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Compounds Related to 4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide. Their Synthesis and Antiarrhythmic Activity

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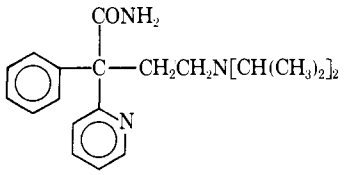
Modification of the carboxamide group of 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide (1, a new antiarrhythmic agent) resulted in compounds which possess considerable antiarrhythmic activity.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide (1, disopyramide) is a potent antiarrhythmic agent first described by Mokler and Van Arman[1] and subsequently shown by Katz[2] and Dreifus[3] to be a clinically useful alternative to quinidine. The tetrazole and oxadiazole analogs of 1 have been reported by Adelstein.[4] This report describes the synthesis and antiarrhythmic activity of the corresponding hydrazides, monosubstituted amides, their thio analogs, and some related compounds.



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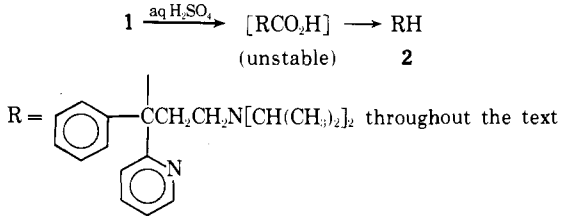
Chemistry. At first we tried to prepare the hydrazide and the thioamide corresponding to 1. Reaction of the ethyl ester **7b** with hydrazine under a variety of conditions failed to yield the hydrazide. Likewise, attempts to prepare the thioamide from 1 yielded, in order of increasing severity of conditions and reagents, starting material, dehydration to the corresponding nitrile, cyclization to various substituted pyrrolidones or cleavage to **2**; the nitrile behaved similarly.† We concluded that steric hindrance prevented the usual conversions and we sought different routes for preparing these compounds. From this search many other analogs were also obtained.

The key intermediate **2** was most conveniently prepared by the hydrolysis and decarboxylation of 1 (eq 1).

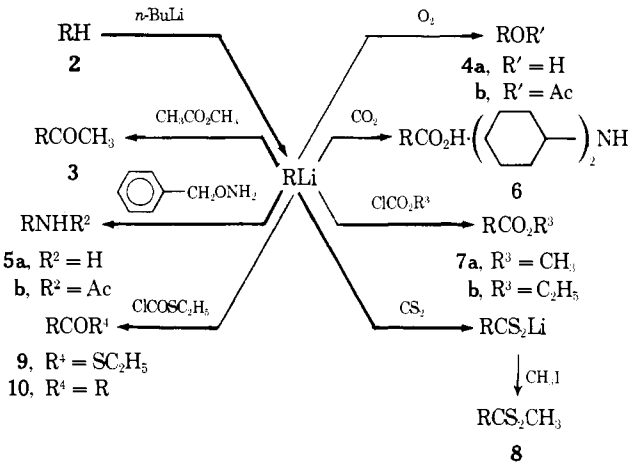


(1)

†H. S. Lowrie, Searle Laboratories, unpublished work.

Erhart and coworkers have reacted sodium or phenylsodium with 3-phenyl-3-(2-pyridyl)propylamines (compounds homologous to **2**) to obtain the corresponding Na salts from which esters and ketones homologous to **7a,b** and **3** have been prepared.[5] In our work **2** was lithiated with *n*-BuLi in a hexane–ether solution. Treatment of the Li salt of **2** with methyl acetate, oxygen,[6] benzyloxyamine,[7] carbon dioxide, and alkyl chloroformates afforded, respectively, **3**, **4a**, **5a**, **6**, and **7a,b**. Reaction of lithiated **2** with carbon disulfide furnished the lithium salt of a dithio acid that with methyl iodide afforded **8**. Addition of lithiated **2** to ethyl chlorothiolformate in ether at −70° afforded **9**, but inverse addition at −4 to −2° afforded the dimer **10** (Scheme I and Table I).

