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Carbonyl and Thiocarbonyl Compounds. XIX* Intramolecular Cyclization of (2-Nitroethenyl)aryl *N*-Arylcarbamates: Synthesis of Newer Series of 3,4-Dihydro-2*H*-1,3-oxazin-2-ones and Their Antimicrobial Activities†

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Abstract

The hitherto unknown 2-(2-nitroethenyl)aryl and 1-(2-nitroethenyl)naphthalen-2-yl *N*-arylcarbamates (2) and (5) are readily obtained through the uncatalysed interaction of aryl isocyanates with the corresponding 2-nitroethenyl phenols (1) and (4). The carbamates (2) and (5) cyclize readily at ambient temperature under base catalysis to the corresponding 3-aryl-4-nitromethyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-ones (3) and 2-aryl-1-nitromethyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-ones (6). The oxazinones (3) are cleaved by hot pyridine affording the corresponding 2-(2-nitroethenyl)phenols and *N*,*N*′-diarylurea, whereas, with butylamine, the corresponding aryl(butyl)urea and salicylaldehyde are obtained. The antimicrobial properties of the carbamates and benzoxazinones are evaluated.

Previously, we have reported on the broad-spectrum biological activity of different β-nitrostyrenes and analogous compounds.[1] In an attempt to elucidate a possible chemical–biological relationship in the nitroalkene series, the preparation of different carbonate derivatives has been required. Although several 3- and 4-(2-nitroethenyl)-phenyl carbamates have been described,[2] the preparation of the 2-analogues has not been previously reported.

Reactions

In an attempt to prepare 2-(2-nitroethenyl)phenyl *N*-phenylcarbamate (2a) by treating 2-(2-nitroethenyl)phenol (1a) with phenyl isocyanate in the presence of triethylamine, according to the familiar method used for the preparation of aryl carbamates, the colourless 4-nitromethyl-3-phenyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (3a) was obtained, whereas the expected carbamate (2a) could not be isolated. The latter was, however, readily obtained without oxazine formation when the reaction was conducted without amine catalysis.

When (2a) was allowed to stand in benzene solution in the presence of catalytic amounts of triethylamine, at room temperature, ring closure smoothly took place affording readily the benzoxazinone (3a), and thus confirming the speculation that

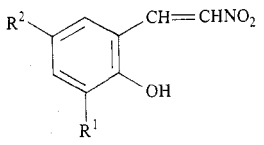
* Part XVIII, *Indian J. Chem.*, 1980, **19B**, 301.

† Presented before the 8th International Congress of Heterocyclic Chemistry, Graz, Austria, 1981.

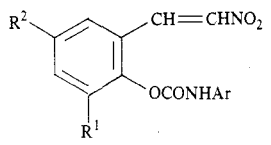
[1] Latif, N., Mishriky, N., Girgis, N. S., and Hussein, A., *J. Prakt. Chem.*, 1973, **315**, 419; Latif, N., Mishriky, N., Girgis, N. S., and Arnos, S., *Indian J. Chem.*, 1980, **19B**, 301.

[2] Cf. Sarbahai Research Centre, Patents (*Chem. Abstr.*, 1977, **86**, 5133, 72178, 106203).

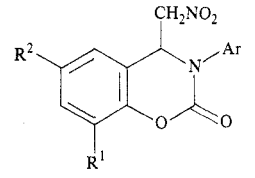
the direct production of the latter from the base-catalysed interaction of phenyl isocyanate with 2-(2-nitroethenyl)phenol proceeds through the intermediate carbamate formation.



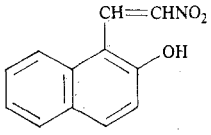
	R^1	R^2
(1a)	H	H
(1b)	H	Cl
(1c)	H	Br
(1d)	OMe	H



	R^1	R^2	Ar
(2a)	H	H	Ph
(2b)	H	H	C_6H_4Cl-*p*
(2c)	H	Cl	Ph
(2d)	H	Cl	C_6H_4Cl-*p*
(2e)	H	Br	Ph
(2f)	H	Br	C_6H_4Cl-*p*
(2g)	OMe	H	Ph
(2h)	OMe	H	C_6H_4Cl-*p*
(2i)	H	Cl	1-naphthyl



