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Antiinflammatory Activity and Structure–Activity Relationships of Some 1,2,3,4-Tetrahydro-1-naphthoic Acids and Related Compounds

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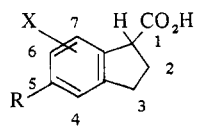
6-Substituted 1,2,3,4-tetrahydro-1-naphthoic acids and related compounds were prepared as potential antiinflammatory agents. A few of the compounds showed moderate antiinflammatory activity when tested orally in the rat. The effect of the geometry of the fused alicyclic ring on activity is discussed and a resemblance noted between structural requirements for arylacetic acid type antiinflammatory agents and certain plant growth regulators.

In a previous paper[1] we described some indan-1-carboxylic acids (**1**, R = alkyl, cycloalkyl; X = monosubstituent) with potent antiinflammatory activity. We have now prepared some 1,2,3,4-tetrahydro-1-naphthoic acids (**2**, R = alkyl, cycloalkyl, phenyl) and related compounds.[2,†] Whereas the indan compounds contain a conformationally fixed car-



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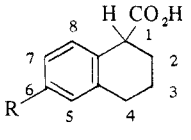


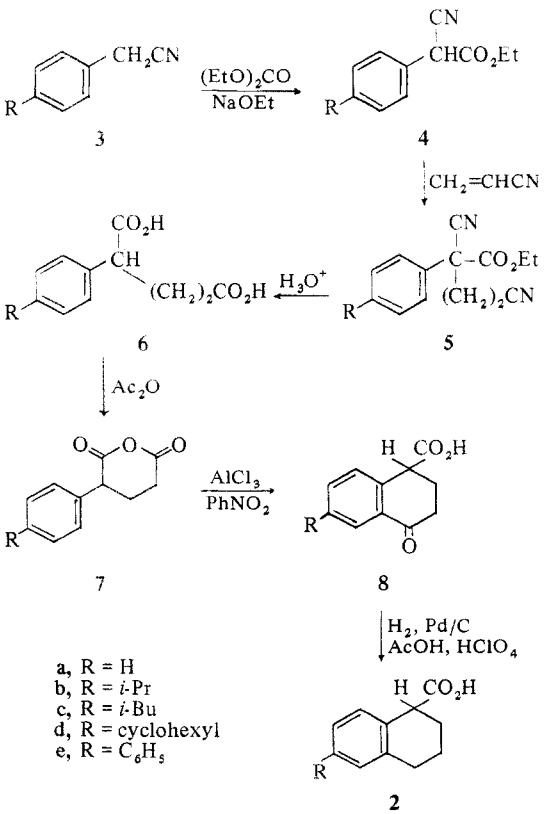
2

boxyl group attached to a fairly rigid system, the tetrahydronaphthoic acids contain a carboxyl group which is only partially restrained by the larger, more flexible cyclohexene ring. The consequences of this flexibility are discussed. Some conclusions are drawn which are used to elaborate on observed similarities between the structural requirements of some acidic antiinflammatory agents and certain plant growth regulators.[1]

Chemistry. Compounds of type **2** were prepared as outlined in Scheme I. These products were not resolved into their optical antipodes. Intermediates and products are listed in Tables I–VI.

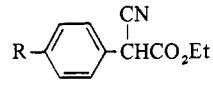
Dehydro analogs (**10**, **13**, **14**, and **15**) of **2d** were obtained as outlined in Scheme II (see Table VII). The two isomers

Scheme I



†A Ciba group has recently reported on some similar compounds with antiinflammatory and analgetic activity.[3]

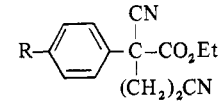
Table I. Ethyl α-Cyano-α-phenylacetates



No.	R	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Analyses
4b	*i*-Pr	100 (0.05)		87	$C_{14}H_{17}NO_2$	C, H, N
4c	*i*-Bu	117-118 (0.05)		78	$C_{15}H_{19}NO_2$	C, H, N
4d	Cyclohexyl	160-163 (0.1)		77	$C_{17}H_{21}NO_2$	C, H, N
4e	C_6H_5	85-86.5	EtOH	93	$C_{17}H_{15}NO_2$	*a*

[a]See ref 10.

