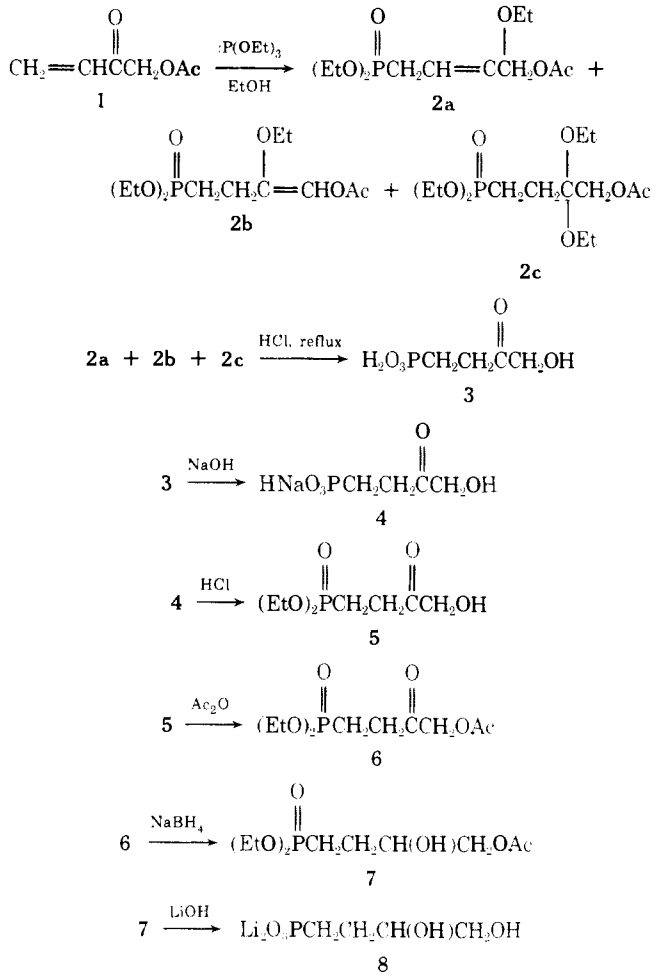
Scheme I



absolute ethanol and then with anhydrous ether. The filtrate and wash solvents were combined and evaporated to give an oil which was retitrated. The powder was dried *in vacuo* over P_2O_5 and gave 6.0 g (93%) of pure 4: ir (Nujol) 3.00, 5.90, 6.95, 7.90, 8.17, 8.80, 9.45, 9.97, 10.20, 11.20 μ; nmr (TFA) δ 2.15–3.10 (m, 4 H, PCH_2CH_2), 4.68 (s, 2 H, CH_2O). *Anal.* Calcd for $C_4H_8O_5NaP$: C, 25.26; H, 4.21. Found: C, 25.05; H, 4.51.‡

Diethyl 4-Acetoxy-3-oxobutyl-1-phosphonate (6). A mixture of 29.4 g (0.1 mol) of the mixture **2a–c** with 4 ml of 3% HCl was stirred overnight and heated at 60–70°. Volatile components were removed under reduced pressure and the resulting mixture of the keto alcohol **5** and keto acetate **6** was treated with 20 g (0.2 mol) of acetic anhydride. The solution was heated on a steam bath for 2 hr and distilled. The yield of pure **6** was 19 g (71%): bp 142° (0.3 mm); ir (film) 3.35, 3.42, 5.78, 7.10, 7.32, 8.25, 8.65, 9.90, 10.58, 12.10 μ; nmr (CCl_4) δ 1.18 (t, J = 7 Hz, 6 H, CH_3CH_2O), 1.50–2.90 [2 m and s (2.02), total 7 H, PCH_2CH_2 and $C(O)CH_3$], 3.92 (m, 4 H, CH_3CH_2O), 4.70 (s, 2 H, CH_2OAc). *Anal.* Calcd for $C_{10}H_{19}O_6P$: C, 45.12; H, 7.19. Found: C, 45.24; H, 7.44.