	R^1	R^2	Ar
(3a)	H	H	Ph
(3b)	H	H	C_6H_4Cl-*p*
(3c)	H	Cl	Ph
(3d)	H	Cl	C_6H_4Cl-*p*
(3e)	H	Br	Ph
(3f)	H	Br	C_6H_4Cl-*p*
(3g)	OMe	H	Ph
(3h)	OMe	H	C_6H_4Cl-*p*
(3i)	H	Cl	1-naphthyl



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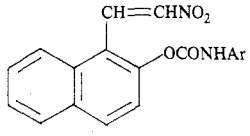
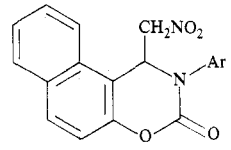


(5a) Ar = Ph
(5b) Ar = C_6H_4Cl-*p*



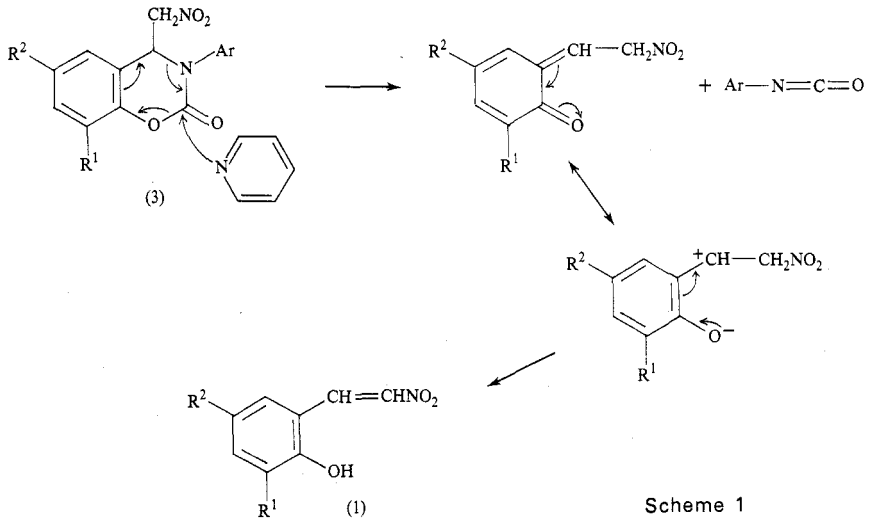
(6a) Ar = Ph
(6b) Ar = C_6H_4Cl-*p*

Structures (2a) and (3a) are inferred from analytical data and supported by absorption and n.m.r. spectra. Thus, the infrared spectrum of compound (2a) shows strong sharp NH and C=O absorptions at 3400 and 1740 cm^{-1}, respectively, as well as a strong band at 960 cm^{-1} due to *trans* ethylenic hydrogen deformations. The n.m.r. spectrum of (2a) shows the expected downfield doublets at δ 7·4 and 8 with a coupling constant of about 7 Hz, due to the coupled ethylenic protons. In contrast to (2a), the infrared spectrum of (3a) lacks ν(NH) and shows ν(C=O) at 1712 cm^{-1}. The n.m.r. spectrum of (3a) shows the expected doublet and triplet at δ 4·5 and 5·25 due to the $CHCH_2NO_2$ moiety. The u.v. spectrum of (3a) lacks the absorption at longer wavelengths which is exhibited by (2a) and is due to extended conjugation of the nitroethenyl side chain with the aromatic nucleus (see Table 1); this will be discussed below. The molecular weights of both (2a) and (3a), determined by mass spectrometry, are the same and thus exclude assignment of possible dimeric or polymeric structures to (3a).

The carbamates (2b–i) and 5a,b) were readily obtained, similarly to (2a), by treating the appropriate nitroethenyl phenols (1) and (4) with the appropriate isocyanates. The spectral characteristics of all the carbamates are mainly similar (Table 1). Compounds (2) and (5) represent a hitherto unknown series of (nitroethenyl)aryl *N*-arylcarbamates for biological evaluation. Such remarkable enhanced reactivity of the nitroethenyl phenols towards reaction with isocyanates in the absence

of a base is presumably due to resonance stabilization of the highly nucleophilic phenoxide anion by the conjugated nitroethenyl side chain. Actually, very little has been reported on the preparation of carbamates through the uncatalysed reaction of isocyanates with hydroxy compounds. Brady and Dunn[3] have previously reported that 2-formylphenyl *N*-phenylcarbamate is obtained by treating salicylaldehyde with phenyl isocyanate; however, their results could not be reproduced by other authors.[4]

