Synthesis and Antiinflammatory Activity of Some 1,2,3- and 1,2,4-Triazolepropionic Acids

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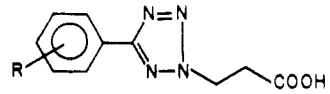
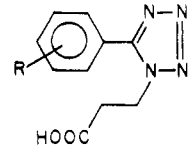
All possible "nonadjacent" phenyltriazolepropionic acids were synthesized and tested for antiinflammatory activity. Two of the isomers displayed activity approximately equal to phenylbutazone: the 4-phenyl-1,2,3-triazole-2-propionic acid (**7**) and its reverse counterpart, 2-phenyl-1,2,3-triazole-4-propionic acid (**6**). The other five isomers were inactive. Since these seven acids are geometrically congruent and possess similar lipophilic characters, antiinflammatory activity must depend on some property that is a function of how the carbon and nitrogen atoms are arranged in the triazole ring.

Some time ago, we found that certain substituted (5-phenyl-2-tetrazolyl)propionic acids I possessed high levels



I



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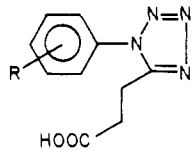

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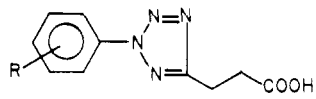
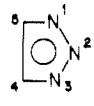


IV

of antiinflammatory activity.[2] The geometrical isomers II and III, which have the phenyl and the propionic acid groups attached to adjacent ring atoms, were inactive. This led us to conclude that the linear geometry of I was necessary for activity. We next prepared two examples of IV, the reverse positional isomer of I, and found both to be about equal in activity to their I isomer counterparts. Since the biological activities of series I are modulated by the nature of the aromatic substituent R, we suggested that the phenyl ring and the carboxyl group fulfill some binding function at the receptor and that the tetrazole ring merely serves to keep them in the proper geometrical relationship.[3] To confirm this hypothesis, we synthesized the analogous phenyltriazolepropionic acids.

There are two kinds of triazoles, the 1,2,4-triazoles V

V

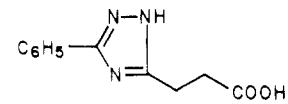


VI

(sometimes called symmetrical) and the 1,2,3-triazoles VI (vicinal triazoles), and there are seven ways that two nonidentical substituents can be attached "nonadjacently" to them.

The *s*-triazoles V give rise to three nonadjacent phenylpropionic acid isomers, compounds **1**–**3** (**2** and **3** are the reverse of each other). The *v*-triazoles VI give rise to four nonadjacent phenylpropionic acid isomers: **4** and its reverse counterpart, **5**, and **6** and its reverse counterpart, **7**. Our earlier work on the tetrazoles implied that all seven of these "linear" phenyltriazolepropionic acids should be roughly equal to each other in antiinflammatory activity and to the tetrazoles I and IV in potency. When prepared, however, isomers **1**–**7** displayed activities ranging from inactive to equal in potency to the reference drug, phenylbutazone.

Chemistry. We prepared triazoles **1**–**7** and at least two substituted derivatives of each (see Table I). The first



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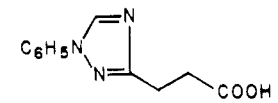

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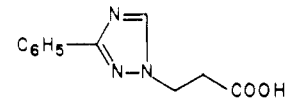

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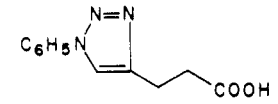

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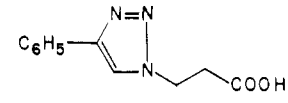

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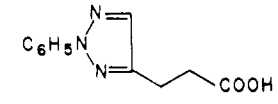

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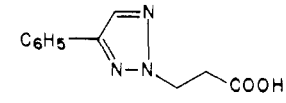
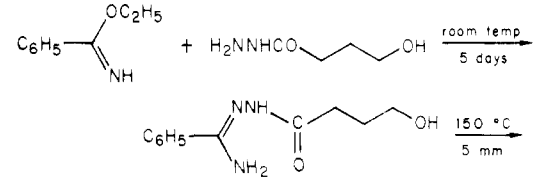


7

of these, triazole **1**, was made by allowing an ethanol solution of benzimido ethyl ether and 4-hydroxybutyrohydrazide to stand for 1 week to produce the acylamidrazone **8** in 50% yield.[4] When heated to 150 °C under



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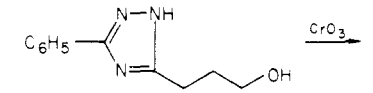
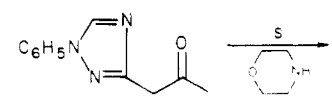


9

vacuum, **8** cyclized to the triazole alcohol **9**. Chromic oxide oxidation of **9** gave 3-[3-phenyl-1*H*-1,2,4-triazol-5-yl]-propionic acid (**1**). The 3-chloro- and 3-bromophenyl analogues **1a** and **1b** were also made.

The second isomer type, **2**, was made from the corresponding acetone derivative **10**, a known compound.[5] This



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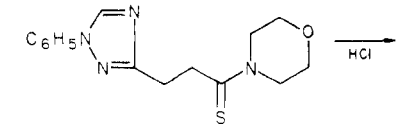

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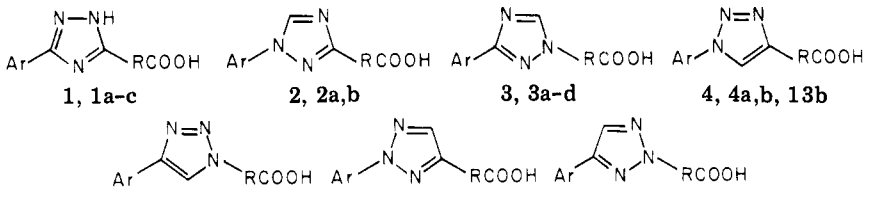
Table I. Aryltriazolealkanoic and -alkenoic Acids



