benzyl)propylamino]-2-nitrobenzonitrile **(24)**, respectively, with **24** being added in a hot HOAc soln to the $SnCl_2$.

2,4-Diamino-6-(alkylamino)quinazolines (IX) (31-35, Table V). 2,4-Diamino-6-(ethylamino)-5-methylquinazoline (32). A mixt of 12.5 g (0.050 mole) of 5-methyl-2,4,6-triaminoquinazoline·HOAc,[3] 100 ml of $MeO(CH_2)_2OH$, 2.5 g of MeCHO, and 1 g of 10% Pt/C under an initial H_2 pressure of 3.55 kg/cm² was shaken at 24-26° for 23 hr. After removal of the catalyst, the filtrate was concd to dryness, dissolved in H_2O, and treated with charcoal. Addn of excess NaOH gave a ppt which was crystd from EtOH, mp 222-225°.

The other 6-(alkylamino)quinazolines **(31, 33-35)** were prepd in the same manner except that no HOAc was present in the redn mixt for **34** and **35.**

3,4-Dichloro-α,*N*-dimethylbenzylamine (36). A mixt of 100 g (0.53 mole) of 3',4'-dichloroacetophenone, 124 g (2.1 moles) of *N*-methylformamide, and 50 ml of 90% HCO_2H was heated for 7 hr at 160-205° while H_2O was removed through a short distn head. After cooling and diln with H_2O, the mixt was extd with Et_2O. Concn of the combined exts gave an oil which was treated with 200 ml of concd HCl and heated under reflux for 6 hr. The resulting soln was cooled, dild with 1.2 l. of H_2O, and washed with Et_2O. Excess NaOH was added to the aqueous layer and the mixt was extd with three 500-ml portions of Et_2O. The combined exts were washed with H_2O, dried (K_2CO_3), treated with excess HCl in *i*-PrOH, and concd to dryness. Recrystn from EtOH-Et_2O gave 81 g (64%): mp 213-215°. *Anal.* ($C_9H_{11}Cl_2N$·HCl) C, H, N.

***N*-Methyl-3,4-dichlorobenzylamine (37).** A mixt of 240 g (1.37 moles) of 3,4-dichlorobenzaldehyde and 65 g (2.1 moles) of $MeNH_2$ in 1.2 l. of C_6H_5Me was allowed to stand 18 hr at 25°. $MgSO_4$ (120 g) was added and the mixt was filtered after cooling to room temp. The filtrate was charged with 7 g of 5% Pt/C and hydrogenated under an initial pressure of 3.52 kg/cm². After removal of the catalyst by filtration, the filtrate was distilled to give 217 g (84%) of colorless liquid: bp 119-121° (10 mm), $n^{25}D$ 1.5557. *Anal.* ($C_8H_9Cl_2N$) C, H, N.

The other *N*-alkylbenzylamines[21-25] required as intermediates for the synthesis of the 2,4-diamino-6-(alkylamino)quinazolines prepd *via* route I were obtained in the same manner in yields of 79-86%.

Acknowledgments. The authors are indebted to Dr. Leo Rane of the University of Miami and Dr. Paul E. Thompson of Parke, Davis and company for the antimalarial testing. We also thank Mr. R. A. Fisken, Mr. J. L. Schardein, and Dr. S. M. Kurtz for the toxicological studies, Mr. W. Pearlman for carrying out the hydrogenations employed, Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the spectral data.

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Metabolism of Diphenidol.† Urinary Products in Humans and Dogs

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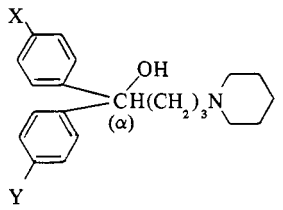
Following oral administration of [α-^{14}C]diphenidol (**1**) to humans and dogs the majority of the radioactive label was detected in urinary excretion within 2-3 days. The products of **1** metabolism, most of which were identified, are similar in the two species. Only 5-10% of unchanged **1** was found in the urine. The predominant metabolite, representing more than 50% of the total radioactivity, was *N*-(4,4-diphenyl-4-hydroxybutyl)-δ-aminovaleric acid. This compound was isolated from dog urine and identified in human specimens; its structure was confirmed by synthesis. Smaller amounts of diphenidol glucuronide were noted in both species. Minor urinary products, indicated by chromatographic comparison with compounds synthesized as potential metabolites, included a phenolic derivative of diphenidol, a lactam derived from the major metabolite, and their glucuronides. Neither the major metabolite nor its lactam afforded diphenidol-like protection against apomorphine-induced emesis in dogs.