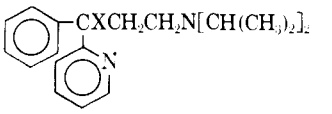
Scheme I



The thio hydrazide **11** was prepared by heating **8** with hydrazine in THF (method A, Scheme II) while the hydrazide **12a** was obtained by refluxing methyl ester **7a** with 85% hydrazine hydrate in methanol (method B, Scheme II). Two derivatives of **12a** were prepared: *N*-acetyl derivative **12b** and hydrazone **12c** (Table II).

Unfortunately, substituted hydrazides could not be prepared by heating methyl ester **7a** with substituted hydrazine, probably due to steric hindrance. Yang has reported

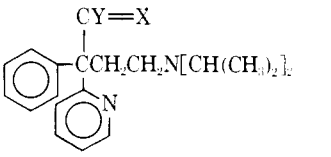
Table I



Compd	X	Crystn solvent[a]	Yield, %	Mp or bp (mm), °C	Formula	Analyses
2	H		39	124–127 (0.2)	$C_{20}H_{28}N_2$	C, H, N
3	$COCH_3$		27	90–102 (0.03)	$C_{22}H_{30}N_2O$	C, H, N
4a	OH	L	52[b]	86–88	$C_{20}H_{28}N_2O$	C, H, N, O
4b	OAc		11	156–160 (0.1)	$C_{22}H_{30}N_2O_2$	C, H, N
5a	NH_2		12	160–168 (0.2)	$C_{20}H_{29}N_3$	H, N; C[c]
5b	NHAc	M	80	104–106	$C_{22}H_{31}N_3O$	C, H, N
6	CO_2H	N	24	90–91.5	$C_{21}H_{28}N_2O_2$·$(c\text{-}C_6H_{11})_2NH$	C, H, N, O
7a	CO_2CH_3		77	141–158 (0.6)	$C_{22}H_{30}N_2O_2$	C, H, N
7b	$CO_2C_2H_5$		74	156–158 (0.2)	$C_{23}H_{32}N_2O_2$	N
8	CS_2CH_3		71[b]			
9	$COSC_2H_5$		75[b]	185–195 (0.5)		
10	$C(C_6H_5)(C_5H_4N\text{-}2)COCH_2CH_2N(i\text{-}Pr)_2$	O	50	146–147.5	$C_{41}H_{54}N_4O$	H, N; C[d]

[a] L, C_2H_5OH–H_2O; M, ether–Skellysolve B; N, CH_2Cl_2–*n*-pentane; O, CH_2Cl_2–Skellysolve B. [b] Yield of crude product. [c] C: calcd, 77.12; found, 77.65. [d] C: calcd, 79.57; found, 79.13.

Table II. Hydrazides



Compd	X	Y	Crystn solvent[a]	Yield, %	Mp or bp (mm), °C	Method	Formula	Analyses
11	S	$NHNH_2$	P	35[b]	87–90	A	$C_{21}H_{30}N_4S$	C, H, N, S
12a	O	$NHNH_2$	P	47	66–68	B	$C_{21}H_{30}N_4O$	C, H, N
12b	O	$NHNHCOCH_3$	P	54	117–119		$C_{23}H_{32}N_4O_2$	C, H, N
12c	O	$NHN{=}C(CH_3)_2$	P	72	104.5–106.5		$C_{24}H_{34}N_4O$	C, H, N
13	O	$NHNHCH_3$		70	176–180 (0.2)	C	$C_{22}H_{32}N_4O$	C, H, N
14	O	$NHN(CH_3)_2$	Q	44	70–75	C	$C_{23}H_{34}N_4O$·$(CO_2H)_2$·CH_3OH	C, H, N
15	O	$N(CH_3)N(CH_3)_2$		19	175–205 (0.1)	D	$C_{24}H_{36}N_4O$	C, H, N

[a] P, ether–*n*-pentane; Q, CH_3OH–ether. [b] Yield of crude product.

