amide (VIIb and h) was formed, solid product could be obtained by triturating the resulting syrup with acetone rather than with water.[27]

B. VIIIc and e.—An equimolar mixture of finely ground triaminopyrimidine (free base, *freshly* prepared from the corresponding 5-nitropyrimidine by Raney nickel reduction) and acetylmandelyl chloride was cautiously warmed on the steam bath. At *ca.* 90° a vigorous reaction occurred. After the reaction subdued the heterogeneous mixture was warmed for another 15 min. with constant stirring. The reaction mixture was then diluted with a large amount of acetone. The crude solid product was then filtered and purified.

8-(α-Hydroxybenzyl)purines (Va-i, Table I).—To a potassium ethoxide solution (prepared by dissolving 2.1 g. of K in 20 ml. of absolute ethanol) was added 5 g. of the amide. The mixture was warmed on a steam bath for 4 hr., poured into 250 ml. of water, and acidified with glacial acetic acid. The resulting precipitate was filtered and recrystallized.

6-Hydroxy-8-(α-hydroxybenzyl)purine (Vj).—To a solution of 200 ml. of water, 10 ml. of concentrated HCl and 10 ml. of 30% of H_2O_2 was added 4.5 g. of 6-methylthio-8-(α-hydroxybenzyl)purine (Vd). The mixture was refluxed for 20 min. and, without cooling, excess acid was carefully neutralized with dilute NaOH. After refrigeration overnight, 2.0 g. of white, analytically pure product was isolated from the reaction mixture (see Table I for additional data).

Preparation of Vj by the cyclization of 4-amino-5-acetylmandelamino-6-hydroxypyrimidine (VIIIj) in potassium ethoxide yielded a yellow solid which gave an additional ultraviolet absorption maximum at 380–390 mμ. Proper analysis for Vj was obtained (*Anal.* Calcd. for $C_{12}H_{10}N_4O_3$: C, 59.5; H, 4.17; N, 23.1. Found: C, 59.3; H, 3.78; N, 23.0.) after the crude product was repeatedly recrystallized from water and ethanol. However, the 380–390-mμ absorption was still present in the final product and paper chromatographic measurements of the recrystallized product still indicated the presence of a trace amount of a fluorescent substance. Work on the formation of this by-product, which is believed to be a pteridine, is not included in the present work.

6-Thio-8-(α-hydroxybenzyl)purine (Vk).—To a three-necked 500-ml. flask equipped with stirrer, Dry Ice cold finger, and drying tube was introduced 200–250 ml. of liquid ammonia followed by the addition of 5.0 g. of 6-benzylthio-8-(α-hydroxybenzyl)purine (Vi). To the light yellow solution was added portionwise, with stirring, 0.9 g. of sodium. After the addition was complete, the mixture was stirred for 30 min. Excess NH_3 was allowed to evaporate and the residue was dissolved in 60 ml. of water. This was then acidified with glacial acetic acid and the resulting yellow gum was recrystallized from a mixture of water and ethanol to yield 2.3 g. of a bright yellow solid (see Table I for additional data).

(27) In the case of the preparation of VIIIg, a mixture of mono- and bis(acetylmandelamino)pyrimidine[28] was formed. The monoacetyl derivative was difficult to purify. The bisacetyl derivative, after recrystallization from ethanol, gave the following information: m.p. 208–209°; λ_{max}^{pH1} 231 mμ (ε 23,000), 303 (14,700); λ_{max}^{pH11} 290 mμ (ε 10,400). *Anal.* Calcd. for $C_{35}H_{28}N_8O_8S \cdot 0.5H_2O$: C, 56.4; H, 4.88; N, 12.9. Found: C, 56.5; H, 5.11; N, 12.8. The crude intermediate, however, was readily cyclized to the desired compound Vg by normal procedure in a 60% over-all yield.

(28) Formation of bisacylamido)pyrimidines has also been reported by other investigators; *cf.* A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

Acknowledgment.—The authors wish to express their appreciation to Mr. Hal P. Van Fossen, Mrs. Margaret L. Rounds, and Mr. John R. Gravatt for the analytical and instrumental measurements. They are also indebted to Dr. John O. MacFarlane and Mr. R. D. Lamb for the antiviral evaluation.

Substituted 5,6-Dihydro-2-(2-, 3-, and 4-pyridyl)-4H-1,3,4-oxadiazines[1]

DONALD L. TREPANIER, PAUL E. KRIEGER, AND JOHN N. EBLE

Chemistry Research and Biomedical Departments, Pitman-Moore Division of The Dow Chemical Company, Indianapolis, Indiana