In an investigation of the metabolism of diphenidol (**1**),[1] a potent antiemetic agent in man and animals,[2] chromatograms of urine obtained from humans and dogs after oral administration of the α-^{14}C-labeled compound showed a small amount of unchanged drug, a major, and several minor metabolic products. The major metabolite was characterized following its isolation from dog urine. Identification of the other products was undertaken by chromatographic compar-

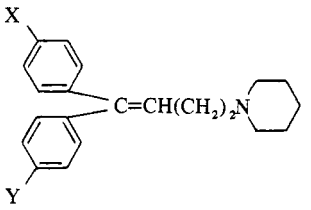
†Diphenidol is the generic name for α,α-diphenyl-1-piperidinebutanol hydrochloride.

ison with various compounds which, on the basis of the metabolism of structurally similar substances,[3,4] were considered potential metabolites. In this article we describe the isolation and characterization of the main product of diphenidol metabolism in humans and dogs, the synthesis of some potential metabolites, and the results of their chromatographic comparison with the urinary products.

Compounds prepared for comparative purposes, as described in the Experimental Section, included an *N*-oxide (**2**) and ring para-hydroxylated derivatives (**3, 4**) of **1** and a related series of olefins (**5-8**).



1, X = Y = H
2, X = Y = H (N → O)
3, X = H; Y = OH
4, X = Y = OH



5, X = Y = H
6, X = Y = H (N→O)
7, X = H; Y = OH
8, X = Y = OH

Results and Discussion

As can be seen from the data in Tables I and II most of the radioactivity appeared in the urinary excretion of humans (about 84% of the total dose) and dogs (about 70% of the total dose) within 2-3 days following oral administration of [α-^{14}C]diphenidol. Results of paper chromatography presented in Table III for a pooled dog urine sample and representative human samples obtained from one subject indicate the products of diphenidol metabolism are comparable in the two species; *i.e.*, a major radioactive area was seen at R_f 0.85 with lesser ones appearing at R_f 0.52, 0.42, and 0.20. In this acidic chromatographic system, the major peak was comprised of a mixture of diphenidol, the major and a minor metabolite which was readily separated by the neutral system (2, Table IV). The neutral system indicated that in both species 5-10% of the radioactivity was unchanged **1**. This was verified by hexane extraction from urine at pH 8.4 (conditions which permit quantitative extraction of **1**) and demonstration of the chromatographic identity of the extracted product with **1** in tlc systems 4 and 5 (Table IV).

After hydrolysis of the hexane-extracted urine samples from either species with β-glucuronidase, the minor peak at R_f 0.2 (Table III) disappeared and a new one, corresponding to **1** (system 4, Table IV), appeared. The newly developed product was characterized by its extraction with hexane and demonstration of its identity with **1** in chromatographic systems 4 and 5 (Table IV). Thus, the original minor peak (R_f 0.2, Table III), which is greater in dog urine than in the human sample, is attributed to **1** glucuronide.

The predominant product of diphenidol metabolism was identified after its isolation from the urine of dogs. It was isolated as colorless crystals having an elemental composition and ir spectrum in agreement with *N*-(4,4-diphenyl-4-hydroxybutyl)-δ-aminovaleric acid (**11**). Physical, spectral, and chromatographic properties of the metabolite were identical with those of authentic **11** obtained by synthesis from **9**[5] as outlined in Scheme I. Because heating the residue of pH-7 urine samples at 120° for 1 hr transformed the major metabolite into a hexane-soluble product which was chromatographically identical with the lactam **10** (system 3, Table IV), lactamization of **11** was investigated. Under comparable thermal conditions **11** is almost quantitatively cyclized to **10**.

Table I. Total Urinary Excretion of [α-^{14}C]Diphenidol Radioactivity in Humans[a]

	Collection period, hr[b]							
Subject	0-3	3-6	6-9	9-12	12-24	24-32	32-48	Total
A	19.2	20.0	12.4	8.6	13.8	3.8	2.5	80.3
B	18.8	12.9	23.8	3.2	15.5	2.4	2.9	79.5
C	13.5	18.3	12.7	7.1	21.0	7.6	8.4	88.6
D	19.7	22.8	12.3	7.9	17.2	3.0	4.7	87.6
Average	17.8	18.5	15.3	6.7	16.9	4.2	4.6	84.0

[a]Percentage of total dose (25 mg, 50 μCi, po) of [α-^{14}C]diphenidol radioactivity in urine collected at indicated times. [b]Time following drug administration.