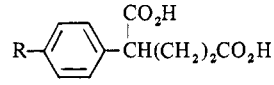
Table II. α-Carbethoxy-α-phenylglutaronitriles



No.	R	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Analyses
5b	*i*-Pr	153-163 (0.05)		92	$C_{17}H_{20}N_2O_2$	C, H, N
5c	*i*-Bu	159-160 (0.03)		91	$C_{18}H_{22}N_2O_2$	C, H, N
5d	Cyclohexyl	69-70.5	Petr ether	88	$C_{20}H_{24}N_2O_2$	C, H, N
5e	C_6H_5	170 (0.01)		100[a]	$C_{20}H_{18}N_2O_2$	C, H, N

[a]Crude product.

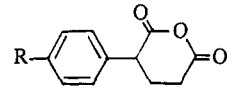
Table III. α-Phenylglutaric Acids



No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
6b	*i*-Pr	Decomp	EtOH-H_2O	64	$C_{14}H_{17}KO_4$	K
6c	*i*-Bu	106-107.5	C_6H_6-Skelly B[a]	67	$C_{15}H_{20}O_4$	C, H
6d	Cyclohexyl	86-93	CCl_4		$C_{17}H_{22}O_4$	*b*
6e	C_6H_5	170.5-172.5	Toluene	82	$C_{17}H_{16}O_4$	C, H

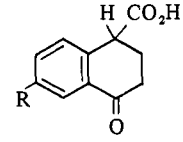
[a]Skellysolve B. [b]See Experimental Section.

Table IV. α-Phenylglutaric Anhydrides



No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
7b	*i*-Pr	80-81.5	Cyclohexane	65	$C_{14}H_{16}O_3$	C, H
7c	*i*-Bu	75-76	Cyclohexane	96	$C_{15}H_{18}O_3$	C, H
7d	Cyclohexyl	102.5-103.5	Cyclohexane	42	$C_{17}H_{20}O_3$	C, H
7e	C_6H_5	236-238	*i*-BuCOMe	75	$C_{17}H_{14}O_3$	C, H

Table V. 1,2,3,4-Tetrahydro-4-oxo-1-naphthoic Acids



No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	Antiinflam ED_{30}, mg/kg
8a	H	93-94.5	C_6H_6		$C_{11}H_{10}O_3$	*a*	>128
8b	*i*-Pr	70-72	Cyclohexane	77	$C_{14}H_{16}O_3$	C, H	80
8c	*i*-Bu	69-71	C_6H_6-Skelly B[b]	65	$C_{15}H_{18}O_3$	C, H	>64
8d	Cyclohexyl	103-105	C_6H_6-Skelly B[b]	53	$C_{17}H_{20}O_3$	C, H	60
8e	C_6H_5	182-184	EtOH-H_2O	47	$C_{17}H_{14}O_3$	C, H	128

[a]See ref 11. [b]Skellysolve B.

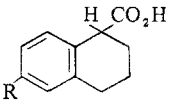
of the hydroxy acid **9** were isolated, but we were unable to assign cis or trans configurations.

Pharmacology. The tetrahydro-, dihydro-, and 1-naphthoic acids were tested orally for antiinflammatory activity using the carrageenin-induced foot edema method in the fasted rat.[4] The results, expressed as the doses which inhibited 30% of the edema (ED_{30}), are recorded in Tables V-VII.‡ Phenylbutazone had an ED_{30} of 20 mg/kg in this assay.

Structure-Activity Relationships. Among the racemic 1,2,3,4-tetrahydro-1-naphthoic acids (Table VI), only the 6-

‡The ED_{30} was determined from a dose-response curve for which five animals per dose were used.

