tiles were removed under vacuum to yield 18.1 g of crude tetrachloro compound containing inorganic salts. A 0.5-g sample sublimed at 0.02 mm (bath temperature 220–230°) gave 150 mg of orange sublimate. An analytical sample was prepared by subliming crude material three times at 0.02 mm (bath temperature 220–290°). The compound did not melt below 360°. The chlorine value was low, possibly due to the extreme ease with which the compound reacts with moisture. It reacts violently with the common primary and cyclic secondary amines.

Anal. Calcd for $C_9Cl_4N_6$: C, 29.84; Cl, 44.05; N, 26.10. Found: C, 29.66; Cl, 43.10, 43.37; N, 25.91.

2,4,7,9-Tetrapiperidinopyrimido[4,5-*g*]pteridine (II, R = piperidino).—To 50 ml of dry piperidine was added, with vigorous stirring, 6.0 g of crude 2,4,7,9-tetrachloropyrimido[4,5-*g*]-pteridine (containing about 70% of inert material.) After the initial exothermic reaction had subsided, the mixture was kept at reflux for 2 hr and allowed to stand over the weekend. The mixture was stirred with ether, and the solids were filtered, washed with ether, and dried. The purple solid was leached with 100 ml of boiling water, filtered, and washed with ligroin to give 4.2 g of crude product, mp 345–348°. An analytical sample was prepared by dissolving the compound in 60 ml of boiling CH_2Cl_2, adding 60 ml of cyclohexane, distilling 60 ml of the mixed solvent, and cooling to give small purple-red needles, mp 349–351.5°.

Anal. Calcd for $C_{28}H_{40}N_{10}$: C, 65.09; H, 7.80; N, 27.11. Found: C, 65.27; H, 7.87; N, 26.84.

2,4,7,9-Tetra(4-hydroxypiperidino)pyrimido[4,5-*g*]pteridine (II, R = 4-hydroxypiperidino).—To 8.73 g (86.5 mmoles) of 4-hydroxypiperidine, at a temperature just above the melting point, was added 1.45 g (4.5 mmoles) of 2,4,7,9-tetrachloropyrimido[4,5-*g*]pteridine, and the mixture was stirred at 110–120° overnight. Pure diethylene glycol dimethyl ether (5 ml) was added, and heating was continued for 4 hr. Hot water (25 ml) was added, and the product was filtered from the cooled solution. The dark purple solid weighed 2.62 g (93%) and melted at 318–327°. Recrystallization from dimethylformamide and then from methanol raised the melting point to 335–336° (sealed, evacuated capillary). The analytical sample was sublimed (with difficulty) at 260–280° (0.001 mm) to yield a red powder, mp 343–344° (sealed, evacuated capillary).

Anal. Calcd for $C_{28}H_{40}N_{10}O_4$: C, 57.91; H, 6.94; N, 24.14. Found: C, 57.75; H, 7.20; N, 23.93.

2,4,7,9-Tetra(diethanolamino)pyrimido[4,5-*g*]pteridine (II, R = diethanolamino).—A mixture of 50 g of diethanolamine and 3.0 g of crude 2,4,7,9-tetrachloropyrimido[4,5-*g*]pteridine was warmed on the steam bath with thorough agitation; a vigorous exothermic reaction occurred. After heating at 90–95° for 18 hr, the excess diethanolamine was removed under high vacuum (*ca.* 1 mm) and the dark red residue was triturated with 150 ml of ice–water and filtered. The crude product was dissolved in dilute acetic acid and filtered, and the filtrate was made alkaline with aqueous NH_3. The product separated as small red needles which, when dry, weighed 0.86 g (16%), mp 225–226° (sealed, evacuated capillary). Recrystallization from water and then from diethanolamine–water (1:2) raised the melting point to 239–240° (sealed, evacuated capillary).

