

SUNDARESAN PRABHAKAR

Faculty of Science and Technology
New University of Lisbon
and
Centro de Química Estrutural
Complexo Interdisciplinar
I.S.T. 1096 Lisboa Codex
PORTUGAL

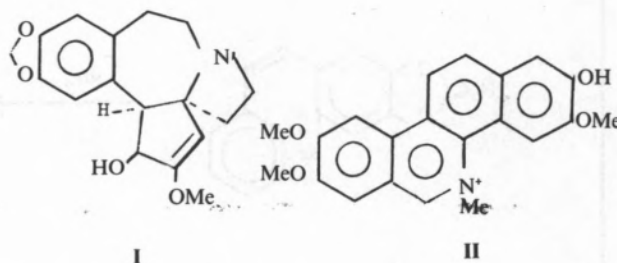


SOME NEW DEVELOPMENTS IN THE CHEMISTRY OF ARYL HYDROXYLAMINES AND THEIR DERIVATIVES

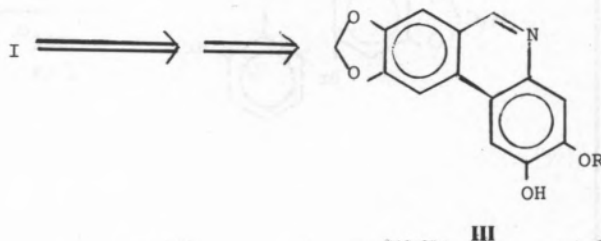
This review is not a detailed account of all the new developments in the chemistry of arylhydroxylamines and their derivatives. Instead it is confined essentially to those new reactions discovered in our laboratory during the past five years.

One of the persisting problems in organic synthesis is to develop new and better methods for effecting a C-C bond connection. Simple as it may seem, it remains, even today, a challenge in terms of regiospecificity, enantioselection and chemical yield when applied to synthesis of complex organic molecules.

The content of the review is a "spin-off", as it were of our efforts to synthesize the anti-leukaemic alkaloids, cephalotaxine (I) and fagaronine (II).



By retrosynthesis (I) could be reduced to a simple synthon (III) — a phenanthridine derivative.

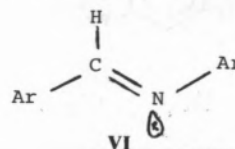


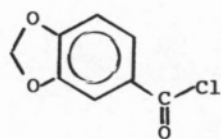
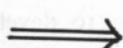
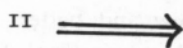
By one of many disconnection processes available (II) could be reduced to two simple units (IV) and (V).

The literature describes various methods to obtain the phenanthridine skeleton and to give only a few examples, the yields are usually low (Table 1). The basic problem in the photocyclisation processes resides essentially in two factors.

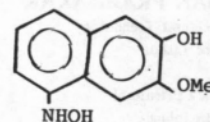
- a) entropic
- b) electronic

Schiffs'bases, normally tend not only to adopt the *trans*-geometry (VI) [3b] (unfavourable situation for C-C bond formation) but also suffers $n-\pi^*$





IV



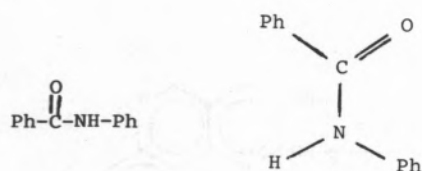
V

Table 1

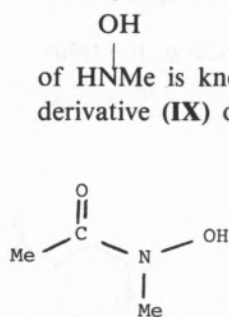
	Reference
	1
	2
	3a 3b
	4

excitation on absorption of light which is non-productive in terms of intramolecular cyclisation [3b].

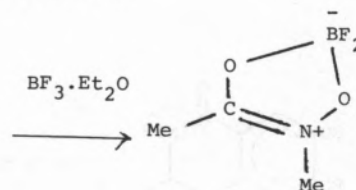
Secondary amides, such as benzanilide, exist predominantly in the *trans*-configuration (VII) and the principal reason for low yield in photocyclisation is due to entropic reasons [3c].



VII



VIII



IX

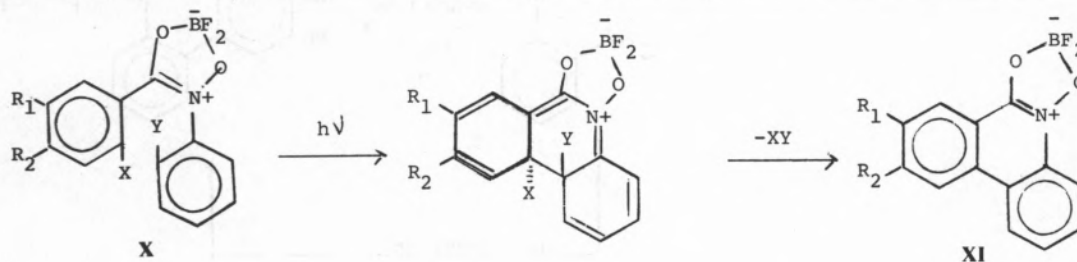
Question

How to overcome these adverse effects-entropic and electronic?