Similarly to (2a), the carbamates (2b–i) and (5a,b) cyclized readily under base catalysis affording the benzoxazinones (3b–i) and the naphthoxazinones (6a,b), respectively, and this possibly permits generalization of this intramolecular cyclization, which successfully leads to novel series of 3,4-dihydro-2*H*-1,3-oxazin-2-ones that are apparently practically inaccessible by other methods. Cyclization presumably proceeds through nucleophilic attack of the carbamoyl nitrogen on the highly electrophilic β-carbon of the nitroethenyl side chain. The strong electron-withdrawing power of the nitro group and the driving force of oxazine cyclization are apparently responsible for promotion of the reaction. It is of interest to mention that the preparation of 3,4-dihydro-2*H*-1,3-oxazin-2-ones by the action of isocyanates on hydroxy compounds has been previously described,[5,6] and occasionally it has been assumed that an intermediate carbamate is formed; however, the carbamate has not been isolated in any case. Meanwhile, nothing has been reported on the preparation of the nitroalkyl derivatives of any of the known oxazine ring systems.[7]



Scheme 1

When the benzoxazinones (3a,c) were heated with pyridine, the parent 2-(2-nitroethenyl)phenols (1a,b) were obtained, respectively, along with *N*,*N*′-diphenylurea. Apparently, cleavage may proceed through the initial attack of pyridine on the carbonyl carbon to give (1) and an aryl isocyanate (Scheme 1); the aryl isocyanate furnishes the diarylurea on workup. An alternative mechanism which immediately

[3] Brady, O. L., and Dunn, F. P., *J. Chem. Soc.*, 1916, **109**, 675.
[4] Strube, R. E., and Mackellar, F. A., *Recl Trav. Chim. Pays-Bas*, 1964, **83**, 1191.
[5] Cf. Shapiro, S. L., Bandurco, V., and Freedman, L., *J. Org. Chem.*, 1961, **26**, 3710.
[6] Bobowski, G., and Shavel, J., Jr, *J. Org. Chem.*, 1967, **32**, 953.
[7] Cf. Eckstein, Z., and Urbanski, T., *Adv. Heterocycl. Chem.*, 1963, **2**, 311; 1978, **23**, 1.

presents itself involves tautomerism of the type (3) ⇌ (2) (see below); the open-chain carbamate form (2) undergoes the expected cleavage in pyridine to give the isocyanate and the nitroethenyl phenol. (*N*-Phenyl substituted carbamates are known to give phenyl isocyanate and the corresponding alcohol through an *E*1cB mechanism.[8])

Butylamine reacted with the oxazinones in boiling ethanolic solution to give the corresponding salicylaldehyde and aryl(butyl)urea. It is believed that the corresponding nitroethenyl phenol is first formed, which affords the aldehyde under the basic conditions of the reaction. This is supported by the fact that (1a,b) reacted with butylamine under the same conditions to give salicylaldehyde and 5-chlorosalicylaldehyde, respectively.

Table 1. Ultraviolet and infrared spectra of 2-(2-nitroethenyl)phenyl *N*-arylcarbamates (2) and benzoxazinones (3)

Ultraviolet spectra were determined in ethanol

Compound	λ_{max} (nm)	ε_{max} (l. mol^{-1} cm^{-1})	ν(NH) (cm^{-1})	ν(C=O) (cm^{-1})	Compound	λ_{max} (nm)	ε_{max} (l. mol^{-1} cm^{-1})	ν(C=O) (cm^{-1})
(2a)	233	13490	3400	1740	(3a)	229	5110	1700
	305	5960				254	7100	
	352	3550			(3b)	230	16850	1725
(2b)	240	17950	3360	1750		260	4770	
	300	6550			(3c)	230	9280	1720
	360	5730				277	1676	
(2c)[A]	235	18200	3358	1745	(3d)[B]	230	15120	1725
	300	6940				280	3000	
	360	4250				360	1260	
(2d)	240	23910	3360	1752	(3e)[B]	233	9310	1715
	290	8540				284	2365	
	360	5635				360	1100	
(2e)	230	16940	3375	1760	(3h)[B]	232	10620	
	285	6800				275[C]	2490	
	365	4535				318	3070	
(2f)	240	20100	3360	1755				
	285	7215						
	365	3280						
(2g)	230	18050	3315	1735				
	275	3770						
	320	7850						
(2h)	236	29900	3350	1740				
	320	13980						