Anal. Calcd for $C_{24}H_{40}N_{10}O_8$: C, 48.31; H, 6.76; N, 23.48. Found: C, 48.42; H, 6.96; N, 23.26.

2,4,6,8-Tetrachloropyrimido[5,4-*g*]pteridine (III, R = Cl). A mixture of 7.15 g (0.0288 mole) of 2,4,6,8-tetrahydroxypyrimido[5,4-*g*]pteridine,[5] 25 g (0.12 mole) of PCl_5, and 70 ml of $POCl_3$ was refluxed for 3 hr. The mixture was cooled and filtered. The filter cake was washed with ether and dried to yield 7.39 g (82%) of product, mp >360°. The analytical sample was prepared by sublimation [160° (*ca.* 0.001 mm)].

Anal. Calcd for $C_8Cl_4N_8$: C, 29.85; Cl, 44.05; N, 26.10. Found: C, 29.68; Cl, 43.84; N, 26.13.

2,4,6,8-Tetrapiperidinopyrimido[5,4-*g*]pteridine (III, R = piperidino).—To 5.25 g (0.062 mole) of piperidine, cooled in an ice bath, was added 2 g (0.0062 mole) of 2,4,6,8-tetrachloropyrimido[5,4-*g*]pteridine in small portions with stirring. An additional 5.25 g of piperidine was added, and the mixture was heated on a steam bath overnight. The cooled mixture was ground with water, and the crude product obtained by filtration was recrystallized from ethanol to yield 1.45 g (45%) of material melting at 315–318°. The product was chromatographed on alumina and eluted with acetone. Evaporation of the acetone and washing with petroleum ether gave the analytical sample, yellow needles, mp 326–327°.

Anal. Calcd for $C_{28}H_{40}N_{10}$: C, 65.08; H, 7.81; N, 27.11. Found: C, 64.86; H, 7.89; N, 26.98.

Acknowledgment.—We are grateful to Mr. Arnold Lewis and his group for the analyses and Mr. Robert Puchalski for the infrared and ultraviolet spectra.

(5) E. C. Taylor, *J. Am. Chem. Soc.*, **77**, 2246 (1955).

Synthesis and Pharmacological Activity of a Series of 2-Substituted Pyridazinones

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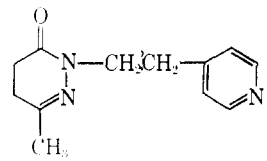
In the course of our investigations into the chemistry and pharmacology of certain pyridazinones, 4,5-dihydro-6-methyl-2-[2-(4-pyridyl)ethyl]-3-pyridazinone (I)[1a] was prepared. This compound was found to have



I

the interesting property of potentiating, in laboratory animals, the action of drugs that affect the central nervous system, such as pentobarbital, hexobarbital, chloral hydrate, chlorpromazine, mephenesin, strychnine, and diphenylhydantoin.[1b] Although I itself has no detectable action on the central nervous system, its administration along with the above named drugs greatly increases the duration of their action at a given dose level or enables a decrease in the dose required to give a desired effect. In view of this property of I, it became of interest to prepare a series of related structures in an endeavor to correlate structure with activity.

The compounds prepared are shown in Tables I and II. All of the compounds in Table I were prepared by reaction of the appropriately substituted hydrazine with levulinic acid. Of these substituted hydrazines, 2-(4-pyridyl)ethyl-,[1a] 2-hydroxyethyl-,[2] 2-cyanoethyl-,[3] phenethyl-,[4] 2-dimethylaminoethyl-,[5] 4-pyridylmethyl-,[6] 4-pyridyl-,[7] 2-(2-pyridyl)ethyl-,[8] and 2-(4-morpholinyl)-ethylhydrazine[9] have been previously described. Certain properties of the hydrazines prepared in the present work are given in Table III. These hydrazines were prepared by one of the following three methods.

(1) (a) G. Gever and J. G. Michels, U. S. Patent 3,012,032 (1961); (b) R. H. Buller, W. T. Rockbold, J. A. Buzard, and I. J. Stern, *J. Pharmacol. Exptl. Therap.*, **134**, 95 (1961).