Table II. Total Urinary Excretion of [α-^{14}C]Diphenidol Radioactivity in Dogs[a]

	Collection period, days[b]				
Dog no.	1	2	3	4	Total
1	58.0	11.6	2.7		72.3
2	43.6	21.1	5.5		70.2
3	56.8	13.3			70.1
4	51.1	18.4			69.5
5[c]	43.7	18.0	3.4	1.1	66.2
Average	50.6	16.5	2.3	0.2	69.6

[a]Percentage of total dose, 5.65 mg (containing 7.5 μCi)/kg, po, of [α-^{14}C]diphenidol radioactivity in urine collected at indicated times. [b]Time following drug administration. [c]This dog received 10 mg (containing 13.3 μCi)/kg, po, of [α-^{14}C]diphenidol. Percentage of total radioactivity was calcd accordingly.

Table III. Chromatographic Distribution of Urinary Radioactivity[a]

	Human[b]						Dog[c]
R_f	0-3	3-6	6-9	9-12	12-24	0-24[d]	0-24
0.85	82.1	75.9	69.1	63.4	57.4	71.3	66.5
0.52	1.5	1.7	2.0	2.6	6.3	2.8	6.5
0.42	1.4	4.4	5.8	7.3	4.5	4.2	Trace
0.20	1.9	3.2	3.6	4.4	4.7	3.4	14.8

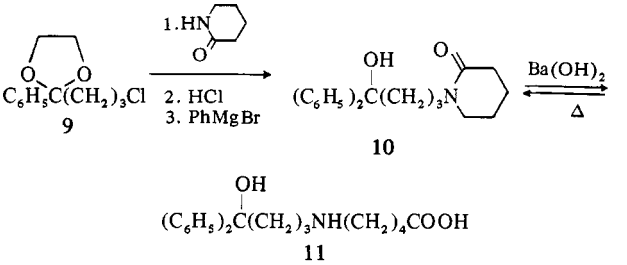
[a]Chromatographic system 1, Experimental Section, was used. Radioactivity is given as % of total in specimen at indicated R_f. Total radioactivity is less than 100% because nonlocalized chromatographic streaking is not included. [b]Urine samples were collected at indicated time (hr) following [α-^{14}C]diphenidol administration to subject D, Table I. [c]A pooled urine sample, obtained as described in the Experimental Section, was used. [d]Pooled 24-hr urine sample, subject D, Table I.

Table IV. R_f Values for Diphenidol and Metabolites

	Chromatographic system[a]						
Compd	1	2	3	4	5	6	7
1	0.85	0.58	0.90	0.70	0.85		0.45
3	0.42				0.35		
10	0.85	0.95	0.90	0.90		0.70	
11	0.85	0.10	0.70	0.35			

[a]Described in Experimental Section.

Scheme I



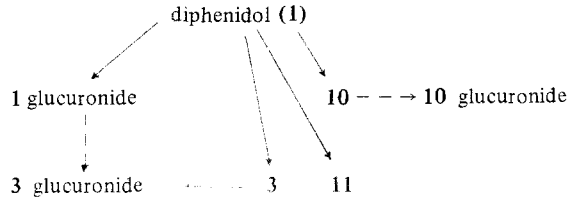
The presence of **11** as the principal metabolite of diphenidol in human urine was established by its thermal conversion (in the same manner described for dog urine) to a hexane-soluble product identical with **10** in tlc systems 2, 3, and 6 (Table IV). In addition, chromatography of *n*-BuOH extracts of human urine gave major spots identical with **11** in R_f (systems 2, 3, and 4, Table IV) and in their ability to produce an intense blue color with sodium nitroprusside-acetaldehyde, a reagent specific for secondary aliphatic amines.[6] Small amounts of metabolic product having the same R_f as the lactam **10** were detected in unheated human and dog urine (systems 2 and 4, Table IV). As the intensity of this peak was increased after treatment of the urine samples with β-glucuronidase apparently this minor lactam metabolite occurs mainly as a glucuronide. This result may possibly be artifactual, however, since a control experiment was not performed to establish that **10** is not formed *via* lactamization of **11** during β-glucuronidase hydrolysis. That neither lactamization of **11** to **10** nor hydrolysis of **10** to **11** contributes to the presence of either product is indicated by experiments in which ^{3}H-labeled **10** and **11** in control urine were shown to be unaltered by the identical conditions of storage and processing used to detect the metabolites.

