lized ($CHCl_3$-hexane) to give 1.0 g (80%) of white crystals, mp 154–156°.

Anal. ($C_8H_7N_3O$) C, H, N.

1-Methyl-4-(3-methyl-5-isoxazolyl)pyridazinium Iodide (5a) and 1-Methyl-5-(3-methyl-5-isoxazolyl)pyridazinium Iodide (6a). A solution of 0.5 g (3.1 mmol) of **7a** and 10 ml of MeI in 20 ml of MeOH was stirred at room temperature for 48 hr. The solution was cooled and 0.2 g of deep orange solid was collected. Recrystallization (EtOH) gave **5a** as deep orange crystals: mp 210–211° dec; nmr δ 4.68 (s, 3, N^+CH_3), 7.47 (s, 1, =CH), 9.73 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.91 (d, 1, $J_{H_bH_c}$ = 2.5 cps, H_b).

Anal. ($C_9H_{10}IN_3O$) H, I, N; C: calcd, 35.7; found, 35.2.

Addition of Et_2O to the mother liquors gave 0.4 g of orange solid which was recrystallized (MeOH) several times to give 68 mg of orange crystals of **6a**:§ mp 166–167° dec; nmr δ 4.75 (s, 3, N^+CH_3), 7.33 (s, 1, =CH), 9.55 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.80 (broad m, 1, H_b).

Anal. ($C_9H_{10}IN_3O$) C, H, I, N.

4-(4-Methyl-2-thiazolyl)pyridazine (7b). A solution of 2.1 g (15.0 mmol) of **8**[12] and 1.9 g (20.0 mmol) of 1-chloro-2-propanone in 100 ml of EtOH was heated under reflux for 6 hr and concentrated *in vacuo*. The solid residue was dissolved in H_2O and the aqueous solution was made alkaline with 1 *N* NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to a brown solid which was recrystallized ($CHCl_3$-hexane) to give 0.4 g (15%) of 7b as a yellow crystalline solid, mp 131–133°.

Anal. ($C_8H_7N_3S$) C, H, N; S: calcd, 18.1; found, 17.3.

1-Methyl-4-(4-methyl-2-thiazolyl)pyridazinium Iodide (5b) and 1-Methyl-5-(4-methyl-2-thiazolyl)pyridazinium Iodide (6b). A solution of 0.4 g (2.25 mmol) of **7b** and 1 ml of MeI in 15 ml of MeOH was stirred at room temperature for 48 hr, cooled, and filtered to give 0.28 g of red solid. Recrystallization (MeOH) gave 0.22 g of **5b** as deep red crystals: mp 220–222° dec; nmr δ 4.67 (s, 3, N^+CH_3), 7.79 (d, 1, J = 1 cps, =CH), 9.63 (d, 1, $J_{H_aH_c}$ = 6.5 cps, H_a), 9.87 (d, 1, $J_{H_bH_c}$ = 2.5 cps, H_b).

Anal. ($C_9H_{10}IN_3S$) C, H, I, N, S.

Addition of Et_2O to the mother liquors gave 0.4 g of orange solid which was recrystallized (twice MeOH, twice Me_2CO) to give 0.172 g of orange crystals of **6b**:§ mp 171° dec; nmr δ 4.75 (s, 3, N^+CH_3), 7.69 (d, 1, J = 1 cps, =CH), 9.50 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 9.87 (d, 1, $J_{H_bH_c}$ = 1 cps, H_b).

Anal. ($C_9H_{10}IN_3S$) C, H, I, N, S.

4-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridazine (7c). A solution of 0.7 g (5.0 mmol) of **9**[12] in 5 ml of Ac_2O was heated under reflux for 3 hr, concentrated *in vacuo* to an oil, and diluted with H_2O. The aqueous mixture was adjusted to pH 6 with dilute aqueous $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to a tan solid. Sublimation at 100–110° (13 mm) followed by recrystallization (hexane) gave 0.18 g (22%) of white crystals, mp 133–134°.

Anal. ($C_7H_6N_4O$) C, H, N.