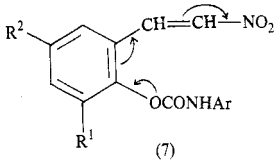
[A] In dioxan (2c) showed λ_{max} (ε_{max}) 255 (9290), 295 (11675).
[B] When the spectra of (3d,e,h) were determined in chloroform, the following bands were exhibited, λ_{max} (ε_{max}): for (3d), 280 (1985); for (3e), 280 (2105); for (3h), 275 (2985).
[C] Plateau.

Ultraviolet Absorption Spectra

The spectra of the 2-(2-nitroethenyl)phenyl *N*-arylcarbamates are generally characterized by three main bands: a short-wavelength band in the region 230–240 nm, and two longer-wavelength bands in the regions 280–300 and 340–365 nm (Table 1), reflecting the polychromophoric nature of the molecules [in the case of

[8] Barton, D., (Sir), and Ollis, W. D., *Compr. Org. Chem.*, 1979, **2**, 1084.

(2h) the two long-wavelength bands fuse together and appear as a strong band at 320 nm]. The short-wavelength absorption can be ascribed mainly to the *N*-arylcarbamoyloxy chromophore which is apparently acting independently, and is rather similar to that of phenylurethanes. The band is more intense, as expected, in the case of the *N*-*p*-chlorophenyl analogues than in the *N*-phenyl compounds. The two longer-wavelength bands are presumably due to the whole conjugated system. The first band is mainly in the same position where nitrostyrene itself absorbs; the second band, in the region 340–365 nm, is apparently due to possible larger contribution of dipolar resonance structures as a result of cross conjugation throughout the whole molecule involving the carbamoyloxy moiety, the nitroethenyl side chain and the phenyl ring [see (7)]. This is supported by finding that this absorption, exemplified by that of (2c), is enhanced at the expense of the shorter one in the 300 nm region when the spectrum is determined in ethanol and suppressed when determination is conducted in the less polar aprotic dioxan solution. Meanwhile, these two long-wavelength bands are more intense in the 4-halophenyl *N*-arylcarbamates than in the corresponding phenyl *N*-arylcarbamates.



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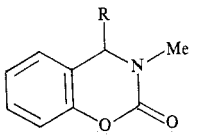

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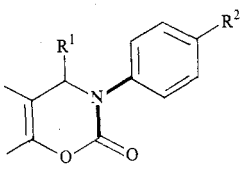

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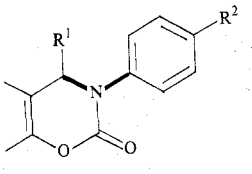

(9)

The spectra of the benzoxazinones, in contrast to the carbamates, are devoid of the long-wavelength bands mentioned above, and thus support the assigned non-conjugated cyclic structures. The spectra, however, generally exhibit a strong short-wavelength absorption in the region 230–260 nm, and, in the majority of cases, a weak absorption in the region 270–285 nm. This spectral pattern would suggest that the *N*-phenyl ring is coplanar with the oxazinone ring. Consequently, the strong short-wavelength bands can be ascribed to an aniline and/or a phenylurethane absorption[9]* (see Table 1) which usually occur mainly in this region, or occasionally are shifted under the effect of substituents. If the phenyl ring is out of plane, the substituted aniline spectra would not be observed, and the spectral pattern would be mainly as that of an *N*-alkylbenzoxazinone such as (10),[6] lacking such a short-wavelength absorption. An out-of-plane *N*-phenyl ring in 3,4-dihydro-2*H*-1,3-oxazin-2-one structures has been previously reported.[5] Actually, group conformations in the

* When the electron pair on nitrogen, and the aryl group and the N–CO bond are coplanar, spectral characteristics similar to those of substituted phenylurethanes could be expected [see (8)]. When the electron pair on nitrogen, and the phenyl ring and the N–CH bond [see (9)] are coplanar, an *N*-alkylaniline absorption is expected.