Solution:

Force the molecule to adopt the *cis*-configuration

It was considered that *C, N*-diarylhydroxamic acids would also form compounds of this type and if properly substituted undergo rapid cyclisation in high yield. Given the fact that the bond strength between **B-O** and **B-F** is relatively high it was anticipated that these complexes would not only be photostable but also possess ideal condi-



- | | |
|--|---|
| i) $R_1 = R_2 = \text{OMe}; X = Y = \text{H}$ | i) $R_1 = R_2 = \text{OMe}$ |
| ii) $R_1 = R_2 = \text{OMe}; X = \text{Br}; Y = \text{H}$ | ii) $R_1 = R_2 = \text{OMe}$ |
| iii) $R_1 = R_2 = \text{OCH}_2\text{O}; X = \text{Br}; Y = \text{H}$ | iii) $R_1 = R_2 = \text{OCH}_2\text{O}$ |
| iv) $R_1 = R_2 = \text{OMe}; X = \text{H}; Y = \text{Cl}$ | iv) $R_1 = R_2 = \text{OMe}$ |
| v) $R_1 = R_2 = \text{OMe}; X = \text{H}; Y = \text{OTs}$ | |
| vi) $R_1 = R_2 = \text{OMe}; X = \text{H}; Y = \text{BR}$ | vi) $R_1 = R_2 = \text{OMe}$ |

Compound X	Mp/°C	Product XI	M.p/°C	% yield	Irradiation time/h
i	199-200	i	318-320	96*	33
ii	158-159	i	318-320	92	4
iii	176-176.5	iii	325-328	93	6
iv	189-191	i	318-320	91	13
v	168-170	—	—	0	18
vi	167-169	i	318-320	92	9

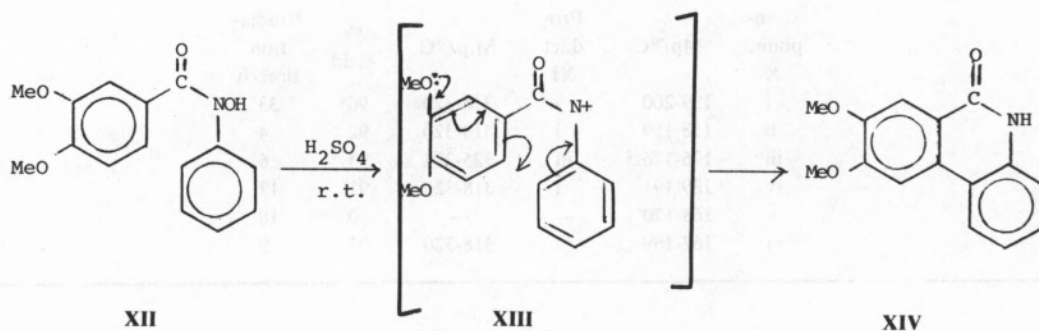
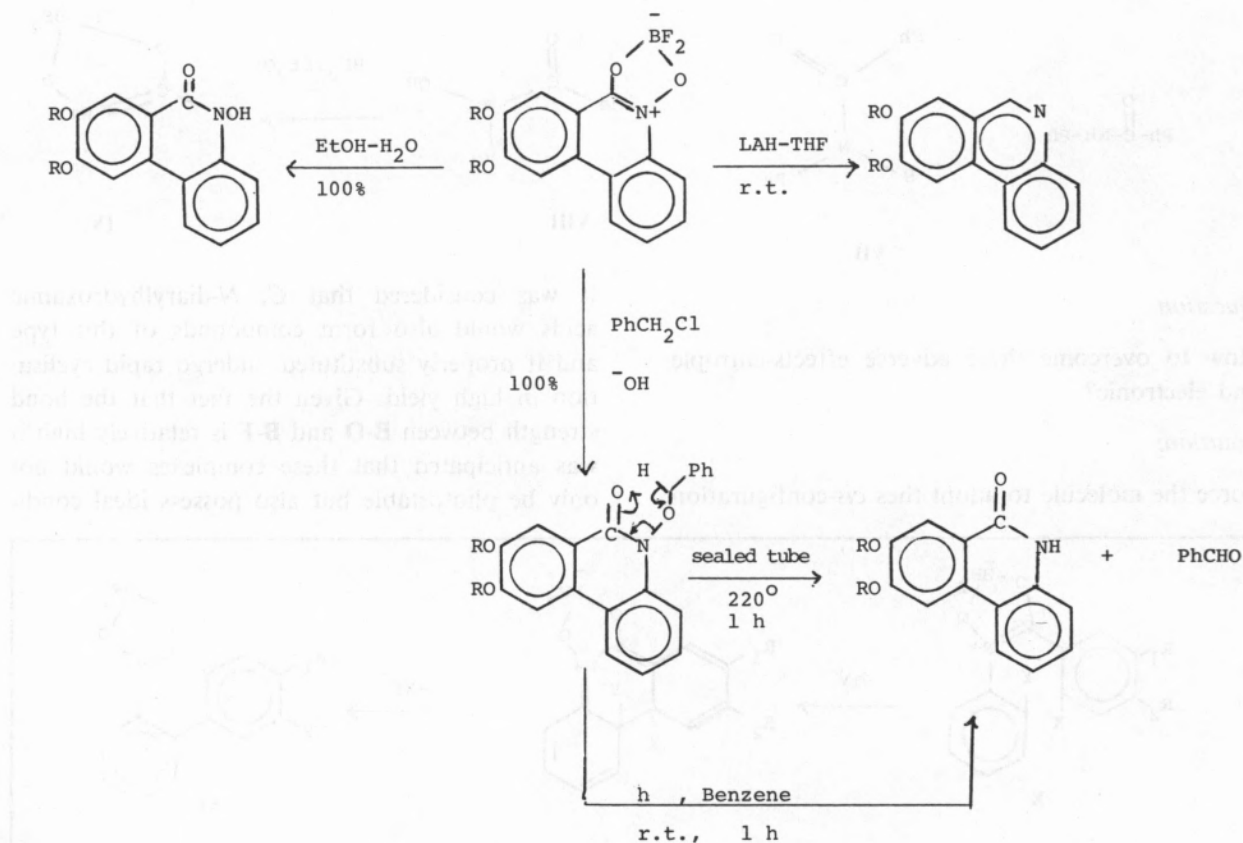
* In the presence of 1 equiv. of iodine.