1-Methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)pyridazinium Iodide (5c) and 1-Methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyridazinium Iodide (6c). A solution of 0.75 g (4.6 mmol) of **7c** and 1.5 ml of MeI in 30 ml of MeOH was stirred at room temperature for 72 hr and concentrated to dryness. The solid residue was taken up in 50 ml of boiling Me_2CO and cooled to give 0.33 g of red solid. Recrystallization (Me_2CO) gave 0.17 g of **5c** as deep red crystals: mp 186–187° dec; nmr δ 4.75 (s, 3, N^+CH_3), 9.83 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 10.0 (d, 1, $J_{H_bH_c}$ = 2 cps, H_b).

Anal. ($C_8H_9IN_4O$) C, H, I, N.

Addition of Et_2O to the mother liquors gave 0.5 g of brown solid which was recrystallized (EtOH–Et_2O) to 0.35 g of very hygroscopic crystals of **6c**:§ mp 126–127° dec; nmr δ 4.83 (s, 3, N^+CH_3), 9.60 (d, 1, $J_{H_aH_c}$ = 6 cps, H_a), 10.3 (broad m, 1, H_b).

Anal. ($C_8H_9IN_4O \cdot H_2O$) C, N; H: calcd, 3.44; found, 2.84.

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§Analytical samples of **6a**, **6b**, and **6c** were found to contain about 25% of the isomeric **5a**, **5b**, and **5c**, respectively (3:1 relative integrated intensity of the nmr N^+CH_3 and =CH signals).

Synthesis of Some *cis*- and *trans*-2-(Substituted amino)cyclohexyl Phenyl Ketones†

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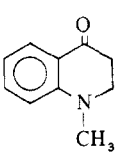
A number of β-amino ketones prepared in this laboratory have been shown to possess analgetic activity. When evaluated by the Hafner tail pinch method,[1] *N*-methyl-2,3-dihydro-4-quinolone (**1**) was found to have an ED_{50} of 250 mg/kg[2] while an open-chain analog, α,α-dimethyl-β-dimethylaminopropiophenone (**2**), was shown to have an ED_{50} of 35 mg/kg.[2] Since the possibility exists that the lower potency of the more rigid 1-methyl-2,3-dihydro-4-quinolone (**1**), might result from its inability to fit the receptor as readily as the open-chain analog (**2**), it was decided to study the biological activity of other β-amino ketones with the hope of ascertaining the stereochemical requirements for the analgetic activity of such compounds.



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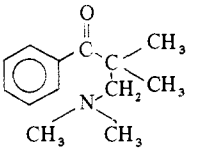

2

Among the compounds selected to study were the cis and trans isomers of a number of 2-(substituted amino)cyclohexyl substituted-phenyl ketones. In these compounds the spatial relationship between the amino and carbonyl groups, which appear to be necessary for analgetic activity,[3] is varied.

The cis isomers were prepd by the catalytic redn of the enamine of substituted 2-benzoylcyclohexanones (**3**) (Table I). The diketones **3** were allowed to react with amines in the presence of TsOH. The amine reacted exclusively with the carbonyl of the cyclohexanone ring to form the enamine **4**.

Infrared spectra of the diketones **3** showed peaks attributed to carbonyl absorption at approximately 1685 and 1710 cm^{-1}. The peak at 1685 cm^{-1} is attributed to the

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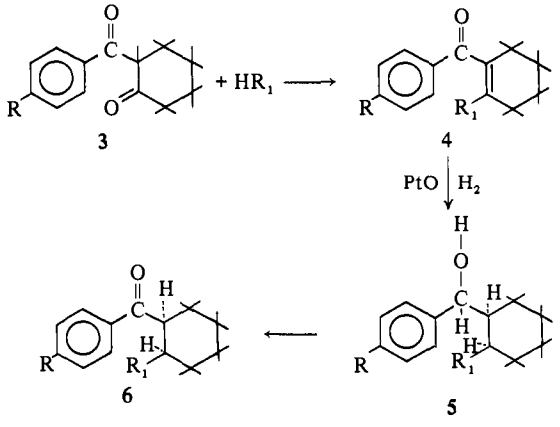
‡A portion of this study was abstracted from the dissertation of J. C. Letton submitted to the Graduate College of the University of Illinois at the Medical Center, Chicago, Ill., in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address, Kentucky State College, Frankfort, Ky.



