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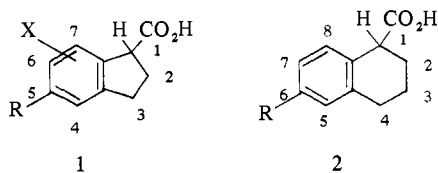
Antiinflammatory Activity and Structure-Activity Relationships of Some 1,2,3,4-Tetrahydro-1-naphthoic Acids and Related Compounds

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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 paper¹ 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-

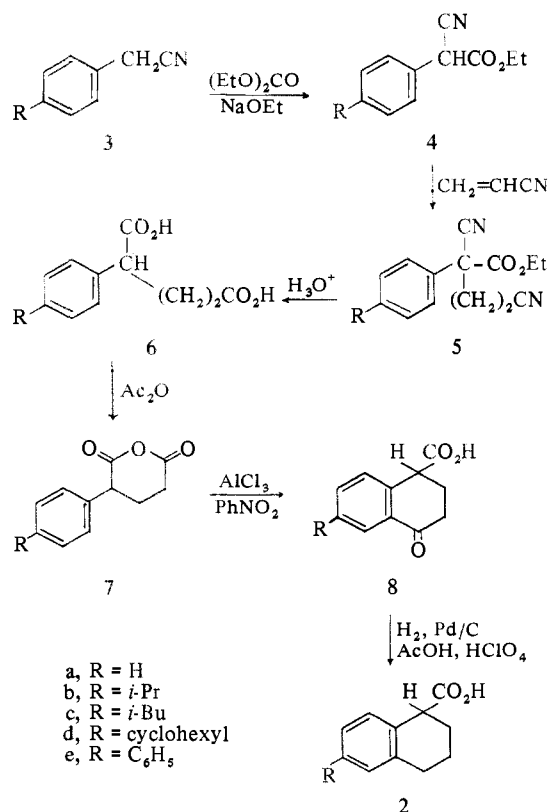


boxyl group attached to a fairly rigid system, the tetrahydro-naphthoic acids contain a carboxyl group which is only partially restrained by the larger, more flexible cyclohexene ring. The consequences of this flexibility are discussed. Some conclusions are drawn which are used to elaborate on observed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

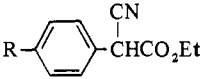
Chemistry. Compounds of type 2 were prepared as outlined in Scheme I. These products were not resolved into their optical antipodes. Intermediates and products are listed in Tables I-VI.

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

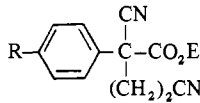
Scheme I



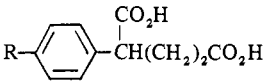
†A Ciba group has recently reported on some similar compounds with antiinflammatory and analgetic activity.³

Table I. Ethyl α -Cyano- α -phenylacetates


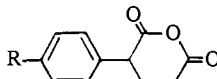
No.	R	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Analyses
4b	<i>i</i> -Pr	100 (0.05)		87	C ₁₄ H ₁₇ NO ₂	C, H, N
4c	<i>i</i> -Bu	117-118 (0.05)		78	C ₁₅ H ₁₉ NO ₂	C, H, N
4d	Cyclohexyl	160-163 (0.1)		77	C ₁₇ H ₂₁ NO ₂	C, H, N
4e	C ₆ H ₅	85-86.5	EtOH	93	C ₁₇ H ₁₅ NO ₂	<i>a</i>

^aSee ref 10.Table II. α -Carboxy- α -phenylglutaronitriles


No.	R	Mp or bp (mm), °C	Recrystn solvent	Yield, %	Formula	Analyses
5b	<i>i</i> -Pr	153-163 (0.05)		92	C ₁₇ H ₂₀ N ₂ O ₂	C, H, N
5c	<i>i</i> -Bu	159-160 (0.03)		91	C ₁₈ H ₂₂ N ₂ O ₂	C, H, N
5d	Cyclohexyl	69-70.5	Petr ether	88	C ₂₀ H ₂₄ N ₂ O ₂	C, H, N
5e	C ₆ H ₅	170 (0.01)		100 ^a	C ₂₀ H ₁₈ N ₂ O ₂	C, H, N

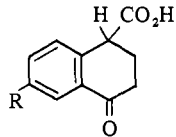
^aCrude product.Table III. α -Phenylglutaric Acids


No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
6b	<i>i</i> -Pr	Decomp	EtOH-H ₂ O	64	C ₁₄ H ₁₇ KO ₄	K
6c	<i>i</i> -Bu	106-107.5	C ₆ H 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	<i>b</i>
6e	C ₆ H ₅	170.5-172.5	Toluene	82	C ₁₇ H ₁₆ O ₄	C, H

^aSkellysolve B. ^bSee Experimental Section.Table IV. α -Phenylglutaric Anhydrides