(2) S. Gabriel, *Ber.*, **47**, 3032 (1914).

(3) U. Hoffmann and B. Jacobi, German Patent 598,185 (1934); U. S. Patent 1,992,615 (1935).

(4) E. Votocek and O. Leminger, *Collection Czech. Chem. Commun.*, **4**, 271 (1932).

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(6) Y. Takeda, Y. Maejima, and H. Namekata, *Japan. J. Tuberc.*, **2**, 184 (1954).

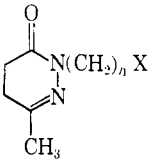
(7) E. Koenigs, W. Weiss, and A. Zscharn, *Ber.*, **59B**, 316 (1926).

(8) A. N. Kost, S. I. Sukhinov, E. V. Vinogradora, and V. Kozler, *Zh. Obshch. Khim.*, **33**, 3606 (1963).

(9) A. Halpern, U. S. Patent 3,080,375 (1963).

TABLE I

2-SUBSTITUTED 4,5-DIHYDRO-6-METHYL-3-PYRIDAZINONES

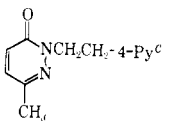
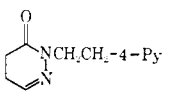
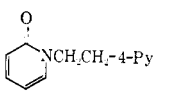
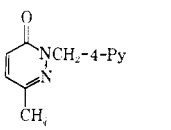
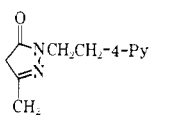
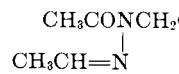
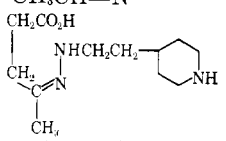


No.	n	X	Mp, °C	Bp, °C (mm)	Solvent[a]	Yield, %	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N	Hexobarbital potentiation[b]
1	2	4-Py[c]	92–93	157–158 (0.3)	i-Pr_2O	49	66.3	6.96	19.3	66.4	6.68	19.7	160/215
2	2	2-Py	73–74	150–155 (0.5)	Hex	52	66.3	6.96	19.3	66.5	6.88	19.6	360/0
3	0	2-Py[d]	132–133	...	Alc	36							220/0
4	2	5-C_2H_5-2-Py	48–49	175–176 (0.5)	Et_2O	86	68.5	7.81	17.1	68.5	7.86	17.1	170/7
5	0	4-Py	32–35	141–155 (0.2)	...	67	63.5	5.86	22.2	63.6	5.91	22.5	34/19
6	1	4-Py	99–100	*Ca.* 145 (0.3)	i-Pr_2O	30	65.0	6.45	20.7	64.9	6.49	21.0	75/235
7	3	4-Py	56–57	160–164 (0.3)	i-Pr_2O	82	67.5	7.41	18.2	67.4	7.73	18.7	85/354
8	1	3-Py	56–57	...	i-Pr_2O	80	65.0	6.45	20.7	65.0	6.60	21.4	130/>85
9	2	$-NC_5H_{10}$·fumarate	149–151	120–124 (0.3)[e]	Alc	83[e]	56.6	7.43	12.4	56.6	7.45	12.5	100/0
10	2	$-NC_4H_8O$·fumarate	165–166	141–145 (0.5)[e]	Alc	83[e]	52.8	6.79	12.3	52.7	7.03	12.5	300/22
11	2	$-N(CH_3)_2$·HCl	161–162	91–95 (0.6)[e]	Alc	73		16.1[f]	19.1		16.2[f]	19.0	100/9
12	2	C_6H_5	52–53	140–152 (0.8)	i-Pr_2O	73	72.2	7.46	13.0	72.2	7.48	13.4	100/0
13	2	CN	36–37	133–134 (0.6)	Et_2O	78	58.2	6.71	25.4	58.2	6.70	25.4	77/0
14	2	OH	91–92	...	Bz	51	53.8	7.75	17.9	53.9	7.50	17.8	1000/0
15	0	H[g]	103–104	...	H_2O	60							130/0

