and the filtrate was stripped. The residue was purified by preparative chromatography (chloroform/methanol, 23:2): 0.260 g of compound **10** was obtained (yield 31%); TLC (chloroform/methanol, 24:1) R_f (S) 0.67; IR (chloroform) 1735 (m), 1720 (s), 1700 (s), 1655 (m), 1625 (s), 1595 (s) cm^{-1}.

Synthesis of 3-[(*p*-Bromoanilino)carbonyl]rifamycin S (11). *p*-Bromoaniline (0.400 g, 2.3 mmol) was added to a solution of 1.0 g (1.3 mmol) of **4** in 25 mL of anhydrous dioxane. The reaction was carried out at room temperature, being stirred for 2 h. MnO_2 (2 g) was then added, and 20 min later, the manganese dioxide was removed by filtration. Chloroform (100 mL) was added, and the organic phase was repeatedly washed first with 0.01 N hydrochloric acid and later with water. The dried solution was stripped. The residue was purified by preparative chromatography (chloroform/methanol, 22.5:2.5), R_f (S) 0.9. The light brown product was precipitated from chloroform with hexane: yield 0.400 g (34%); IR (chloroform) 1740 (s), 1710 (s), 1685 (m), 1635 (s), 1605 (s), 1575 (w) cm^{-1}; ^1H NMR δ 7.5–7.8 (m, 4 H, aromatic), 9.75 (br s, 1 H, CONH).

Biological Test. Antimicrobial Activity. MIC values were determined in a liquid medium, by means of the serial dilution method in test tubes. The medium employed was brain–heart infusion (BHI, Difco). The inoculum size was always 10^6 cells/mL. The MIC was defined as the lowest antibiotic concentration that prevented a visible growth after 24 h of incubation at 35 °C.

Acknowledgment. The authors are indebted to Dr. A. P. Venturini for MIC determination and to Dr. L. Cellai, Gruppo di Strutturistica Chimica "G. Giacomello", CNR-Roma, for the studies on RNAP isolated from *E. coli*.

Synthesis and Antibacterial Activity of 1-(Arylamino)-1*H*-pyrroles and 4-(1*H*-Pyrrol-1-ylimino)-2,5-cyclohexadienes

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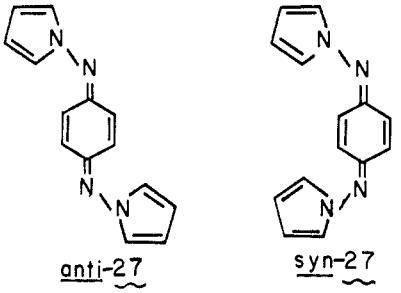
The syntheses of 1-(arylamino)-1*H*-pyrroles and 4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadienes are described. Several of these compounds express in vitro antibacterial activity or can be metabolized to show in vitro antibacterial activity, and a few examples have shown efficacy against tuberculosis in mice. One compound, *N,N'*-(2,5-cyclohexadiene-1,4-diylidene)bis-1*H*-pyrrol-1-amine, is completely effective at 6.25 mg/kg against *Mycobacterium tuberculosis* H37Rv.

The efficacy of the experimental antitubercular agent *N,N'*-(2,5-cyclohexadiene-1,4-diylidene)bis-1*H*-pyrrol-1-amine (azarole, *anti*-**27**) has been reported to be due to its



stimulation of cell-mediated immunity.[1] This unique compound is one of a series of structurally related 1-(arylamino)-1*H*-pyrrol-1-amines and 4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadienes that were investigated for in vitro antibacterial activity and in vivo antitubercular activity. The purpose of this paper is to describe the synthesis of this series of compounds and to relate some of the structural requirements necessary for their antibacterial effects.

Chemistry. The compounds described in Tables I and II were prepared utilizing the procedures outlined in Scheme I.

1-(Arylamino)-1*H*-pyrroles **3–13** were prepared by a sequence of reactions starting with the condensation of benzoic acid 1-arylhydrazides[2-4] [e.g., **1** (R = Bz; X = 4-OCH_2Ph)] and 2,5-diethoxytetrahydrofuran or 2,5-hexanedione in hot glacial acetic acid, followed by alkaline hydrolysis of the intermediate benzamides, and then catalytic hydrogenolysis of the benzyl ethers where appropriate. In a similar manner, **14** was prepared by the catalytic debenzylation of the reaction product of 1-methyl-1-[4-(phenylmethoxy)phenyl]hydrazine (**2**) and 2,5-diethoxytetrahydrofuran.

The synthesis of **16** was accomplished by basic H_2O_2 oxidation, followed by catalytic debenzylation of **15**, which was the reaction product of **4** and oxalyl chloride.

Monoacetylated products **17** or **31** resulted when **8** or **30** were reacted with excess acetic anhydride in pyridine. Similarly, **8** was treated with either 1 or 2 equiv of 4-methylbenzoyl chloride to give **19** or **20**, respectively. Diacetylated **18** was produced when **17** was combined with acetic anhydride using sodium hydride as base.