Dilithium 3,4-Dihydroxybutyl-1-phosphonate (8). To a solution of 1.59 g (6 mmol) of keto acetate **6** in 25 ml of anhydrous 2-propanol was added 76 mg (2 mmol) of $NaBH_4$. The mixture was heated at 50° for 1 hr and stirred overnight at room temperature. The solution was treated with 1 ml of 3 *N* HCl and the volatile components were removed under reduced pressure. To the residue was added 50 ml of water and 2.5 g (100 mmol) of LiOH, and the resulting solution was heated in an autoclave for 6 hr at 120°. A white precipitate was isolated by filtration, washed with absolute ethanol and anhydrous ether, and dried under vacuum to yield 0.88 g of **8**. This material was identical with that prepared by the route previously described[4] as indicated by ir and nmr spectra, tlc, and enzymatic assay.† This reaction was subsequently repeated on a smaller scale using tritium-labeled sodium borohydride yielding **8** labeled at the 3 position with tritium.

Biological Data. The ability of the monosodium salt of the 4-hydroxy-3-oxobutyl-1-phosphonic acid (**4**) to serve as a substrate for L-glycerol 3-phosphate:NAD oxidoreductase (EC 1.1.1.8) was determined by the procedure of Black.[5] Kinetic studies of **4** and dihydroxyacetone phosphate yielded K_m's of 182 and 133 μM, respectively. These values are similar to one another and relatively close to the value of 80 μM for dihydroxyacetone phosphate which was reported by Black. Preliminary evidence indicates that the phosphonic acid analog **4** can also serve as a substrate for the biosynthetic L-glycerol 3-phosphate dehydrogenase from *E. coli* which was initially described by Kito and Pizer.[1]

The 3,4-dihydroxybutyl-1-phosphonic acid (**8**) with tritium labeling at the 3 position was used to determine an apparent K_m for L-glycerol 3-phosphate CMP phosphatidyl transferase. A value of 1.8×10^{-5} M was determined,§ adding to our previous data on this compound.[6]

The data obtained substantiate the value of the synthesized compounds as analogs of natural substrates both for the investigation of biological action and as a metabolic regulator.

Acknowledgment. This work was supported by a grant from the National Science Foundation (GB-33718) and a Biomedical Sciences Support Grant from the National Institutes of Health (5-SO5-FR-07064-07).

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‡ All elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Inc., Woodside, N. Y., and were within acceptable limits.

§ P. J. Cheng, R. Hickey, R. Engel, and B. Tropp, unpublished results of this laboratory; manuscript in preparation.

Cyclization of Lactamimide Ketones to Imidazo[1,2-*a*]-azacycloalkanes with Hypoglycemic Activity

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We have prepared many lactamimides in order to evaluate their pharmacological properties, especially hypoglycemic effects.[1-3] When α-amino ketone hydrochlorides I were allowed to react with lactim ethers II, the resulting products were found to be imidazo[1,2-*a*]azacycloalkane hydrochlorides IV. These resulted from cyclization of the lactamimides III, which could be isolated in some instances. Compounds IV lacked the carbonyl absorption seen in the infrared spectra of III at 1700–1710 cm^{-1} and the benzoyl chromophore at 246 nm (ϵ 16,300) seen in the ultraviolet spectra of III. On treatment with concentrated hydrochloric acid, compounds IV dehydrated to the aromatic compounds V that showed the characteristic phenylimidazole ultraviolet chromophore at 234–237 nm (ϵ 11,700). The isomeric compound Vd has recently been described (Scheme I).[4]