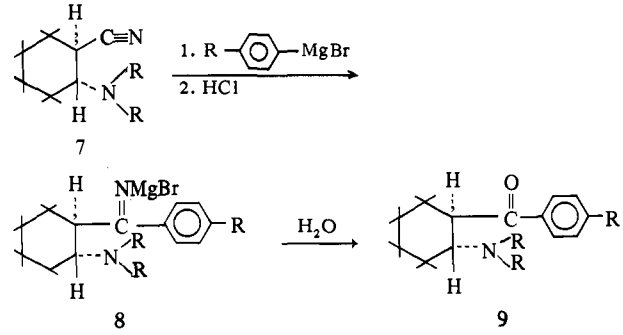
3 4 5 6

HR_1 = primary or secondary amine

carbonyl absorption of the benzoyl group since it is conjugated with the aromatic ring and might be expected to absorb at lower wave numbers than the carbonyl of cyclohexanone. This absorption band varied when the benzoyl group was substituted in the para position while the absorption at 1710 cm^{-1} remained virtually constant in all compounds substituted on the benzoyl group. Since the enamine showed a single band which could be attributed to carbonyl absorption and since it was always below 1700 cm^{-1}, it can be assumed that the reaction with amines occurred only with the carbonyl group of the cyclohexanone ring.

Catalytic redn of the enamine gave the amino alcohols **5** (Table II), which were readily oxidized with Jones reagent to the desired amino ketones **6** (Table III).

trans-2-(*N,N*-Dimethylamino)cyclohexyl phenyl ketone and *trans*-2-(*N,N*-dimethylamino)cyclohexyl *p*-methoxyphenyl ketone were prepared by allowing *trans*-aminohexahydrobenzonitrile (**7**) to react with the appropriate Grignard reagent and hydrolyzing the resulting imine.



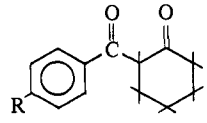
7 8 9

Structure Assignment. The assignment of configuration of the amino alcohols and the amino ketones was based upon both their method of preparation and nmr analysis. The amino alcohols **5** were prepared by hydrogenation of the vinylogous amides **4** which have a planar, conjugated system.

Hydrogenation gives the cis alcohol which upon oxidation yielded the cis amino ketones since oxidation of the benzyl alcohol does not involve the stereochemistry of the cyclohexane ring. Nmr analysis supported this assignment of configuration. The cis ketones **6** showed a peak at 3.90 ppm having a broad base, but singlet character corresponding to the hydrogen α to the carbonyl. In the case of several of the *p*-methoxyphenyl substituted-aminocyclohexyl ketones, the signal for this hydrogen is overlapped by the methoxy hydrogen. In these cases, the area integrates for 4 protons. The hydrogen attached to the carbon holding the amino group appears at approximately 2.66 ppm. It is overlapped by the signals of the methylene protons of the *N*-alkyl groups. While overlapping does occur, it is possible to interpret the spectra taking advantage of the fact that the coupling constant between axial hydrogens on adjacent carbons (J_{aa} = 8-10 Hz) is larger than between hydrogen in any other orientation on adjacent carbons (J_{ae} = 2-5 Hz). When the compounds were examined using an applied frequency of 90 MHz, the coupling constant between the hydrogens α and β to the carbonyl groups was observed to be 3-4.5 Hz.

The trans ketones were similarly examined. While again some overlapping of signal occurred it was possible to

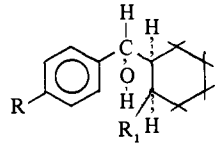
Table I. 2-(Substituted benzoyl)cyclohexanones



R	Mp, °C	Crystn solvent[a]	Yield, %	Formula	Analysis
H	89-91	A	43	$C_{13}H_{14}O_2$	C, H
Cl	101-103	B	51	$C_{13}H_{13}O_2Cl$	C, H
OCH_3	116-118	A	69	$C_{14}H_{16}O_3$	C, H

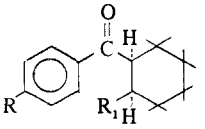
[a] Solvents used in recrystallization: A = methanol, B = ethanol.