To investigate aromatic-ring hydroxylation as a possible metabolic course for diphenidol, test urine was examined for mono- (**3**, **7**) and dihydric (**4**, **8**) phenols. Urine samples, after being adjusted to pH 11, were extracted with Et_2O—conditions shown to permit extraction of the comparative phenolic compounds. Chromatography of the extracts thus obtained from human urine gave a minor radioactive peak having the same R_f as **3** (systems 1 and 7, Table IV), whereas similarly treated dog urine (a pooled sample collected for 12 hr after the last of 4 100-mg, po, doses of unlabeled **1** given at 12-hr intervals to a 12-kg female beagle dog) showed only a trace of this product. Thus, as indicated by the relative intensities of the R_f 0.42 peaks in Table III, the phenolic metabolite may be more significant in humans than in dogs. Following hydrolysis with β-glucuronidase this product was significantly intensified in the Et_2O extracts of basic urine from both species. In the human sample it represented about 5–10% of the total radioactivity excreted; the relative activity following glucuronidase treatment indicated about 90% was originally present as glucuronide. Although this metabolite was not characterized unambiguously, further evidence for its phenolic composition was afforded by demonstration that, like **3**, it gives a yellow color with fast scarlet GG spray,‡ an analytical reagent for phenols.[7,8] A similar color was observed with the olefinic monophenol **7**, whereas the diphenolic derivatives **4** and **8** gave a dark orange color with this reagent. The phenols **4**, **7**, and **8** (R_f 0.20, 0.65, and 0.55, respectively in tlc system 7) were not detected in the Et_2O extracts of pH-11 urine of either species.

Neither the olefin **5** nor the *N*-oxides **2** and **6** were detected in urinary excretion. Absence of **5**, which is readily formed by dehydration of diphenidol,[9,10] was established by tlc and the uv absorption of hexane extracts of pH-8.4 adjusted human and dog urine (conditions shown to permit extraction of both **1** and **5**). Chromatography (system 7, Table IV) of the extracts showed a single radioactive peak identical with that of **1**. The uv spectrum of the extracts also indicated only **1** [λ_{max} (hexane) 258 mμ (ε 440)] and none of the more strongly uv-absorbing **5** [λ_{max} (hexane) 249 mμ (ε 13,700)]. Absence of **2** and **6** was demonstrated using untreated and β-glucuronidase-hydrolyzed urine samples from both species. After Et_2O extraction of urine adjusted to pH 11 (conditions under which the *N*-oxides are not extracted), chromatography (system 3) of the aqueous phase did not produce a peak at R_f 0.9—the value noted for both **2** and **6** in control and test urine.

As summarized in Scheme II (dotted arrows indicate the products were not characterized with certainty) possible pathways to the products of diphenidol metabolism detected in the urine of humans and dogs arise from aromatic hydroxylation (possibly more significant in humans than in dogs), conjugation with glucuronic acid (perhaps more significant in dogs than in humans), and, most importantly, fission of the piperidine ring to give **11**.

Scheme II



The latter type of oxidative ring opening is a significant metabolic route for several related tertiary N-heterocycles. For example, δ-methylaminovaleric acid is a product of metabolism of *N*-methylpiperidine in dogs.[11] The homologous pyrrolidine derivatives, nicotine and tremorine, also yield amino acids as metabolic products of ring fission. In addition, they give lactam (2-pyrrolidone) derivatives. McKennis, *et al.*,[12,13] proposed two pathways for the formation of the lactam, cotinine, from nicotine in dogs, *i.e.*, (1) oxidation of the pyrrolidine to an amino acid with subsequent spontaneous ring closure, and (2) direct oxidation. *In vitro*, rat liver microsomes metabolize nicotine mainly by α-hydroxylation of the pyrrolidine ring followed by dehydrogenation of the resulting α-hydroxypyrrolidine to cotinine.[14] Two pathways, both involving an α-hydroxypyrrolidine, perhaps arising from an intermediate *N*-oxide,[15] are important for the formation of the 2-pyrrolidone, oxotremorine, from tremorine in rats.[16] In one of these pathways the α-hydroxy derivative is dehydrogenated. The other involves oxidation of the ring-opened equilibrium product of the hydroxy intermediate, an amino aldehyde, to an amino acid, which then lactamizes. *In vivo* formation of the lactam from the amino acid was demonstrated; however, the reverse reaction did not occur.

The formation of an amino acid (**11**) and the corresponding lactam (**10**) from diphenidol might involve mechanistic pathways similar to those of nicotine and tremorine.

Pharmacological Results. The major metabolite **11** and its lactam **10** were examined for their ability to diminish the frequency of apomorphine-induced emesis in dogs by a modification[2] of the method of Chen and Ensor.[17] In this test diphenidol has ED_{50} 1.5 (0.4–2.9) mg/kg, po, at a 1-hr time of peak effect.[2] Under the same conditions, using a 1-hr pretreatment time, neither **11** (3.0 mg/kg, po) nor **10** (2.5, 5.0 mg/kg, po) caused a significant reduction of apomorphine-induced emesis as compared to controls.