1, 1a-c 2, 2a,b 3, 3a-d 4, 4a,b, 13b

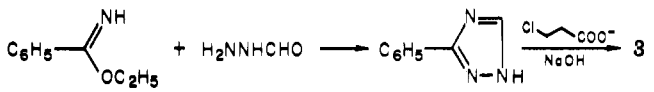
5, 5a-i 6, 6a,b, 20, 20a,b 7, 7a-g

no.	Ar	R	mp, °C	formula	recrystn solvent	analyses
1	C_6H_5	CH_2CH_2	117-118	$C_{11}H_{11}N_3O_2 \cdot H_2O$	EtOAc	C, H[a]
1a	3-ClC_6H_4	CH_2CH_2	165	$C_{11}H_{10}ClN_3O_2$	xylene	C, H
1b	3-BrC_6H_4	CH_2CH_2	167	$C_{11}H_{10}BrN_3O_2$	*i*-PrOH-H_2O	C, H
1c	3-$CH_3C_6H_4$	CH_2CH_2	136	$C_{12}H_{13}N_3O_2$	Me_2CO-pentane	C, H
2	C_6H_5	CH_2CH_2	175	$C_{11}H_{11}N_3O_2$	EtOH	C, H
2a	3-ClC_6H_4	CH_2CH_2	158	$C_{11}H_{10}ClN_3O_2$	EtOH	C, H
2b	3,5-$Cl_2C_6H_3$	CH_2CH_2	200	$C_{11}H_9Cl_2N_3O_2$	EtOH	C, H
3	C_6H_5	CH_2CH_2	141	$C_{11}H_{11}N_3O_2$	*i*-PrOH	C, H
3a	3-ClC_6H_4	CH_2CH_2	143	$C_{11}H_{10}ClN_3O_2$	*i*-PrOH-H_2O	C, H
3b	3-BrC_6H_4	CH_2CH_2	155	$C_{11}H_{10}BrN_3O_2$	*i*-PrOH-H_2O	C, H
3c	3-$CH_3C_6H_4$	CH_2CH_2	162	$C_{12}H_{13}N_3O_2$	EtOAc	C, H
3d	3-$CH_3C_6H_4$	CH_2	163	$C_{11}H_{13}N_3O_2$	EtOAc	C, H
4	C_6H_5	CH_2CH_2	138	$C_{11}H_{11}N_3O_2$	EtOH-H_2O	C, H
4a	3-FC_6H_4	CH_2CH_2	134	$C_{11}H_{10}FN_3O_2$	toluene	C, H
4b	3-ClC_6H_4	CH_2CH_2	166	$C_{11}H_{10}ClN_3O_2$	MeOH-H_2O	C, H
13a	3-FC_6H_4	CH=CH	251	$C_{11}H_{10}FN_3O_2$	THF-MeOH	C, H
5	C_6H_5	CH_2CH_2	181[b]	$C_{11}H_{11}N_3O_2$	*i*-PrOH	C, H
5a	3-FC_6H_4	CH_2CH_2	148	$C_{11}H_{10}FN_3O_2$	MeOH	C, H
5b	3-ClC_6H_4	CH_2CH_2	174	$C_{11}H_{10}ClN_3O_2$	MeOH	C, H
5c	3-BrC_6H_4	CH_2CH_2	179	$C_{11}H_{10}BrN_3O_2$	MeOH	C, H
5d	3-$CH_3C_6H_4$	CH_2CH_2	143	$C_{12}H_{13}N_3O_2$	*i*-PrOH-H_2O	C, H
5e	3-$C_2H_5OC_6H_4$	CH_2CH_2	138	$C_{13}H_{15}N_3O_3$	C_6H_6	C, H
5f	3-$NH_2C_6H_4$	CH_2CH_2	178[c]	$C_{11}H_{12}N_4O_2$	EtOAc	C, H
5g	3-$CH_3CONHC_6H_4$	CH_2CH_2	237[d]	$C_{13}H_{14}N_4O_3$	MeOH	C, H
5h	3-$NO_2C_6H_4$	CH_2CH_2	170	$C_{11}H_{10}N_4O_4$	MeOH	C, H
5i	3-pyridyl	CH_2CH_2	207	$C_{10}H_{10}N_4O_2$	MeOH	C, H
6	C_6H_5	CH_2CH_2	75[e]	$C_{11}H_{11}N_3O_2$	C_6H_6-hexane	
6a	3-ClC_6H_4	CH_2CH_2	107	$C_{11}H_{10}ClN_3O_2$	C_6H_6	C, H
6b	3-BrC_6H_4	CH_2CH_2	97	$C_{11}H_{10}BrN_3O_2$	C_6H_6	C, H
20	C_6H_5	CH=CH	180[f]	$C_{11}H_9N_3O_2$	MeOH	
20a	3-ClC_6H_4	CH=CH	183	$C_{11}H_8ClN_3O_2$	EtOH	C, H
20b	3-BrC_6H_4	CH=CH	229	$C_{11}H_8BrN_3O_2$	AcOH	C, H
7	C_6H_5	CH_2CH_2	143[g]	$C_{11}H_{11}N_3O_2$	MeOH-H_2O	C, H
7a	3-ClC_6H_4	CH_2CH_2	90	$C_{11}H_{10}ClN_3O_2$	pentane	C, H
7b	3-BrC_6H_4	CH_2CH_2	90	$C_{11}H_{10}BrN_3O_2$	hexane	C, H
7c	3,5-$Cl_2C_6H_3$	CH_2CH_2	123	$C_{11}H_9Cl_2N_3O_2$	C_6H_6-hexane	C, H
7d	3-$CH_3CONHC_6H_4$	CH_2CH_2	191	$C_{13}H_{14}N_4O_3$	Me_2CO	C, H
7e	3-$CH_3C_6H_4$	CH_2CH_2	93	$C_{12}H_{13}N_3O_2$	C_6H_6-hexane	C, H
7f	3-$NO_2C_6H_4$	CH_2CH_2	124	$C_{11}H_{10}N_4O_4$	C_6H_6	C, H
7g	3-pyridyl	CH_2CH_2	191[h]	$C_{10}H_{11}ClN_4O_2$	AcOH-EtOAc	C, H

[a] Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11. Found: C, 60.52; H, 4.92 [after drying at 130 °C (0.1 mm) for 15 min]. [b] Reference 10 reports mp 180-181 °C. [c] Prepared by reduction of 5h. [d] Prepared by acetylization of 5f. [e] Reference 11 reports mp 75 °C. [f] Reference 11 reports mp 180 °C. [g] Reference 13 reports mp 145-146 °C. [h] Hydrochloride salt.

methyl ketone was subjected to a Willgerodt-Kindler reaction and the resulting thiomorpholide 11 hydrolyzed to the desired *s*-triazole acid 2. The 3-chloro- and 3,5-dichlorophenyl isomers 2a and 2b were also prepared by this method.