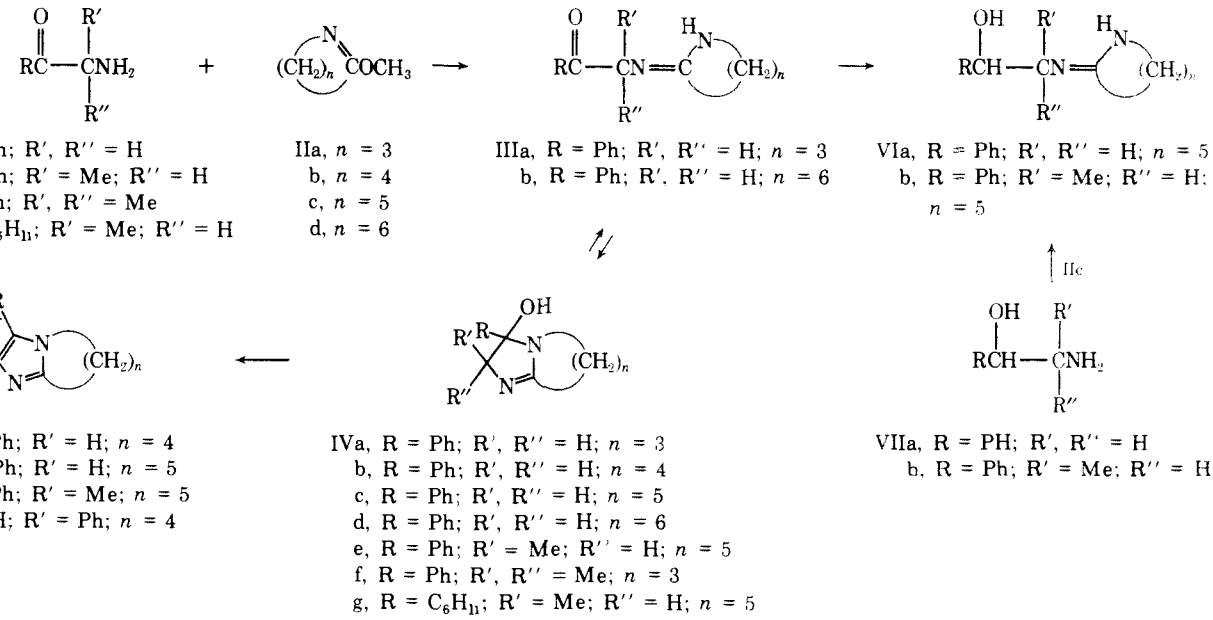
Compounds III and IV are interconvertible and there appears to be a preference for one or the other form, which depends on the size of the azacycloalkane ring (n). Thus, the hydrochloride salts of the lactamimide ketones IIIa and IIIb were isolated from the reaction of the hydrochloride of Ia with lactim ethers IIa or IId, respectively. Ketone IIIa was stable to refluxing concentrated hydrochloric acid. When converted to free base, IIIa and IIIb spontaneously cyclized to IVa and IVd, respectively; IVa opened to IIIa in a solution of ethanol or deuteriochloroform, and thus only the infrared spectrum (KBr) provides evidence for its existence (*cf.* Table I). Compound IVd, on

Table I. Physical, Chemical, and Biological Data on Compounds III–VI, VIII, and IX

