NEW COMPOUNDS

Studies in the Furan Series. 22. *N*-Arylfurfuryl- and *N*-Aryl-5-methylfurfurylamines and Their *N*-Allyl Derivatives†

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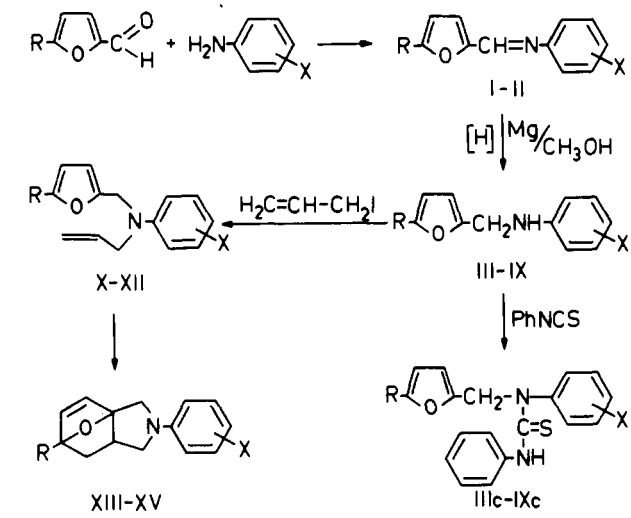
The title compounds, where aryl is a meta- or para-substituted chlorophenyl, methoxyphenyl, or methylphenyl group, were prepared by reduction of corresponding azomethines. Their allylation with allyl iodide or allyl bromide yielded tertiary *N*-arylfurfurylamines which under spontaneous intramolecular Diels–Alder reaction isomerize to *N*-arylepoxyisoindolines.

Several reports from our laboratory deal with the intramolecular Diels–Alder reaction of *N*-allylfurfurylamines (*1*, *2*) and the influence of substituents on the rate of *N*-aryl-5,7a-epoxy-4*H*-isoindoline formation (*3*, *4*). In continuation of previous work, as a consequence of our general interest in furane chemistry (*5*) and potential biological (pesticidal) activity with similar compounds (*6*, *7*), in the present paper we report details of the preparation of tertiary *N*-allyl-*N*-aryl-*N*-furfurylamines and their precursors, corresponding *N*-arylfurfurylamines. (See Scheme I.)

Scheme I



Experimental Section

Melting and boiling points are uncorrected. UV spectra were recorded on a Unicam SP-800 spectrometer with ethanolic solutions. ^{1}H NMR spectra in deuterated chloroform were obtained with a Jeol JNM-FX 90 Q spectrometer, and shifts (δ) are given in ppm relative to internal Me_4Si. Refractive indices were measured with a Carl Zeis Jena refractometer. Elemental analyses on all new compounds were submitted for review and were within ±0.3% of the expected values.

Azomethines. All furfurylidenearylamines were prepared according to reported or modified procedures (*8–10*) exemplified by compounds I and II.

***N*-Furfurylidene-*m*-anisidine (*I*).** To freshly distilled furfural (19.2 g, 0.2 mol) was added on equimolar quantity of *m*-anisidine (24.6 g, 0.2 mol) in portions with cooling. The mixture was stirred for 2 h and fractionated under reduced pressure; 86% (34.5 g) of crude product, bp 186–188 °C/18 mmHg was obtained. An analytically pure sample had bp 173 °C/7 mmHg.

***N*-Furfurylidene-*m*-chloroaniline (*II*).** The compound was prepared by substantially the same procedure, but reactants were used as benzene solutions (50%). The reaction mixture was kept for 2 h over dry magnesium sulfate, the solvent was evaporated, and the crude product was fractionated: yellow oil (90%), bp 155–157 °C/7 mmHg. An analytically pure sample had bp 151–152 °C/5 mmHg.