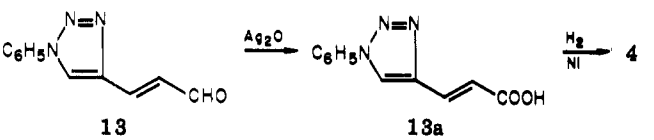
The third of the 1,2,4-triazole isomers, 3, was made by reaction of benzimido ethyl ether with formylhydrazine to give 3-phenyl-1*H*-1,2,4-triazole (12) in good yield.[6] At



12

this point we had trouble attaching the propionic acid side chain to 12. The sodium salt of 12 reacted with ethyl 3-bromopropionate to give only ethyl acrylate via β-elimination of Br rather than 3 via displacement of Br. After examining a variety of reaction conditions, we finally obtained a 60% yield of 3 by heating a water solution of the sodium salt of 12 with sodium 3-chloropropionate for 3 days. The ionized carboxyl group of the latter suppressed α-proton abstraction leading to β-elimination and allowed β-displacement to take place. The nonadjacent 1 isomer 3 was the major product. Other workers have shown that steric hindrance by the phenyl moiety suppresses the formation of isomers derived from attack at N-2 or N-4 in 12.[7] Also prepared were the 3-chloro-, 3-bromo-, and 3-methylphenyl analogues 3a-c.

The first representative of the *v*-triazoles, isomer 4, was prepared from the known acrolein 13.[8] This compound

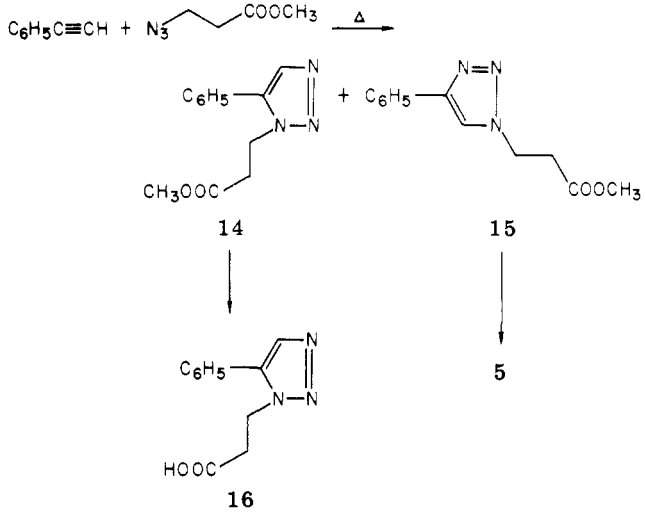


13 13a

was oxidized and hydrogenated to the triazolepropionic acid 4. The 3-fluoro- and 3-chlorophenyl analogues 4a and

4b were also prepared in this fashion.

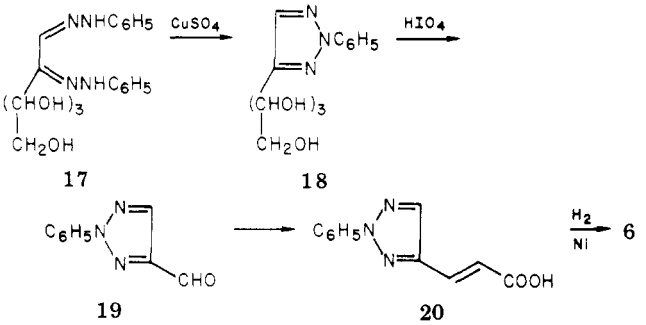
Isomer **5** and its analogues were obtained by thermal addition of methyl 3-azidopropionate to the appropriately substituted phenylacetylene. This reaction produced chiefly the desired 4 isomer **15** as well as smaller amounts



of the 5-phenyl-1-propionate isomer **14**.[9] The mixtures were separated by column chromatography on silicic acid and each ester was hydrolyzed to the corresponding free acid, **5** and **16**.

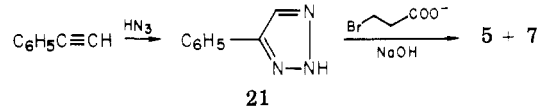
The less polar, lower melting ester and acid were assigned the structures of the 5-phenyl isomers **14** and **16** by analogy with previously reported isomers of triazoles[8,10] and by their ^{1}H NMR spectra. The 4-phenyl ester and acid (both in C_5D_5N) displayed the phenyl protons as two multiplets: 2 H centered on 485 Hz and 3 H centered on 442 Hz. The triazole H occurred as a singlet at about 507 Hz. The 5-phenyl isomers (C_5D_5N) exhibited the phenyl protons as a 5 H singlet at 476 Hz. For steric reasons, the phenyl ring in the 5-phenyl isomers **14** and **16** is skewed out of the plane of the triazole ring. It no longer interacts strongly enough with it to provide the ortho protons with different chemical shifts, and the phenyl protons collapse to a singlet. Additionally, this skewing of the phenyl ring puts the triazole proton into the phenyl shielding zone, shifting it upfield 31 Hz relative to the 4-phenyl isomers **15** and **5**. In all, eight substituted 4-aryl-1*H*-1,2,3-triazole-1-propionic acids were made (**5a–i**).

Compound **6**, the parent of the 2-aryl-2*H*-1,2,3-triazole-4-propionic acids, is a known compound.[11] It was prepared by converting the osazone of glucose **17** to the



glucosotriazole **18**, followed by periodate oxidation to the aldehyde **19**. When treated with malonic acid in pyridine, this aldehyde gave the acrylic acid **20**, which was hydrogenated to the propionic acid **6**. This route was used to make the 3-chloro- and the 3-bromophenyl analogues **6a** and **6b**. To prepare the bromo compound **6b** it was necessary to use nickel boride as the catalyst in the hydrogenation step.[12] Platinum catalysts caused debromination of **20b** to **6**.

The last of the seven isomers, 3-[4-phenyl-2*H*-1,2,3-triazol-2-yl]propionic acid (**7**), was made by reacting phenylacetylene with either hydrazoic acid or trimethylsilyl azide to give 4-phenyl-*v*-triazole (**21**).[10] The sodium salt

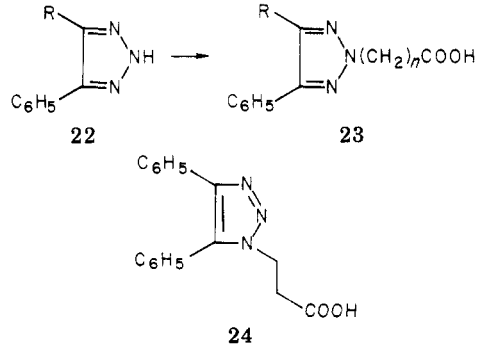


of **21** was alkylated with the anion of 3-bromopropionic acid to give mainly isomer **7** in the manner described for the preparation of **3**. Nevertheless, a substantial amount of the 4-phenyl-1-propionic acid isomer **5** was isolated from the reaction mixture. Thus, isomer **5** occurred in two reactions, the one leading to **7** as well as the one leading to **16**. This served to unequivocally distinguish **5**, **7**, and **16**, since the isomer appearing in both reaction mixtures could only be **5**. Therefore **7** was identified by elimination.[13]

When chromatographed on silicic acid, isomer **7** eluted first, followed by **5**. The two isomers were also distinguished by their ^{1}H NMR spectra (C_5D_5N). The triazole H of **7** appears at 489 Hz and the triazole H of **5** at 507 Hz. These parameters were used to assign the structures of analogues **7a–c,e–g** as well as **23b** (see Experimental Section).