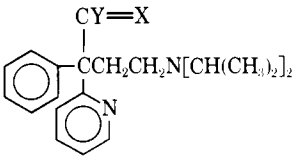
successful aminolysis of hindered esters with the lithium derivative of amines[8] and this method was extended to the hydrazinolysis of the methyl ester **7a** to yield the alkylated hydrazides **13** and **14** (method C, Scheme II). However, the trimethyl hydrazide **15** was prepared from phenylacetyl chloride by the two-step sequence of method D, Scheme II. These hydrazides are listed in Table II.

Yang's method of aminolysis was also applied to prepare several *N*-alkyl and *N*-aryl derivatives (**17**–**20**) of **1** (method C, Scheme II). However, the *N*-methylamide **16** was prepared by heating the thiol ester **9** with methylamine in 2-propanol, indicating that **9** is a useful active ester (method E, Scheme II). The *N*-methylolamide **21** was prepared by refluxing **1** with formaldehyde in aqueous ethanol (method F, Scheme II).

The thioamide **22** was prepared by heating the dithio ester **8** with ammonia in THF at 60° (method G, Scheme II), but at 100° the corresponding nitrile was the only product. The monosubstituted amides and thioamide are listed in Table III.

Biology. Multifocal ventricular tachycardia was induced in anesthetized dogs with intravenous injections of ouabain as described by Lucchesi;[9] this method minimizes mortality from ouabain overdosage. Compounds were given intravenously at ≲20 mg/kg and rated active if normal sinus rhythm supervened for at least 15 min in at least half of the dogs. Active compounds were then tested in dogs subjected to a two-stage ligation of the anterior descending coronary artery.[10] On the first postoperative day these dogs exhibited arrhythmias analogous to those observed in man following acute myocardial infarction. Compounds given intravenously at ≲20 mg/kg were rated