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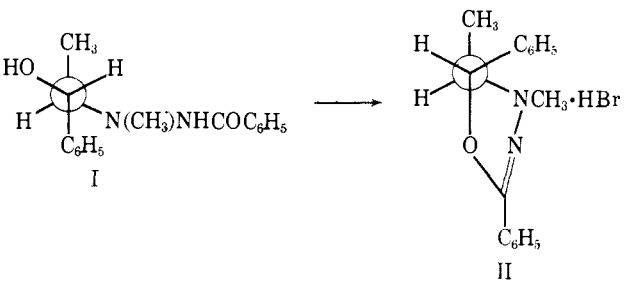
Various 2-(β-hydroxyalkyl)nicotinic, -isonicotinic, and -picolinic acid hydrazides were prepared by treating appropriate hydrazino alcohols with either the chloride, mixed anhydride, or anhydride of nicotinic, isonicotinic, and picolinic acids. Cyclodehydration of the 2-(β-hydroxyalkyl)nicotinic, isonicotinic, and picolinic acid hydrazides, containing either a primary, secondary, or tertiary hydroxyl group, to substituted 5,6-dihydro-2-(2-, 3-, and 4-pyridyl)-4H-1,3,4-oxadiazines was accomplished utilizing the four following methods: (1) concentrated H_2SO_4, (2) hydrogen bromide in acetic acid, (3) O-tosylation followed by solvolysis, and (4) replacement of OH by Cl followed by NaOH dehydrochlorination. All 2-(4-pyridyl)oxadiazines in this series antagonized the effects of tremorine in mice. The 2-(2- and 3-pyridyl) isomers were inactive in this test. It is suggested that the 2-(4-pyridyl)oxadiazines interfere with the metabolic conversion of tremorine since they did not antagonize its active metabolite oxotremorine.

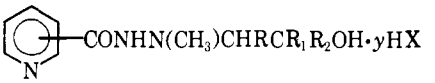
As part of a continuing exploratory research program in heterocyclic syntheses, we turned our attention to the substituted 5,6-dihydro-2-(2-, 3-, and 4-pyridyl)-4H-1,3,4-oxadiazines. Previously,[2] we had discovered that the acid-catalyzed dehydration of certain 2-(β-hydroxyalkyl)carboxylic acid hydrazides proceeds *via* neighboring-group participation with concomitant formation of a substituted 5,6-dihydro-4H-1,3,4-oxadiazine. For example, treatment of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazide (I) with gaseous hydrogen bromide in glacial acetic acid (HBr–AcOH) at ambient temperature gave *cis*-(−)-4,5-dimethyl-2,6-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine hydrobromide (II) in 87% yield.[2d]



(1) Presented in part before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965.

(2) (a) D. L. Trepanier, V. Spranemanis, and K. G. Wiggs, *J. Org. Chem.*, **29**, 668 (1964); (b) D. L. Trepanier and V. Spranemanis, *ibid.*, **29**, 673 (1964); (c) *ibid.*, **29**, 2151 (1964); (d) D. L. Trepanier, V. Spranemanis, D. S. Tharpe, and P. E. Krieger, *J. Heterocyclic Chem.*, in press.

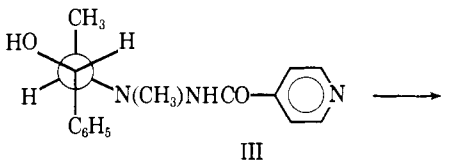
Table I
2-(β-Hydroxyalkyl)nicotinic, -isonicotinic, and -picolinic Acid Hydrazides



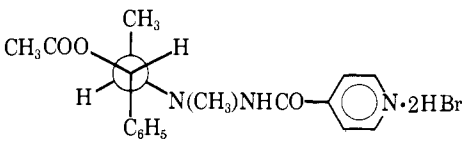
NC_5H_4 position	R	R_1	R_2	y	X	M.p., °C.[a]	Recrystn. solvent	Method[b]	Yield, %[c]	Calcd., % C	Calcd., % H	Calcd., % N	Found,[d] % C	Found,[d] % H	Found,[d] % N
4-	CH_3	H	C_6H_5	0		142–144	EtOAc	A	23	67.35	6.71		67.48	6.89	
3-[e]	CH_3	H	C_6H_5	0		119–122	EtOH	B	9	67.35	6.71	14.68	67.37	7.06	14.59
3-	H	H	C_6H_5	1	Br	206–207 dec.	MeOH-H_2O	A	13	51.14	5.15	22.68[f]	50.76	5.52	22.89
4-	H	H	CH_3	0		127.5–133	Acetone–ether	C	51	57.39	7.22	20.08	58.04	7.16	19.80
3-	H	H	CH_3	0		106–107.5	MeOH–ether	C	10	57.39	7.22	20.08	57.22	7.43	20.14
4-	H	CH_3	CH_3	0		89–91	Acetone–ether	C	75	59.17	7.67	18.82	59.47	8.01	18.76
3-	H	CH_3	CH_3	1	Br	102–104 dec.	MeOH–ether	C	52	43.43	5.96	26.27[f]	41.88	6.35	25.48
4-	H	H	C_6H_5	0		125–127	*i*-PrOH–ether	C	52	66.40	6.32	15.48	67.39	6.16	15.58
2-[e]	CH_3	H	C_6H_5	0		121–123	*i*-PrOH	B	38	67.35	6.71	14.73	67.54	6.01	14.67
4-	H	H	H	0		112–113.5 dec.	MeOH–ether	C	29	55.37	6.71	21.53	54.86	7.40	21.53
3-	H	H	H	0		109–112	MeOH–ether	C	40	55.37	6.71	21.53	55.41	6.83	20.85

[a] Thomas–Hoover capillary melting point apparatus; corrected. [b] For description of methods, see Experimental Section. [c] No effort was made to determine the conditions for optimum yield. [d] Midwest Microlab, Inc., Indianapolis, Ind. [e] *erythro*-(−) isomer. [f] Bromine.