Compound **16**, the isomer produced by attack at N-1 in **21**, is not seen in the reaction of **21** with 3-bromopropionate. Apparently steric hindrance by the phenyl group prevents attack at the adjacent nitrogen just as it does in the alkylation of the *s*-triazole **12**.

Because the 4-phenyl-2*H*-1,2,3-triazole-2-propionic acids turned out to be the most interesting, pharmacologically, of the seven types of triazoles studied, a number of other variations on isomer **7** were made (see Tables II and III). The alkylation of 4-phenyl-*v*-triazole (**21**) with ethyl chloroacetate and ethyl 4-chlorobutyrate gave, after hydrolysis, acetic acid **23a** and butyric acid **23b**, respectively.

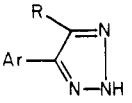


a, R = H; *n* = 1 **d**, R = C_6H_5; *n* = 2
b, R = H; *n* = 3 **e**, R = $COCH_3$; *n* = 2
c, R = CH_3; *n* = 2 **f**, R = $N(CH_3)_2$; *n* = 2

Also, four disubstituted acetylenes were reacted with trimethylsilyl azide to give the disubstituted *v*-triazoles **22c–f**. Triazoles **22c** and **22d** were alkylated with sodium 3-chloropropionate and gave mainly the 2 isomers **23c** and **23d**. In the reaction of **23d**, a substantial amount of the 1 isomer **24** was isolated. Triazoles **22e** and **22f** were alkylated with propiolactone in DMF. This reaction also yielded chiefly the 2 isomers **23e** and **23f**. The structural assignments of **23a–f** were made by analogy with the products of the alkylation of triazoles **12** and **21**.

For purposes of comparison with the triazoles, 3-(2-phenyl-5-tetrazolyl)propionic acid (**25**) was prepared from

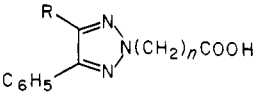
Table II. 5-Substituted 4-Aryl-*v*-triazoles



no.	Ar	R	mp, °C	method[a]	formula	% yield	recrystn solvent	analyses
21a	3-ClC_6H_4	H	140	A	$C_8H_6ClN_3$	45	toluene	C, H
21b	3-BrC_6H_4	H	140	B	$C_8H_6BrN_3$	83	toluene	C, H
21c	3,5-$Cl_2C_6H_3$	H	206	B	$C_8H_5Cl_2N_3$	54	xylene	C, H
21e	3-$CH_3C_6H_4$	H	93	A	$C_9H_9N_3$	75	C_6H_6-pentane	H; C[b]
21f	3-$NO_2C_6H_4$	H	208	A	$C_8H_6N_4O_2$	56	DMF-xylene	C, H
21g	3-pyridyl	H	197	A	$C_7H_6N_4$	43	DMF-H_2O	C, H
22c	C_6H_5	CH_3	176	B	$C_9H_9N_3$	87	MeOH	C, H
22d	C_6H_5	$COCH_3$	119	B	$C_{10}H_9N_3O$	50	MeOH	C, H
22f	C_6H_5	$N(CH_3)_2$	138[c]	B	$C_{10}H_{13}ClN_4$	21	*i*-PrOH	H; C[d]

[a] A = hydrazoic acid; B = trimethylsilyl azide. [b] C: calcd, 67.90; found, 68.40. [c] Hydrochloride salt. [d] C: calcd, 53.45; found, 54.08.

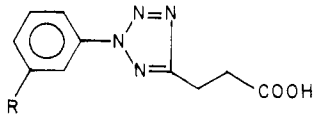
Table III. 5-Substituted 4-Phenyl-2*H*-1,2,3-triazole-2-alkanoic Acids



no.	R	*n*	mp, °C	formula	% yield	recrystn solvent	analyses
23a	H	1	199[a]	$C_{10}H_9N_3O_2$	35	MeOH-H_2O	
23b	H	3	99	$C_{12}H_{13}N_3O_2$	50	C_6H_6-pentane	C, H
23c	CH_3	2	115	$C_{12}H_{13}N_3O_2$	39	C_6H_6	C, H
23d	C_6H_5	2	166	$C_{17}H_{15}N_3O_2$	20	MeOH-H_2O	H; C[b]
23e	$COCH_3$	2	113	$C_{13}H_{13}N_3O_3$	28[c]	hexane	C, H
23f	$N(CH_3)_2$	2	210	$C_{13}H_{15}N_4O_2Na$	41[d]	*i*-PrOH	N, Na[e]

[a] Reference 13 reports mp 199-200 °C. [b] C: calcd, 69.61; found, 69.11. [c] Prepared by alkylating **22e** with propiolactone. [d] Prepared by alkylating **22f** with propiolactone. [e] Sodium salt.

the known ethyl 2-phenyltetrazolyl-5-carboxylate. Also prepared was the 3-bromo analogue **26**.



25, R = H
26, R = Br

Discussion

The way that changes in chemical structure in a series of compounds bring about changes in biological activity is often proportional to the way these changes alter the geometry, electronic state, lipophilicity, and steric size of each molecule. Although a detailed explanation will be offered in a later paper, some general observations can be made here about the way changes in these four factors affect the antiinflammatory activity of the triazoles.

Our previous suggestion that the activity of the tetrazoles I requires the linear geometry associated with the nonadjacent attachment of the phenyl and propionic acid groups received additional support: the adjacent isomer **16** of the active triazole **7** was inactive (see Table IV). Furthermore, shortening or lengthening the side chain of **7** gave acetic acid **23a** and butyric acid **23b**, both inactive.