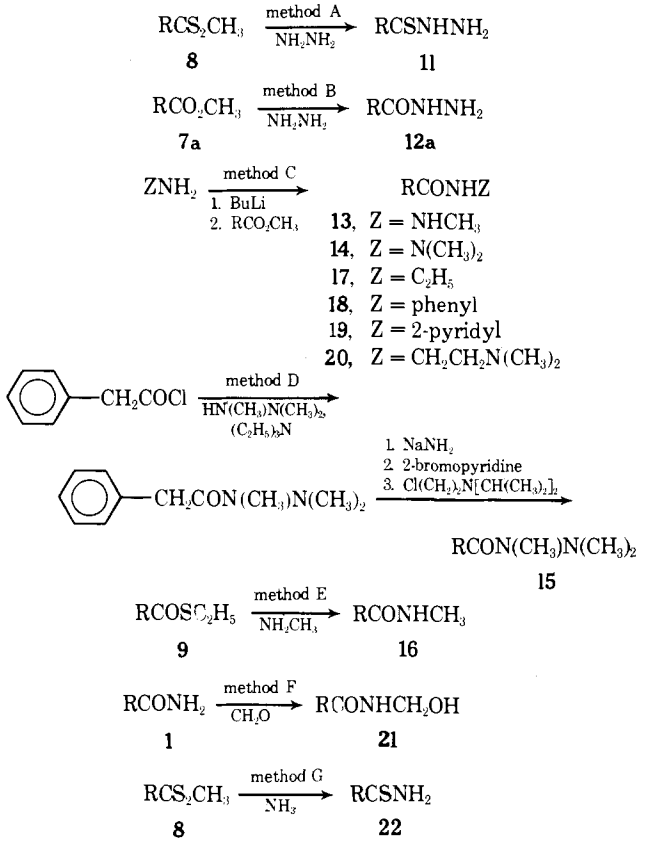
Table III. Amides



Compd	X	Y	Crystn solvent[b]	Yield, %	Mp or bp (mm), °C	Method	Formula	Analyses
16	O	$NHCH_3$	R	67	88–90	E	$C_{22}H_{31}N_3O$	C, H, N
17	O	NHC_2H_5	P	63	89.5–92	C	$C_{23}H_{33}N_3O$	C, H, N
18[a]	O	NHC_6H_5	S	29	184–186 dec	C	$C_{27}H_{33}N_3O \cdot H_3PO_4 \cdot 0.5H_2O$	C, H, N
19[a]	O	$NH\text{-}2\text{-}C_5H_4N$	Q	37	200.5–202 dec	C	$C_{26}H_{32}N_4O \cdot H_3PO_4$	C, H, N
20[a]	O	$NH(CH_2)_2N(CH_3)_2$		73	174–180 (0.1)	C	$C_{25}H_{38}N_4O$	C, H, N
21	O	$NHCH_2OH$	P	39	94–96	G	$C_{22}H_{31}N_3O_2$	C, H, N, O
22	S	NH_2	O	57[c]	113–115	H	$C_{21}H_{29}N_3S$	C, H, N, S

[a] Ether was used as solvent. [b] See footnotes *a*, Tables I and II; R, *n*-pentane; S, C_2H_5OH. [c] Crude yield.

Scheme II



active if the ectopic ventricular rate was reduced by ≥25% in more than half of the dogs.

Analysis of antiarrhythmic activity should consider six factors.[11] We have combined three of these by calculating an "activity ratio" (AR) which normalizes test-to-test variation and provides a single numerical index for comparing antiarrhythmic potency. The formula for this ratio is

$$AR = \sum_{i=1}^{n} (\text{Red. ER} \times \text{THR})_i / 5 \sum_{i=1}^{n} ED_i$$

where n = number of dogs, Red. ER = maximal reduction of extrasystolic rate/pretreatment extrasystolic rate, THR = pretreatment total heart rate, and ED = minimum effective dose of compound. Table IV summarizes the biological results.

Table IV. Antiarrhythmic Activities

Compd	Ouabain MED (n)[a]	Coronary artery ligation		
		Duration[b]	AR[c]	Acute toxicity
18	5 (2)	25	7.2	Lethal
10	5 (1)	<10	6.0	Lethal
15	5 (1)	>27	4.8	Toxic[d]
4a	10 (1)	60	4.7	Toxic[d]
1·H_3PO_4	6.6 (3)	35	4.1	None
17	12.5 (1)	22	3.6	Slightly toxic[e]
22	15 (1)	20	3.2	Lethal
13	5 (1)	51	3.0	Toxic[d]
7b	10 (1)	18	2.9	None
12b	15 (1)	32	2.8	None
3	10 (2)	17	2.4	Toxic[d]
16	10 (1)	<10	2.4	Toxic[d]
12a	10 (1)	>21	2.3	Slightly toxic[e]
5b	15 (1)	12	2.1	Slightly toxic[e]
11	15 (1)	15	2.1	Toxic[d]
12c	15 (1)	10	2.0	None
14	10 (1)	<10	1.8	None
7a	5 (1)	<10	1.4	Lethal
21	12.5 (1)	<10	1.0	None

[a] Average minimum effective dose (number of dogs). [b] Minutes. [c] Activity ratio. See text. [d] Toxicity is defined as the appearance of one or more of the following symptoms in a moderate or severe degree: emesis, convulsion, labored breathing, head wobbling, and muscle tremor. [e] A compound is considered slightly toxic when the symptoms listed in footnote *d* are weak.