No.	R	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
7b	<i>i</i> -Pr	80-81.5	Cyclohexane	65	C ₁₄ H ₁₆ O ₃	C, H
7c	<i>i</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 ₆ H ₅	236-238	<i>i</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 ₆ H ₆		C ₁₁ H ₁₀ O ₃	<i>a</i>	> 128
8b	<i>i</i> -Pr	70-72	Cyclohexane	77	C ₁₄ H ₁₆ O ₃	C, H	80
8c	<i>i</i> -Bu	69-71	C ₆ H ₆ -Skelly B ^b	65	C ₁₅ H ₁₈ O ₃	C, H	> 64
8d	Cyclohexyl	103-105	C ₆ H ₆ -Skelly B ^b	53	C ₁₇ H ₂₀ O ₃	C, H	60
8e	C ₆ H ₅	182-184	EtOH-H ₂ O	47	C ₁₇ H ₁₄ O ₃	C, H	128

^aSee ref 11. ^bSkellysolve 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 (ED₃₀), are recorded in Tables

V-VII.[‡] Phenylbutazone had an ED₃₀ 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-

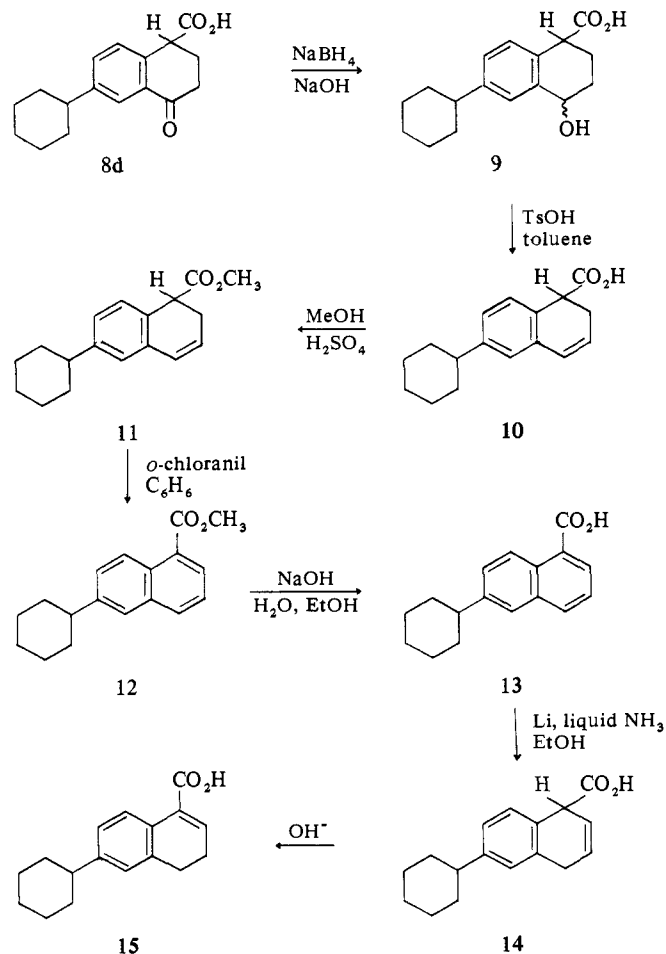
[‡]The ED₃₀ was determined from a dose-response curve for which five animals per dose were used.

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	<i>b</i>	>128
2b	<i>i</i> -Pr	67.5-68.5	Petr ether	72	C ₁₄ H ₁₈ O ₂	C, H	>128
2c	<i>i</i> -Bu	76-78	<i>n</i> -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 ₆ H ₅	154.5-156	Cyclohexane	82	C ₁₇ H ₁₆ O ₂	C, H	>128

^aSkellysolve B. ^bSee ref 12.

Scheme II

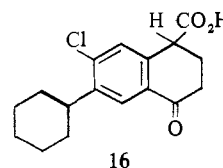


cyclohexyl compound 2d showed significant activity, and this activity (ED₃₀ = 64 mg/kg) is weak relative to the analogous indan (1, R = cyclohexyl, X = H; ED₃₀ = 3.7 mg/kg).¹ In contrast, all but the 6-H compound (8a) of the 4-oxo precursors (Table V) showed significant activity,⁸ the most active compound being 8d (ED₃₀ = 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 (ED₃₀ = 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 ED₃₀ of 16 mg/kg.

In the paper¹ on the 5-alkylindan-1-carboxylic acid anti-inflammatory agents (1) we defined six structural require-

ments 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 reported³ comparable activity for a 7-chloro derivative 16.



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

⁸A compound is considered to show significant activity if it has an ED₃₀ ≤ 128 mg/kg.