[a] i-Pr_2O = isopropyl ether, Hex = hexane, Et_2O = ether, Alc = ethanol, Bz = benzene. [b] Dose (mg/kg *po*, mice)/increase in sleeping time (min). Dose of hexobarbital, 100 mg/kg ip. The dose of the pyridazinone used was at or less than the AD_0. [c] Py = pyridyl. [d] W. N. Haworth and L. F. Wiggins, British Patent 656,228 (1951). [e] Of the free base. [f] Chlorine analysis. [g] W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239 (1947).

TABLE II

MISCELLANEOUS RELATED STRUCTURES

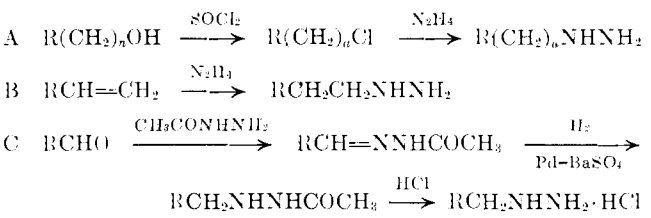
No.	Structure	Mp, °C	Solvent[a]	Yield, %	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N	Hexobarbital potentiation[b]
16		148–149	EtOAc	56	67.0	6.09	19.5	66.8	6.06	19.5	170/206
17		74–75	Cyhex	51	65.0	6.45	20.7	65.2	6.19	21.1	130/283
18		121-123	Bz	45	72.0	6.04	14.0	72.1	6.43	14.2	100/155
19		97-98	Et_2O	45	65.7	5.51	20.9	65.6	5.52	21.4	280/>178
20		149–150	Bz–alc	30	65.0	6.45	20.7	64.7	6.25	20.9	100/13
21		131–142 (0.4)[d]	...	40	64.4	7.37	...	64.6	7.28	...	77/>90
22		179–181	Aq alc	74	59.7	9.61	17.4	59.5	9.77	17.5	280/13
23	$H_2NNHCH_2CH_2$-4-Py·2HCl	157–159	Aq alc		40.0	6.24	33.8[e]	39.9	6.33	33.7[e]	25/48

[a] EtOAc = ethyl acetate, Cyhex = cyclohexane, Bz = benzene, Et_2O = ether, Alc = ethanol. [b] See footnote *b*, Table I. [c] 4-Py = 4-pyridyl. [d] Boiling point, °C (mm). [e] Cl analysis.

TABLE III
SUBSTITUTED HYDRAZINES
$R(CH_2)_nNHNH_2$

R	n	Bp, °C (mm)	Method	Yield, %	Salt	Mp, °C	% calcd C	H	N	Cl	% found C	H	N	Cl
3-Py[a]	1	...	C	88[b]	2HCl	184–186	36.8	6.66	21.4	36.2	36.8	6.04	21.3	36.2
4-Py	3	128–130 (0.8)	A	37[c]	$1.5(CO_2H)_2 \cdot H_2O$	...	43.4	5.32	13.8	...	43.7	5.31	13.9	...
5-C_2H_5-2-Py	2	101–104 (0.4)	B	75	2HCl	85–95	45.1	7.20	17.6	29.8	45.3	7.12	17.6	29.9
$H_2C<\frac{CH_2CH_2}{CH_2CH_2}>N-$	2	79–81 (1.1)	A	21	2HCl	151–152	38.9	8.86	19.4	32.8	39.1	9.46	19.1	32.7
$HN<\frac{CH_2CH_2}{CH_2CH_2}>CH-$	2	83–88 (0.6)	..	28	$2(CO_2H)_2 \cdot 2H_2O$	169–171	36.8	7.01	11.7	...	36.8	7.01	11.9	...