In contrast, treatment of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)isonicotinic acid hydrazide (III) with HBr–AcOH at ambient temperature did not give the isosteric pyridyloxadiazine but rather produced in 46% yield, *erythro*-(−)-2-methyl-2-(α-methyl-β-acetoxy-β-phenethyl)isonicotinic acid hydrazide dihydrobromide (IV). This observation of the



III

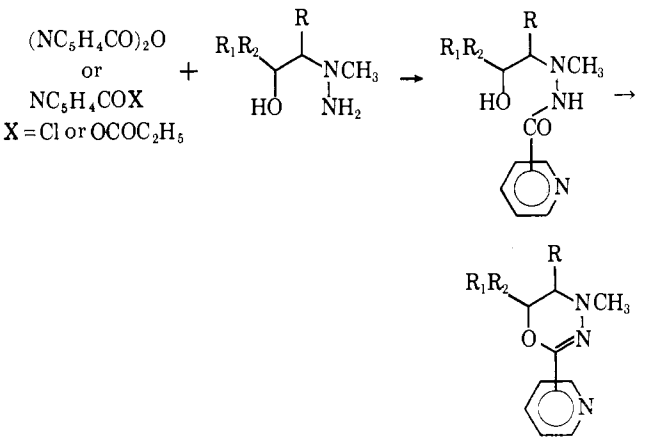


IV

influence exerted by the basic pyridyl nitrogen on the course of this reaction prompted us to prepare various 2-(β-hydroxyalkyl)carboxylic acid hydrazides having differing types of hydroxyl groups and differing types of nitrogen-containing acyl moieties, such as isonicotinoyl, nicotinoyl, and picolinoyl, and determine how they behaved when treated with various acidic dehydrating agents.

The 2-(β-hydroxyalkyl)nicotinic, -isonicotinic, and -picolinic acid hydrazides (Table I) were prepared by treating appropriate hydrazino alcohols with either the chloride, mixed anhydride, or anhydride of nicotinic, isonicotinic, and picolinic acids (Scheme I). Cyclization of the hydrazides in which the hydroxyl group is either primary, secondary, or tertiary, to give substituted 5,6-dihydro-2-(2-, 3-, and 4-pyridyl)-4H-1,3,4-oxadiazines was accomplished using the four following methods: (1) concentrated H_2SO_4, (2) HBr–AcOH, (3) O-tosylation followed by solvolysis, and (4) replacement of OH by Cl followed by base-catalyzed dehydrochlorination.