Discussion

Crude compounds **5a**, 8, and **9** were not tested. The other compounds are active against the ouabain-induced ventricular arrhythmia except **2**, **4b**, 6, 19, and **20**. These compounds are also active against the coronary artery ligation-induced ventricular arrhythmia and are arranged in Table IV in decreasing order of AR. Compounds **18**, **10**, **15**, **4a**, and **17** show potency equal to or greater than disopyramide phosphate (Norpace) but have varying degrees of acute toxicity. Compounds **7b**, **12b**, and **12c** are free of acute toxicity but are less potent. Duration of activity less than 10 min is considered to be too short to be useful:

compounds **10**, **16**, **14**, **7a**, and **21**. We conclude that modification of the carboxamide group of disopyramide failed to produce a clearly superior compound in terms of potency, acute toxicity, and duration of action.[4] There is a relationship between the AR's of the carbonyl-containing compounds (except **10**) in Table IV and certain physicochemical parameters. This has been reported.[12]

Experimental Section‡

3-Diisopropylamino-1-phenyl-1-(2-pyridyl)propane (2). A solution of **1** (354 g) and concentrated H_2SO_4 (250 ml) in water (2 l.) was refluxed for 18 hr. After cooling the solution was made alkaline with excess powdered K_2CO_3. The liberated oil was extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residual oil was stirred in *n*-pentane and after cooling to −10° the solid was filtered off to afford 173 g of unreacted **1**. The filtrate was evaporated and the residue was distilled to give 120 g (39%) of **2** as a light yellow oil: bp 124–127° (0.2 mm). *Anal.* ($C_{20}H_{28}N_2$) C, H, N.

General Procedure for Preparing Lithiated 2. A solution of *n*-BuLi (10–20% excess) in hexane was added dropwise to a stirred solution of **2** in dry ether in an ice–water bath under N_2. The deep red solution was stirred at ≤25° for about 1 hr.

5-Diisopropylamino-3-phenyl-3-(2-pyridyl)-2-pentanone (3). To a stirred solution of lithiated **2** (0.1 mol) in ether (300 ml) was added dropwise a solution of methyl acetate (60.0 g, 0.81 mol) in dry ether (60 ml) at −5 to 0° under N_2. The brown mixture was stirred for 0.5 hr, allowed to stand overnight at room temperature, washed with water, and extracted with dilute HCl. The acidic extract was made alkaline with dilute NaOH and the liberated oil extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residual oil was distilled through a spinning-band column§ affording 9.3 g (27%) of viscous purple oil: bp 90–102° (0.03 mm). *Anal.* ($C_{22}H_{30}N_2O$) C, H, N.

The oxime of **3** (from CH_2Cl_2–*n*-pentane) melted at 129–132°. *Anal.* ($C_{22}H_{31}N_3O$) C, H, N.

3-Diisopropylamino-1-phenyl-1-(2-pyridyl)propanol (4a). Dry oxygen gas was passed through a stirred solution of lithiated **2** (0.28 mol) in dry ether (1 l.) at −10 to −5° until the red color discharged. After warming to >0°, the mixture was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residual brown oil was crystallized from ethanol–water affording 45.3 g (52%) of white crystals, mp 82–86°, that on recrystallization melted at 86–88°. *Anal.* ($C_{20}H_{28}N_2O$) C, H, N, O.

3-Diisopropylamino-1-phenyl-1-(2-pyridyl)propyl Acetate (4b). *n*-BuLi in hexane (0.035 mol) was added dropwise to a stirred solution of **4a** (10.0 g, 0.032 mol) in dry ether (150 ml) under N_2. After stirring for 25 min a solution of acetic anhydride (6.0 ml, 0.064 mol) in dry ether (80 ml) was added dropwise at 15–20°. After stirring for 1.5 hr, the mixture was worked up conventionally. The oil obtained, a mixture of the alcohol **4a** and the acetate **4b**, was chromatographed on silica gel and the desired fraction was distilled affording 1.2 g (11%) of **4b** as a yellow oil: bp 156–160° (0.1 mm), which crystallized on standing, mp 44–47°. *Anal.* ($C_{22}H_{30}N_2O_2$) C, H, N.