No.	Mp, °C	Recrystn solvent[a]	Yield, %	Ir (KBr), cm^{-1}	Uv, λ max (ε)	Mol formula	Analyses	Plasma glucose, rats: mg/kg po	Plasma glucose, rats: % reduction
IIIa	192–193 dec	A	71	1710, 1680	246 (14,300)	$C_{12}H_{14}N_2O \cdot HCl$	C, H, Cl	100	0
IIIb	155–157 dec	A	51	1710, 1660	266 (500), 278 (300)	$C_{15}H_{26}N_2O \cdot HCl$	C, H, N	100	29[b]
IVa	112–119 dec	B	45	1680, 1610 •	244 (11,900)	$C_{12}H_{14}N_2O$	C, H, N		
IVb	162–163 dec	A	61	1620	266 (300)	$C_{13}H_{16}N_2O \cdot HCl$	C, H, N	100	22
IVc	160–161 dec	A	64	1620	267 (300)	$C_{14}H_{16}N_2O \cdot HCl$	C, H, Cl	100	31[b]
IVd	166–168 dec	A	20	1600	265 (sh)	$C_{15}H_{20}N_2O$	C, H, N	100	25[b]
IVe[c]	173–174 dec	A	79	1650	267 (200)	$C_{15}H_{20}N_2O \cdot HCl$	C, H, Cl	100	50[b]
								50	42[b]
								25	35[b]
								12.5	4
IVf	217–219 dec	A	36	1650	256 (300)	$C_{14}H_{16}N_2O \cdot HCl$	C, H, Cl	100	16[b]
IVg	172–173 dec	A	57	1620	224 (6,600)	$C_{15}H_{26}N_2O \cdot HCl$	C, H, Cl	100	33[b]
Va	213–215 dec	A	78	1620	237 (11,700)	$C_{13}H_{14}N_2 \cdot HCl$	C, H, N	100	0[d]
Vb	98–101	C	56	1610	260 (10,800)	$C_{14}H_{16}N_2$	C, H, N	100	0[d]
Vc	217–219 dec	A	62	1600	234 (11,700)	$C_{15}H_{16}N_2 \cdot HCl$	C, H, N	100	12[b]
VIa	171–173 dec	A	83	1650–1660	263 (100), 257 (200)	$C_{14}H_{20}N_2O \cdot HCl$	C, H, Cl	100	0
VIb	212–214 dec	A	55	1660	263 (100), 257 (200)	$C_{15}H_{22}N_2O \cdot HCl$	C, H, Cl	100	0
VIII	134–136 (10 mm)[e]		80	1730, 1635	232 (4,400)	$C_9H_{14}N_2O$	C, H, N	100	0
IXa	213–219[f]	C	62	1820, 1590		$C_8H_{15}N_3 \cdot HCl$	C, H, N	100	0
IXb	130–132[g]			1530	233 (11,000)	$C_{13}H_{15}N_3$	C, H, N	100	0
2-[*cis*-2-(Cyclohexylcyclopentyl)imino]hexahydroazepine hydrochloride (RMI 11894)[h]								100	53[b]
								50	49[b]
								25	42[b]
								12.5	33[b]
								6	15[b]
2-(9-Fluorenylimino)hexahydroazepine hydrochloride (RMI 10026)[i]								100	47[b]
								50	44[b]
								25	49[b]
								12.5	32[b]
								6	22[b]
								3	0
Tolbutamide								100	41[b]
								50	43[b]
								25	29[b]
								12.5	16

[a] A = MeOH–Me_2CO, B = Me_2CO, C = Et_2O. [b] Statistically significant at $p \leq 0.05$. [c] RMI 11,945A. [d] Hyperglycemic. [e] $n^{25}D$ 1.5073. [f] Reference 7 gives mp 214°. [g] Reference 7 gives mp 133°. [h] Reference 2. [i] Reference 3.

Scheme I



Ia, R = Ph; R′, R″ = H
b, R = Ph; R′ = Me; R″ = H
c, R = Ph; R′, R″ = Me
d, R = C_6H_{11}; R′ = Me; R″ = H

IIa, n = 3
b, n = 4
c, n = 5
d, n = 6

IIIa, R = Ph; R′, R″ = H; n = 3
b, R = Ph; R′, R″ = H; n = 6

VIa, R = Ph; R′, R″ = H; n = 5
b, R = Ph; R′ = Me; R″ = H; n = 5

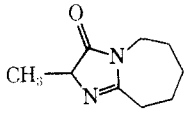
Va, R = Ph; R′ = H; n = 4
b, R = Ph; R′ = H; n = 5
c, R = Ph; R′ = Me; n = 5
d, R = H; R′ = Ph; n = 4

IVa, R = Ph; R′, R″ = H; n = 3
b, R = Ph; R′, R″ = H; n = 4
c, R = Ph; R′, R″ = H; n = 5
d, R = Ph; R′, R″ = H; n = 6
e, R = Ph; R′ = Me; R″ = H; n = 5
f, R = Ph; R′, R″ = Me; n = 3
g, R = C_6H_{11}; R′ = Me; R″ = H; n = 5