[9] Cf. Shapiro, S. L., Rose, I. M., Testa, F. C., Roskin, E., and Freedman, L., *J. Am. Chem. Soc.*, 1959, **81**, 6498.

3,4-dihydro-2*H*-1,3-benzoxazin-2-one series, as far as we are aware, have not been previously discussed and related to their ultraviolet spectra.

It is of interest to report that the spectra of some of the benzoxazinones exhibit weak absorptions at longer wavelength, in the same position where the corresponding carbamates show strong absorption (Table 1); this would suggest the existence of ring–chain tautomerism of the type (3) ⇌ (2) in ethanolic solution, with the contribution of a very small amount of the open-chain form.

Table 2. Microanalytical data of the products

Except where stated otherwise, the compounds were recrystallized from benzene

Compound	M.p. (°C)	Yield (%)	Molecular formula	Found (%) C	H	Cl	N	Requires (%) C	H	Cl	N
(2a)	136–138	70	$C_{15}H_{12}N_2O_4$	63·7	4·2		9·9	63·4	4·2		9·8
(2b)	150	65	$C_{15}H_{11}ClN_2O_4$	56·9	3·7	11·5	9·3	56·5	3·5	11·1	8·8
(2c)	169–170	72	$C_{15}H_{11}ClN_2O_4$	56·5	3·6	11·4	8·4	56·5	3·5	11·1	8·8
(2d)	183–184	84	$C_{15}H_{10}Cl_2N_2O_4$	51·0	3·0		7·8	51·0	2·8		7·9
(2e)[A]	176–177	60	$C_{15}H_{11}BrN_2O_4$	49·4	3·1		7·6	49·6	3·0		7·7
(2f)[B]	190–192	60	$C_{15}H_{10}BrClN_2O_4$	45·9	2·6		7·2	45·3	2·5		7·1
(2g)	158–160	60	$C_{16}H_{14}N_2O_5$	61·1	4·3		9·0	61·1	4·5		8·9
(2h)	170–172	60	$C_{16}H_{13}ClN_2O_4$	54·9	3·8	10·6	7·7	55·1	3·7	10·2	8·0
(2i)[B]	163–164	57	$C_{19}H_{13}ClN_2O_4$	62·0	3·8		7·6	61·9	3·5		7·6
(3a)	188–190	85	$C_{15}H_{12}N_2O_4$	63·2	4·0		9·7	63·4	4·2		9·9
(3b)	185–186	80	$C_{15}H_{11}ClN_2O_4$	56·7	3·6	11·5	8·5	56·5	3·5	11·1	8·8
(3c)	167–168	60	$C_{15}H_{11}ClN_2O_4$	56·5	3·4	11·5	8·8	56·5	3·5	11·1	8·8
(3d)	186–187	70	$C_{15}H_{10}Cl_2N_2O_4$	51·4	3·0	19·7	8·3	51·0	2·8	20·1	7·9
(3e)	165	50	$C_{15}H_{11}BrN_2O_4$	49·7	3·2		7·7	49·6	3·0		7·7
(3f)	174–176	60	$C_{15}H_{10}BrClN_2O_4$	45·2	2·6		7·1	45·3	2·5		7·1
(3g)	160–162	60	$C_{16}H_{14}N_2O_4$	61·6	4·6		9·1	61·1	4·5		8·9
(3h)	177–178	70	$C_{16}H_{13}ClN_2O_5$	55·1	3·7	9·9	8·1	55·1	3·7	10·2	8·0
(3i)[C]	189–190	60	$C_{19}H_{13}ClN_2O_4$	62·1	3·9		7·3	61·9	3·5		7·6
(5a)	177–178	75	$C_{19}H_{14}N_2O_4$	68·7	4·4		8·1	68·3	4·2		8·4
(5b)[C]	180–181	88	$C_{19}H_{13}ClN_2O_4$	62·1	3·7	9·8	7·9	61·9	3·5	9·6	7·6
(6a)	205–206	70	$C_{19}H_{14}N_2O_4$	68·4	4·4		8·7	68·3	4·2		8·4
(6b)[C]	215–217	70	$C_{19}H_{13}ClN_2O_4$	61·9	3·8	9·6	7·7	61·9	3·5	9·6	7·6

[A] Found: Br, 22·3. $C_{15}H_{11}BrN_2O_4$ requires Br, 22·0%.
[B] Recrystallized from benzene/dioxan.
[C] Recrystallized from dioxan.

