine. In V the basic side chain is rigid and is not attached to the phenyl bearing carbon of indan as it is in II and III. Therefore, superimposition of N and the two phenyl rings of V and imipramine is restricted to one conformation of the imipramine side chain. In this conformation the three carbon atoms of the imipramine side chain also are superimposed on the three atoms of the oxazoline ring. Thus, it is likely that V would be able to interact with an imipramine receptor but that its structural requirement for interaction would be much more demanding. The divergence in structural similarity between imipramine and

(1) P. V. Petersen and I. Moeller-Nielson, *Antidepressant Drugs, Proc. Int. Symp. 1st. Milan 1966*, 217–21 (1967); *Chem. Abstr.*, **68**, 1724 (1968).

(2) J. H. Biel, *Ann. Rep. Med. Chem.*, 11 (1966); M. A. Davis, *ibid.*, 15–17 (1967).