The 4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadienes **21–24** and compound **32** were obtained by mild oxidation of **8**, **12**, **13**, **5**, and **30**, respectively, with yellow HgO or Ag_2O. Other cyclohexadienes, **25–28**, were directly prepared by the trifluoroacetic acid catalyzed reaction of 1*H*-pyrrol-1-amine[5] (**36**) with the appropriate benzoquinone. Separation of **27** into anti and syn isomers was accomplished by fractional crystallization. The 100-MHz NMR spectrum of *anti*-**27** showed quinone signals at 7.38 and 7.12 ppm with ortho coupling ($J \simeq 10$ Hz), and *syn*-**27** showed quinone signals at 7.35 and 7.09 ppm with no ortho coupling. These NMR results are similar to those reported for *anti*- and *syn-N,N'*-(2,4-cyclohexadien-1,4-diylidene)-bis(2,6-diethylaniline).[6]

(1) J. R. O'Connor, R. A. Dobson, and R. E. Johnson, "Abstracts of Papers", 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sept 1980, American Society for Microbiology, Washington, DC, 1980, Abstr 745.
(2) W. Metlesics, R. F. Tavares, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1311 (1965).
(3) M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Jpn.*, **34**, 668 (1961).
(4) H. Yamamoto, M. Nakao, and A. Kobayashi, *Chem. Pharm. Bull.*, **16**, 647 (1968); *Chem. Abstr.*, **69**, 51931*m* (1968).
(5) R. Epton, *Chem. Ind. (London)*, 425 (1965).
(6) R. W. Layer and C. J. Carman, *Tetrahedron Lett.*, 1285 (1968).

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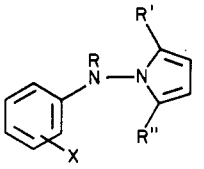
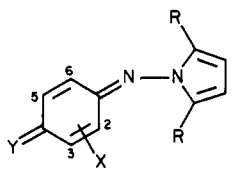
Table I. 1-(Arylamino)-1*H*-pyrroles



compd	X	R	R′, R″	procedures[a] (% yield)	mp or bp (mm), °C	crystn solvent	formula[b]
3	4-OCH_2Ph	Bz	H, H	C (54)	120-122	cyclohexane	$C_{24}H_{20}N_2O_2$
4	4-OCH_2Ph	H	H, H	D (95)	68-70	hexane	$C_{17}H_{16}N_2O$
5	4-NHPh	H	H, H	A-D (20)	110-112	cyclohexane	$C_{16}H_{15}N_3$
6	4-OMe	H	H, H	C, D (50)	38-40		$C_{11}H_{12}N_2O$
					117-119 (0.05)		
7	H	H	H, H	C, D (57)	44-46	pentane	$C_{10}H_{10}N_2$
8	4-OH	H	H, H	E (54)	99-102		$C_{10}H_{10}N_2O$
					143-147 (0.02)		
9	3-OH	H	H, H	A-E (19)	133-135	sublimed	$C_{10}H_{10}N_2O$
10	2-OH	H	H, H	F, B-E (21)	98-100	sublimed	$C_{10}H_{10}N_2O$
11	3,4-diOH	H	H, H	A-E (9)	122-124	PhH	$C_{10}H_{10}N_2O_2$
12	4-OH-2,3-CH=CHCH=CH	H	H, H	F, B-E (13)	148-150	pentane	$C_{14}H_{12}N_2O$
13	4-OH	H	Me, Me	C-E (31)	127-129	cyclohexane	$C_{12}H_{14}N_2O$
14	4-OH	Me	H, H	C, D (32)	70-72	cyclohexane	$C_{11}H_{12}N_2O$
16	4-OH	H	H, COOH	E (47)	158-159	Et_2O/pentane	$C_{18}H_{16}N_2O_3$
17	4-OAc	H	H, H	J (41)	88-91		$C_{12}H_{12}N_2O_2$
					128-134 (0.10)		
18	4-OAc	Ac	H, H	(50)	108-111	cyclohexane	$C_{14}H_{14}N_2O_3$
19	4-(4-MeBz)O	H	H, H	J (86)	137-139	cyclohexane	$C_{18}H_{16}N_2O_2$
20	4-(4-MeBz)O	4-MeBz	H, H	J (18)	178-180	EtOAc	$C_{26}H_{22}N_2O_3$
29	4-(1*H*-pyrrol-1-yl)NH	H	H, H	(95)	176-178	DMF/H_2O	$C_{14}H_{14}N_4$
30	4-OH-2-Cl	H	H, H	(50)	77-80	hexane	$C_{10}H_9ClN_2O$
31	4-OAc-2-Cl	H	H, H	J (83)	118-120	cyclohexane	$C_{12}H_{11}ClN_2O$
37	4-NO	H	H, H	(33)	77-80	PhH	$C_{10}H_9N_3O$

[a] General procecures A-J are detailed under Experimental Section, as are procedures to prepare 18, 29, 30, and 37. Reported yields are overall yields for the procedures indicated. [b] All compounds were analyzed for C, H, and N, and results are within ±0.4% of theoretical values.