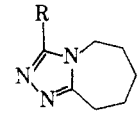
VIIa, R = PH; R′, R″ = H
b, R = Ph; R′ = Me; R″ = H

the other hand, was stable as free base but opened to IIIb hydrochloride on treatment with 1 equiv of methanolic hydrogen chloride. Reactions of the hydrochloride of Ia with lactim ethers IIb and IIc led to formation of the hydrochloride salts of IVb and IVc, respectively. Similarly, the products from reactions of the hydrochlorides of Ib–d were isolated in the cyclized form IVe–g, respectively. An attempt to open IVe to form III failed. An attempt to separate the diastereoisomers of IVe by fractional crystallization of the hydrochloride salt also failed, presumably due to isomerization by interconversion of open and cyclized form. On the other hand, sodium borohydride reduction of IVc in ethanol gave about 30% of the lactamimide carbinol VIa; this finding indicated that IVc had opened to the corresponding lactamimide ketone. The same compound VIa was obtained by reaction of the β-hydroxyamine hydrochloride VIIa with lactim ether IIc. It is evident from these experiments that it is difficult to predict whether a particular compound of this series will exist in the cyclized form IV or in the lactamimide ketone form III when in solution at physiological pH and under physiological conditions. In addition, when in the lactamimide form III, the compounds can occur in two tautomeric forms.[5]

The cyclization of lactamimide ketones to imidazo[1,2-*a*]azacycloalkanes IV and V is analogous to the cyclization of the lactamimide derived from alanine to VIII and of lactamimides derived from acetyl- and benzoylhydrazine leading to IXa and IXb, respectively, reported earlier by Petersen and Tietze.[6,7]



VIII



IXa, R = CH_3
b, R = Ph

Biological Evaluation, Results, and Conclusion

Hypoglycemic activity was determined by the method of Gerritsen and Dulin.[8] Young male rats (Sprague–Dawley strain) were fasted overnight. Six animals were given a glucose load of 1 g/kg sc immediately after dosing of the test compound by stomach tube. Two hours later, blood was withdrawn and plasma glucose was determined by the glucose oxidase procedure.[9] Results are recorded in the last column of Table I.

Compound IVe was by far the most potent hypoglycemic agent in this series. Only one pair was available in both the open and the cyclized form, IIIb and IVd; as expected, both compounds showed very nearly the same degree of activity. Of the aromatized compounds V, only Vc was active but of very low potency. Compounds VI, VIII, and IX showed no hypoglycemic activity.

2,3,6,7,8,9-Hexahydro-2-methyl-3-phenyl-5*H*-imidazo-[1,2-*a*]azepin-3-ol hydrochloride (IVe, RMI 11,945A) was selected from this series for extended biological evaluation. Although somewhat less potent than related hypoglycemic lactamimides, reported earlier from this laboratory,[2,3] preliminary experiments show IVe to have a different pharmacological profile. The possibility of metabolic dehydration of a compound containing a strongly basic amidine function (IVe) to an aromatic and only weakly basic imidazole derivative (Vc) is intriguing. Compound Vc did not show strong hypoglycemic activity and is therefore not the active metabolite of IVe; but it may nevertheless be formed. Studies are now in progress to determine tissue specificity and therapeutic ratio of IVe for comparison to other hypoglycemic lactamimides.

Experimental Section

Melting points are corrected and were taken on a Thomas-Hoover capillary melting point apparatus. Ir spectra were taken on a Perkin-Elmer 521 instrument. Uv spectra were taken on a Cary 17 instrument; unless otherwise indicated, they were run in 95% EtOH. Nmr spectra were taken on a Varian Model A-60 instrument (Me_4Si as internal standard). Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4%.

2,3,6,7,8,9-Hexahydro-2-methyl-3-phenyl-5*H*-imidazo[1,2-*a*]-azepin-3-ol Hydrochloride (IVe). To 50.0 g (0.269 mol) of powdered α-aminopropiophenone hydrochloride (Ib·HCl) was added 60 ml (*ca.* 0.42 mol) of *O*-methylcaprolactim (IIc) and the components were stirred into a slurry. During the first 6 hr of reaction time, the mixture was kept at room temperature and was stirred frequently; several 25-ml portions of anhydrous EtOH were added to keep the thick slurry stirrable. The mixture was then allowed to stand at room temperature for 4 days. It was cooled (−20°), and the precipitate was collected, washed with anhydrous Et_2O, and recrystallized from MeOH–Me_2CO to give 51.4 g (68%) of IVe (Table I). A second crop of 7.4 g (10%) was recovered from the mother liquor.