Table II. *cis*-2-(Substituted amino)cyclohexyl-substituted-phenylmethanols



							Hydrochloride				
R	R_1	Mp, °C	Yield, %	Crystn solvent	Formula	Analysis	Mp, °C	Crystn solvent	Yield, %	Formula	Analyses
H	$NHCH_3$	89-91	46	A	$C_{14}H_{21}NO$	C, H, N					
H	$N(CH_3)CH_2C_6H_5$						220-222	B	58	$C_{21}H_{28}ClNO$	C, H, N, Cl
H	NC_4H_8	142-144	78	B	$C_{17}H_{25}NO$	C, H, N					
H	NC_4H_8O	95-97	55	B	$C_{17}H_{25}NO_2$	C, H, N					
Cl	$N(CH_3)CH_2C_6H_5$						241-242	B	65	$C_{21}H_{27}Cl_2NO$	C, H, N
Cl	NC_4H_8	143-145	40	C	$C_{17}H_{24}NOCl$	C, H, N					
Cl	NC_4H_8O						256-257	B	45	$C_{17}H_{25}Cl_2NO$	C, H, N, Cl
OCH_3	$NHCH_3$	87-90	54	D	$C_{15}H_{23}NO_2$	C, H, N					
OCH_3	$N(CH_3)CH_2C_6H_5$						220-221	B	65	$C_{22}H_{30}ClNO_2$	C, H, N, Cl
OCH_3	NC_4H_8						213-215	B	89	$C_{18}H_{28}ClNO_2$	C, H, N, Cl
OCH_3	NC_4H_8						210-211	B	72	$C_{18}H_{28}ClNO_3$	C, H, N, Cl

Table III. *cis*-2-(Substituted amino)cyclohexyl Substituted-phenyl Ketones



							Hydrochloride				
R	R_1	Mp, °C	Crystn solvent	Yield, %	Formula	Analyses	Mp, °C	Yield, %	Crystn solvent	Formula	Analyses
H	$NHCH_3$						170–172	66	C	$C_{14}H_{20}ClNO$	C, H, N, Cl
H	$N(CH_3)CH_2C_6H_5$	55–57	A	49	$C_{21}H_{25}NO$	C, H, N					
H	NC_4H_8						155–157	74	C	$C_{17}H_{24}ClNO$	C, H, N, Cl
H	NC_4H_8O	78–80	B		$C_{17}H_{23}NO_2$	C, H, N					
Cl	$N(CH_3)CH_2C_6H_5$						137–139	59	C	$C_{21}H_{25}Cl_2NO$	C, H, N, Cl
Cl	NC_4H_8	86–88	A		$C_{17}H_{22}ClNO$	C, H, N, Cl					
Cl	NC_4H_8O	100–101	B		$C_{17}H_{22}ClNO_2$	C, H, N, Cl					
OCH_3	$N(CH_3)CH_2C_6H_5$	57–59	A	78	$C_{22}H_{27}NO_2$	C, H, N					
OCH_3	NC_4H_8	95–97	B	75	$C_{18}H_{25}NO_2$						
OCH_3	NC_4H_8O	74–76	B	83	$C_{18}H_{25}NO_3$						
OCH_3	$NHCH_3$						188–190	66	D	$C_{15}H_{22}ClNO_2$	C, H, N, Cl

measure a coupling constant of approximately 8 Hz between the same protons examined in the cis series of compounds.

Biological Activity. The compounds prepared in this study showed no analgetic activity in white female Swiss mice when tested by the Hafner tail pinch method.[1] The compounds were administered intraperitoneally. 2-Benzoylcyclohexanone, when similarly administered to mice in doses of 200/kg, markedly increased the activity of the animals. No such action was noted in the compounds bearing a substituent in the para position.

Conclusions

Lack of analgetic activity in the compounds reported may be due to their inability to be transported to the site of action or to their ability to fit the receptor. Because of their complete lack of analgetic activity and their close resemblence to active compounds, the latter seems more likely. If this assumption is true, it would appear that the spacial arrangement between the phenyl, amino, and carbonyl groups, previously suggested essential for activity, is not suitable for the proper interaction with the receptor.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary melting point apparatus. Microanalysis for C, H were performed by Microtech Microanalytical Laboratories, Skokie, Ill.; where analyses are indicated only by symbols of the elements the results were within ±0.4% of the theoretical values.

trans-**2-Dimethylaminohexahydrobenzonitrile.** *trans*-2-Dimethylamino-Δ^3-tetrahydrobenzonitrile (50 g, 0.3 mole) in MeOH (100 ml) was reduced in a Parr hydrogenator using 1.0 g of PtO_2 as catalyst at 30-lb pressure. When the theoretical amount of H_2 was absorbed the catalyst was removed by filtration and the solvent removed by distn. The residue was converted to the picrate for identification. After recrystn from EtOH, it melted at 158–159°. *Anal.* ($C_{15}H_{19}O_7N_5$) C, H, N.