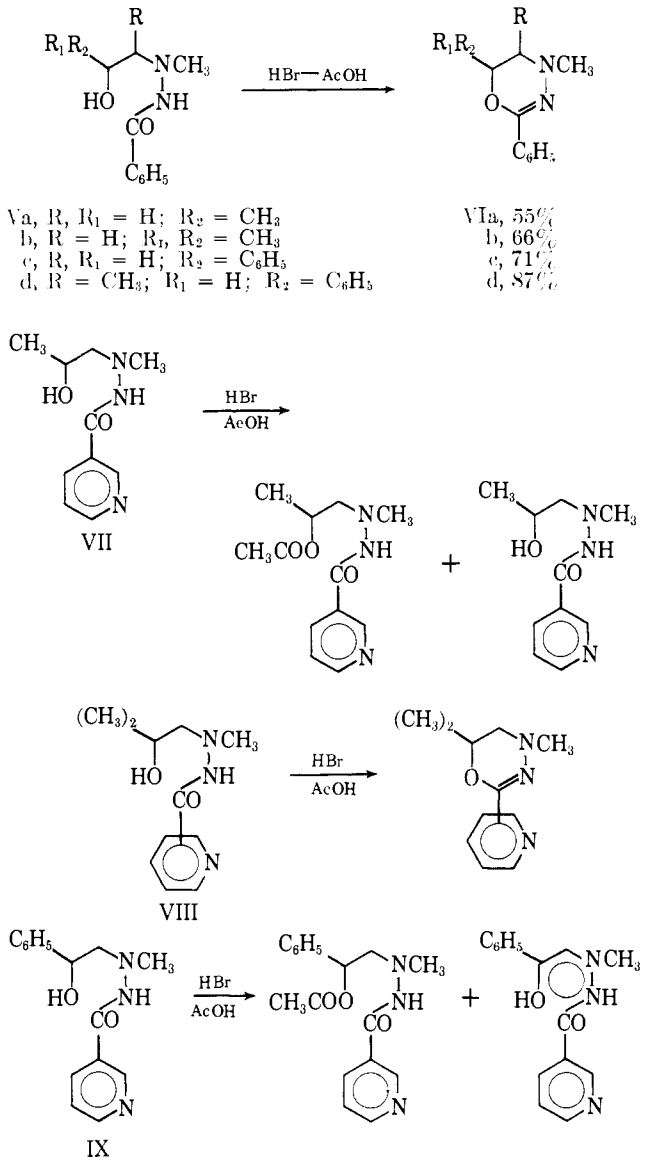
Scheme I



The choice of the method used for cyclization is dictated by the influence the hydroxyl group and the basic pyridyl nitrogen exert on the course of the reaction. For example, whereas 2-methyl-2-(β-hydroxypropyl), 2-methyl-2-(β-hydroxyisobutyl), 2-methyl-2-(β-hydroxy-β-phenethyl), and *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)benzoic acid hydrazides are all cyclodehydrated by HBr–AcOH into substituted 5,6-dihydro-4H-1,3,4-oxadiazines,[2d] the isosteric nicotinic and isonicotinic acid hydrazides do not all behave similarly (Scheme II).

The 2-methyl-2-(β-hydroxyisobutyl)nicotinic and isonicotinic acid hydrazides (VIII) were cyclodehydrated with HBr–AcOH into substituted 5,6-dihydro-4H-1,3,4-oxadiazines. However, treatment of 2-methyl-2-(β-

SCHEME II



hydroxyisopropyl)- and 2-methyl-2-(β-hydroxyphenethyl)nicotinic acid hydrazides (VII and IX) with HBr–AcOH gave mixtures composed mainly of unchanged hydroxy hydrazide and O-acetylated hydroxy hydrazide. Because we had found[2d] that 2-(β-hydroxyethyl)benzoic acid hydrazides could not be cyclodehydrated with HBr–AcOH, this method was not attempted with 2-(β-hydroxyethyl)nicotinic and -isonicotinic acid hydrazides. The 2-methyl-2-(β-hydroxyalkyl)niciotnic, -isonicotinic, and -picolinic acid hydrazides containing secondary benzylhydroxyl were all successfully cyclodehydrated with concentrated sulfuric acid at ambient temperature.

The 2-methyl-2-(β-hydroxyisopropyl)nicotinic and -isonicotinic acid hydrazides were successfully cyclodehydrated by converting them to O-tosyl derivatives, and then subjecting the O-tosylates to solvolyzing conditions, *i.e.*, refluxing water–acetone in the presence of sodium carbonate.

The 2-methyl-2-(β-hydroxyethyl)nicotinic and -isonicotinic acid hydrazides were converted to 2-(β-chloroethyl)nicotinic and -isonicotinic acid hydrazides with thionyl chloride, and the chlorides were cyclodehydrochlorinated with sodium hydroxide in ethanol–water at steam-bath temperature.

The foregoing data indicate that the strong electron-withdrawing effect of the protonated pyridyl nitrogen retards the rate of HBr–AcOH cyclodehydration to the extent that, with those 2-(β-hydroxyalkyl)nicotinic, -isonicotinic, and -picolinic acid hydrazides possessing either a secondary benzyl or a secondary aliphatic hydroxyl, a competing reaction, O-acetylation, predominates. This competing reaction is insignificant in the HBr–AcOH cyclodehydration of 2-methyl-2-(β-hydroxyisobutyl)nicotinic and -isonicotinic acid hydrazides. Retardation of HBr–AcOH cyclodehydration by the presence of a positive charge on pyridyl nitrogen is to be expected since our previous studies[2d] indicate that cyclodehydration in this medium proceeds *via* attack of hydroxylic oxygen upon polarized carbonyl carbon followed by loss of protonated carbonyl oxygen. The loss of carbonyl oxygen as hydroxide is more difficult with a strong electron-withdrawing substituent attached to the carbonyl carbon.

Concentrated H_2SO_4 cyclodehydration was not adversely affected by the presence of protonated pyridyl nitrogen as evidenced by the fact that the reaction proceeded as expected in all cases attempted. Since our previous studies[2d] showed that concentrated H_2SO_4 cyclodehydration proceeds by attack of carbonyl oxygen upon carbonium carbon resulting from dissociation of protonated hydroxyl, the presence of positive pyridyl nitrogen would not be expected to affect the rate-determining step (carbonium ion formation). The cyclization of nicotinic, isonicotinic, and picolinic hydroxyl hydrazides containing secondary aliphatic or primary hydroxyl was not attempted with concentrated H_2SO_4 because previously[2b] we had observed that concentrated H_2SO_4 treatment of 2-(β-hydroxyalkyl)benzoic acid hydrazides possessing either secondary or primary hydroxyl produced cleavage of the hydrazide linkage to give a quantitative yield of benzoic acid. Hydrogen bromide–acetic acid cyclization of those with primary hydroxyl was not attempted because previously[2d] we had observed that the treatment of 2-hydroxyalkylbenzoic acid hydrazides containing primary hydroxyl gave only O-acetyl derivatives. Instead, the hydroxyl group was converted to a better leaving group (chloride), and cyclization was effected under basic conditions.