Antimicrobial Activity of the Compounds

The toxicity of the carbamates and the benzoxazinones towards various types of bacteria and phytopathogenic fungi were tested. The microorganisms used in the tests were: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeroginosa*, *Bacillus subtilis*, *Bacillus cereus*, *Sarcina leutea*, *Candida albicans*, *Aspergillus flavus*, *Botrytis alli*, *Fusarium oxysporum* and *Fusarium moniliforma*. The results obtained* revealed broad-spectrum antimicrobial activity of the compounds. The majority of the compounds showed general activity towards the tested microorganisms in concentrations ranging between 12·5 and 100 μg/ml. However, the carbamates proved to be generally more active, especially on bacteria.

* Quantitative data are available on request from the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, Vic. 3002.

Experimental

*Preparation of 4-Nitromethyl-3-phenyl-3,4-dihydro-2*H*-1,3-benzoxazin-2-one (3a)*

Phenyl isocyanate (1·2 g, 0·01 mol) was added to a solution of 2-(2-nitroethenyl)phenol (1·6 g, 0·01 mol) in dry benzene (25 ml) containing a few drops of triethylamine. The solution was left at room temperature (20–25°) for 3 h. The separated solid was filtered off and recrystallized from benzene to give (3a) as colourless crystals, m.p. 188–190° (2·1 g) (see Table 2).

Preparation of (2-Nitroethenyl)aryl N*-Arylcarbamates (General Method)*

A mixture of the 2-nitroethenyl phenol (1) or (4) (0·01 mol) and aryl isocyanate (0·015 mol) in dry benzene (50 ml) was refluxed for a few hours, and left to cool. The separated solid was filtered off and recrystallized from the appropriate solvent to give the corresponding carbamates (2) or (5) (see Table 2).

Cyclization of (2-Nitroethenyl)aryl N*-Arylcarbamates (General Method)*

The (2-nitroethenyl)aryl *N*-arylcarbamates (2) or (5) (0·01 mol) were dissolved in hot benzene or dioxan and 5–8 drops of triethylamine were added. The mixtures were then left overnight. The solvent was evaporated to dryness under reduced pressure, the residue was cooled and a few millilitres of methanol were added. The separated solid was filtered off and recrystallized from the appropriate solvent to give the corresponding 3,4-dihydro-2*H*-1,3-benzoxazin-2-one (3) or 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-one (6) (see Table 2).

Cleavage of the 1,3-Benzoxazinones with Pyridine

The benzoxazinone (3a,c) (2 g) in pyridine (30 ml) was heated on a boiling water bath for 3 h; the mixture was cooled, then poured into acidified ice-cold water. The precipitate formed was filtered off, dried, then extracted with hot benzene. The undissolved material (0·5 g) proved to be *N,N'*-diphenylurea (by m.p. and mixed m.p.). The benzene solution was concentrated, left to cool and the separated solid was recrystallized from benzene to give (1a,b) (m.p. and mixed m.p.).

Reaction of 1,3-Benzoxazinones with Butylamine

A suspension of the benzoxazinone (3a,c) (1 g) and butylamine (1 ml) in absolute ethanol (15 ml) was refluxed for 3 h, then left to cool. The precipitate formed was filtered off and proved to be *N*-butyl-*N'*-phenylurea.[10] To the parent mother liquor, 2,4-dinitrophenylhydrazine reagent was added. The precipitate formed proved to be the dinitrophenylhydrazone of the corresponding salicylaldehyde.

Antimicrobial Activity

The antimicrobial activity of the compounds was measured by determining the minimum inhibition concentration according to the bioassay technique of antibiotics specified in the United States Pharmacopeia. Antibiotic medium No. 2 was used as the base agar in the plate assay for bacterial cultures. Czapeck agar medium was used with yeast and mould cultures. The tested compounds were dissolved in dimethyl sulfoxide. Concentrations down to 12·5 μg/ml of the compounds in dimethyl sulfoxide were used.

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[10] Boehmer, J. W., *Recl Trav. Chim. Pays-Bas*, 1936, **55**, 379.