3-Diisopropylamino-1-phenyl-1-(2-pyridyl)propylamine (5a). A solution of benzyloxyamine (2.5 g, 0.02 mol) in dry ether (20 ml) was added to a stirred solution of lithiated **2** (0.05 mol) in ether (100 ml) under N_2 during 13 min at −70°. After removing the cooling bath, the red solution was stirred for 0.5 hr, allowed to stand overnight, and worked up conventionally. The oil obtained was chromatographed on silica gel and the desired fraction was distilled to afford 1.8 g (12%) of **5a** as a colorless oil: bp 160–168° (0.2 mm). *Anal.* ($C_{20}H_{29}N_3$) H, N; C: calcd, 77.12; found, 77.65. Tlc on silica gel (benzene–ethanol–concentrated ammonia, 35:14:1) of this oil showed the presence of a small amount of **2**.

In another run starting with 104 g (0.35 mol) of **2**, the oil was distilled without chromatography to give 94.8 g of oil containing 23% of **5a** and 77% of **2** by glc. This mixture was used to prepare **5b**.

***N*-Acetyl-3-diisopropylamino-1-phenyl-1-(2-pyridyl)propylamine (5b).** A solution of 30 g of crude **5a** (23% pure) and 140 ml of acetic anhydride in 500 ml of dry ether was allowed to stand for 3 days. Conventional work-up afforded 7.2 g (92%) of white crystals (from ether–*n*-pentane), mp 100–104°, which on recrystallization from ether–Skellysolve B gave 5.7 g (80%) of white prisms: mp 104–106°. *Anal.* ($C_{22}H_{31}N_3O$) C, H, N.

Dicyclohexylammonium 4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyrate (6). Carbon dioxide gas was passed through a stirred solution of lithiated **2** (0.1 mol) in dry ether (400 ml) until the red color discharged. The resultant cloudy solution was quickly extracted repeatedly with ice-cold water. The combined aqueous extracts were washed with ice-cold *n*-pentane, adjusted to pH 8.7 with cold dilute HCl, and extracted repeatedly with CH_2Cl_2. These combined extracts were treated with dicyclohexylamine (28 ml) and evaporated with N_2 to 50 ml of volume. After diluting with *n*-pentane (450 ml) and additional dicyclohexylamine (18 ml), the solution was cooled to 0°. The solid precipitate was filtered off, washed with *n*-pentane, and dried *in vacuo*: 12.5 g (24%) of white prisms; mp 90–91.5°. *Anal.* ($C_{33}H_{51}N_3O_2$) C, H, N, O. The product decarboxylated rapidly when dissolved in a solvent at room temperature.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyric Acid Methyl Ester (7a) and Ethyl Ester (7b). A solution of methyl chloroformate (15.0 g, 0.16 mol) in dry ether (45 ml) was added dropwise to a stirred solution of lithiated **2** (0.135 mol) in dry ether (500 ml) at −5 to 0° under N_2. After stirring for 1.5 hr at room temperature, the mixture was worked up in the usual manner. Distillation afforded 37.1 g (77%) of **7a** as a red oil: bp 141–158° (0.6 mm). *Anal.* ($C_{22}H_{30}N_2O_2$) C, H, N. The product turned yellow on standing.

The ethyl ester **7b** was prepared from ethyl chloroformate and lithiated **2** in a similar manner in 74% yield as a red-brown oil: bp 156–158° (0.2 mm). *Anal.* ($C_{23}H_{32}N_2O_2$) N.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)dithiobutyric Acid Methyl Ester (8). Carbon disulfide (24 ml) was added dropwise to a stirred solution of lithiated **2** (0.19 mol) in dry ether (550 ml) under N_2. After stirring for 2.5 hr, the precipitated solid was filtered off, washed with ether, and dried *in vacuo*, affording 5.50 g of the Li salt as a yellow solid. This was suspended in CH_2Cl_2 (2.1 l.) and a solution of MeI (20.3 g, 0.145 mol) in CH_2Cl_2 (140 ml) was added. After standing for 3 days, the mixture was evaporated; the residual oil was taken up in *n*-pentane (300 ml) and filtered. The filtrate was evaporated under reduced pressure affording 52.6 g (71%) of red oil (crude **8**) which was used to prepare **11** and **22** without purification.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)thiolbutyric Acid Ethyl Ester (9). A solution of lithiated 2 (0.3 mol) in dry ether (1.1 l.) was added during 2.5 hr to a stirred solution of $ClCOSC_2H_5$ (78.5 g, 0.6 mol) in dry ether (700 ml) under N_2 at −70°. The mixture was warmed to 0°, washed with ice-cold dilute K_2CO_3 and water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was distilled affording 86 g (75%) of a brown oil (crude **9**), bp 185–195° (0.5 mm), which was used to prepare **16**.