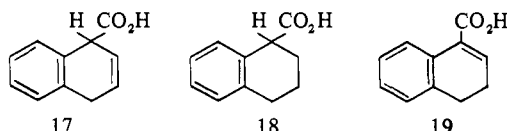
Table VII. 6-Cyclohexylnaphthalenes

No.	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses	Antiinflam ED ₅₀ , mg/kg
9a	177.5-179	EtOH-H ₂ O	15	C ₁₇ H ₂₂ O ₃	C, H	>128
9b	143-144.5	C ₆ H 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

^aSkellysolve B. ^bOil, see Experimental Section. ^cCrude 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



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. Comps 4b-4e (Table I) were prep'd from the corresponding phenylacetoneitriles, (EtO)₂CO, and NaOEt in EtOH by a method similar to that described for the prep'n of ethyl α -cyanophenylacetate.⁸

α -Carbethoxy- α -phenylglutaronitriles. Comps 5b-5e (Table II) were prep'd from the corresponding α -cyano- α -phenylacetates, CH₂=CHCN, and KOH in *tert*-BuOH by a method similar to that described for the prep'n of α -carbethoxy- α -phenylglutaronitrile.⁹

α -Phenylglutaric Acids. Comps 6b-6e (Table III) were prep'd 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 H₂O and EtOAc-Et₂O (1:1). The organic layer was washed (aqueous NaCl), dried (Na₂SO₄), and concentrated. The residue was recrystallized from C₆H₆-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 CCl₄ solvent of crystallization.

α -Phenylglutaric Anhydrides. Comps 7b-7e (Table IV) were prep'd by a method similar to that described for 7d as follows. A soln of 6d (1.2 g) in Ac₂O (25 ml) was heated under reflux for 1.5 hr. The soln was conc'd and the residue crystallized from C₆H₆-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. Comps 8a-8e (Table V) were prep'd 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-H₂O), stirred mixt of AlCl₃ (1.08 g, 0.00808 mole) in C₆H₅NO₂

(12 ml). The mixt was heated at ca. 50° for 2 hr. Ice-cold H₂O (15 ml) followed by 1 N HCl (10 ml) were added to the cooled mixt, and the C₆H₅NO₂ removed by steam distn. The aqueous residue was extracted with Et₂O. The Et₂O extract was washed (H₂O), dried (Na₂SO₄), and concentrated. The residue was chromatographed on silicic acid (Mallinckrodt SilicAR, CC-4, 100-200 mesh) with C₆H₆-Me₂CO (20:1) to give material which was crystallized from C₆H₆-Skellysolve B to give 8d (0.528 g), mp 102-104°. Recrystallization from C₆H₆-Skellysolve B gave colorless crystals, mp 103-105°.

1,2,3,4-Tetrahydro-1-naphthoic Acids. Comps 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% HClO₄ (1 ml) and 10% Pd/C (0.2 g) was shaken with H₂ at 3.5 kg/cm² until no further H₂ was absorbed. NaOAc·3H₂O (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 Et₂O and H₂O. The Et₂O layer was washed (saturated aqueous NaCl), dried (Na₂SO₄), 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). NaBH₄ (3.78 g, 0.1 mole) was added rapidly to a cooled (ice-H₂O), 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 Et₂O-EtOAc (2:1). The extract was washed (H₂O, saturated aqueous NaCl), dried (Na₂SO₄), and concentrated. Two comps, 9a (3.1 g) and 9b (12.4 g), were obtained by fractional recrystallization of the residue from EtOH-H₂O. Compd 9a was recrystallized from toluene followed by EtOH-H₂O to give colorless crystals, mp 177.5-179°. Compd 9b was recrystallized successively from C₆H₆, EtOH-H₂O, C₆H₆-Skellysolve B, EtOHc, and C₆H₆ 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 (H₂O), dried (Na₂SO₄), 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 (CDCl₃) δ 6.43 (d, 1 H, CH=CHCH₂), 5.94 (m, 1 H, CH=CHCH₂), 3.75 (d of d, 1 H, >CHCO₂H) and 2.60 ppm (broad m, 3 H, CH=CHCH₂ and >CH of cyclohexyl).

Methyl 6-Cyclohexyl-1,2-dihydro-1-naphthoate (11). A soln of 10 (3.3 g, 0.0129 mole), H₂SO₄ (0.15 ml, sp gr 1.84), and MeOH (1.2 ml) in CH₂Cl₂ (20 ml) was refluxed for 17 hr. The cooled soln was washed (H₂O, 5% aq NaHCO₃, H₂O, saturated aqueous NaCl), dried (Na₂SO₄), 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 C₆H₆ (325 ml) was heated at 45° under N₂ for 20 hr. Excess 5% aqueous K₂CO₃ was added to the cooled mixt. The solids were removed by filtration with Et₂O washing. The organic layer of the filtrate was dried (Na₂SO₄) 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), H₂O (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 $\pm 0.4\%$ 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, $\text{CH}=\text{CHCH}_2$), 5.92 (m, 1 H, $\text{CH}=\text{CHCH}_2$), 4.37 (m, 1 H, $>\text{CHCO}_2\text{H}$), and 3.40 ppm (m, 2 H, $\text{CH}=\text{CHCH}_2$).

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, $(\text{CH}_2)_6$].

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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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