2,3,6,7-Tetrahydro-2,2-dimethyl-3-phenyl-5*H*-pyrrolo[1,2-*a*]imidazol-3-ol Hydrochloride (IVf). A slurried mixture of 3.3 g of α-amino-α-methylpropiophenone hydrochloride (Ic·HCl) and 5 ml of *O*-methylbutyrolactim (IIa) was allowed to stand at room temperature for 10 days. The mixture was cooled (−20°), and the precipitate was collected and recrystallized from MeOH–Me_2CO to give 1.6 g (36%) of IVf (Table I).

2-[(Octahydroazocin-2-ylidene)amino]acetophenone Hydrochloride (IIIb). To 50.0 g (0.292 mol) of powdered α-aminoacetophenone hydrochloride (Ia·HCl) was added 50 ml (*ca.* 0.35 mol) of *O*-methylenantholactim (IId); the reactants were thoroughly mixed and were allowed to stand at room temperature for 4 days. (After 3 days, 25 ml of anhydrous EtOH was added.) The mixture was cooled (−20°) and the precipitate was collected and washed with anhydrous Et_2O to give 71.0 g of product of mp 149–155°. Two recrystallizations from MeOH–Me_2CO resulted in 41.7 g (51%) of IIIb·HCl (Table I).

To a solution of 10.0 g of IIIb·HCl in MeOH was added 1 equiv of methanolic KOH, the precipitating KCl was filtered off, and the filtrate was evaporated to dryness. The resulting residue was recrystallized three times from MeOH–Me_2CO to give 1.7 g of IVd (Table I). In a duplicate experiment, the residue was reacidified with 1 equiv of methanolic HCl and the resulting salt was recrystallized twice from MeOH–Me_2CO to give 2.6 g of IIIb·HCl (not IVd·HCl).

6,7,8,9-Tetrahydro-2-methyl-3-phenyl-5*H*-imidazo[1,2-*a*]azepine Hydrochloride (Vc). A solution of 22.3 g (0.0795 mol) of IVe in 60 ml of concentrated HCl was refluxed for 3 hr. The mixture was evaporated to dryness under reduced pressure and the residue was recrystallized twice from MeOH–Me_2CO to give 12.8 g (62%) of Vc (Table I): nmr (D_2O) δ 2.30 (s, 3).

α-[(Hexahydroazepin-2-ylidenamine)methyl]benzyl Alcohol Hydrochloride (VIa). A. From 2,3,6,7,8,9-Hexahydro-3-phenyl-5*H*-imidazo[1,2-*a*]azepin-3-ol Hydrochloride (IVc). To 5.0 g of $NaBH_4$ in 100 ml of absolute EtOH at room temperature was added 5.0 g (0.0187 mol) of IVc·HCl (Table I, prepared from Ia·HCl and IIc as described for IVe) and the resulting mixture was stirred for 3 hr. The reaction mixture was then poured into 300 ml of H_2O; the solution was acidified with 2 *N* HCl to destroy excess reagent and made basic again with 2 *N* NaOH. The product was extracted into Et_2O, the extract was washed (4 × H_2O) and dried (Na_2SO_4), ethereal HCl was added, and the solvent was evaporated. The residue crystallized after trituration with Me_2CO, 1.5 g (30%), mp 168–173° dec; the material was identical (mixture melting point and ir) with VIa prepared by method B.

B. From 2-Amino-1-phenylethanol Hydrochloride (VIIa) and IIc. A mixture of 94.4 g (0.543 mol) of VIIa·HCl, 100 ml (0.7 mol) of IIc, and 50 ml of EtOH was allowed to react at room temperature with cooling in an ice bath and was allowed to stand at room temperature for 3 days. The mixture was cooled (−20°) and the precipitate was collected, washed with anhydrous Et_2O, and recrystallized twice from MeOH–Me_2CO to give 120.8 g (83%) of VIa (Table I).