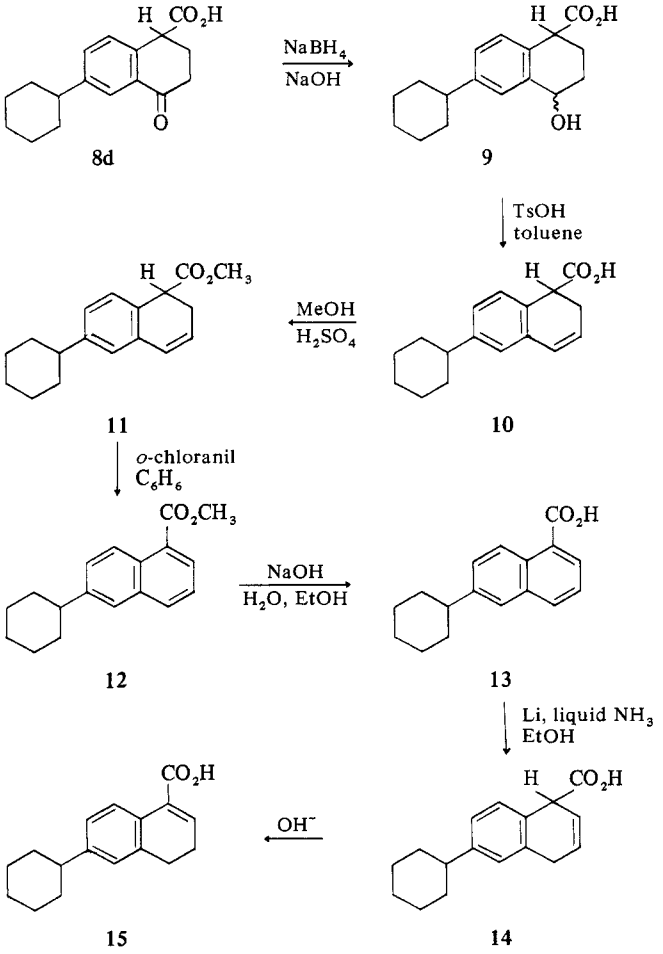
Table VI. 1,2,3,4-Tetrahydro-1-naphthoic Acids



No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	Antiinflam ED_{30}, mg/kg
2a	H	82.5-84	Skelly B[a]	89	$C_{11}H_{12}O_2$	*b*	>128
2b	*i*-Pr	67.5-68.5	Petr ether	72	$C_{14}H_{18}O_2$	C, H	>128
2c	*i*-Bu	76-78	*n*-Pentane	87	$C_{15}H_{20}O_2$	C, H	>128
2d	Cyclohexyl	129-130	Skelly B[a]	63	$C_{17}H_{22}O_2$	C, H	64
2e	C_6H_5	154.5-156	Cyclohexane	82	$C_{17}H_{16}O_2$	C, H	>128

[a]Skellysolve B. [b]See ref 12.

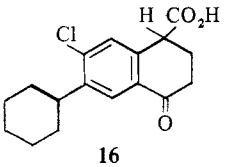
Scheme II



cyclohexyl compound **2d** showed significant activity, and this activity (ED_{30} = 64 mg/kg) is weak relative to the analogous indan (**1**, R = cyclohexyl, X = H; ED_{30} = 3.7 mg/kg).[1] In contrast, all but the 6-H compound (**8a**) of the 4-oxo precursors (Table V) showed significant activity,§ the most active compound being **8d** (ED_{30} = 60 mg/kg). The two 4-hydroxy acids **9a** and **9b** (Table VII) were devoid of activity, but the 1,2-dihydro-1-naphthoic acid **10** showed activity (ED_{30} = 64 mg/kg) comparable to **8d**. Neither the fully aromatized acid **13** nor the 3,4-dihydro analog **15** showed significant activity. The most potent member of the series was the 1,4-dihydro derivative **14**, with an ED_{30} of 16 mg/kg.

In the paper[1] on the 5-alkylindan-1-carboxylic acid antiinflammatory agents (**1**) we defined six structural requirements which are necessary for optimal activity in the indan series. These requirements are: (1) a carboxyl group separated by one carbon atom from a flat, aromatic nucleus, (2) the carboxyl group deviating considerably from the plane of the nucleus, (3) a free hydrogen at position 1, (4) the *S* configuration at position 1, (5) optional substitution at position 6 by a small group, preferably chlorine, and (6) a cyclohexyl ring para to the acetic acid residue.

The compounds which show the highest activity in the current naphthalene series, **2d, 8d, 10,** and **14**, meet all these requirements, except number 4 which was not investigated. We did not examine the effect of substitution at position 7, which corresponds to position 6 of the indan compounds, but the Ciba group reported[3] comparable activity for a 7-chloro derivative **16**.