trans-**2-(Dimethylamino)cyclohexyl Phenyl Ketone.** The Grignard reagent was prepared using 15.7 g (0.1 mole) of bromobenzene, 2.4 g (0.1 g-atom) of magnesium, and 50 ml of Et_2O. 2-Dimethylaminohexahydrobenzonitrile (10.0 g, 0.66 mole) in 50 ml of Et_2O was added dropwise while the Et_2O was heated under reflux. After the mixture was heated to reflux for 2 hr, the addition was completed. The mixture was poured over iced dil H_2SO_4, washed with Et_2O, made alkaline with $NaHCO_3$, and extd with Et_2O. The Et_2O ext were washed with H_2O and dried ($MgSO_4$), and the solvent was evapd. The residue was recrystd from Et_2O–petr ether (1:1). It melted at 96–97°, lit. 96–97°.[4]

trans-**2-(Dimethylamino)cyclohexyl *p*-Methoxyphenyl Ketone.** This compound was prepared following the procedures reported for the preparation of *trans*-2-(dimethylamino)cyclohexyl phenyl ketone, but substituting *p*-methoxybromobenzene for BrC_6H_5. After recrystallizing from Et_2O–petr ether (1:1), it melted at 74–76°, yield 77%. *Anal.* ($C_{16}H_{23}O_2N$) C, H, N.

2-(Substituted benzoyl)cyclohexanones. The procedure for the preparation of 2-(*p*-chlorobenzoyl)cyclohexanone was employed for the synthesis of 2-benzoylcyclohexanone and 2-(*p*-methoxybenzoyl)cyclohexanone. Cyclohexanone, 49 g (0.5 mole), 71 g (1.0 mole) of pyrrolidine, and 500 ml of C_6H_6 were mixed and heated under reflux for 2.5 hr using a Dean–Stark trap. At the end of this period, 9 ml (0.5 moles) of water was collected.

The solvent was then removed *in vacuo*. The liquid residue was dissolved in 750 ml of $CHCl_3$ and chilled to 0° in an ice–CH_3OH bath. $(C_2H_5)_3N$ (60 g, 0.7 mole) was added. This was followed by the dropwise addition of 95.0 g (0.56 mole) of anisoyl chloride, in 50 ml of $CHCl_3$ over a 30-min period. Reaction temp was maintained below 10°. The reaction was allowed to stir for 2 hr at ice-bath temp. Stirring was continued overnight at ambient temp.

The reddish soln was poured over 800 g of crushed ice and made acid by the addition of 20% HCl. The acidified mixture was stirred for 2 hr in an ice bath before the organic layer was separated.

The aqueous layer was extracted with two 100-ml portions of $CHCl_3$, and the combined $CHCl_3$ layers were washed with H_2O, 10% $NaHCO_3$, and finally with H_2O until neutral. The neutral $CHCl_3$ solution was dried (Na_2SO_4) overnight then concentrated *in vacuo* to a solid residue (Table I).

cis-**2-(Substituted aminocyclohexyl)phenylmethanols.** A soln of the properly substituted 2-benzoylcyclohexanone (0.05 mole), amine (0.15 mole), and *p*-toluenesulfonic acid (0.1 g) in 50 ml of C_6H_6 was heated at reflux for 12 hr using a Dean–Stark trap. Approximately 0.9 ml of H_2O was collected. The mixture was evapd to dryness, the residue dissolved in 175 ml of absolute C_2H_5OH, 0.5 g of PtO_2 added, and the mixture hydrogenated at 50 lb until the theoretical quantity of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate evapd to dryness. The residue was dissolved in Et_2O and this solution extracted with 10% AcOH. The AcOH extract was made alkaline with 20% sodium hydroxide solution to ppt the amino alcohol. It was removed by filtration or extd with Et_2O. It was either characterized as the free base or extracted with Et_2O or converted to the hydrochloride by the usual procedure.