[a] Py = pyridyl. [b] As the dihydrochloride. [c] From 3-(4-pyridyl)-1-propanol.



It is interesting to note the variations in the reactivities of the vinylpyridines with hydrazine hydrate (method B) under the same reaction conditions. The reaction with 4-vinylpyridine took place about as fast as the addition could be carried out (as indicated by the cessation of the exothermic reaction at the end of the addition). With the 2 isomer, the exothermic reaction continued for about 30 min beyond the end of the addition. With 5-ethyl-2-vinylpyridine, no evolution of heat occurred and it was necessary to reflux the mixture to obtain a yield comparable to those of the other vinyl compounds.

In the reaction of 2-(4-piperidyl)ethylhydrazine with levulinic acid, the substituted hydrazone of levulinic acid (**22**) was obtained instead of the desired cyclized pyridazinone. That **22** exists as an inner salt is indicated by its high melting point, solubility characteristics, and infrared spectrum.

A comparison of the potentiating effects of the compounds prepared was obtained by measuring the prolongation of hexobarbital narcosis in mice. The results are shown in the right-hand columns of Tables I and II. Although the dosage of the potentiating compounds is based on the AD_0 (the maximum dose showing no ataxia), and hence varies, certain conclusions can be drawn. The two most important structural features required for maximum activity are the 4-pyridyl group and the number of CH_2 groups in the side chain. Increasing the length of the side chain has an alternating effect on the activity. Thus, with no CH_2 groups (**5**) the activity is quite low; with one CH_2 (**6**), good activity is observed; with two CH_2 (**1**), the activity is less than **6** but more than **5**; and with three CH_2 (**7**) the highest activity of any of the compounds prepared is found. The 3-pyridyl isomer is apparently somewhat less active than the 4 isomer (compare **8** with **6**) and the 2 isomer is devoid of activity (compare **2**, **3**, and **4** with **1**). The state of unsaturation of the pyridazinone ring appears to be relatively unimportant (compare **1** with **16**, and **6** with **19**). The loss of the 6-methyl group is associated with a slight increase in activity (compare **1** with **17**). Replacement of the pyridyl group with other functions causes complete loss of activity (**9**–**15**). Decreasing the size of the pyridazinone ring to a pyrazolinone ring (**20**) causes an almost complete loss of activity, while the compound in which the pyridazinone ring has been split between the 4 and 5 carbons (**21**) still retains a degree of activity. Some activity is found even when one nitrogen is replaced in the pyridazinone ring to give the pyridone (**18**) and even in the parent pyridylethylhydrazine (**23**) itself.

Experimental Section[10]

Preparation of Hydrazines (Table III). Method A.—3-(4-Pyridyl)-1-propanol[11] was converted to 3-(4-pyridyl)propyl chloride hydrochloride by the action of thionyl chloride in chloroform.[12] The above salt, as well as 2-(1-piperidyl)ethyl chloride hydrochloride,[13] was treated with 10 molar equiv of 85% hydrazine hydrate and 2 molar equiv of NaOH to give the corresponding hydrazine.

Method B.—2-Vinyl-, 4-vinyl-, and 5-ethyl-2-vinylpyridines[14] were each added to 3 molar equiv of 100% hydrazine hydrate at 85–90°. The reaction was continued for about 30 min beyond the cessation of the exothermic reaction. In the case of the 5-ethyl-2-vinylpyridine, it was necessary to reflux the mixture for 23 hr at 117°. The products were recovered by stripping off the excess hydrazine on the aspirator and vacuum distilling the residues.

Method C.—3-Pyridinecarboxaldehyde acetylhydrazone, mp 156–157°, was prepared in 78% yield by condensing 3-pyridinecarboxaldehyde[11] and acetylhydrazine in 2-propanol solution. Catalytic reduction of the hydrazone in absolute ethanol with Pd-$BaSO_4$ catalyst at 2.8 kg/cm², followed by removal of the acetyl group with 10% HCl, gave 3-pyridylmethylhydrazine dihydrochloride in 88% yield.