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We suggest that the relatively weak activity of the 1,2,3,4-tetrahydro-1-naphthoic acid **2d** as compared to **1** (R = cyclohexyl; X = H) is due to the nature of the fused alicyclic ring. The carboxyl group is not held rigidly out of the plane of the aromatic ring as is the case for the indan compound. Instead, the carboxyl group can exist in two conformations, pseudoaxial and pseudoequatorial. In the latter case, the carboxyl becomes almost coplanar with the aromatic ring. In addition, all the carbon atoms of the fused alicyclic ring are not coplanar with the benzene ring, a condition which is largely met in the indan system. The keto group of the 4-oxo derivative **8d** and the additional double bond of the 1,2-dihydro acid **10** both tend to flatten the alicyclic ring slightly. The compound in which all the carbon atoms of the alicyclic ring most closely approach coplanarity with the benzene ring is **14**, the most potent antiinflammatory agent of the naphthalene series. The alicyclic ring of 1,4-dihydro-1-naphthoic acid has been shown to be slightly puckered, with the carboxyl group existing in a pseudoaxial conformation.[5]

The significance of this requirement for coplanarity of the alicyclic ring carbons with the benzene ring may lie in the need for one flat, unhindered surface for this part of the molecule. This could explain the requirement of a free hydrogen at position 1, on the side opposite to the carboxyl group. For optimal activity in both the indan and naphthalene series we now restate requirement 3 to read: one flat, unhindered surface for the benzocycloalkene-1-carboxylic acid moiety. The other five requirements remain as before. As noted previously,[1] the more potent examples of the

§A compound is considered to show significant activity if it has an $ED_{30} \leq 128$ mg/kg.

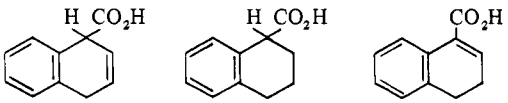
Table VII. 6-Cyclohexylnaphthalenes

No.	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	Antiinflam ED_{30}, mg/kg
9a	177.5-179	EtOH-H_2O	15	$C_{17}H_{22}O_3$	C, H	>128
9b	143-144.5	C_6H_6	61	$C_{17}H_{22}O_3$	C, H	>128
10	129-130	Skelly B[a]	72	$C_{17}H_{20}O_2$	C, H	64
11	*b*		86	$C_{18}H_{22}O_2$	C, H	>128
12	*c*		72	$C_{18}H_{20}O_2$	*c*	>128
13	202.5-203.5	Methylcyclohexane	81	$C_{17}H_{18}O_2$	C, H	>128
14	120-122	Skelly B[a]	65	$C_{17}H_{20}O_2$	C, H	16
15	182-183	Skelly B[a]	48	$C_{17}H_{20}O_2$	C, H	>128

[a]Skellysolve B. [b]Oil, see Experimental Section. [c]Crude oil, not characterized.

open-chain antiinflammatory aryl- and heteroarylalkanoic acids can adopt conformations which satisfy most of these requirements.

Once again we are struck by the close similarity between requirements for these nonsteroidal antiinflammatory agents and the requirements for optimum activity among plant growth regulators of the arylalkanoic acid, benzocycloalkene-1-carboxylic acid, and indole-3-acetic acid types.[6,#] One of the most potent members of the benzocycloalkene-1-carboxylic acid series of plant growth regulators is 1,4-dihydro-1-naphthoic acid (**17**). Slightly less active is 1,2,3,4-tetrahydro-1-naphthoic acid (**18**). 3,4-Dihydro-1-naphthoic



17 **18** **19**

acid (**19**) shows only weak activity. Among these growth regulators which contain a carboxyl group attached to an asymmetric center, it is the *S* isomer which possesses most of the activity.[7] The growth regulators do not, however, require a large lipophilic substituent such as cyclohexyl on the aromatic nucleus in order to show optimal activity.