Table II. 4-(1*H*-Pyrrol-1-ylimino)-2,5-cyclohexadienes

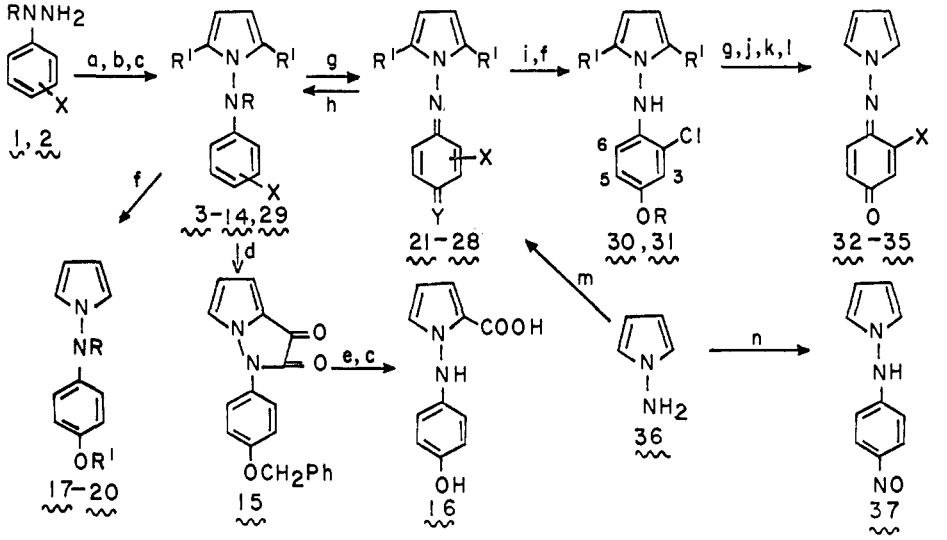


compd	X	Y	R	procedures[a] (% yield)	mp or bp (mm), °C	crystn solvent	formula[b]
21	H	O	H	G (31)	89-91	cyclohexane	$C_{10}H_8N_2O$
22	2,3-CH=CHCH=CH	O	H	H (59)	83-84	Et_2O	$C_{14}H_{10}N_2O$
23	H	O	Me	H (15)	50-54		$C_{12}H_{12}N_2O$
					94-122 (0.1)		
24	H	PhN	H	I (76)	146-147	Me_2CO	$C_{16}H_{13}N_3$
25	3,5-Me_2	O	H	G (80)	68	pentane	$C_{12}H_{12}N_2O$
26	3,5-*t*-Bu_2	O	H	G (79)	77	EtOH/H_2O	$C_{18}H_{24}N_2O$
anti-27	H	(1*H*-pyrrol-1-yl)N	H	(42)	162-164	EtOAc	$C_{14}H_{12}N_4$
syn-27	H	(1*H*-pyrrol-1-yl)N	H	(7)	110-112	EtOAc	$C_{14}H_{12}N_4$
28	2-Me	(1*H*-pyrrol-1-yl)N	H	(40)	167-169	EtOAc	$C_{15}H_{14}N_4$
32	2-Cl	O	H	I (80)	116-118	Et_2O	$C_{10}H_7ClN_2O$
33	2-Me_2N	O	H	(46)	128-130	CCl_4	$C_{12}H_{13}N_3O$
34	2-N_3	O	H	(53)	104-106	cyclohexane	$C_{10}H_7N_5O$
35	2-NH_2	O	H	(53)	163-165	CCl_4	$C_{10}H_9N_3O$

[a] General procedures G-I are detailed under Experimental Section, as are procedures to prepare 27, 28, 33, 34, and 35. [b] All compounds were analyzed for C, H, and N, and results are within ±0.4% of theoretical values.

1-(Arylamino)-1*H*-pyrroles **29** and **8** were prepared by sodium hydrosulfite reduction of **27** and **21**, respectively. Addition of HCl (g) to **21** gave **30**. Structural identification of **30** was made by comparing the 100-MHz NMR spectra of the three aromatic protons of **30** [H^6, 6.11 ppm ($J \simeq$ 8.6 Hz); H^5, 6.53 ppm ($J \simeq$ 2.6 and 8.6 Hz); H^3, 6.79 ppm ($J \simeq$ 2.6 Hz)] and the acetate of **30** (**31**) [H^6, 6.13 ppm ($J \simeq$ 8.6 Hz); H^5, 6.75 ppm ($J \simeq$ 2.6 and 8.6 Hz); H^3, 7.04 ppm ($J \simeq$ 2.6 Hz)]. The 0.22–0.25 ppm downfield shift of the H^5 and H^3 protons of **31** relative to **30** indicate that

Scheme I



[a] (a) 2,5-diethoxytetrahydrofuran or 2,5-hexanedione in hot AcOH, (b) KOH, MeOH, (c) H_2, Pd/C, (d) $(COCl)_2$, Et_2O, (e) OH^-, H_2O_2, (f) Ac_2O or 4-MeBzCl, base, (g) Ag_2O or HgO, (h) $Na_2S_2O_4$, (i) HCl(g), Et_2O, (j) $MeNH_2$, (k) NaN_3, (l) $Na_2S_2O_4$, OH^-, (m) sub-1,4-benzoquinone, H^+, (n) 4-nitrosophenol, *p*-TsOH, MeOH.

their attachments are ortho to the oxygen function.[7]

When **32** was treated with dimethylamine or sodium azide, **33** or **34** resulted, respectively, and **35** was obtained by sequential treatment of **34** with sodium hydrosulfite and sodium hydroxide.

The method of Hayes, Young, and Espy[8] furnished **37** from **36** and 4-nitrosophenol.

Biology. Several 1-(arylamino)-1*H*-pyrroles and 4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadienes were antibacterial at MIC ≤ 31.3 μg/mL against *Staphylococcus aureus* and *Proteus mirabilis* (Table III). Antibacterial activity against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* was only observed for these compounds at MIC ≥ 62.5 μg/mL (data not shown). The most susceptible organism was *Staphylococcus aureus*, which **8**, **10–13**, **21**, and **23** inhibited at ≤7.8 μg/mL. These and other less effective agents, **5**, **22**, **25**, **32**, and **35**, were components of hydroquinone/benzoquinone pairs. Three hydroquinone/benzoquinone pairs, **8/21**, **12/22**, and **13/23**, were antibacterial. All compounds closely related to **8** that were not capable of undergoing this redox interconversion, **6**, **7**, **14**, and **17–20**, were not inhibitory. Although fewer compounds were antibacterial toward *Proteus mirabilis*, the same necessity of hydroquinone/benzoquinone interconversion was suggested. Only phenols **8**, **10**, and **13** had MIC ≤ 31.3 μg/mL, and the quinone analogues of **8** and **13**, **21** and **23**, had MIC = 62.5 μg/mL.