cis-**2-(Substituted amino)cyclohexyl Substituted-phenyl Ketones.** To a soln of *cis*-2-(substituted aminocyclohexyl)substituted-phenylmethanol (6.5 mmoles) in 100 ml of Me_2CO, 10 ml of dioxane, and 6 ml of H_2O was added Jones reagent (10.68 mmoles). The solution was allowed to stand for 2 hr. The Me_2CO was removed by vacuum distilln and the residue treated with 200 ml of H_2O and cooled in an ice bath. CH_2Cl_2 (100 ml) was added, and the mixture made basic by the dropwise addition of 20% NaOH. The basic mixt was allowed to stir for 1 hr in the cold, and the organic layer was sepd. The aqueous layer was extd with 2 portions of CH_2Cl_2 (50 ml each) and these combined were washed twice with H_2O (200 ml each) and then dried (Na_2SO_4). The CH_2Cl_2 was removed by distn. If the residue did not crystallize, the liquid was dissolved in a mixture of

anhydrous Et_2O (20 ml) and absolute C_2H_5OH. Anhydrous HCl was passed through the soln. On cooling, the hydrochloride was isolated.

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Synthesis and Biological Activity of 2,4-Diamino-6- and -7-(1-adamantyl)pteridines†

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As part of an effort to synthesize new folate antagonists[1] of potential anticancer activity, we would like to report the preparation and some biological properties of 2,4-diamino-6-(1-adamantyl)pteridine (**1**) and its isomer, 2,4-diamino-7-(1-adamantyl)pteridine (**2**). Compound **1** was obtained by condensation of 1-adamantylglyoxal hydrazone§ (**3**) with 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in aqueous methanol. Isomeric pteridine **2** was prepared by condensation of 1-adamantylglyoxal[4] with 2,4,5,6-tetraaminopyrimidine[3] in methanol.#

The structural assignments of the two isomers were established by comparison of their uv maxima with the literature values recorded for 2,4-diamino-6- and -7-methylpteridines (Table I), **4** and **5**, respectively. Hydrolysis of the diaminoadamantylpteridines (**1** and **2**) gave the respective 2-amino-4-hydroxypteridines (**6** and **7**) which had uv spectra (Table I) and tlc characteristics (Experimental Section) similar to the literature values for 2-amino-4-hydroxy-6- and -7-methylpteridines (**8** and **9**, respectively).

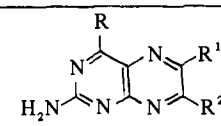
Compound **1** was found to inhibit the growth of mouse mammary adenocarcinoma (TA3) cells *in vitro* culture[6] with an ID_{50} of $1.4 \times 10^{-7} M$. This compound also inhibited the growth of *Streptococcus faecium*[7] with an ID_{50} of $1.44 \times 10^{-8} M$ but was an ineffective growth inhibitor of *Escherichia coli*[8] at a concentration of $10^{-5} M$.

Compound **2** demonstrated growth inhibition of the TA3 cells with ID_{50} $4.8 \times 10^{-6} M$. Compound **2** also inhibited the growth of *Strep. faecium*[7] with ID_{50} $1.96 \times 10^{-6} M$ but was an ineffective growth inhibitor of *E. coli*[8] at a concentration of $10^{-5} M$.

It is possible that the activity of the 7 isomer (**2**) is affected by very minor amounts of the 6 isomer present as an impurity. The biological data seem to negate this objection because the ratios of the ID_{50}'s (2:1) for the TA3 cells and *Strep. faecium* are 35 and 136, respectively. One would expect these ratios to be nearly the same if the activity of **2** were an artifact caused by isomeric contamination of the analytical sample.

Work is continuing in our laboratories to determine if other adamantylpteridines will exhibit biological activity.

Table I. Ultraviolet Data[a]



No.	R	R^1	R^2	λ_{max}, mμ pH 1	λ_{max}, mμ pH 13
1	NH_2	$C_{10}H_{15}$[b]	H	338	369
2	NH_2	H	$C_{10}H_{15}$[b]	331	360
4	NH_2	CH_3	H	337[c]	369[c]
5	NH_2	H	CH_3	332[c]	361[c]
6	OH	$C_{10}H_{15}$[b]	H	324	364
7	OH	H	$C_{10}H_{15}$[b]	316	357
8	OH	CH	H	326[d]	367[d]
9	OH	H	CH_3	319[d]	359[d]

[a] Other maxima present in each spectrum are not presented here for the sake of clarity. Shifts of the maxima not presented are in the same direction as those reported in this Table. [b] 1-Adamantyl. [c] Seeger, *et al.*[5a] [d] Mowat, *et al.*[5b]

Experimental Section

Analytical data were obtained by G. I. Robertson, Jr., Florham Park, N. J.; where analyses are indicated by the symbols of the elements, analytical results were within ±0.3% of the theoretical values. Ultraviolet spectra were run on a Perkin-Elmer 202. Tlc plates were Brinkman silica gel F-254 on aluminum. Melting points were determined on a Fisher-Johns apparatus.