Experimental Section**

Ethyl α-Cyano-α-phenylacetates. Compds **4b-4e** (Table I) were prepd from the corresponding phenylacetonitriles, $(EtO)_2CO$, and NaOEt in EtOH by a method similar to that described for the prepn of ethyl α-cyanophenylacetate.[8]

α-Carbethoxy-α-phenylglutaronitriles. Compds **5b-5e** (Table II) were prepd from the corresponding α-cyano-α-phenylacetates, CH_2=CHCN, and KOH in *tert*-BuOH by a method similar to that described for the prepn of α-carbethoxy-α-phenylglutaronitrile.[9]

α-Phenylglutaric Acids. Compds **6b-6e** (Table III) were prepd by a method similar to that described for **6c** as follows. A mixt of **5c** (203 g), glacial AcOH (1200 ml), and concentrated HCl (1200 ml) was heated under reflux for 16.5 hr. The mixt was concentrated and the residue partitioned between H_2O and EtOAc-Et_2O (1:1). The organic layer was washed (aqueous NaCl), dried (Na_2SO_4), and concentrated. The residue was recrystallized from C_6H_6-Skellysolve B to give **6c** (119.7 g), mp 105-107.5°. Two recrystallizations gave colorless crystals, mp 106-107.5°.

Compd **6b** failed to crystallize and was characterized as its monopotassium salt. Compd **6d** gave poor analytical data due to retention of variable amounts of CCl_4 solvent of crystallization.

α-Phenylglutaric Anhydrides. Compds **7b-7e** (Table IV) were prepd by a method similar to that described for **7d** as follows. A soln of **6d** (1.2 g) in Ac_2O (25 ml) was heated under reflux for 1.5 hr. The soln was concd and the residue crystallized from C_6H_6-Skellysolve B to give **7d** (0.47 g), mp 102-104°. Recrystallization from cyclohexane gave colorless crystals, mp 102.5-103.5°.

1,2,3,4-Tetrahydro-4-oxo-1-naphthoic Acids. Compds **8a-8e** (Table V) were prepd by a method similar to that described for **8d** as follows. Compd **7d** (1.0 g, 0.00367 mole) was added to a cooled (ice-H_2O), stirred mixt of $AlCl_3$ (1.08 g, 0.00808 mole) in $C_6H_5NO_2$ (12 ml). The mixt was heated at *ca.* 50° for 2 hr. Ice-cold H_2O (15 ml) followed by 1 *N* HCl (10 ml) were added to the cooled mixt, and the $C_6H_5NO_2$ removed by steam distn. The aqueous residue was extracted with Et_2O. The Et_2O extract was washed (H_2O), dried (Na_2SO_4), and concentrated. The residue was chromatographed on silicic acid (Mallinckrodt SilicAR, CC-4, 100-200 mesh) with C_6H_6-Me_2CO (20:1) to give material which was crystallized from C_6H_6-Skellysolve B to give **8d** (0.528 g), mp 102-104°. Recrystallization from C_6H_6-Skellysolve B gave colorless crystals, mp 103-105°.

1,2,3,4-Tetrahydro-1-naphthoic Acids. Compds **2a-2e** (Table VI) were prepared by a method similar to that described for **2d** as follows. A soln of **8d** (0.545 g) in glacial AcOH (50 ml) containing 60% $HClO_4$ (1 ml) and 10% Pd/C (0.2 g) was shaken with H_2 at 3.5 kg/cm² until no further H_2 was absorbed. NaOAc·$3H_2O$ (1.5 g) was added to the mixt which was then filtered to remove catalyst. The filtrate was concentrated and the residue treated with 3 portions of toluene, the mixt being concentrated after each addition. The residue was partitioned between Et_2O and H_2O. The Et_2O layer was washed (saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. The residue was recrystallized from Skellysolve B to give **2d** (0.323 g), mp 127-130°. Two recrystallizations from Skellysolve B gave off-white crystals, mp 129-130°.

6-Cyclohexyl-1,2,3,4-tetrahydro-4-hydroxy-1-naphthoic Acids (9). $NaBH_4$ (3.78 g, 0.1 mole) was added rapidly to a cooled (ice-H_2O), stirred soln of **8d** (20.0 g, 0.0735 mole) in 0.5 *N* NaOH (200 ml, 0.1 mole). The mixt was stirred for 40 min with cooling and for 1.25 hr at 25°. The mixt was treated with 1 *N* HCl, and then extracted with Et_2O-EtOAc (2:1). The extract was washed (H_2O, saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. Two compds, **9a** (3.1 g) and **9b** (12.4 g), were obtained by fractional recrystallization of the residue from EtOH-H_2O. Compd **9a** was recrystallized from toluene followed by EtOH-H_2O to give colorless crystals, mp 177.5-179°. Compd **9b** was recrystallized successively from C_6H_6, EtOH-H_2O, C_6H_6-Skellysolve B, EtOHc, and C_6H_6 to give colorless crystals, mp 143-144.5°.