Only two classes of triazoles were active: the *v*-triazole **7** and its reverse isomer **6**. The other five were inactive, clearly demonstrating that the triazole ring or some part of it has a major role in determining antiinflammatory activity, although how is not immediately apparent. The arrangement of carbon and nitrogen atoms within the heterocyclic rings has little effect on geometry or lipophilicity.[14] The lipophilicities of the triazoles, as reflected in the octanol–H_2O partition coefficients calculated by the method of ref 14, range from 0.04 to 0.23. This range is too small to account for the large differences in activity among compounds **1**–**7**. Thus activity must depend either on some electronic property at a particular position of the triazole ring or on some electronic property peculiar to the ring as a whole. The active triazoles **6** and **7** and the active tetrazoles I and IV all possess one feature in common: a nitrogen atom at the ring position between the two atoms bearing the phenyl and propionic acid substituents.

In the two active series, analogues having phenyl substituents with negative σ values were not active. Halogens seem to be the best phenyl substituents although their presence merely maintained activity; it did not increase it. Substitution in the triazole ring tended to lower activity except in the case of the phenyl-substituted **23d** which was relatively unchanged in activity from **7**.

Experimental Section[15]

Below are listed the preparations of propionic acids **1**–**7**, **23f**, **25**, and **26**. Substituted acids were made by the method used for the parent unless otherwise indicated in Table I. The intermediate triazoles that are new compounds are listed in Table II. Other intermediates were isolated but not usually characterized.

3-[3-Phenyl-1*H*-1,2,4-triazol-5-yl]propan-1-ol (9). A suspension of 37 g (0.2 mol) of benzimido ethyl ether hydrochloride[16] in 400 mL of warm absolute EtOH was neutralized with a solution of 1 equiv of NaOEt in 200 mL of absolute EtOH. The precipitate of NaCl was filtered and 23.6 g (0.2 mol) of 4-hydroxybutyrohydrazide[17] was added. After standing for 8 days at room temperature in the dark, the solvent was removed under reduced pressure to give a gummy residue of crude amidrazone **8**. Heating at 170 °C for 7 h cyclized it to the triazole. The dark, glassy residue was partitioned between 250 mL of 1 N NaOH and 250 mL of ether. The aqueous phase was separated, back washed with 250 mL of ether, and neutralized with CO_2. A solid precipitated that was twice recrystallized from EtOAc to give 13 g (31%) of the triazole alcohol **9** as fine white needles, mp 118 °C. Anal. ($C_{11}H_{13}N_3O$) C, H. This gave a diacetate when treated with Ac_2O–pyridine: white plates from EtOH; mp 95 °C.[18] Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.97. Found: C, 62.61; H, 5.95.

Table IV. Antiinflammatory Activity of Some Aryltriazolealkanoic and -alkenoic Acids

no.	pleural effusion model[a]	adjuvant arthritis model[b] injected foot day 7	injected foot day 21	uninjected foot, day 21
1	−1.7	9.1	4.2	30
1a	2.9	3	3	3
1b	−9.0	−13	−1.2	30
1c	−3.0	c	c	c
2	12	1.3	−0.6	−15
2a	7.5	c	c	c
2b	5.2	23	30[d]	71[d]
3	−3.7	4.4	8.6	10
3a	1.1	3.0	11	14
3b	8.9	6.2	0.1	18
3c	−3.2	−5.1	7.1	50
3d	3.0	0.2	6.0	−15
4	1.6	2.3	−1.6	−3.2
4a	−4.1	22	2.4	−2.0
4b	10	10	−1.9	21
13a	2.3	−19	−2.7	18
5	0.0	8.9	2.2	12
5a	1.7	−9.9	−10	1.6
5b	−1.4	−1.1	3.5	8.2
5c	11	0.0	7.2	23
5d	0.0	10	7.8	22
5e	0.6	0.4	9.0	28
5f	1.4	2.8	11	6.7
5g	9.9	1.7	20	19
5i	5.1	9.3	18	30
6	28[d]	9.1	21[d]	36[d]
6a	33	13	32[d]	11
6b	14	11	35[d]	39
20	13	11	20[d]	17[d]
20a	18	c	c	c
20b	20	12	14	16
7	42[d]	36[d]	57[d]	63[d]
7a	19	28	42[d]	26
7b	29	19	30[d]	25
7c	0.0	35	33[d]	38
7d	−3.2	8.1	−0.1	−24
7e	−1.3	13	4.5	9.6
7g	−1.3	c	c	c
25a	−5.0	−17	−9.0	45
25b	13	−1.8	14	1.4
25c	17	c	c	c
25d	26	21	23	34
25e	2.6	13	−8.0	−30
25f	0.0	c	c	c
22	40[d]	20	59[d]	62[d]
23	33[d]	c	c	c
16	5	c	c	c
26	21	17	34[d]	22
I (R = H)	c	c	c	c
aspirin	29[d,f]	37[d,g]	5[g]	11[g]
phenylbutazone	28[h]	33[d,h]	39[d,h]	36[d,h]

[a] Percent reduction from controls of the pleural fluid volume (see ref 24). [b] Percent reduction from controls of the volume of the foot (see ref 25). [c] Not tested in the rat adjuvant arthritis model. [d] $p < 0.05$. [e] Potency = 0.9 × phenylbutazone in the pleural effusion model (see ref 2). [f] 0.83 mmol/kg (150 mg/kg). [g] 72 mg/kg. [h] 0.2 mmol/kg (62 mg/kg).

Also prepared in this fashion were 3-[3-(3-chlorophenyl)-1*H*-1,2,4-triazol-5-yl]propan-1-ol (**9a**) [mp 114 °C. Anal. ($C_{11}H_{12}ClN_3O$) C, H], 3-[3-(3-bromophenyl)-1*H*-1,2,4-triazol-5-yl]-propan-1-ol (**9b**) [mp 105 °C. Anal. ($C_{11}H_{12}BrN_3O$) C, H], and 3-[3-(3-methylphenyl)-1*H*-1,2,4-triazol-5-yl]propan-1-ol (**9c**) [mp 98 °C. Anal. ($C_{12}H_{15}N_3O$) C, H].