Bis[3-diisopropylamino-1-phenyl-1-(2-pyridyl)propyl] Ketone (10). A solution of $ClCOSC_2H_5$ (19.2 g, 0.146 mol) in ether (20 ml) was added to a stirred solution of lithiated **2** (0.133 mol) in dry ether (700 ml) under N_2 at −4 to 0° during 20 min. After stirring at room temperature for 1.5 hr, the mixture was washed with water, dried (Na_2SO_4), and evaporated. The residual solid was triturated with *n*-pentane (400 ml), filtered off, and crystallized from CH_2Cl_2–Skellysolve B affording 20.4 g (50%) of off-white crystals: mp 146–147.5°. *Anal.* ($C_{41}H_{54}N_{40}O$) H, N; C: calcd, 79.57; found, 79.13.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)thiobutyric Acid Hydrazide (11) (Method A, Scheme II). A biphasic mixture of crude **9** (37.0 g, 0.096 mol), 97% NH_2NH_2 (100 ml), and dry THF (700 ml) was refluxed while being stirred for 5 hr under N_2. After cooling and evaporating under reduced pressure, the residual gum was partitioned between ether and water. The ether phase was dried (Na_2SO_4) and diluted with *n*-pentane until no more gum precipitated; the supernate was decanted. This process was repeated several times until the gum crystallized: 12.6 g (35%) of tan solid; mp 80–85°. Recrystallization from ether–*n*-pentane afforded white crystals: mp 87–90°. *Anal.* ($C_{21}H_{30}N_4S$) C, H, N, S.

4-Diisopropyl-2-phenyl-2-(2-pyridyl)butyric Acid Hydrazide (12a) (Method B, Scheme II). A solution of **7a** (38.0 g, 0.0107

‡Melting points were taken in a Hershberg apparatus and were uncorrected. We thank Mr. A. Damascus and his staff for ir and nmr spectra, which were consistent with assigned structures, and Mr. E. Zielinski and staff for elemental analyses, which were within 0.4% of the theoretical values where only symbols of the elements are listed. Likewise, we are indebted to Mr. R. Nicholson, Mr. B. Smith, and Mr. W. Aksamit and their staffs, respectively, for column, thin-layer, and gas chromatographies.

§We thank Mr. E. Saugstad of the Hydrogenation Group for spinning-band distillations.

mol) and 85% $NH_2NH_2 \cdot H_2O$ (260 ml) in MeOH (420 ml) was refluxed for 18 hr, cooled, and evaporated. The residual oil was dissolved in ether. The ether solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ether–*n*-pentane affording 18.0 g (47%) of white crystals: mp 66–68°. *Anal.* ($C_{21}H_{30}N_4O$) C, H, N.

***N*-Acetyl Derivative of 12a (12b).** A solution of **12a** (0.03 mol) and 4-nitrophenyl acetate (0.03 mol) in dry ether (155 ml) after standing for 4 days afforded (by conventional work-up) 6.4 g (54%) of **12b** (from ether–*n*-pentane) as white crystals: mp 117–119°. *Anal.* ($C_{23}N_{32}N_4O_2$) C, H, N.