6-Cyclohexyl-1,2-dihydro-1-naphthoic Acid (10). A mixt of **9b** (3.0 g, 0.0109 mole) and TsOH (400 mg) in toluene (300 ml) was heated under reflux (Dean-Stark trap) for 17 hr. The cooled soln was washed (H_2O), dried (Na_2SO_4), and concentrated. The residue was recrystallized from Skellysolve B to give **10** (2.03 g), mp 128.5-130°. Recrystallization from Skellysolve B gave colorless crystals: mp 129-130°; nmr ($CDCl_3$) δ 6.43 (d, 1 H, CH=$CHCH_2$), 5.94 (m, 1 H, CH=$CHCH_2$), 3.75 (d of d, 1 H, >$CHCO_2H$) and 2.60 ppm (broad m, 3 H, CH=$CHCH_2$ and >CH of cyclohexyl).

Methyl 6-Cyclohexyl-1,2-dihydro-1-naphthoate (11). A soln of **10** (3.3 g, 0.0129 mole), H_2SO_4 (0.15 ml, sp gr 1.84), and MeOH (1.2 ml) in CH_2Cl_2 (20 ml) was refluxed for 17 hr. The cooled soln was washed (H_2O, 5% aq $NaHCO_3$, H_2O, saturated aqueous NaCl), dried (Na_2SO_4), and concentrated to give **11** (3.0 g). Evaporative distillation gave analytical material.

Methyl 6-Cyclohexyl-1-naphthoate (12). A soln of **11** (16.4 g, 0.06 mole) and *o*-chloranil (25.2 g, 0.10 mole) in dry C_6H_6 (325 ml) was heated at 45° under N_2 for 20 hr. Excess 5% aqueous K_2CO_3 was added to the cooled mixt. The solids were removed by filtration with Et_2O washing. The organic layer of the filtrate was dried (Na_2SO_4) and concentrated. The residue was chromatographed over acid-washed alumina (Merck 71695) with toluene to give **12** (11.7 g) as an oil.

6-Cyclohexyl-1-naphthoic Acid (13). A mixt of **12** (11.7 g, 0.04 mole), NaOH (2.6 g, 0.06 mole), H_2O (60 ml), and EtOH (60 ml) was refluxed for 15 min. The cooled soln was acidified (HCl). The ppt was collected, dried, and recrystallized from methylcyclohexane to give **13** (9.0 g), mp 200-203°. Recrystallization from methylcyclohexane gave analytical material, mp 202.5-203.5°.

6-Cyclohexyl-1,4-dihydro-1-naphthoic Acid (14). Lithium (0.090 g, 0.013 g-atom) was added in 3 portions over 15 min to a

#See ref 1 and ref cited therein.

**Satisfactory nmr and ir spectra were obtained for all compounds. Where analyses are indicated only by symbols of the elements, results obtained for these elements were within ±0.4% of the theoretical values. Melting points are uncorrected.

stirred mixt of **13** (1.0 g, 0.0039 mole) in liquid NH_3 (60 ml) and Et_2O (25 ml). After 2 hr, EtOH (5 ml) was added and the NH_3 removed. The residual mixt was cooled (ice) and acidified with dil HCl. The aqueous layer was separated and extracted with Et_2O. The combined Et_2O soln was washed (saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. The residual solid was recrystallized from Skellysolve B to give **14** (0.65 g), mp 117–119°. Two recrystallizations gave analytical material: mp 120–122°; nmr ($CDCl_3$) δ 6.16 (m, 1 H, $CH{=}CHCH_2$), 5.92 (m, 1 H, $CH{=}CHCH_2$), 4.37 (m, 1 H, $>CHCO_2H$), and 3.40 ppm (m, 2 H, $CH{=}CHCH_2$).