3-[3-Phenyl-1*H*-1,2,4-triazol-5-yl]propionic Acid (1). A solution of 60 g (0.60 mol) of CrO_3 in 700 mL of 90% aqueous AcOH was cooled to 5 °C with stirring. To this was added 60 g (0.30 mol) of the triazole alcohol **9** in 200 mL of AcOH. After 5 h at 5 °C, the reaction was let stand at room temperature overnight. The dark green solution was evaporated to dryness. The residue was taken up in aqueous $NaHCO_3$ solution and filtered, and the acid was precipitated with dilute HCl. It was recrystallized from H_2O and then from EtOAc to give 27 g of white needles, mp 112–118 °C, of the acid monohydrate **1**. Treatment with diazomethane and recrystallization from benzene gave the methyl ester, methyl 3-[3-phenyl-1*H*-1,2,4-triazol-5-yl]propionate, mp 117 °C. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 62.32; H, 5.67. Found: C, 62.39; H, 5.62. Saponification of this ester by heating in aqueous NaOH, followed by acidification and recrystallization from EtOAc, gave back the acid **1**, still as the monohydrate: mp 112–117 °C; mass spectrum (70 eV) 217 (M^+). When dried over xylene under vacuum, this acid melted with effervescence and set to a glass. Anal. ($C_{11}H_{11}N_3O_2$) C, H. Also prepared in this manner were analogues **1a–c**, none of which showed evidence of hydrate formation.

3-[1-Phenyl-1*H*-1,2,4-triazol-3-yl]propionic Acid (2). A mixture of 2 g (10 mmol) of 1-[1-phenyl-1*H*-1,2,4-triazol-3-yl]-propan-2-one (**10**),[5] 0.32 g (10 mg-atom) of sulfur, and 0.87 g (10 mmol) of morpholine was heated at 110 °C for 5 h. The intermediate thiomorpholide **11** was not isolated but was hydrolyzed directly by heating for 5 h in 200 mL of 1:1 v/v AcOH–HCl, 20 mL/g of compound. Evaporation gave a residue that was taken up in aqueous $NaHCO_3$ and filtered. Neutralization with HCl, followed by recrystallization from EtOAc, gave the desired acid **2** as tan crystals in 40% yield from **10**.

3-[3-Phenyl-1*H*-1,2,4-triazol-1-yl]propionic Acid (3). Sodium, 2.3 g (0.1 g-atom), was dissolved in 100 mL of absolute EtOH and added to a solution of 18.3 g (0.1 mol) of benzimidoethyl ether hydrochloride in 200 mL of EtOH.[16] The precipitated NaCl was filtered and 6 g (0.1 mol) of freshly prepared formylhydrazine was added. After standing for 3 days at room temperature, the solution was concentrated under reduced pressure, leaving a gummy residue that was taken up in 500 mL of ether. This was extracted with 1 N NaOH and the basic, aqueous solution neutralized with solid CO_2. The precipitate was recrystallized from toluene to give 10 g (70%) of 3-phenyl-1*H*-1,2,4-triazole (**12**), mp 117 °C.[19] Also prepared by this method was the previously unknown 3-(3-methylphenyl)-1*H*-1,2,4-triazole (**12c**) as fine white needles from toluene, mp 96 °C. Anal. ($C_9H_9N_3$) C, H.

A solution consisting of 29 g (0.2 mol) of 3-phenyl-1*H*-1,2,4-triazole, 22 g (0.2 mol) of 3-chloropropionic acid, and 16 g (0.4 mol) of NaOH in 300 mL of H_2O was refluxed for 3 days. It was cooled and carefully neutralized with dilute HCl. The precipitate was collected and recrystallized from *i*-PrOH to give 9.5 g of the desired acid **3** as off-white needles, mp 141 °C.

3-[1-Phenyl-1*H*-1,2,3-triazol-4-yl]propionic Acid (4). The published procedure was followed to prepare 3-[1-phenyl-1*H*-1,2,3-triazol-4-yl]acrolein (**13**).[8] This was converted to the unsaturated acid **13a** with Ag_2O and hydrogenated over Raney nickel or nickel boride[12] to give the propionic acid **4**, mp 138 °C, in 70% yield.

3-[1-Phenyl-1*H*-1,2,3-triazol-1-yl]propionic Acid (5) and 3-[5-Phenyl-1*H*-1,2,3-triazol-1-yl]propionic Acid (16). A solution consisting of 10.2 g (0.1 mol) of phenylacetylene and 14.2 g (0.1 mol) of methyl 3-azidopropionate in 50 mL of dry toluene was refluxed under an argon atmosphere for 4 days. On cooling, a mass of crystals deposited that was recrystallized from toluene to give 8.7 g of methyl 3-[4-phenyl-1*H*-1,2,3-triazol-1-yl]propionate (**15**) as stubby white needles, mp 114 °C. Anal. ($C_{12}H_{13}N_3O_2$) C, H. The combined mother liquors were evaporated to give a semisolid residue that was chromatographed on 350 g of silica gel and eluted with 9:1 v/v CCl_4–acetone. Twenty-milliliter fractions were collected. Fractions 71–80 were combined and evaporated to give 2 g of methyl 3-[5-phenyl-1*H*-1,2,3-triazol-1-yl]propionate (**14**) as a pale yellow oil. Anal. ($C_{12}H_{13}N_3O_2$) C, H.

The methyl esters of analogues **5a–h** were isolated but not characterized as was also the case for the other 5-phenyl analogues of **14** and **16**.

Each ester was hydrolyzed by heating for 16 h in 1:1 v/v AcOH–HCl (20 mL/g of ester). When cool, the solutions were diluted with H_2O and the acids collected and dried. The constants for the 4-phenyl isomer **5** are listed in Table I. The 5-phenyl isomer **16** was recrystallized from benzene–EtOAc, giving tan

crystals, mp 140 °C. Anal. ($C_{11}H_{11}N_3O_2$) C, H.

3-[2-(3-Chlorophenyl)-2*H*-1,2,3-triazol-4-yl]propionic Acid (6a). A solution of 207 g (1.2 mol) of fructose[20] in 1.5 L of H_2O was stirred at 55 °C under N_2. Over a 15-min period, 400 g (2.8 mol) of 3-chlorophenylhydrazine in 700 mL of AcOH was added. After 8 h, the yellow reaction mixture was cooled to room temperature. The precipitate was filtered, washed well with cold *i*-PrOH, and dried to give 300 g (75%) of crude (3-chlorophenyl)glucosazone (**17a**) as an orange-yellow solid, mp 205 °C dec. This was suspended in 2 L of hot dioxane and added to a solution of 1.5 mol of $CuSO_4$ in 4 L of H_2O. After 40 min at 90 °C, the black solution was cooled to 5 °C and filtered. The precipitate was recrystallized twice from EtOH to give 41 g (20%) of (3-chlorophenyl)glucosotriazole (**18a**) as fine white needles, mp 206 °C. Anal. ($C_{12}H_{14}ClN_3O_4$) C, H. In a like manner we prepared the (3-bromophenyl)glucosotriazole (**18b**) as fine white needles from EtOH, mp 212 °C. Anal. ($C_{12}H_{14}BrN_3O_4$) C, H.