Secondary Amines. General Procedure. A mixture of an azomethine (0.2 mol) and 1 g-atom of *magnesium turnings* in 400 mL of dry methanol was left to react until the evolution of hydrogen ceased. If necessary, the start of the reaction was induced by adding a few milligrams of iodine and local heating. The surplus of methanol was evaporated, and the residue was dissolved in diluted acetic acid and after neutralization with ammonia extracted into ether. After drying the solvent was evaporated and the residue fractionated under reduced pressure. Secondary amines III–IX (Table I) were obtained in good yields and all except crystalline IX were light-yellow oils. A typical example is *N*-*furfuryl*-*m*-*chloroaniline* (*IV*): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.33 (dd, J = 1.7 Hz, J' = 0.9 Hz, 1 H), 6.62 (dd, J = 3.2 Hz, J' = 0.9 Hz, 1 H), 6.29 (dd, J = 3.2 Hz, J' = 1.7 Hz, 1 H) for furanic H_5, H_3, and H_4, respectively; 4.54 (br s, 1 H) exchangeable with D_2O for NH; 4.33 (s, 2 H) for CH_2 and the usual pattern for meta-substituted benzene ring 7.27–6.20 (m, 4 H).

Amine Hydrochlorides IIIa–IXa. These compounds (Table I) were obtained by addition of concentrated hydrochloric acid to an equimolar solution of an amine in absolute ethanol. After evaporation to dryness, the residue was recrystallized from an appropriate solvent.

Picrates IIIb–IXb. These compounds (Table I) were obtained from corresponding amines and equimolar amounts of picric acid in appropriate solvent or from amine hydrochloride and sodium picrate in aqueous solution. Analytically pure samples were obtained by repeated recrystallization.

***N,N,N'*-Three-Substituted Thioureas IIIc–IXc.** These compounds (Table I) were prepared by heating a mixture of equimolar quantities (3 mmol) of a secondary amine and phenyl isothiocyanate in ethanol (1 mL). After short heating (5 min) on a steam bath the mixture was left for several days at room temperature. Crystalline products were purified by recrystallization from ethanol.

Allylation. General Procedure. To an appropriate, freshly distilled secondary amine (0.05 mol) was added dropwise a surplus of allyl iodide or allyl bromide (0.055 mol) with stirring

† For part 21, see ref *5*.

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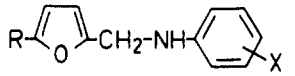
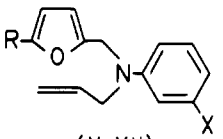
Table I. *N*-Arylfurfurylamines and *N*-Aryl-5-methylfurfurylamines[a]



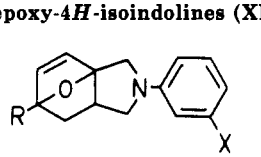
compd	R	X	deriv (salt)	yield, %	bp, °C/mmHg	mp, °C	n^{20}_D
III	H	*m*-OCH_3		80	162–163/5		1.5814
IIIa			hydrochloride[b]			111–112	
IIIb			picrate[c]			114–115	
IIIc			thiourea[d]			146–147	
IV[e]	H	*m*-Cl		70	157–158/5		1.5912
IVa			hydrochloride[f]			120–121	
IVb			picrate[d]			96–97	
IVc			thiourea[d]			75–76	
V[g]	H	*p*-Cl		78	166–167/7		
Va			hydrochloride[d]			182–183	
Vb			picrate[d]			117–118	
Vc			thiourea[d]			99–100	
VI	CH_3	H		74	144–145/6		1.5730
VIa			hydrochloride[h]			113–114	
VIb			picrate[i]			92–93	
VIc			thiourea[d]			121–122	
VII	CH_3	*p*-CH_3		66	152–153/5		1.5672
VIIa			hydrochloride[b]			136–137	
VIIb			picrate[d]			112–113	
VIIc			thiourea[d]			73–74	
VIII	CH_3	*p*-OCH_3		65	172–173/5		1.5730
VIIIa			hydrochloride[b]			120–121	
VIIIb			picrate[c]			100–101	
VIIIc			thiourea[d]			112–113	
IX[j]	CH_3	*p*-Cl		77	166–167/6		
IXa			hydrochloride[b]			121–122	
IXb			picrate[k]			92–93	
IXc			thiourea[d]			100–101	

[a] Elemental analyses (C, H, N) in agreement with theoretical values were obtained and submitted for review. [b] From dry ethanol/ether. [c] From ethanol/water. [d] From ethanol. [e] Lit. (*6*, *7*) no experimental data. [f] From acetone. [g] Lit. (*11*) mp 30–31 °C. [h] From ethyl acetate. [i] From methanol/water. [j] Lit. (*3*) mp 48–49 °C. [k] From ether.