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Aryl 5-Nitro-2-furyl Ketone Antifungal Agents

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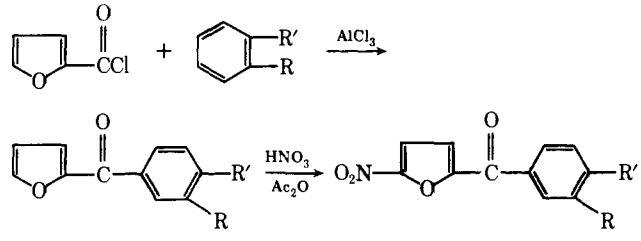
In the course of work directed at the synthesis of furans containing a 5-nitro group and a 2 side chain, 5-nitro-2-furyl phenyl ketone (**1**) was prepared and found to possess antifungal activity. In this paper we describe the synthesis and biological properties of some aryl 5-nitro-2-furyl ketones II and derivatives.

Chemistry. The aryl 5-nitro-2-furyl ketones II were prepared by nitration of the corresponding aryl 2-furyl ketones I with nitric acid and Ac_2O. The position of nitration had been established previously.[1] Compounds I were prepared by Friedel–Crafts reaction from furoyl chloride and appropriately substituted benzenes in the presence of $AlCl_3$. The synthesis of the aryl 2-furyl ketones I which were precursors for **1–5**, **7**, and **8** had been reported previously.[2] Acylation of *o*-dichlorobenzene to prepare Ia occurred para to the halogen as indicated by the nmr spectrum and analogous acylations.[3] The product from the acylation of *o*-fluoroanisole was assigned structure Ib since the position of acylation of analogous reactions had been reported to be para to the methoxy group,[4,5] and oxidative degradation of Ib with $KMnO_4$ gave the known acid, 3-fluoro-4-methoxybenzoic acid.[6,7]

An alternative synthesis of II by reaction of 5-nitro-2-furoyl chloride with substituted benzenes in the presence of $AlCl_3$ failed to give appreciable amounts of pure product with the exception of **1**. Variation of the order of addition of the reactants, the use of $SnCl_4$ and BF_3·Et_2O as catalyst, and the use of various solvents failed to improve the reaction. The derivatives of II listed in Table I were prepared by standard procedures as described in the Experimental Section.



Ia, R = R′ = Cl
b, R = F; R′ = OCH_3

II (**1–9**)

Biological Activity. All compounds prepared were tested *in vitro* for antifungal activity against *Candida albicans* and *Microsporum canis* by the agar diffusion–cylinder cup method.[8] The data are presented in Table I, and the reference standard nystatin is included for comparison. The ketones were found to possess the most significant activity, compounds **1**, **4**, and **8** being the most active. Formation of the oxime and *O*-methyloxime derivatives (**10–13**) decreased activity, while formation of the other derivatives (**14–18**) caused complete loss of activity at the concentrations tested.

Additional testing of **4** and **8** at 200 μg/ml against *C. albicans* under kinetic fungicidal test conditions showed them to be active, reducing a viable cell count of 3 × 10^5/ml to 0 after 2 hr; no growth was evident on subsequent subculture after 72 hr.

Experimental Section†

Aryl 5-Nitro-2-furyl Ketones (1–9). Nitric acid (70%, 95 ml, 1.5 mol) containing 2 ml of concentrated H_2SO_4 was added dropwise to 330 ml (3.5 mol) of Ac_2O with stirring and cooling to maintain the temperature at 25–30°. The aryl 2-furyl ketone (0.5 mol) was added in portions over 20 min at 0°. After the mixture was stirred for 0.5 hr, 300 ml of H_2O and 570 g (1.5 mol) of Na_3PO_4·$12H_2O$ were added. The mixture was heated with stir-

† Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. The ir spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. The nmr spectra were determined with a Varian Associates Model A-60A spectrometer (Me_4Si).