6-Cyclohexyl-3,4-dihydro-1-naphthoic Acid (15). A soln of **14** (2.5 g) in 2 *N* NaOH (125 ml) was heated under reflux for 2.5 hr. The warm soln was treated with Norit, filtered, cooled, and acidified with 5 *N* H_2SO_4. The ppt was dried and recrystallized from Skellysolve B to give **15** (1.21 g), mp 171–178°. Recrystallizations from MeOH (Norit) followed by Skellysolve B gave **15** as colorless crystals: mp 182–183°; nmr ($CDCl_3$) δ 7.80 (d, 1 H, ArH), 7.30 (t, 1 H, vinylic), 7.04 (m, 2 H, ArH), 2.55 (broad m, 5 H, allylic and benzylic), and 1.55 ppm [broad m, 10 H, $(CH_2)_5$].

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Folic Acid Analogs. Modifications in the Benzene-Ring Region. 2. Thiazole Analogs†

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Two thiazole analogs of folic acid, in which the benzene ring is replaced by a thiazole ring, were synthesized as part of a continuing program to design and obtain folic acid analogs with a potentially altered ability to function as one-carbon transfer agents. The reductive condensation of 2-acetamido-6-formylpteridin-4(3*H*)-one (**3**) with diethyl *N*-[(2-amino-4-thiazolyl)carbonyl]glutamate (**2**) followed by hydrolysis of the blocking groups afforded thiazole analog **6**. Thiazole analog **10** was obtained similarly from **3** and diethyl *N*-[(2-amino-5-thiazolyl)carbonyl]glutamate (**8**). Compounds **2**, **6**, **8**, and **10** were not active against leukemia L1210 in mice in tests on a single-dose schedule and were not cytotoxic to HEp-2 cells in culture. Analogs **6** and **10** displayed modest inhibition of *Streptococcus faecalis* ATCC 8043 but were noninhibitory toward pigeon liver dihydrofolate reductase.

Tetrahydrofolate derivatives serve as agents in the transfer of one-carbon units in biological systems.[1] The manner in which certain structural alterations in the folic acid molecule may alter its capacity ultimately to function as a one-carbon transfer agent has been described.[2] For example, the potential of reduced folic acid type molecules for forming one-carbon transfer agents may possibly be decreased by decreasing the electron availability at position 10 (N^{10}). In the two folic acid analogs herein reported, in which the benzene ring is replaced by the thiazole ring, the electron availability at N^{10} may be expected to be diminished. Additionally, because of its attachment to a five-membered instead of a six-membered ring, the geometric and spatial relationship of the carbonylglutamate moiety to the remainder of the molecule has been altered. Either or both of these structural changes may affect folic acid metabolism at stages other than, or in addition to, the reduction by dihydrofolate reductase. These folic acid analogs were synthesized as part of a continuing program whose goal is to obtain potentially useful antineoplastic agents.

Chemistry. The method of synthesis of the folic acid analogs **6** and **10** is based on the method of Sletzinger, *et al.*,[3] in which folic acid had been obtained *via* the reductive condensation of **3** with *p*-aminobenzoylglutamic acid in the presence of *p*-toluenethiol. The syntheses of 2′-azafolic acid and 3′-azafolic acid have been accomplished similarly.[2] Intermediate **2**, obtained by the coupling of **1**[4] with diethyl glutamate, was condensed reductively with **3**, and the crude N^2-deacetylated product **4** was obtained. Acetylation of **4** yielded **5**, and purification was accomplished at this stage. Complete and selective hydrolysis in 0.1 *N* NaOH of the glutamate ester groups and the N^2- and N^{10}-acetamide functions of **5** afforded the desired thiazole analog **6**. Analog **6** was obtained more conveniently from **4** by direct hydrolysis of the ester functions.

Similarly, reductive condensation of **3** with **8**, obtained by the coupling of **7b** with diethyl glutamate, afforded **9**. Hydrolysis of the ester functions of **9** yielded thiazole analog **10** (Scheme I).

Hydrated samples of **6** and **10** having satisfactory elemental analyses and uv and pmr spectral properties were obtained by DEAE-cellulose column chromatography, but tlc analysis of the analogs revealed the presence of a blue-fluorescent impurity in **6**. Its identity was established as 2-amino-6-formylpteridin-4(3*H*)-one (**11**) by tlc compari-

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