Metabolites present in urine from medicated rats expressed the antibacterial activities against *Staphylococcus aureus* and *Proteus mirabilis* that are reported in Table III. Activity against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* at dilutions greater than 1:2 was not observed (data not shown). This selective activity against *Staphylococcus aureus* and *Proteus mirabilis* in this assay is the same as that observed for the in vitro antibacterial assay. Noteworthy are **6**, **7**, and **17**, which cannot take part in hydroquinone/benzoquinone redox reactions and showed no in vitro antibacterial activity, yet are metabolically activated to show similar antibacterial activities to the hydroquinone/benzoquinone pair **8/21**. This activation suggests that the metabolism of **6**, **7**, and **17** may involve formation of antibacterial

Table III. In Vitro and Metabolite Antibacterial Activity of 1-(Arylamino)-1*H*-pyrroles and 4-(1*H*-Pyrrol-1-ylimino)-2,5-cyclohexadienes[a]

	Staphylococcus aureus		*Proteus mirabilis*	
compd	MIC[b]	MID[c]	MIC[b]	MID[c]
5	31.3	<1:2	>250	<1:2
6	>125	1:32	>125	1:16
7	250	1:128	>125	1:192
8	≤7.8	1:64	31.3	1:16
9	62.5	<1:2	500	<1:2
10	≤7.8	<1:2	15.6	<1:2
11	≤7.8	1:8	62.5	<1:2
12	≤7.8	1:4	62.5	<1:2
13	≤7.8	1:4	15.6	<1:2
14	125	<1:2	>250	<1:2
16	500	1:16	500	1:8
17	>62.5	1:16	>62.5	<1:2
18	>250	1:2	>125	<1:2
19	>250	1:4	>250	<1:2
20	125	<1:2	>62.5	<1:2
21	<7.8	1:32	62.5	1:4
22	31.3	1:2	>62.5	<1:2
23	≤7.8	1:2	62.5	<1:2
24	>62.5	<1:2	>62.5	<1:2
25	31.3	1:4	>125	<1:2
26	>62.5	<1:2	>62.5	<1:2
anti-27	>125	1:16	>62.5	1:16
syn-27	>62.5	1:8	>125	1:32
28	>62.5	<1:2	>62.5	<1:2
29	125	<1:2	>250	<1:2
30	62.5	<1:2	>125	1:2
32	31.3	<1:2	>125	<1:2
33	62.5	<1:2	>125	<1:2
34	125	<1:2	>250	<1:2
35	15.6	1:2	125	1:4
37	125	<1:2	250	<1:2
naladixic acid	62.5	1:16	15.6	1:128
chloramphenicol	3.9	1:16	>62.5	1:8
furadantin	15.6	1:32	>62.5	1:2

[a] See Experimental Section for details of assay systems. [b] Minimum inhibitory concentration in micrograms per milliliter. Compounds were considered active if their MIC was ≤ 31.3 μg/mL. [c] Minimum inhibitory dilution (MID) of medicated rat urine. Compounds were considered active if their MID was > 1:4.

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, p 202.
(8) J. T. Hayes, H. L. Young, and H. H. Espy, *J. Org. Chem.*, 32, 158 (1967).

Table IV. Antitubercular Activity of 1-(Arylamino)-1*H*-pyrroles and 4-(1*H*-Pyrrol-1-ylimino)-2,5-cyclohexadienes in the 31-Day Murine Model[a]

		% survival after 31 days[b]					
compd	dose, mg/kg:	3.1	6.25	12.5	25	50	100
8		0	30	100	100	100	
21		0	60	100	100	100	
anti-27		10	80	100	100	100	100
syn-27		70	100	80	100	100	
29			0	0	40	0	0
isoniazid		100	100	100			
ethambutol				0	30	90	100

[a] See Experimental Section for details of assay method. [b] Compounds were considered active if the survival rate was ≥80%.

metabolites that can oxidatively/reductively interconvert. Anomalously, *anti*- and *syn*-27 show metabolic activation to become antibacterial, and metabolism of their reduced form (29) showed no antibacterial activity.

More important than the in vitro and metabolite antibacterial activity is the curative effect that four of these compounds, 8, 21, *anti*-27, and *syn*-27 have on mice infected with *Mycobacterium tuberculosis* H37Rv (Table IV). This antitubercular effect appears to be unrelated to the activity of these compounds against *Staphylococcus aureus* and *Proteus mirabilis*. The most potent antituberculars, *anti*-27 and *syn*-27, did not inhibit the other two bacteria, and 8 and 21 showed efficacy against tuberculosis; yet other analogues that were effective against *Staphylococcus aureus* and *Proteus mirabilis* were ineffective against tuberculosis. Almost any manipulation of or substitution on the 8 or 21 structure (e.g., 6, 7, 9–14, 16–20, 22–26, 30, and 32–37) resulted in complete loss of antitubercular activity. As noted previously, 8 and 21 are related by an oxidative/reductive interconversion and their equipotent antitubercular activity may be a consequence of this property. Surprisingly, the reduced form of 27 (29) was totally ineffective in the antitubercular assay. Analogous to 8 and 21, minor modification of the 27 structure (e.g., 5, 24, and 28) resulted in complete loss of antitubercular activity. Equipotency of *anti*-27 and *syn*-27 was anticipated in that in solution either compound equilibrates to the same isomeric mixture (ca. 1:1). Due to difficulties in preparing the syn isomer, further evaluation of 27 has been on the more easily prepared *anti*-27.

The antitubercular *anti*-27 appears to be unique when compared to biologically active analogues. The total inactivity of the reduced form, 29, is contrasted by the activities of other hydroquinone/benzoquinone pairs in the three assays studied. Also, unlike 8 and 21, the other effective antituberculars studied, *anti*-27 was without effect in the in vitro antibacterial assay, although it did have activity in the metabolite assay. Because of its antitubercular potency and unique profile, *anti*-27 has undergone further investigations to determine its mechanism of action. Evidence has previously been presented that at least a significant portion of the antitubercular effect of *anti*-27 may be due to an influence on cell-mediated immunity and that efficacy in other animal models of disease, such as adjuvant arthritis (rat), streptozotocin-induced diabetes (rat), and spontaneous hypertension (rat), may also be due in part to regulation of the immune system.[1]

Experimental Section

Biology. Microbial Assay. The compounds were assayed for antimicrobial activity by the method of Goss and Cimijotti[9] as either H_2O solutions or H_2O solutions containing the minimum amount of Me_2SO necessary to maintain solution. The minimal inhibitory concentration (MIC) of compounds prefaced by a "greater than" sign indicates that the solvent blank containing Me_2SO was inhibitory at that concentration. The test organisms were *Staphylococcus aureus* and *Proteus mirabilis*. Compounds were considered active if their MIC was 31.3 μg or less per milliliter of assay medium.