Pharmacology. Hexobarbital Sleeping Times.—Adult male mice, in groups of 10, were injected intraperitoneally with the test compound 1 hr. before they were injected intraperitoneally with 100 mg./kg. of hexobarbital. The time in minutes between injection of the hexobarbital and the regain of the righting reflex was taken as the duration of sleeping times. The results are presented as a ratio with the sleeping times of a control group tested simultaneously.

Tremorine and Oxotremorine Tests.—Groups of 10 mice were given the test compounds intraperitoneally 1 hr. before a tremorine[3] or oxotremorine challenge (200 mg./kg.). Twenty minutes later they were observed for signs of salivation, defecation, lacrimation, piloerection, and distinctive tremor. The results are given as a ratio of the number of mice protected to the number challenged with tremorine or oxotremorine.

(3) G. M. Everett, *Nature*, **177**, 1238 (1956).

Maximal Electroshock Test.—Groups of 10 mice were given the test compounds intraperitoneally 1 hr. prior to being subjected to supramaximal electroshock delivered through corneal electrodes.[4] The results are expressed as a ratio of the number of mice protected from the tonic hind limb extensor phase of the seizure to the number shocked.

The results of these pharmacological tests are summarized in Table II. All but three of the compounds greatly prolonged hexobarbital sleep times. The three inactive compounds were 3-pyridyls which did not have either a methyl group in the 5-position or two methyl groups in the 6-position.

Compounds of the 4-pyridyl series antagonized the effects (tremor, salivation, defecation) of injecting tremorine in mice (standard anti-Parkinson screen); the 2- and 3-pyridyl isomers were inactive. Leslie and Maxwell[5] have suggested that the pharmacological actions of tremorine may be entirely due to the metabolically formed oxotremorine. So, antagonism to this substance by our active compounds was investigated and they were found to be inactive. We conclude then, that these compounds are inhibiting the oxidation of tremorine to oxotremorine rather than antagonizing the central actions of its metabolically formed oxo derivative. Compounds in this series which antagonized tremorine were found to be active also in the electroshock test.

Experimental Section

General Procedures for the Preparation of the Compounds Listed in Table I. Method A.—To a stirred mixture of 0.50 mole of α-(1-methylhydrazinomethyl)benzyl alcohol, 250 ml. of triethylamine, and 750 ml. of methylene chloride was added, over a 0.5-hr. period, a suspension of 0.55 mole of nicotinoyl chloride hydrochloride (prepared from nicotinic acid and thionyl chloride) in 350 ml. of methylene chloride. The mixture was stirred and refluxed for 3 hr., stirred for 16 hr., treated with 500 ml. of $CHCl_3$, and washed with water. The organic solution was evaporated *in vacuo*, and the residual oil was dissolved in methanol and treated with gaseous HBr. The hydrobromide was precipitated with ether, removed by suction filtration, and recrystallized from an appropriate solvent.

Method B.—To a stirred, cooled (5°) mixture of 0.50 mole of picolinic acid, 75 ml. of triethylamine, 150 ml. of benzene, and 200 ml. of chloroform was added dropwise, 0.5 mole of ethyl chloroformate. The reaction was stirred at 5° for 1 hr. To the stirred mixture was added a solution of 0.5 mole of N-amino-(−)-ephedrine in 200 ml. of $CHCl_3$. The mixture was stirred at ambient temperature overnight, washed with water, and evaporated *in vacuo*. The residue was crystallized with an appropriate solvent.

Method C.—To a stirred solution of 0.50 mole of 1-(1-methylhydrazino)-2-propanol in 200 ml. of methylene chloride there was added over a period of 2 hr., a solution of 0.50 mole of nicotinic acid anhydride (prepared from potassium nicotinoate and oxalyl chloride) in 500 ml. of methylene chloride. The mixture was stirred and refluxed for 1 hr., cooled, and filtered, and the filtrate was evaporated *in vacuo*. The residual oil was dissolved in 200 ml. of hot ethanol, treated with 200 ml. of 1 *N* NaOH, and refluxed for 1.5 hr. The cooled mixture was treated with Na_2SO_4 and thoroughly extracted with $CHCl_3$. The washed (water) and dried ($MgSO_4$) $CHCl_3$ solution was evaporated *in vacuo*, and the residue was crystallized with an appropriate solvent.

General Procedures for the Preparation of the Compounds Listed in Table II. Method A.—To a beaker containing 20 ml. of stirred concentrated H_2SO_4 was added, dropwise, a solution of 2.0 g. of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)isonicotinic acid hydrazide in 20 ml. of $CHCl_3$. The mixture was stirred and the $CHCl_3$ was evaporated with a stream of nitrogen. The mixture was allowed to stand at ambient temperature for 2 hr., poured onto crushed ice, and basified with Na_2CO_3. The basic mixture was extracted with methylene chloride. The methylene chloride extract was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residual oil was either crystallized with an appropriate solvent or converted to an acid addition salt by dissolving in dry ether and treating with either HCl, HBr, or maleic acid.