Experimental Section§

Materials and Methods. Urine Samples. Humans. A single oral dose of 25 mg of diphenidol containing 50 μCi of [α-^{14}C]-**1** was ad-

‡A stabilized diazonium salt of 2,5-dichloroaniline; obtained from American Aniline Products, Inc., Paterson, N. J.

§All mp's were determined by the capillary method and are uncorrected. Microanalyses were obtained by the Analytical and Physical Chemistry Section of Smith Kline and French Laboratories.

ministered to four male volunteers. Urine specimens were collected at the time periods indicated in Table I for 48 hr following drug administration. Unless indicated otherwise samples employed for chromatographic studies were combined 0- to 24-hr specimens from the four volunteers. All samples were frozen and stored at −10°.

Dogs. Three female beagle dogs averaging about 12 kg were given three oral doses of 100 mg of **1** (containing 50 μCi of [α-^{14}C]-**1**) at 6-hr intervals. Animals were placed in individual metabolism cages where urine was collected under PhMe for 24 hr after the final dose. Samples were collected every 12 hr, pooled, and frozen. Unless indicated otherwise, *e.g.*, Table II, these samples were employed for the study.

Chromatography. Paper and tlc# systems (support, solvent, proportions) were as follows: (1) Whatman No. 3MM paper, *i*-AmOH-*tert*-AmOH-HCO_2H-H_2O, 5:5:2:10; (2) Whatman No. 3MM paper, impregnated with 40% aqueous $HCONH_2$ in MeOH and blotted prior to sample application, BuOAc-$HCONH_2$-H_2O, 20:1:1; (3) Whatman No. 3MM paper, *n*-BuOH-28% aqueous NH_3, 4:1; (4) silica gel G, MeOH-Me_2CO-Et_3N, 50:50:1.5; (5) silica gel G, $CHCl_3$-MeOH, 80:20. These plates were developed 3 times: (6) silica gel G, $CHCl_3$-MeOH, 97:3; (7) silica gel G containing 20% $AgNO_3$, EtOAc-MeOH, 80:20. For the paper systems (1-3) descending development for 16 hr was used. Radioactive zones were detected by scanning on a Farro chromatograph scanner or by ^{14}C analysis of 1-cm paper segments or 8-mm tlc scrapings. Color sprays were iodoplatinate,[18] iodine vapor, sodium nitroprusside-acetaldehyde,[6] Dragendorff's reagent,[18] and a 0.1% solution of fast scarlet GG‡ in H_2O containing a trace of HCl.[7,8]

Radioassay Methods. Analysis for ^{14}C activity was carried out in a Packard Tri-Carb liquid scintillation spectrometer (Model 3375) in an aqueous phosphor mixt consisting of 2,5-bis(5-*tert*-butyl-2-benzoxazolyl)thiophene (8 g), naphthalene (80 g), PhMe (400 ml), dioxane (400 ml), and a sufficient quantity of EtOH to make 1 l. Quenching was corrected by internal standardization.

Hydrolysis of Glucuronides. A β-glucuronidase soln** (1 ml, 5000 units) was added to 10 ml of urine which had been adjusted to pH 5. A drop of $CHCl_3$ was added, and the mixt was incubated at 37° for 48 hr.

Isolation of the Major Metabolite. After being hydrolyzed with β-glucuronidase, a pooled 36-hr urine sample from 3 dogs treated with 3 100-mg (50 μCi), po, doses of **1** at 6-hr intervals was brought to pH 11 (NaOH) and extd with Et_2O. The aqueous phase was then extd with *n*-BuOH. The *n*-BuOH ext was concd *in vacuo* at 40°, and the residue was dissolved in 100 ml of EtOH. Solid, which pptd upon cooling the soln to −10°, was filtered. The filtrate was concd to half its original vol under a stream of N_2, then it was again cooled and filtered. Vol redn, cooling, and removal of the pptd solid were repeated once more to give about 30 ml of a pale yellow soln. The entire EtOH soln was applied to paper strips (chromatography system 3). After development of the chromatograms, the single radioactive spot was eluted from each strip with EtOH. Eluates were combined and concd to 5 ml *in vacuo* to give 105 mg of colorless crystals, mp and mmp with **11**, 207–209 dec; ir identical with that of **11**. *Anal.* ($C_{21}H_{27}NO_3$) C, H, N.