1-Adamantylglyoxal Hydrazone (3). 1-Adamantylglyoxal[4] (1.68 g, 8.75 mmoles) was dissolved in the min amt of abs Et_2O. A few drops of hydrazine were added to this soln. A ppt began to form almost immediately and was collected after 0.5 hr. The crude material (1.2 g) was recrystallized from Et_2O to give 300 mg: mp 132–135°; single spot in tlc ($CHCl_3$–THF, 1:1) R_f 0.33. *Anal.* ($C_{12}H_{18}N_2O$) C, H, N.

2,4-Diamino-6-(1-adamantyl)pteridine (1). 1-Adamantylglyoxal hydrazone (**3**) (300 mg, 1.46 mmoles) in MeOH (40 ml) was added to a soln of 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in a hot soln of 35 ml of MeOH and 5 ml of H_2O. This reaction mixt was stirred under N_2 for 18 hr; during this period of time, the vol decreased from 75 to 40 ml. The reaction mixt was then evapd to dryness. The resulting residue was extracted twice with hot EtOH–THF (1:4). The insol solid was unreacted pyrimidine (140 mg) (tlc). The filtrates were evapd to dryness and triturated with Et_2O to give 90 mg of gray-white solid which was dissolved in hot EtOH and filtered. Enough H_2O was added to the soln to make it opaque, and the soln was allowed to cool to room temperature. The solid was collected by filtration, washed with Et_2O, and dried at 138° *in vacuo* over P_2O_5 for 4 hr to give 1: 50 mg yield; mp 326–328° dec; tlc (ϵ 9.8×10^3) (THF–$CHCl_3$, 1:1) single spot, R_f 0.18; λ_{max} (pH 1) 243 (ϵ 1.76×10^4), 279 (3.8×10^3), 338 mμ; λ_{max} (pH 13) 257 (ϵ 1.65×10^4), 369 mμ (5.76×10^3). *Anal.* ($C_{16}H_{20}N_6 \cdot 0.75HCl$) C, H, C; N: calcd, 26.00; found, 25.42.

2,4-Diamino-8-(1-adamantyl)pteridine (2). A soln of 1-adamantylglyoxal[4] (905 mg, 4.0 mmoles) in hot MeOH (100 ml) was added to a soln of 2,4,5,6-tetraaminopyrimidine hydrochloride[3] in MeOH (100 ml, hot). The reaction mixt turned yellow immediately and was refluxed for 2.5 hr. The vol was reduced to 30 ml, the reaction mixt cooled, and 360 mg of product collected on filtration. Recrystallization from abs EtOH gave 460 mg: mp (darkens from 265°) 307–309° dec, after drying at 138° over P_2O_5 *in vacuo* for 2 hr; tlc (THF–$CHCl_3$, 1:1) R_f 0.36 (single spot); λ_{max} (pH 1) 239 (ϵ 1.92×10^4), 277 (7.84×10^3), 331 mμ (1.63×10^4); λ_{max} (pH 13) 252 (ϵ 1.33×10^4), 360 mμ (6.47×10^3). *Anal.* ($C_{16}H_{20}N_6 \cdot C_2H_5OH \cdot HCl$) C, H, N, Cl.

Hydrolysis of 2,4-Diamino-6- and -7-(1-adamantyl)pteridines. 2-Amino-4-hydroxy-6-(1-adamantyl)pteridine (6). 2,4-Diamino-6-(1-adamantyl)pteridine (**1**) (3 mg) was refluxed under N_2 with 3 ml of 0.1 *N* NaOH for 2 hr when soln occurred. After 2 hr more, the reaction mixt was cooled and the basic soln neutralized with 1 *N*

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§ Use of the hydrazone has been shown to produce the 6 isomer in analogous systems (see ref 2).

Use of these conditions has been shown to lead to the 7 isomer in analogous systems (see ref 2).