2-(4-Piperidyl)ethylhydrazine.—A mixture of 13.7 g (0.1 mole) of 2-(4-pyridyl)ethylhydrazine, 140 ml of absolute ethanol, 40 ml of glacial acetic acid, and 10 g of 5% Pd-C was hydrogenated for 16 hr at an initial pressure of about 2.8 kg/cm². The combined filtrates from ten such runs were stripped of solvent at the aspirator on a steam bath. The syrupy residue was cooled in an ice bath and treated slowly with 1.1 l. of saturated KOH. Two layers formed and were allowed to separate. The organic layer was extracted with toluene, the extract was stripped of toluene and the residue was vacuum distilled.

Preparation of Pyridazinones (Table I).—To the appropriate hydrazine was added slowly while cooling in an ice bath 1 molar equiv of levulinic acid. The use of an equal volume of water to help dissipate the heat did not increase the yields. The reaction mixture was then freed of volatile materials by heating under reduced pressure and the residue was distilled under vacuum where possible. Purification was accomplished by recrystallizations from the solvents indicated.

4,5-Dihydro-2-[2-(4-pyridyl)ethyl]-3-pyridazinone (17) was prepared exactly as for the pyridazinones using ethyl 3-formylpropionate[14] instead of levulinic acid.

1-[2-(4-Pyridyl)ethyl]-2-pyridone (18).—A mixture of 47.5 g (0.5 mole) of 2-pyridone, 52.5 ml (0.5 mole) of freshly distilled 4-vinylpyridine, and 0.5 g of NaOH was heated on the steam bath

(10) All melting points were taken on a micro hot stage (Fisher-Johns apparatus) and are uncorrected.
(11) Aldrich Chemical Co.
(12) J. P. Mason and H. W. Block, *J. Am. Chem. Soc.*, **62**, 1443 (1940).
(13) Reilly Tar and Chemical Corp.
(14) Union Carbide Chemicals Co.

overnight. Purification was effected by recrystallization from benzene using charcoal.

3-Methyl-1-[2-(4-pyridyl)ethyl]-2-pyrazolin-5-one (20).—The condensation of 1 mole of ethyl acetoacetate with 1 mole of 2-(4-pyridyl)ethylhydrazine was carried out by the general procedure above. The recrystallization solvent was ethanol–benzene (1:10).

1-Acetyl-2-ethylidene-1-[2-(4-pyridyl)ethyl]hydrazine (21).—To 68.5 g (0.5 mole) of 2-(4-pyridyl)ethylhydrazine was added slowly 40 ml (0.7 mole) of acetaldehyde while cooling in an ice bath. Water was removed from the resulting mixture by adding 200 ml of benzene and refluxing over a Dean–Stark trap. The dried benzene solution was treated with 130 ml (1.38 moles) of acetic anhydride and refluxed for 45 min. The volatile materials were removed on the steam bath at reduced pressure and the product was obtained by vacuum distillation of the residue.

6-Methyl-2-[2-(4-pyridyl)ethyl]-3-pyridazinone (16) and 6-Methyl-2-(4-pyridylmethyl)-3-pyridazinone (19).—To a boiling solution of 0.5 mole of the corresponding dihydropyridazinone (**1** or **6**) in 1 l. of glacial acetic acid was added dropwise during 1.5 hr 25.5 ml (0.5 mole) of bromine. The solution was then allowed to cool to about 85–90° and treated with a solution of 98 g (1 mole) of anhydrous potassium acetate in 650 ml of glacial acetic acid. The mixture was refluxed for 1 hr, then cooled in ice. The crystallized KBr was removed by filtration, and the filtrate was stripped of acetic acid by distillation under reduced pressure. The residue was extracted and crystallized from the solvent indicated in Table II.