Syntheses. α,α-[α-^{14}C]Diphenyl-1-piperidinebutanol·HCl [α-^{14}C]-1). A soln of 1.46 g (12 mmoles) of [7-^{14}C]PhCOOH (sp activity 2.08 mCi/mmole) and 2.1 ml of $SOCl_2$ was refluxed for 2 hr, then it was concd. To a stirred soln of the residual [7-^{14}C]BzCl in 5 ml of PhH at 0° was added 1.7 g (13 mmoles) of $AlCl_3$. After being stirred at 0° for 30 min, the mixt was refluxed for 2 hr. Excess PhH was distd and the residue was dild with a mixt of 20 g of ice H_2O and 1.2 ml of 12 *N* HCl. The mixt was extd with Et_2O, and the exts were washed (2.5 *N* NaOH, H_2O), dried, and concd. [α-^{14}C]-Benzophenone (2.02 g, 92%) was obtained by crystn of the residue (*i*-PrOH-H_2O). A soln of 1.95 g (10.7 mmoles) of this ketone (sp activity 2.08 mCi/mmole) in 4 ml of THF was added slowly to a stirred and refluxing soln of Grignard reagent prepd from Mg (0.365 g, 15 mg-atoms) and 1-(3-chloropropyl)piperidine[19] (2.42 g, 15 mmoles) in 15 ml of THF. After being refluxed for 2 hr, the mixt was concd *in vacuo*, and the residue was dild with a soln of 5 g of NH_4Cl in 20 ml of ice H_2O. The product (2.59 g, 74.6%) was removed by centrifugation, mp 102.5–103° (EtOH-H_2O). A soln of this base in *i*-PrOH-PhMe was adjusted to pH 6 with HCl to give colorless crystals of [α-^{14}C]-**1** (sp activity 5.3 μCi/mg), mp 220–221°.[19] Radiochemical purity was demonstrated by production of a single radioactive peak having the same R_f as authentic **1** on paper chromatography (system 2).

#Tlc's were carried out on Analtech silica gel G (250 μ) uniplates, Analtech, Inc., Newark, Del.

**Ketodase, Warner-Chilcott Laboratories, Morris Plains, N. J.

α,α-Diphenyl-1-piperidinebutanol *N*-Oxide (2). To a stirred soln of 3.1 g (10 mmoles) of **1**[19] in 25 ml of MeOH at 0° was added dropwise 2.15 g (12.5 mmoles) of *m*-chloroperbenzoic acid in 15 ml of MeOH. The soln was stirred for 30 min and concd. The residue was dissolved in H_2O and the soln was made alk (NaOH) to give a cryst ppt (1.5 g, 46%), mp 180–181°, after recrystn (H_2O). *Anal.* ($C_{21}H_{27}NO_2 \cdot 0.25H_2O$) C, H, N.

A maleate, mp 129–130°, was prepd in EtOH-Et_2O. *Anal.* ($C_{25}H_{31}NO_6$) C, H, N.

1,1-Diphenyl-4-piperidinylbutene *N*-Oxide (6). A mixt of 2.0 g (5.5 mmoles) of **2** and 25 ml of 12 *N* HCl was stirred and refluxed for 3 hr, then it was concd *in vacuo*. A soln of the residue in H_2O was made alk (NaOH), and the mixt was extd with EtOAc. The exts were dried and concd to give 1.3 g (68%) of **6** as a colorless liquid. For analysis it was converted to a **methanesulfonate,** mp 159–160°, after recrystn (MeOH-EtOAc). *Anal.* ($C_{22}H_{29}NO_4S$) C, H, N.

4,4′-Dibenzyloxybenzophenone. A soln of 30.5 g (0.24 mole) of $PhCH_2Cl$ in 100 ml of EtOH was added dropwise to a stirred suspension of 21.4 g (0.1 mole) of 4,4′-dihydroxybenzophenone, 30.4 g (0.22 mole) of K_2CO_3, and 2.3 g of KI in 170 ml of EtOH. The mixt was stirred and refluxed for 6 hr, then it was filtered to give 37 g (94%) of pale yellow crystals, mp 189–191°, after washing with H_2O, EtOH, and Et_2O. *Anal.* ($C_{27}H_{22}O_3$) C, H.

α-(4-Benzyloxyphenyl)-α-phenyl-1-piperidinebutanol·HCl. A soln of 47.8 g (0.166 mole) of 4-benzyloxybenzophenone[20] in 100 ml of THF was added dropwise at 20° to a soln of Grignard reagent prepd from 40.5 g (0.25 mole) of 1-(3-chloropropyl)piperidine[19] and 6.1 g (0.25 g-atom) of Mg in 125 ml of THF. The soln was stirred and refluxed for 1 hr, then it was poured into ice H_2O contg an excess of NH_4Cl. The mixt was extd with Et_2O, and the exts were dried and concd. A soln of the residue in EtOH was treated with dry HCl to give 55.0 g (73%) of colorless crystals, mp 183–185°, after recrystn from MeOH-EtOAc-Et_2O. *Anal.* ($C_{28}H_{33}NO_2 \cdot HCl$) C, H, N.