Metabolite Antibacterial Assay. Female Sprague–Dawley rats wieghing 160 to 200 g were divided into groups of three. Each group received 50 mg/kg of test compound, followed in 8 h by a second 50 mg/kg medication. Compounds were administered orally in 1 mL of 1.0% gum tragacanth/100 g of body weight. The urine from each group was collected for 24 h starting at the time of first medication. At the end of the collection period, the samples were measured, centrifuged for clarification, sterilized by ultrafiltration, and frozen in sealed vials at −20 °C until they were thawed for testing against the following bacterial organisms: *Staphylococcus aureus*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Antibacterial activity of the urine samples was determined on the Autotiter by serial, two-fold dilutions of the urine in tryptose phosphate broth to which the bacterial inoculum was added. The inoculum was prepared by diluting an 18-h broth culture to a 0.1 optical density before diluting to 1:250 in tryptose phosphate broth. Urine dilutions were incubated for 18 h at 37 °C. The highest dilution that showed no visible growth was considered to be the maximum inhibitory dilution (MID). Compounds were considered active if their MID was greater than 1:4.

Murine Antituberculosis Assay. Female Swiss mice weighing 14 to 16 g were divided into groups of 10 for each treated group with 20 mice in an infected control group. Infection was established by an intravenous inoculation of 0.1 mL of a 2 mg/mL suspension of *Mycobacterium tuberculosis*, strain H37Rv, grown in Yoman's media for 2 weeks at 37.0 °C. Medication was administered in a volume of 0.5 mL of 1.0% gum tragacanth orally and was initiated 3 days postinfection and continued twice daily 5 days a week for 4 weeks. The percent survival of mice in each treatment group was recorded when the test was terminated at 31 days postinfection. Compounds were considered active if the survival rate was consistently >80% at the doses tested.

Chemistry. Microanalytical determinations were obtained on all new compounds reported and were carried out by Instranal Laboratories, Inc., Rensselaer, NY, and Galbraith Laboratories, Inc., Knoxville, TN. Analyses for the indicated elements were within ±0.4% of the theoretical values. Melting points are uncorrected. NMR spectra were determined on a 100-MHz Varian instrument. Chemical shifts (δ) are reported relative to Me_4Si (δ 0.00, internal standard).

Noncommercial starting materials were benzoic acid 1-(4-methoxyphenyl)hydrazide[4] for 6, benzoic acid 1-phenylhydrazide[10] for 7, *N*-(2-hydroxyphenyl)benzamide[11] for 10, 3,4-bis(phenylmethoxy)benzenamine[12] for 11, and *N*-(4-hydroxy-1-naphthalenyl)benzamide[13] for 12. The following alphabetized procedures are examples of general procedures utilized to prepare

(9) W. A. Goss and E. B. Cimijotti, *Appl. Microbiol.*, 16, 1414 (1968).

(10) G. Lockemann, *Chem. Ber.*, 43, 2223 (1910).
(11) H. Hubner, *Justus Liebigs Ann. Chem.*, 210, 387 (1881).
(12) W. Baker, A. Kirby, and L. Montgomery, *J. Chem. Soc.*, 2876 (1932).
(13) K. Nishida, N. Ohgoshi, T. Akimoto, and M. Tsuchimoto, *Sen'i Gakkaishi*, 25, 141 (1969); *Chem. Abstr.*, 72, 13798c (1970).

many of the compounds listed in Tables I and II. Yields throughout have not been optimized.

Procedure A. *N*-[4-(Phenylmethoxy)phenyl]benzamide. A solution of 23.5 g (0.10 mol) of 4-(phenylmethoxy)benzenamine hydrochloride in 150 mL of pyridine was prepared by warming. This solution was stirred at 20–30 °C with ice-bath cooling while 15.5 g (0.11 mol) of BzCl was added dropwise. The mixture was stirred for 15 min without cooling, then 200 mL of H_2O was added, and the solid that formed was collected and dried to give 29.3 g (90%), mp 228–229 °C (lit.[14] mp 235–236.5 °C).

Procedure B. Benzoic Acid 1-[4-(Phenylmethoxy)-phenyl]hydrazide (1). To a stirred suspension of 12 g (0.29 mol) of NaH (57% mineral oil dispersion) in 250 mL of DMF was added in portions 74 g (0.24 mol) of *N*-[4-(phenylmethoxy)phenyl]-benzamide. This mixture was stirred for 1 h. An Et_2O solution of chloramine was prepared by adding 105 mL of concentrated NH_4OH dropwise in 5 min to a stirred mixture of 2.5 L of Et_2O and 650 mL of Clorox (5.25% aqueous NaOCl) maintained at 0 ± 2 °C, stirring the resulting mixture for 15 min at 0 °C, separating the Et_2O layer, drying this Et_2O layer by vigorous stirring over pulverized $CaCl_2$ for 15 min, and finally filtering this mixture to give the desired ethereal chloramine. This solution was added rapidly to the previously prepared DMF solution. The mixture was stirred for 4 h and filtered, and the filtrate was washed with 1 L of 1:1 H_2O/saturated brine. The product precipitated at this point from the Et_2O solution and was collected, washed with Et_2O, and suspended in 500 mL of EtOH, and 25 mL of 10 N HCl (EtOH) was added to give 79 g (92%) of 1·HCl, mp 183 °C. A small sample was recrystallized from EtOH, mp 191–193 °C. Anal. ($C_{20}H_{18}N_2O_2$·HCl) C, H, N.