Levulinic Acid 2-(4-Piperidyl)ethylhydrazone (22).—To 22.1 g (0.15 mole) of 2-(4-piperidyl)ethylhydrazine was added slowly while cooling in ice, 18.0 g (0.15 mole) of levulinic acid. The resulting solid was triturated with alcohol, filtered, and washed with ethanol and ether. The crude product was recrystallized by boiling in ethanol and adding water slowly to complete solution.

Acknowledgment.—We wish to thank Mr. Gordon Ginther and Mr. Marvin Tefft, of the Analytical Chemistry Section of The Norwich Pharmacal Company for the analytical results and Dr. Robert Buller and Dr. William Rockhold, formerly of the Pharmacology Section of The Norwich Pharmacal Company, for the biological testing results.

3-Aminopiperidones.[1a] II. 2-(N,N-Diethylamino)-2-phenylglutarimide[1b,c]

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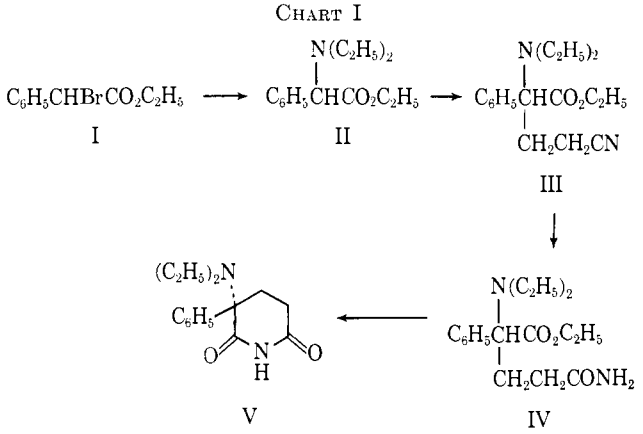
Of the very large number of compounds investigated[2] for antiepileptic activity relatively few carry polar substituents.[3] This fact, coupled with the success of aminoglutethimide, prompted the synthesis of the model compound, 2-(N,N-diethylamino)-2-phenylglutarimide. Steps to the final synthesis of this compound were accomplished after extensive studies of several possible routes. The difficulties experienced in attempts to synthesize certain intermediates along some of these routes and mechanistic studies of problems associated with them have been explored.[1a,4] The most successful route is presented herein.

Ethyl α-bromophenylacetate (I) was prepared by a modification of the procedure of Anschütz,[5] or using the thionyl chloride catalyzed method of Schwenk and Papa.[6] In the subsequent displacement reaction (I → II) using diethylamine as the nucleophile, some aminolysis of the ester (I) was anticipated since it is known that α-halo esters react at elevated temperature with amines to give both α- and β-aminoamides.[7] Since aminolysis reactions are equilibrium controlled, whereas displacement reactions are in general kinetically controlled, a short-time, high-temperature method was chosen (see Experimental Section).

The next step in the reaction sequence, the addition of a 3-carbon chain to ethyl α-N,N-diethylaminophenylacetate (II), proved to be difficult. Electronic and steric effects, operating at close proximity, decrease considerably the acidity of the α-hydrogen and interfere with the approach of the attacking nucleophile.

Efforts toward effecting a Michael condensation of the ester (II) with acrylamide, acrylonitrile, and methyl acrylate failed to achieve the desired addition, and so were attempted alkylations of II with halopropionitriles following several published procedures.[8] However, employing the general procedure recently developed by Zaugg, *et al.*,[9] it was possible to alkylate II with β-bromopropionitrile in fair yields. The treatment of III with polyphosphoric acid[10] gave a 91% yield of the amido ester (IV) (see Chart I). A clean product was obtained, in comparable yield, by heating the carbethoxynitrile in a 1:1 mixture of concentrated sulfuric and glacial acetic acids at steam-bath temperature for 30 min.

CHART I



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