Method B.—To 100 ml. of stirred thionyl chloride was added, portionwise, 15 g. (0.08 mole) of 2-methyl-2-(β-hydroxyethyl)-nicotinic acid hydrazide. After the addition was completed, the mixture was stirred at 50° for 1 hr., cooled, and treated with ether until the precipitation of the hydrochloride was complete. The hydrochloride was removed by suction filtration, washed with dry ether, air dried, dissolved in 120 ml. of ethanol, treated with a solution of 7.0 g. of NaOH in 50 ml. of water, and heated on a steam bath for 2 hr. The mixture was concentrated by distillation *in vacuo*, treated with 100 ml. of water, and extracted thoroughly with $CHCl_3$. The $CHCl_3$ extract was washed (water), dried (Na_2SO_4), and evaporated *in vacuo*. The residual oil either solidified and was recrystallized from an appropriate solvent or was chromatographed on alumina and converted to the hydrochloride.

Method C.—A mixture of 10 g. (0.05 mole) of 2-methyl-2-(β-hydroxypropyl)isonicotinic acid hyrazide, 10 g. (0.05 mole) of *p*-toluenesulfonyl chloride, and 100 ml. of dry pyridine was kept at 4° for 20 hr., poured onto crushed ice, extracted with $CHCl_3$, and then the $CHCl_3$ extract was washed (Na_2CO_3 solution and water) and evaporated *in vacuo*. The residue was dissolved in 100 ml. of acetone, treated with 100 ml. of water and 20 g. of K_2CO_3, heated on a steam bath for 1.5 hr., and allowed to stand at ambient temperature overnight. The solid was removed by suction filtration, and the filtrate was extracted thoroughly with $CHCl_3$. The washed (water) and dried (Na_2SO_4) $CHCl_3$ extract was chromatographed on alumina, and the oil obtained upon evaporation of the eluent was converted to the hydrochloride.

Method D.—2-Methyl-2-(β-hydroxyisobutyl)nicotinic acid hydrazide (10.0 g.) dissolved in 250 ml. of glacial acetic acid was treated with gaseous HBr until the solution was saturated. After standing at ambient temperature for 5 hr., the mixture was evaporated *in vacuo*. The residue was either recrystallized with an appropriate solvent or it was basified and extracted with ether, and the hydrochloride was obtained by treating the ether extract with gaseous HCl.

Attempted HBr–AcOH Cyclodehydration of *erythro*-(—)-2-Methyl-2-(α-methyl-β-hydroxy-β-phenethyl)isonicotinic Acid Hydrazide.—A solution of 15.3 g. of *erythro*-(−)-2-methyl-2-(α-methyl-β-hydroxy-β-phenethyl)isonicotinic acid hydrazide in 300 ml. of glacial acetic acid was saturated with gaseous HBr. After standing at ambient temperature for 1 hr., the mixture was evaporated *in vacuo* and the semisolid, glassy mass crystallized by triturating it with methanol–ether. Recrystallization from methanol–isopropyl ether gave 12.1 g. (46%) of *erythro*-(—)-**2-methyl-2-(α-methyl-β-acetoxy-β-phenethyl)isonicotinic acid hydrazide dihydrobromide**, m.p. 177–178° dec.

Anal. Calcd. for $C_{18}H_{21}N_3O_3 \cdot 2HBr$: C, 44.19; H, 4.74; Br, 32.67. Found: C, 43.86; H, 4.89; Br, 31.80.

Attempted HBr–AcOH Cyclodehydration of 2-Methyl-2-(β-hydroxyisopropyl)nicotinic Acid Hydrazide.—A solution of 2.0 g. of 2-methyl-2-(β-hydroxyisopropyl)nicotinic acid hydrazide in 100 ml. of glacial acetic acid was saturated with gaseous HBr. After standing at ambient temperature for 3 hr., the mixture was evaporated *in vacuo*. The residual oil was dissolved in a minimum of methanol, basified with 5% aqueous Na_2CO_3, and extracted with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ extract was evaporated *in vacuo* leaving an oil (1.8 g.) which by infrared analysis was shown to be a mixture composed mainly of 2-methyl-2-(β-hydroxyisopropyl)nicotinic acid hydrazide and 2-methyl-2-(β-acetoxyisopropyl)nicotinic acid hydrazide; ν_{max} (film) 3300–3200 broad (OH, NH), 1723 (ester carbonyl), and 1668 (hydrazide carbonyl) cm.$^{-1}$.

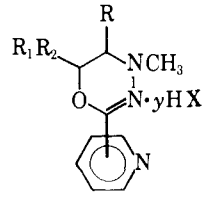
Attempted HBr–AcOH Cyclodehydration of 2-Methyl-2-(β-hydroxyphenethyl)nicotinic Acid Hydrazide.—A solution of 2.0 g. of 2-methyl-2-(β-hydroxyphenethyl)nicotinic acid hydrazide dihydrobromide in 50 ml. of glacial acetic acid was saturated

(4) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Expll. Therap.*, **106**, 319 (1952).

(5) G. B. Leslie and D. R. Maxwell, *Nature*, **202**, 97 (1964).