Table II. *N*-Allyl-*N*-aryl-*N*-furfurylamines (X-XII), *N*-Aryl-5,7a-epoxy-4*H*-isoindolines (XIII-XV), and Their Salts[a]



(X-XII)



(XIII-XV)

compd	R	X	salt	yield, %	bp, °C/mmHg	mp,[b] °C	n^{20}_D
X	H	CH_3		85	149–151/4		1.5695
Xa	H	CH_3	picrate			104–105	
XI	H	OCH_3		72	176–177/5		1.5750
XIa	H	OCH_3	picrate			74–75	
XII	H	Cl		45	178–180/6		1.5872
XIIa	H	Cl	picrate			77–78	
XIII	H	CH_3		67[c]		95–96	
XIIIa	H	CH_3	picrate			121–122	
XIV	H	OCH_3		66[c]		125–126	
XIVa	H	OCH_3	picrate			105–106	
XV	H	Cl		83[c]		86–87	
XVa	H	Cl	picrate			83–84	

[a] Elemental analyses (C, H, N) in agreement with theoretical values were obtained and submitted for review. [b] Analytical sample, recrystallized from ethanol. [c] Isomerization at 50 °C for 3 days.

and ice cooling for 30 min. After the mixture stood overnight in a well-stoppered flask, crystalline hydrohalogenide of tertiary amine was separated. The crude salt, or complete reaction mixture dissolved in 600 mL of water, was treated with 50 mL of 40% sodium hydroxide and extracted with ether. After drying, solvent was evaporated and the crude amine purified by fractional distillations at reduced pressure. Pure *N*-allyl-*N*-aryl-*N*-furfurylamines X–XII (Table II) were obtained as light-yellow oils liable to spontaneous, but at room temperature slow, intramolecular cycloaddition. The data for ortho- and para-substituted analogues have been reported earlier (*3*). A typical example is *N-allyl-N-furfuryl-m-chloroaniline* (*XII*): UV λ_{max} (log ϵ) 226 nm (3.71), 258 (4.31), 302 nm (3.50). ^{1}H NMR (90 Hz, $CDCl_3$) δ 7.32 (dd, J = 0.9 Hz, J' = 1.8 Hz, 1 H), 6.58 (dd, J = 0.9 Hz, J' = 3.2 Hz, 1 H), 6.27 (dd, J = 1.8 Hz, J' = 3.2 Hz, 1 H) for furanic H_5, H_3, and H_4, respectively; 4.39 (s, 2 H) for furfurylic —CH_2—; 6.01–5.60 (m, 1 H), 5.2–5.01 (m, 2 H), and 3.94–3.87 (m, 2 H) for allylic =CH—, =CH_2, and —CH_2—, respectively; 7.17–6.11 (m, 4 H) for the usual pattern for m-substituted benzene ring.

Picrates Xa–XIIa. These compounds (Table II) were prepared by mixing equimolar quantities of tertiary amine and picric acid in ethanol. Analytically pure samples were obtained by repeated recrystallization from ethanol.

Isomerization to Epoxyisoindolines. General Procedure. The sample of about 2 g of freshly distilled tertiary amine (X–

XII) was allowed to stand at room temperature for 60 days or at 50 °C for 3 days. To the semicrystalline mixture of starting amine and isomeric cycloaddition product was added 1–2 mL of ethanol; the crystalline crop was filtered off and washed with small portions of ethanol. Recrystallization from ethanol gave colorless crystals of XIII–XV (Table II). A typical example is *N*-(*m*-chlorophenyl)-5,7a-epoxy-4H-isoindoline (*XV*): UV λ_{max} (log ϵ) 213 nm (4.31), 259 (4.34), and 308 (3.45). ^{1}H NMR (90 Hz, $CDCl_3$) δ 6.69–6.36 (m, 4 H) for meta-substituted phenyl; 7.24 (d, J = 7.6 Hz, 1 H) and 7.07 (d, J = 7.6 Hz, 1 H) for 6-CH and 7-CH but not specifically one or the other; 5.09 (d, J = 4.4 Hz, 1 H) for bridgehead proton 5-CH; 3.84 and 3.63 (q_{AB}, J = 11.7 Hz, 2 H) for 1-CH_2; 3.74 (t, J = 9.1, 1 H), 2.95 (t, J = 9.1, 1 H), and 2.44–1.37 (m, 3 H) for protons 4-CH_2, 3-CH_2, and 3a-CH but not necessarily respectively.