(3-Chlorophenyl)glucosotriazole was oxidized with 4 equiv of periodic acid in aqueous dioxane to give a 75% yield of 2-(3-chlorophenyl)-2*H*-1,2,3-triazole-4-carboxaldehyde (**19a**) as fine white needles from pentane: mp 89 °C. Anal. ($C_9H_6ClN_3O$) C, H. Also made was 2-(3-bromophenyl)-2*H*-1,2,3-triazole-4-carboxaldehyde (**19b**): mp 94 °C; white needles from pentane. Anal. ($C_6H_6BrN_3O$) C, H. A solution of 8 g (39 mmol) of the aldehyde **19a** and 7.8 g (78 mmol) of malonic acid in 20 mL of pyridine containing 1 mL of piperidine was heated on the steam bath for 2 h. When cool, it was poured into 500 mL of cold 1 N HCl and the precipitate collected. Recrystallization from EtOH gave 7.3 g of the unsaturated acid **20a** as white needles, mp 183 °C. The bromo analogue **20b** also gave white needles from EtOH, mp 229 °C. Both were hydrogenated to the propionic acids **6a** and **6b** using nickel boride in EtOH at 3 atm.[12]

3-[4-Phenyl-2*H*-1,2,3-triazol-2-yl]propionic Acid (7). A solution of 6.3 g (45 mmol) of 4-phenyl-*v*-triazole, 6.2 g (45 mmol) of potassium carbonate, and 6.9 g (45 mmol) of 3-bromopropionic acid in 75 mL of H_2O was refluxed for 2 days. This was cooled and 2.5 g of unreacted triazole removed. Acidification of the mother liquor to pH 3 produced 4 g of a mixture of acids **5** and **7**. Chromatography on silicic acid (elution with 9:1 v/v CCl_4–acetone) gave 2 g of each acid. The less polar, front-running isomer was recrystallized from aqueous MeOH to yield 1.8 g of the triazole-2-propionic acid **7** as white silvery platelets, mp 143 °C.[13] Anal. ($C_{11}H_{11}N_3O_2$) C, H. The ^1H NMR spectra (C_5D_5N) displayed the triazole proton at 489 Hz and the phenyl protons as two multiplets, one of 2 H centered at 478 Hz and one of 3 H centered on 445 Hz.

Preparation of 4-Aryl-*v*-triazoles. These were prepared by the reaction of the appropriate acetylenes with either hydrazoic acid or trimethylsilyl azide (see Table II). Some of the precursor arylacetylenes were made by thermal decomposition of the analogous selenodiazoles (**5b–d**)[21] or, in the case of **5e,g,j**, by dehydrochlorination of the products of the reaction of PCl_5 on the corresponding acetophenones.

4-[4-Phenyl-2*H*-1,2,3-triazol-2-yl]butyric Acid (23b). To a solution of 2.07 g (0.09 g-atom) of sodium in 100 mL of absolute EtOH was added 12.6 g (0.09 mol) of 4-phenyl-*v*-triazole. This was heated to reflux with stirring and 13.5 g (0.09 mol) of ethyl 4-chlorobutyrate was added. After heating 16 h, the reaction was cooled and concentrated under reduced pressure. The oily residue was washed with 1 N NaOH to remove unreacted starting material and then chromatographed on silicic acid. Elution with benzene removed 5 g of ethyl 4-[4-phenyl-2*H*-1,2,3-triazol-2-yl]butyrate as an oil. Hydrolysis in HCl–AcOH gave the triazole-2-butyric acid **23b**, mp 99 °C. Anal. ($C_{12}H_{13}N_3O_2$) C, H.

3-(2-Phenyl-5-tetrazolyl)propionic Acid (25). A mixture of 30.5 g (0.17 mol) of 5-(hydroxymethyl)-2-phenyltetrazole[22] and 150 mL of thionyl chloride was warmed to 60 °C for 90 min and then cooled and concentrated under reduced pressure. Benzene was added and then evaporated to remove the last traces of $SOCl_2$. The concentrate was taken up in warm EtOH and added to a solution of 63 g (0.35 mol) of diethyl sodiomalonate in 250 mL of absolute EtOH. After 5 h of heating, the reaction was concentrated to dryness and the residue partitioned between ether and H_2O. The ether phase was separated, dried over anhydrous $MgSO_4$, filtered, and evaporated to give the oily diester. This was saponified and decarboxylated directly with KOH to give 0.7 g of the desired acid, **25**, as white needles from benzene, mp 100 °C. Anal. ($C_{10}H_{10}N_4O_2$) C, H.

3-[2-(3-Bromophenyl)-5-tetrazolyl]propionic Acid (26). An aqueous solution of 111 g (0.5 mol) of (3-bromophenyl)hydrazine hydrochloride was combined with 35 g of 75% aqueous glyoxalic acid. A yellow solid formed at once. It was collected, washed with H_2O, and dried to give 124 g (100%) of the (3-bromophenyl)-hydrazone of glyoxalic acid,[22] mp 103 °C dec. Anal. Calcd for $C_8H_7BrN_2O_2$: C, 39.51; H, 2.88. Found: C, 39.61; H, 2.86. This hydrazone and 190 g (0.50 mol) of 2,4,6-tribromophenyl azide were added to a solution of 1 equiv of sodium ethoxide in 1600 mL of absolute EtOH. After 5 h at reflux, the mixture was poured into 2 L of ice H_2O. The solid precipitate of tribromoaniline was filtered out, washed with H_2O, and discarded. The combined filtrate and washings were acidified with concentrated HCl. A solid precipitated that amounted to 53 g of 2-(3-bromophenyl)tetrazole-5-carboxylic acid, mp 152–153 °C dec. Anal. Calcd for $C_8H_5BrN_4O_2$: C, 35.87; H, 1.86. Found: C, 35.48; H, 1.94. This acid was esterified with EtOH–HCl and recrystallized from hexane to give 52 g of ethyl 2-(3-bromophenyl)tetrazole-5-carboxylate, mp 75 °C. Anal. Calcd for $C_{10}H_9BrN_4O_2$: C, 40.44; H, 3.05. Found: C 40.45; H, 3.04.

A dry THF solution of the ester was added to a hot, stirred suspension of 14.2 g (0.65 mol) of lithium borohydride in 200 mL of dry THF. After 5 h at reflux, the mixture was cooled and treated dropwise with 100 mL of 20% HCl. It was filtered and concentrated, and the residue was taken up in $CHCl_3$ and washed with dilute HCl. Evaporation gave a solid that was recrystallized from benzene–hexane and yielded 43 g of 5-(hydroxymethyl)-2-(3-bromophenyl)tetrazole, mp 83 °C. Anal. Calcd for $C_8H_7BrN_4O$: C, 37.65; H, 2.75. Found: C, 37.81; H, 2.72.