α,α-Bis(4-benzyloxyphenyl)-1-piperidinebutanol. Prepd from 4,4′-dibenzyloxybenzophenone by the same procedure described for prepn of α-(4-benzyloxyphenyl)-α-phenyl-1-piperidinebutanol from the monobenzyloxy deriv, this base melted at 123–125° after recrystn from EtOH-hexane. *Anal.* ($C_{35}H_{39}NO_3$) C, H, N.

α-(4-Hydroxyphenyl)-α-phenyl-1-piperidinebutanol (3). A mixt of 18 g (0.04 mole) of α-(benzyloxyphenyl)-α-phenyl-1-piperidinebutanol·HCl, 1.0 g of 10% Pd/C, 5 ml of H_2O, and 150 ml of EtOH was hydrogenated for 4 hr on a Parr apparatus at 25° using an initial H_2 pressure of 2.1 kg/cm². The mixt was filtered, and the filtrate was concd *in vacuo*. A soln of the residue in H_2O was neutralized with Na_2CO_3 to give 14.0 g (96%) of colorless crystals, mp 218–219°, after recrystn from EtOH-Et_2O. *Anal.* ($C_{21}H_{27}NO_2$) C, H, N.

1,1-Bis(4-hydroxyphenyl)-4-piperidinylbutene (8). Hydrogenation of a mixt of 10.4 g (0.02 mole) of α,α-bis(4-benzyloxyphenyl)-1-piperidinebutanol, 30 ml of AcOH, 70 ml of EtOH, and 1.5 g of 10% Pd/C by the procedure described for synthesis of **3** gave 5.8 g (89%) of colorless crystals, mp 260–262°. *Anal.* ($C_{21}H_{25}NO_2$) C, H, N.

α,α-Bis(4-hydroxyphenyl)-1-piperidinebutanol (4) was prepd from 10.7 g (0.05 mole) of 4,4′-dihydroxybenzophenone and 0.2 mole of 3-(1-piperidinyl)propylmagnesium chloride by the same procedure described for α-(4-benzyloxyphenyl)-α-phenyl-1-piperidinebutanol·HCl. Upon decompn of the reaction mixt with NH_4Cl-H_2O, a cryst product pptd. Recrystn from EtOH gave 3.5 g (21%) of colorless crystals, mp 254–256° dec. *Anal.* ($C_{21}H_{27}NO_3$) C, H, N.

1-(4-Hydroxyphenyl)-1-phenyl-4-piperidinylbutene·HCl (7). Dry HCl was added to a suspension of 6.5 g (0.02 mole) of **3** to give a clear soln. Addn of Et_2O pptd 6.2 g (90%) of colorless crystals, mp 242–243°, after recrystn from MeOH-Et_2O. *Anal.* ($C_{21}H_{25}NO \cdot HCl$) C, H, N.

2-[3-(2-Ketopiperidinyl)propyl]-2-phenyloxirane. To a stirred suspension of 5.4 g (0.124 mole) of a 56% dispersion of NaH in mineral oil in 50 ml of DMF was added dropwise a soln of 12.3 g (0.124 mole) of 2-piperidone in 75 ml of DMF. The stirred mixt was heated at 100° for 10 min, then it was cooled to 0° and a soln of 28 g (0.124 mole) of 2-(3-chloropropyl)-2-phenyloxirane (**9**)[5] in 60 ml of DMF was added dropwise. After stirring and refluxing the mixt for 3 hr, it was poured into 500 ml of ice H_2O. The mixt was extd with Et_2O. The exts were dried and concd. Distn of the residual liquid gave 17.8 g of a nearly colorless liquid, bp 160–178° (0.5 mm). The distillate crystd on standing; it was recrystd from EtOAc-*n*-C_6H_{14} to give 12.0 g (33%) of colorless crystals, mp 76–78°. *Anal.* ($C_{17}H_{23}NO_3$) C, H, N.

4-(2-Ketopiperidinyl)butyrophenone. A soln of 67.5 g (0.23 mole) of 2-[3-(2-ketopiperidinyl)propyl]-2-phenyloxirane in 500 ml of dioxane and 25 ml of 2.5 *N* HCl was refluxed for 1 hr, then it was

concd *in vacuo*. The residue was dild with H_2O, and the mixt was extd with CH_2Cl_2. The exts were washed with H_2O, dried, and concd to leave 55.2 g (96%) of a colorless liquid, bp 169–174° (0.4 mm). *Anal.* ($C_{15}H_{19}NO_2$) H, N; C: calcd, 73.44; found, 72.45.