Procedure C. *N*-[4-(Phenylmethoxy)phenyl]-*N*-(1*H*-pyrrol-1-yl)benzamide (3). A mixture of 49 g (0.14 mol) of 1·HCl, 24 g (0.15 mol) of 2,5-diethoxytetrahydrofuran, 12 g (0.15 mol) of NaOAc, and 150 mL of AcOH was stirred and heated on a steam bath for 15 min. The NaOAc was deleted if free base 1 was used. The mixture was cooled, 200 mL of EtOAc was added, and this mixture was washed with 3 × 1 L of H_2O and 500 mL of saturated $NaHCO_3$. The organic solution was dried ($MgSO_4$) and concentrated to give 40 g of a solid. Recrystallization from cyclohexane gave 28.1 g (54%) of **3**, mp 120–122 °C. Anal. ($C_{24}H_{20}N_2O_2$) C, H, N.

Procedure D. *N*-[4-(Phenylmethoxy)phenyl]-1*H*-pyrrol-1-amine (4). To a solution of 10.6 g (0.16 mol) of KOH in 100 mL of MeOH was added 47 g (0.13 mol) of **3**. This mixture was heated under reflux for 1.5 h, concentrated, diluted with 200 mL of H_2O, and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$), charcoaled, and concentrated to give 32.5 g (95%) of **4** as an oil. A small portion was crystallized from hexane, mp 68–70 °C. Anal. ($C_{17}H_{16}N_2O$) C, H, N.

Procedure E. 4-(1*H*-Pyrrol-1-ylamino)phenol (8). A solution of 30 g (0.11 mol) of **4** in 170 mL of EtOH was hydrogenated over 3.0 g of 10% Pd/C in a Parr apparatus at room temperature under an initial H_2 pressure of 47 psi. After 1.2 equiv of H_2 had been taken up, the catalyst was removed and the solution was concentrated to give 20 g of an oil. The oil was dissolved in Et_2O and extracted with 2 N NaOH. The basic extract was made acidic with 2 N HCl and extracted with Et_2O. This Et_2O extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated to give 17 g of an oil, which was distilled to give 10.7 g (54%) of **8**: bp 143–147 °C (0.02 mm); mp 99–102 °C. Anal. ($C_{10}H_{10}N_2O$) C, H, N.

Procedure F. *N*-Methyl-*N*-nitroso-4-(phenylmethoxy)-benzenamine. A solution of 38.5 g (0.25 mol) of 4-(*N*-methyl-*N*-nitrosoamino)phenol[15] in 150 mL of DMF was added in 15 min to a cooled mixture of 12 g (0.29 mol) of NaH (57% mineral oil dispersion) in 150 mL of PhH. When H_2 evolution was complete, a solution of 36.0 g (0.29 mol) of chloromethylbenzene in 50 mL of PhH was added, and the mixture was allowed to stand for 15 h. The mixture was diluted with H_2O and extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$) and concentrated to give 63 g of a solid, which was recrystallized from cyclohexane to give 52.8 g (88%), mp 95–97 °C. Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

1-Methyl-1-[4-(phenylmethoxy)phenyl]hydrazine (2). A solution of 55 g (0.23 mol) of *N*-methyl-*N*-nitroso-4-(phenylmethoxy)benzenamine in 400 mL of THF was added in 0.5 h to a stirred mixture of 8.5 g (0.23 mol) of $LiAlH_4$ in 300 mL of THF while maintaining the temperature at 30–40 °C. The mixture was stirred for 1 h and then treated with 10 mL of *i*-PrOH and 200 mL of 30% NaOH. The mixture was filtered and the organic layer was separated and concentrated to give 51.5 g of an oil, which solidified and was recrystallized from cyclohexane to give 38.7 g (74%) of **2**, mp 76–77 °C. Anal. ($C_{14}H_{16}N_2O$) C, H, N.

1-[4-(Phenylmethoxy)phenyl]-1*H*-pyrrolo[1,2-*b*]-pyrazole-2,3-dione (15). A solution of 18.0 g (0.068 mol) of **4** in 100 mL of Et_2O was stirred and cooled at −20 °C while a solution of 10.0 g (0.078 mol) of oxalyl chloride in 150 mL of Et_2O was added slowly in 0.5 h. The mixture was stirred without cooling for 1 h, and the solid that formed was collected and air-dried to give 13.3 g (62%) of **15**: mp 140–142 °C dec. A small sample was recrystallized from PhH, mp 181–182 °C. Anal. ($C_{19}H_{14}N_2O_3$) C, H, N.

1-[(4-Hydroxyphenyl)amino]-1*H*-pyrrole-2-carboxylic Acid (16). A solution of 16.8 g (0.053 mol) of **15** in 110 mL of 2 N NaOH and 150 mL of H_2O was obtained by heating the stirred mixture to 50 °C. The solution was cooled to 42 °C and 15 mL (0.17 mol) of 30% H_2O_2 was added dropwise in 5 min, keeping the temperature at 42 °C with an ice bath. The mixture was stirred for 10 min at 42 °C and then overnight at room temperature. The mixture was made acidic to litmus paper by adding concentrated HCl and then extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$), charcoaled, concentrated, and crystallized from PhH/pentane to give 10 g (60%) of 1-[[4-(phenylmethoxy)phenyl]amino]-1*H*-pyrrole-2-carboxylic acid, mp 158–159 °C. A small portion was recrystallized from CCl_4/EtOAc, mp 163–164 °C. Anal. ($C_{19}H_{16}N_2O_3$) C, H, N.