This (hydroxymethyl)tetrazole was converted to the chloride and used to alkylate malonic ester by the procedure used to make **25**. Workup, followed by two recrystallizations from benzene–hexane, gave 25 g of the propionic acid **26**, mp 99 °C. Anal. ($C_{10}H_9BrN_4O_2$) C, H.

3-[4-(Dimethylamino)-5-phenyl-2*H*-1,2,3-triazol-2-yl]-propionic Acid (23f). A solution of 18 g (0.1 mol) of triazole **22f** in 250 mL of DMF containing 1 equiv of NaOEt was cooled to 0 °C. While stirring rapidly, 7.2 g (0.1 mol) of propiolactone was dripped in over 1 h. The reaction was allowed to come to room temperature overnight. Solvent was removed and the residue taken up in 250 mL of H_2O. The solution was saturated with CO_2 which precipitated 2 g of unreacted triazole. It was then filtered and treated with 8.0 mL of concentrated HCl which separated 20 g of a pale yellow oil. TLC (silica gel; 4:1 benzene–MeOH) showed the oil to consist of a major, fast-moving material and a minor, slow-moving one.

The mixture was esterified by heating for 3 h in 200 mL of absolute MeOH containing 3 equiv of BF_3–MeOH complex.[23] Workup gave 21 g of a colorless oil that was chromatographed on 500 g of silicic acid, eluting with 19:1 v/v CCl_4–acetone. The first-eluted material amounted to 16 g of methyl 3-[4-(dimethylamino)-5-phenyl-2*H*-1,2,3-triazol-2-yl]propionate as a colorless oil. Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61. Found: C, 60.68; H, 6.45.

This ester was saponified and acidified to give 15 g of the free acid, **23f**, as a pale yellow oil. Conversion to the sodium salt gave 13 g of white crystals, mp 207–210 °C.

Pharmacology. Two models of inflammation, one acute and one chronic, were used to examine the antiinflammatory activity of the triazole acids (see Table IV). Acute activity was measured in the rat pleural effusion model as described by Sancilio.[24] Here the introduction of a mixture of the irritants, carrageenan and Evans blue dye, into the rat pleural cavity causes an inflammation that results in an increase in the volume of pleural fluid in the following 6 h. This increase can be inhibited by a wide variety of antiinflammatory compounds, and the degree of inhibition is dose dependent.

Each test compound was administered orally to six rats 1 h before the irritants at a dose of 0.4 mmol/kg. Six hours after the irritants were given, the animals were killed and the volumes of their pleural fluid measured. The results are expressed as the percent reduction in pleural fluid volume from the untreated controls produced by the test drug at a dose of 0.4 mmol/kg. Values for aspirin and phenylbutazone are included for reference.

These acids were also examined in the chronic adjuvant-induced rat arthritis model.[25] Adjuvant arthritis was induced in male Lewis rats (125–150 g) by the intradermal injection of 0.05 mL of a 0.65% suspension of *Mycobacterium tuberculosis* in Freund's adjuvant into the plantar surface of the right hind foot (day 0). Negative control groups received only mineral oil. Test compounds were administered once daily, by gavage, at a dose of 0.2 mmol/kg to groups of six rats from day 0 to 21. The change in right and left hind foot volumes over the period from days 0 to 21 was determined plethysmographically for both the injected and uninjected foot of each rat. The significance of differences between treated and untreated control groups was assessed using Dunnet's test.[26]

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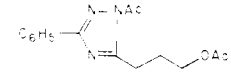

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4-(6-Methoxy-2-naphthyl)butan-2-one and Related Analogues, a Novel Structural Class of Antiinflammatory Compounds[1]

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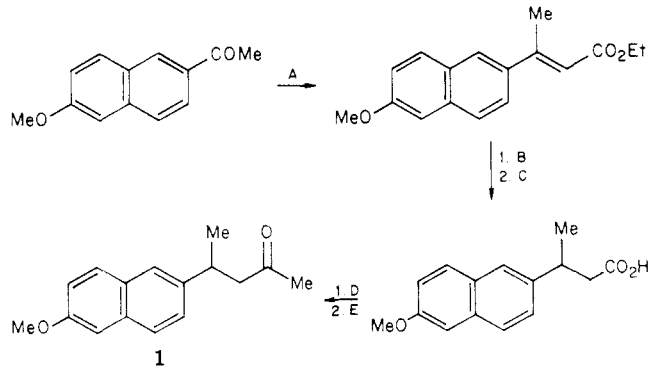
A series of compounds related to 4-(6-methoxy-2-naphthyl)butan-2-one has been prepared and tested for antiinflammatory activity by the cotton pellet granuloma method. Compounds possessing a small lipophilic group such as methoxyl, methyl, or chloro in the 6 position in conjunction with a butan-2-one side chain in the 2 position of the naphthalene ring were most active. The introduction of a methyl group along the side chain was invariably deleterious. Good activity was generally retained by forming esters of a butan-2-ol side chain.

Numerous arylacetic and arylpropionic acids have been synthesized in the search for nonsteroidal antiinflammatory agents. Although many of these acids have been shown to possess good activity, they invariably cause harmful irritation to the gastrointestinal tract. It is thought that this property could be related to the acidic nature of such compounds. In order to overcome this important drawback we decided to screen a variety of compounds lacking a carboxyl group, and from this investigation we have now prepared a structurally novel class of antiinflammatory compounds. This class consists of 2,6-disubstituted naphthylalkanones and derivatives thereof. We hoped that such compounds, when given orally, would be absorbed without causing gastric damage.

Chemistry. The initial lead compound, **1**, was prepared from 2-acetyl-6-methoxynaphthalene[2] according to Scheme I. The majority of compounds which were subsequently synthesized are shown in Scheme II. The reaction of 6-methoxy-2-naphthaldehyde[3] or 6-methyl-2-naphthaldehyde[4] with acetone and dilute NaOH gave the enones **2** and **18**, respectively, and these underwent catalytic

Scheme I[a]



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[a] Reagents: method A, NaH-triethyl phosphonoacetate; B, 10% Pd/C-H_2; C, 10% NaOH; D, $SOCl_2$; E, $(Me)_2CuLi$.

hydrogenation to their corresponding butanones **3** and **19**. The preparation of **3** using an alternative route involving 6-methoxy-2-naphthylacetic acid has previously been

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