1,1-Diphenyl-4-(2-ketopiperidinyl)butanol (10). To a soln of PhMgBr, prepd from 23.5 g (0.15 mole) of PhBr and 2.6 g (0.15 g-atom) of Mg in 150 ml of THF, at 0° was added dropwise a soln of 24.5 g (0.1 mole) of 4-(2-ketopiperidinyl)butyrophenone in 150 ml of THF. After being stirred at 0° for 5 hr, the mixt was concd *in vacuo*. The residue was dild with excess NH_4Cl–H_2O. The resulting mixt was extd with CH_2Cl_2. The exts were dried and concd to leave 23.9 g of colorless crystals, mp 173–174° (EtOH). *Anal.* ($C_{21}H_{25}NO_2$) C, H, N.

A sample of 1-[^{3}H]Ph-**10** was prepd from [*G*-^{3}H]PhBr (sp activity 50 mCi/mg) in the same way.

***N*-(4,4-Diphenyl-4-hydroxybutyl)-δ-aminovaleric Acid (11).** A mixt of 8 g (0.025 mole) of **10** in 275 ml of EtOH and 37 g (0.12 mole) of $Ba(OH)_2 \cdot 8H_2O$ in 165 ml of H_2O was stirred and refluxed for 48 hr. After distn of EtOH, the mixt was cooled to 0° and 150 ml of 2 *N* H_2SO_4 was added dropwise. The mixt was stirred for 15 min, then it was made alk (2 *N* KOH), heated to boiling, and filtered through Super-Cel. The filtrate was cooled to 0° and brought to pH 7 with AcOH. The cryst ppt was filtered and washed (H_2O, EtOH, and Et_2O) to give 6.6 g (78%) of colorless crystals, mp 207–209° dec. *Anal.* ($C_{21}H_{27}NO_3$) C, H, N.

A sample of 4-[^{3}H]Ph-**11** was prepd from 1-[^{3}H]Ph-**10** by the same procedure. Radiochemical purity was 99% as determined by segmentation[21] of the tlc (system 4) and liquid scintillation counting.

Lactamization of 11. A suspension of 0.5 g (1.5 mmoles) of **11** in 35 ml of xylene was stirred and refluxed for 1 hr. The resulting soln was concd *in vacuo* and the residue was crystd from EtOH to give 0.45 g (97%) of colorless crystals, mp and mmp with **10**, 173–174°.

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Design, Synthesis, and Broad Spectrum Antiviral Activity of 1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide† and Related Nucleosides[1,2]

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The first synthetic broad-spectrum, noninterferon-inducing, antiviral agent 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**1**) has been prepared and tested against a variety of both RNA and DNA viruses in tissue culture. The syntheses of **1** and related nucleosides by the silylation–glycosylation procedure and the acid-catalyzed fusion procedure are described. The concepts underlying the development of this agent are discussed. Comparison of antiviral activity is made with the structurally related nucleoside antibiotics pyrazomycin, formycin, and showdomycin. Reproducible broad-spectrum antiviral activity both *in vitro* and *in vivo* at nontoxic dosage levels is shown by **1**. These findings demonstrate the feasibility of practical antiviral chemotherapy despite the problem that viral infection is intimately linked to the biochemistry of the host cell. This nucleoside (**1**) should prove a most useful probe in the study of the molecular biology of virus replication.

Although broad-spectrum antibacterial agents and antibiotics have been developed to wide clinical usefulness over the period of the past 40 years, the comparable screening effort in the direction of the development of antiviral agents has yielded results far short of the same degree of success.[3-6] This situation prevails despite the fact that respiratory diseases, principally of viral origin, are responsible for more than 50% of all acute human illnesses.[7-9]

In searching for a broad-spectrum antiviral agent an effort was made to concentrate on the synthesis of compounds which have the potential to affect enzymatic processes which are common to all known viruses such as viral-induced nucleic acid and protein synthesis. These processes are carried out by enzymes specifically coded for in the viral genome. Another common feature of all viruses is their lack of protein-synthesizing capability. It is conceivable that initiation of virus-specific protein synthesis and/or RNA synthesis may utilize unique viral enzymes which could be specifically inhibited.

Several nucleosides such as 5-iodo-2′-deoxyuridine and 1-β-D-arabinofuranosylcytosine have been used with limited success against herpes virus infection in man.[10-12] One of the more potentially clinically useful agents, 9-β-D-arabino-

†1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide is identified by the International Chemical and Nuclear Corporation by the name Virazole.