Catalytic hydrogenation of 9.2 g (0.030 mol) of this material using procedure E gave 3.1 g (47%) of **16**, mp 154 °C dec (Et_2O–pentane). Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

Procedure G. 4-(1*H*-Pyrrol-1-ylimino)-2,5-cyclohexadien-1-one (21). A freshly prepared solution of 24 g (0.29 mol) of 1*H*-pyrrol-1-amine[5] in 500 mL of H_2O containing 50 mL of 2 N HCl was added rapidly to a solution of 33 g (0.30 mol) of 1,4-benzoquinone in 2 L of H_2O. After the mixture had set at room temperature for 15 min, the orange-red solid that had formed was collected, washed with H_2O, air-dried, and recrystallized from cyclohexane to give 15.5 g (31%) of **21**, mp 89–91 °C. Anal. ($C_{10}H_8N_2O$) C, H, N.

Procedure H. 4-(1*H*-Pyrrol-1-ylimino)-1(4*H*)-naphthalenone (22). A mixture of 8.0 g (0.036 mol) of **12**, 15 g (0.07 mol) of HgO, and 150 mL of PhH was heated with stirring under reflux using a Dean–Stark H_2O trap for 20 min, collecting 0.6 mL of H_2O. The hot mixture was filtered through diatomaceous earth and concentrated to 8 g of a solid, which was dissolved in 500 mL of hot Et_2O, charcoaled, concentrated to 50 mL, and cooled to give 4.7 g (59%) of **22**, mp 83–84 °C. Anal. ($C_{14}H_{10}N_2O$) C, H, N.

Procedure I. *N*-[4-(Phenylimino)-2,5-cyclohexadien-1-ylidene]-1*H*-pyrrol-1-amine (24). To a stirred solution of 12.5 g (0.050 mol) of **5** in 200 mL of acetone was added 25 g (0.20 mol) of Ag_2O. The mixture was stirred for 0.5 h at room temperature, heated to boiling, filtered, and concentrated to 100 mL. The solid which separated was collected to give 9.5 g (76%) of **24**, mp 146–147 °C. Anal. ($C_{16}H_{13}N_3$) C, H, N.

Procedure J. 4-(1*H*-Pyrrol-1-ylamino)phenyl Acetate (17). To a stirred solution of 10.0 g (0.058 mol) of **8** in 50 mL of pyridine was added 15 g (0.15 mol) of Ac_2O in 5 min. The mixture was stirred overnight, diluted with H_2O, and extracted with Et_2O. The Et_2O extract was washed with 2 N HCl and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 12.5 g of an oil. Distillation of the oil yielded 5.1 g (41%) of **17**: bp 128–134 °C (0.10 mm); mp 88–91 °C. Anal. ($C_{12}H_{12}N_2O_2$) C, H, N.

***N*-[4-(Acetyloxy)phenyl]-*N*-1*H*-pyrrol-1-ylacetamide (18).** A slurry of 1.5 g (0.036 mol) of NaH (57% mineral oil dispersion) in 25 mL of DMF was stirred in an ice bath while a solution of 6.0 g (0.028 mol) of **17** in 25 mL of DMF was added. Then 3.5 g (0.034 mol) of Ac_2O was added in portions. The mixture was stirred in the ice bath for 1 h, diluted with H_2O, and extracted

(14) H. M. Blatter, U.S. Patent 3 165 529 (1965); *Chem. Abstr.*, **62**, 7767c (1965).

(15) J. Ehrlich, *J. Am. Chem. Soc.*, **70**, 2286 (1948).

with Et_2O. The Et_2O extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated, and the residue was crystallized from cyclohexane to give 3.8 g (50%) of **18**, mp 108–111 °C. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

***anti*- and *syn*-*N*,*N*′-(2,5-Cyclohexadiene-1,4-diylidene)-bis-1*H*-pyrrol-1-amine (*anti*- and *syn*-27).** To a solution of 74 g (0.90 mol) of **36** and 46 g (0.43 mol) of 1,4-benzoquinone in 700 mL of Et_2O was added 2 mL of CF_3COOH. This solution sat at room temperature overnight, and the red solid that had formed was collected and recrystallized from EtOAc to give 42.6 g (42%) of *anti*-**27** in the first two crops: mp 162–164 °C; NMR ($CDCl_3/Me_2SO$, 3:1) δ 7.38 (dd, 2, ArH, $J \simeq 10$ and 3 Hz), 7.12 (dd, 2, ArH, $J \simeq 10$ and 3 Hz), 7.02 (t, 2, pyrrole H, $J \simeq 3$ Hz), 6.26 (t, 2, pyrrole H, $J \simeq 3$ Hz). Anal. ($C_{14}H_{12}N_4$) C, H, N. A third crop gave 26.7 g (mp 115–120 °C) which was mostly *syn*-**27** as determined by TLC (SiO_2; CH_2Cl_2/hexane, 1:1). This material was pulverized in a mortar and then stirred for 1 h at room temperature with EtOAc. The mixture was filtered and concentrated without heating to 50 mL. The solid which separated was collected and dried to give 7.5 g (7%) of *syn*-**27**: mp 110–112 °C (resolidified and mp 162–163 °C); NMR ($CDCl_3/Me_2SO$, 3:1) δ 7.35 (d, 2, ArH, $J \simeq 2$ Hz), 7.09 (d, 2, ArH, $J \simeq 2$ Hz), 7.03 (t, 2, pyrrole H, $J \simeq 3$ Hz), 6.26 (t, 2, pyrrole H, $J \simeq 3$ Hz). Anal. ($C_{14}H_{12}N_4$) C, H, N.