Hydrazone of 12a (12c). **12c** was prepared from **12a** (0.028 mol), acetone (100 ml), and AcOH (0.03 ml) in 72% yield: mp 104.5–106.5° (from ether–*n*-pentane). *Anal.* ($C_{24}H_{34}N_4O$) C, H, N.

1-[4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyryl]-2-methylhydrazine (13) (Method C, Scheme II). *n*-BuLi (0.12 mol) in hexane was added dropwise to a stirred solution of NH_2NHMe (7.4 g, 0.16 mol) in dry THF (250 ml) at 15–20° under N_2 and resulted in a solid suspension. A solution of **7a** (14.2 g, 0.04 mol) in dry THF (35 ml) was added dropwise at <25°. After stirring for 2 hr, the mixture was quenched with water. Conventional work-up afforded 10.4 g (70%) of purple oil: bp 176–180° (0.2 mm). *Anal.* ($C_{22}H_{32}N_4O$) C, H, N.

[4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyryl]trimethylhydrazine (15) (Method D, Scheme II). A solution of trimethylhydrazine (15.0 g, 0.2 mol) and triethylamine (20.0 g, 0.2 mol) in dry benzene (200 ml) was added to a stirred solution of benzoyl chloride (31.0 g, 0.2 mol) in dry benzene (200 ml) under N_2 at 10–15° during 45 min. After standing at room temperature for several hours, the mixture was washed with dilute NaOH, dried (Na_2SO_4), and evaporated. The residual oil was distilled affording 26.8 g of 1-benzoyl-1-methyl-2,2-dimethylhydrazine: bp 96–100° (0.25 mm).

This material (26 g, 0.135 mol) and 21.4 g (0.135 mol) of 2-bromopyridine were dissolved in dry toluene (150 ml). The stirred solution was heated to 75° and sodium amide (10.9 g, 0.28 mol) was added portionwise under N_2. The stirred mixture was heated to 105° for 15 min. A solution of $ClCH_2CH_2N[CH(CH_3)_2]_2$ (27.6 g, 0.169 mol) in dry toluene (125 ml) was added during 20 min. After refluxing for 3 hr the mixture was cooled and worked up in the usual way. The crude product was chromatographed on a silica gel column and the desired fraction was distilled affording 2.8 g (19%) of yellow oil (15): bp 175–205° (0.1 mm). *Anal.* ($C_{24}H_{36}N_4O$) C, H, N.

***N*-Methyl-4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide (16) (Method E, Scheme II).** A solution of **9** (12.5 g, 0.033 mol) and $MeNH_2$ (4.0 g, 0.13 mol) in 2-propanol (75 ml) was heated in a bomb at 100° for 18 hr.& After cooling, the solution was diluted with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized twice from *n*-pentane to afford 6.2 g (67%) of shiny flakes: mp 88–90°. *Anal.* ($C_{22}H_{31}N_3O$) C, H, N.

***N*-Methylol-4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide (21) (Method F, Scheme II).** A solution of 1 (34.0 g, 0.1 mol) and 38% CH_2O (39 ml) in ethanol (240 ml) was refluxed for 9 hr, cooled, and evaporated. The residual oil was taken up in CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ether–*n*-pentane to give 13.3 g (39%) of fine white needles: mp 94–96°. *Anal.* ($C_{22}H_{31}N_3O_2$) C, H, N, O.

4-Diisopropylamino-2-phenyl-2-(2-pyridyl)thiobutyramide (22) (Method G, Scheme II). Liquid NH_3 (100 ml), 8 (12.0 g, 0.031 mol), and ether (100 ml) were heated at 60° in a bomb for 1 hr. The mixture was cooled and evaporated under reduced pressure. The residue solidified when triturated with Skellysolve B (100 ml) affording 6.3 g (57%) of off-white solid: mp 107–112°. Crystallization from CH_2Cl_2–Skellysolve B gave 4.2 g of white crystals: mp 113–115°. *Anal.* ($C_{21}H_{29}N_3S$) C, H, N, S.

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