TABLE II

PYRIDYLOXADIAZINES



NC_5H_4 position	R	R_1	R_2	y	HX	M.p., °C.[a]	Yield, %[b]	Recrystn. solvent	Method[c]	Calcd., % C	Calcd., % H	Calcd., % N	Found,[d] % C	Found,[d] % H	Found,[d] % N	Dose[e]	Hexobarbitol sleep time test[e]	Tremorine test[e]	Max. electric shock test[e]
3-[f]	CH_3	H	C_6H_5	0	...	95–96	64	Hexane	A	71.88	6.41	...	71.91	6.48	...	100	150/32	2/10	0/10
																100		3/10	
4-[g]	CH_3	H	C_6H_5	1	HCl	239–241 dec.	23	*i*-PrOH	A	63.26	5.97	13.83	63.39	5.99	13.26	100	182/32	9/10	6/10
																100		10/10	
3-	H	H	H	2	HCl	189–190 dec.	23	*i*-PrOH–MeOH	B	43.22	5.24	16.80	43.33	5.18	17.07	50	67/36	0/10	0/10
																100	44/30	0/10	
4-	H	H	H	0	...	80–81	30	Ligroin (30–60°)	B	61.00	6.26	23.71	60.97	6.51	23.46	50	165/36	4/9	3/10
																100		5/10	
																100	245/30	1/10	
3-	H	H	CH_3	2	HCl	197–199 dec.	5.4	MeOH–acetone	C	45.47	5.72	15.91	45.04	6.00	16.00	50	60/36	0/9	0/10
4-	H	H	CH_3	1	HCl	228–229 dec.	7.0	*i*-PrOH–ether	C	52.75	6.20	18.46	53.09	6.21	18.61	50	127/36	4/10	5/9
																100		10/10	
3-	H	CH_3	CH_3	2	HBr	208–209 dec.	24	*i*-PrOH–EtOH	D	35.99	4.67	43.54[h]	35.97	4.86	42.99	50	168/36	1/10	0/10
																100	277/30	0/7	
4-	H	CH_3	CH_3	1	HCl	228–230	87	*i*-PrOH	D	54.65	6.67	17.38	54.31	6.86	17.63	25	215/36	3/10	
																50	220/36	4/10	
																100	295/30	1/10	5/10
																100		3/10	
4-	H	H	C_6H_5	1	(=CHCOOH)$_2$	109–111 dec.	33	*i*-PrOH	A	61.78	5.18	11.38	61.54	5.33	11.16	50	186/36	5/10	3/10
																100		7/10	
2-[i]	CH_3	H	C_6H_5	0	...	182–184	79	*i*-PrOH	A	71.88	6.41	15.72	71.59	6.79	15.32	100	165/32	4/10	0/10
																100		0/10	
																100	130/30	0/10	
																200			9/10
3-	H	H	C_6H_5	1	(=CHCOOH)$_2$	121–123 dec.	41	MeOH–ether	A	61.78	5.18	11.38	61.97	5.46	11.12	100	65/32	2/10	2/10
4-[j]	CH_3	H	C_6H_5	1	HCl	240–242 dec.	37	*i*-PrOH	A	63.26	5.97	13.83	63.22	6.13	13.44	100	170/32	8/10	5/10
																100		7/10	
																50		4/10	

[a] Thomas–Hoover capillary melting point apparatus; corrected. [b] No effort was made to determine the conditions for optimum yield. [c] For description of methods, see Experimental Section. [d] Midwest Microlab, Inc., Indianapolis, Ind. [e] See Pharmacology. [f] *trans*-(+) isomer, $[\alpha]_D$ +112.9° (*c* 4.02, $CHCl_3$), $J_{H_5\text{-}H_6}$ (20% $CDCl_3$) = 7.2 c.p.s.; prior to purification the material which melted at 93–95.5° was shown by n.m.r. to contain ~23% of the *cis* isomer, $J_{H_5\ H_6}$ (20% $CDCl_3$) = 2.9 c.p.s. [g] *trans*-(−) isomer, $J_{H_5\ H_6}$ (20% $CDCl_3$) = 6.1 c.p.s., $[\alpha]_D$ −202.4° (*c* 4.01, water). [h] Bromine. [i] *trans*-(+) isomer, $J_{H_5\ H_6}$ (20% $CDCl_3$) = 6.5 c.p.s., $[\alpha]_D$ +195.5° (*c* 4.02, $CHCl_3$). [j] *trans*-(+) isomer, $J_{H_5\ H_6}$ (20% $CDCl_3$) = 6.1 c.p.s., $[\alpha]_D$ +204.0° (*c* 4.00, water).

with gaseous HBr and allowed to stand at ambient temperature for 18 hr. The mixture was evaporated *in vacuo*. The residual oil was dissolved in a minimum of methanol, basified with 5% aqueous Na_2CO_3, and extracted with $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ extract was evaporated *in vacuo* leaving an oil (1.1 g.) which by infrared analysis was shown to be a mixture composed mainly of 2-methyl-2-(β-hydroxyphenethyl)nicotinic acid hydrazide and 2-methyl-2-(β-acetoxyphenethyl)nicotinic acid hydrazide; ν_{max} (film) 3390–3180 broad (OH, NH), 1726 (ester carbonyl), and 1695 (hydrazide carbonyl) cm.$^{-1}$.