***N*,*N*′-(2-Methyl-2,5-cyclohexadiene-1,4-diylidene)bis-1*H*-pyrrol-1-amine (28).** To a solution of 8.2 g (0.10 mol) of **36** and 6.0 g (0.050 mol) of 2-methyl-1,4-benzoquinone in 50 mL of Et_2O was added 10 drops of CF_3COOH. After 2 days the solid which had formed was collected and recrystallized from EtOAc to give 5.0 g (40%) of **28**, mp 167–169 °C. Anal. ($C_{15}H_{14}N_4$) C, H, N.

***N*,*N*′-Di-1*H*-pyrrol-1-yl-1,4-benzenediamine (29).** A solution of 15 g (0.064 mol) of *anti*-**27** in 500 mL of warm DMF was stirred while a solution of 30 g (0.17 mol) of $Na_2S_2O_4$ in 150 mL of H_2O was added in 0.5 min. The mixture was stirred for 1 h and then poured into 1500 mL of H_2O. The solid was collected, washed with H_2O, and dried to give 14.2 g (95%) of **29**, mp 176–178 °C. Anal. ($C_{14}H_{14}N_4$) C, H, N.

3-Chloro-4-(1*H*-pyrrol-1-ylamino)phenol (30). A solution of 15.0 g (0.087 mol) of **21** in 600 mL of Et_2O was cooled in an ice bath while HCl (g) was bubbled through the solution for 10 min. The resulting solution was washed with H_2O and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 10 g of a solid, which was recrystallized from hexane to give 9.0 g (50%) of **30**: mp 77–80 °C; NMR ($CDCl_3$) δ 6.87 (br s, 1, NH), 6.79 (d, 1, ArH, $J \simeq 2.6$ Hz), 6.71 (t, 2, pyrrole H, $J \simeq 2$ Hz), 6.53 (dd, 1, ArH, $J \simeq 2.6$ and 8.6 Hz), 6.15 (t, 2, pyrrole H, $J \simeq 2$ Hz), 6.11 (d, 1, ArH, $J \simeq 8.6$ Hz), 4.50 (br s, 1, OH). Anal. ($C_{10}H_9ClN_2O$) C, H, N.

3-Chloro-4-(1*H*-pyrrol-1-ylamino)phenyl Acetate (31). From 2.0 g (0.0096 mol) of **30** and 1.2 g (0.012 mol) of Ac_2O, using procedure J, was obtained 2.0 g (83%) of **31**: mp 118–120 °C (cyclohexane); NMR ($CDCl_3$) δ 7.04 (d, 1, ArH, $J \simeq 2.6$ Hz), 7.00 (br s, 1, NH), 6.75 (dd, 1, ArH, $J \simeq 2.6$ and 8.6 Hz), 6.65 (t, 2, pyrrole H, $J \simeq 2$ Hz), 6.13 (t, 2, pyrrole H, $J \simeq 2$ Hz), 6.10 (d, 1, ArH, $J \simeq 8.6$ Hz), 2.23 (s, 3, CH_3CO). Anal. ($C_{12}H_{11}ClN_2O_2$) C, H, N.

3-(Dimethylamino)-4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadien-1-one (33). A solution of 2.0 g (0.04 mol) of dimethylamine in 25 mL of EtOH was added to a solution of 5.0 g (0.024 mol) of **32** in 100 mL of warm EtOH. After 20 min, the mixture was diluted with saturated NaCl and extracted with EtOAc. The EtOAc extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated to give 4.5 g of an oil which was crystallized from CCl_4 to give 2.4 g (46%) of **33**, mp 128–130 °C. Anal. ($C_{12}H_{13}N_3O$) C, H, N.

3-Azido-4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadien-1-one (34). A solution of 5.1 g (0.024 mol) of **32** in 100 mL of EtOH was heated to 60 °C and then mixed with a solution of 3.2 g (0.05 mol) of NaN_3 in 50 mL of H_2O. The mixture was heated at 55–60 °C for 20 min, cooled, and diluted with H_2O, and the solid was collected and recrystallized from cyclohexane to give 2.7 g (53%) of **34**, mp 104–106 °C. Anal. ($C_{10}H_7N_5O$) C, H, N.

3-Amino-4-(1*H*-pyrrol-1-ylimino)-2,5-cyclohexadien-1-one (35). A solution of 4.0 g (0.019 mol) of **34** in 15 mL of EtOAc was combined with a solution of 4.0 g (0.23 mol) of $Na_2S_2O_4$ in 20 mL of H_2O. This mixture was stirred for 1 h, and the organic layer was separated, dried ($MgSO_4$), and concentrated to give 4.0 g of a solid. This solid was dissolved in 50 mL of EtOAc and 10 mL of 2 N NaOH was added. After this mixture was stirred for 1 h under N_2, an additional 10 mL of 2 N NaOH was added, the mixture was stirred overnight, an additional 10 mL of 2 N NaOH was added, and the mixture was again stirred for 1 h. The organic layer was separated, dried ($MgSO_4$), and concentrated, and the residue was recrystallized from CCl_4 to give 1.9 g (53%) of **35**, mp 163–165 °C. Anal. ($C_{10}H_8N_3O$) C, H, N.

***N*-(4-Nitrosophenyl)-1*H*-pyrrol-1-amine (37).** A mixture of 14.0 g (0.11 mol) of 4-nitrosophenol and 3.0 g (0.016 mol) of *p*-toluenesulfonic acid monohydrate in 80 mL of MeOH was stirred at room temperature for 1 h. Then, 8.2 g (0.10 mol) of **36** was added, the mixture was stirred for 3.5 h, treated with 6.0 g (0.07 mol) of $NaHCO_3$ in 80 mL of H_2O, and stirred for another 0.5 h, and the precipitate was collected. Chromatography on SiO_2 using EtOAc/hexane (1:4) as eluate gave a solid that was recrystallized from PhH to give 6.2 g (33%) of **37**, mp 77–80 °C. Anal. ($C_{10}H_9N_3O$) C, H, N.

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