Picrates XIIIa–XVa. These compounds were prepared by the addition of picric acid in ethanol, followed by recrystallization from appropriate solvent.

Acknowledgment

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Registry No. I, 95124-20-2; II, 95124-21-3; III, 95124-24-6; IIIa, 95124-60-0; IIIb, 95124-61-1; IIIc, 95124-25-7; IV, 51597-76-3; IVa, 95124-26-8; IVb, 95124-27-9; IVc, 95124-28-0; V, 33829-87-7; Va, 95124-29-1; Vb, 95124-30-4; Vc, 95124-31-5; VI, 95124-32-6; VIa, 95124-33-7; VIb, 95124-34-8; VIc, 95124-35-9; VII, 95124-36-0; VIIa, 95124-37-1; VIIb, 95124-38-2; VIIc, 95155-93-4; VIII, 95124-39-3; VIIIa, 95124-40-6; VIIIb, 95124-41-7; VIIIc, 95124-42-8; IX, 51305-71-6; IXa, 95124-43-9; IXb, 95124-44-0; IXc, 95155-94-5; X, 95124-48-4; X·HI, 95124-45-1; Xa, 95124-51-9; XI, 95124-49-5; XI·HI, 95124-46-2; XIa, 95124-52-0; XII·HI, 95124-47-3; XII, 95124-50-8; XIIa, 95124-53-1; XIII, 95124-54-2; XIIIa, 95124-55-3; XIV, 95124-56-4; XIVa, 95124-57-5; XV, 95124-58-6; XVa, 95124-59-7; *N*-furfurylidene-*p*-chloroaniline, 13533-22-7; *N*-furfurylideneaniline, 61973-96-4; *N*-(5-methylfurfurylidene)-*p*-methylaniline, 95124-22-4; *N*-(5-methylfurfurylidene)-*p*-anisidine, 95124-23-5; *N*-(5-methylfurfurylidene)-*p*-chloroaniline, 51305-59-0; *N*-(*p*-methylphenyl)furfurylamine, 3139-27-3; furfural, 98-01-1; 5-methyl-2-furfural, 620-02-0; *m*-anisidine, 536-90-3; 3-chlorobenzeneamine, 108-42-9; 4-chlorobenzenamine, 106-47-8; benzenamine, 62-53-3; 4-methylbenzenamine, 106-49-0; 4-methoxybenzenamine, 104-94-9; allyl iodide, 556-56-9; phenyl isothiocyanate, 103-72-0.

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Preparation and Properties of *N*-Methyl- and *N*-(4-Chlorophenyl)-Substituted Hydroxamic Acids

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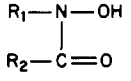
The preparation and properties of several new *N*-methyl- and *N*-(4-chlorophenyl)-substituted hydroxamic acids are described. The proton magnetic resonance and mass spectra of a typical *N*-methyl-substituted hydroxamic acid have also been recorded for characterization.

Hydroxamic acids exhibit biological activity and are used as antitubercular agents (*1*), fungicides (*2*), drugs reducing the cholesterol level (*3*), and antipyretics or analgetics (*4*). In this communication, a number of *N*-(4-chlorophenyl)- and *N*-methyl-substituted hydroxamic acids of the general formula



R_1 = methyl or 4-chlorophenyl

were prepared and characteristized by melting point, elemental analysis, and ultraviolet and infrared spectra. One *N*-methyl-substituted hydroxamic acid was also characterized by ^{1}H NMR and mass-spectral data.

The data on the ^{1}H NMR and mass spectra of a typical compound, *N*-methyl-cinnamohydroxamic acid, are presented in Table I and its ^{1}H NMR spectrum is shown in Figure 1.

Experimental Section

Ultraviolet spectra of hydroxamic acids in 95% ethanol were recorded on a Carl-Zeiss Jena, SPECORD recording spectrophotometer using two 10-mm matched silica cells. Fixed-wavelength measurements for the calculation of molar absorptivity, ϵ, were made with an Electronic Corp. of India, Model GS-865, spectrophotometer. Molar absorptivity is expressed in units of L mol^{-1} cm^{-1}.

Infrared absorption spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer as Nujol mulls. The spectrophotometer was calibrated with polystyrene film.

The ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as internal standard. These were obtained with thanks from Central Drug Research Institute, Lucknow, and their instrument was operated at 90 Hz. Mass spectra were

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