New Sedative and Hypotensive 3-Substituted 2,4(1H,3H)-Quinazolinediones

SHIN HAYAO, HERBERT J. HAVERA, WALLACE G. STRYCKER, T. J. LEIPZIG, RICHARD A. KULP, AND HAROLD E. HARTZLER

Chemical Therapeutics Research Laboratory, Miles Laboratories, Inc., Elkhart, Indiana

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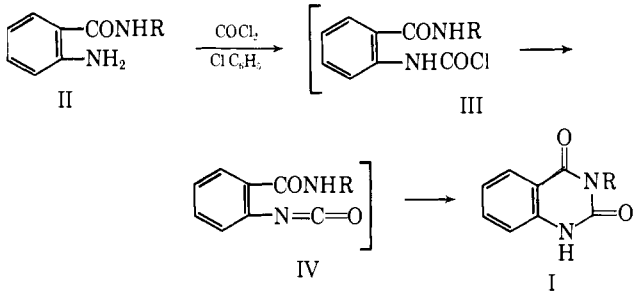
A series of 3-substituted 2,4(1H,3H)-quinazolinediones, mostly 3-(4-aryl-1-piperazinylalkyl)-2,4(1H,3H)-quinazolinediones, was prepared from the corresponding *o*-amino-N-substituted benzamides by treatment with phosgene in boiling chlorobenzene. 1-Methyl-3-substituted 2,4(1H,3H)-quinazolinediones were prepared by the reaction of *o*-methylamino-N-substituted benzamides with ethyl chloroformate, followed by heating at 200° to cyclize. These compounds showed varying degrees of sedative and hypotensive activity in experimental animals.

It has been reported that 2,4(1H,3H)-quinazolinedione[1,2] and 1,3-dimethyl-2,4(1H,3H)-quinazolinedione[1,2] possess anticonvulsant[3] activity against electroshock and pentylenetetrazol seizures in mice. 3-Alkyl-, 3-aralkyl-, and 3-aryl-2,4(1H,3H)-quinazolinediones[4] have been described but no pharmacological screening results were given. Our finding that some amides derived from 4-aryl-1-piperazinylalkylamines,[5] 4-aryl-1-piperazinylalkanoic acids,[5] and N-(4-aryl-1-piperazinylalkyl) derivatives of cyclic imides[6] have shown sedative and hypotensive activities led us to prepare 3-substituted [mostly 3-(4-aryl-1-piperazinylalkyl)-2,4(1H,3H)-] quinazolinediones (I).

The reaction of primary amines with isatoic anhydride gives mainly *o*-aminobenzamides[7] with minor quantities of 1-alkyl-3-(*o*-carboxyphenyl)ureas.[4b] The latter compounds are readily cyclized with dilute mineral acid to give I. In our hands, *o*-amino-N-alkyl- (or aralkyl-) benzamides (II) cyclized readily with phosgene in boiling chlorobenzene to give I in high yield.

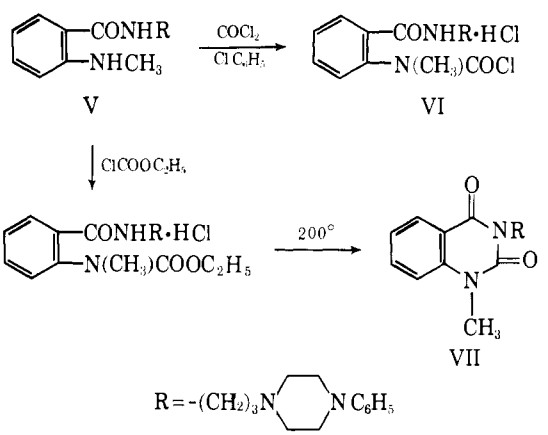
SCHEME I



I was also prepared by treating II with ethyl chloroformate, followed by heating at 200° to cyclize.

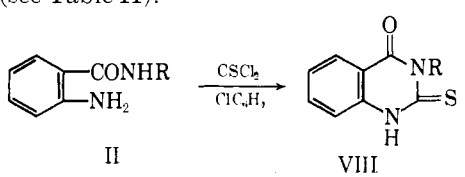
The formation of the quinazolinedione (I) (Scheme I) by treatment of *o*-amino-N-[3-(4-phenyl-1-piperazinyl)-propyl]benzamide (II) with phosgene at the boiling point of chlorobenzene was presumed to proceed through the intermediate isocyanate (IV) formed by dehydrochlorination of the carbamoyl chloride (III). Under the same conditions, *o*-methylamino-N-[3-(4-phenyl-1-piperazinyl)propyl]benzamide (V) gave the carbamoyl chloride (VI) in high yield (Scheme II).

SCHEME II



The dehydrochlorination of VI to give isocyanate is not possible in the latter case. 1-Methyl-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolinedione(VII) was obtained by treating V with ethyl chloroformate, followed by heating at 200°. See Table I for compounds I and VII.

2-Thio-2,4(1H,3H)-quinazolinediones (VIII) were prepared by adding II to a solution of thiophosgene in chlorobenzene, followed by heating under reflux to cyclize (see Table II).



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