tions to undergo in high yield a conrotatory photocyclisation. This expectation was fully realised in practise and our results [6] are presented below.

These cyclised compounds (**XI**) undergo the following reactions:

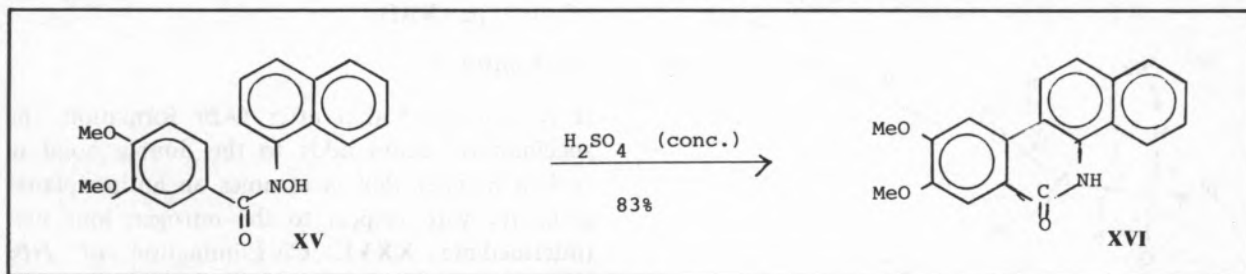
It was subsequently found [7] that properly substituted benzohydroxamic acids, such as (**XII**) cyclise rapidly on treatment with conc. H_2SO_4 , to give the corresponding phenanthridone **XIV** in high yield.

The intermediate is presumed to be the reactive

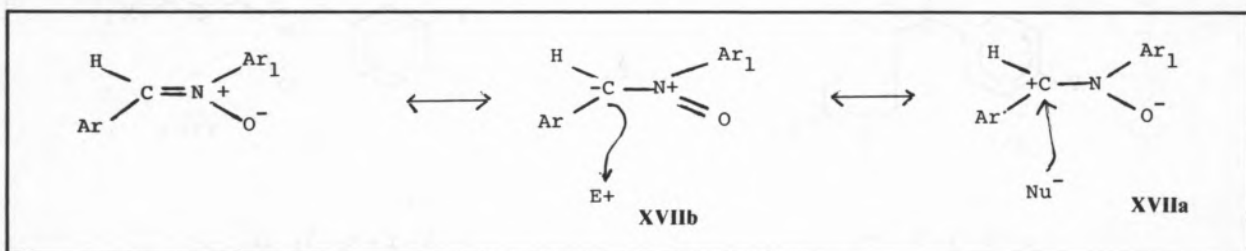
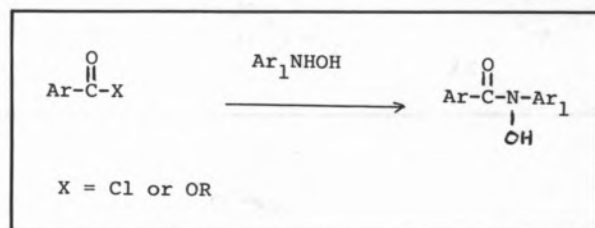


acylnitrenium ion (**XIII**). Similarly (**XV**) yielded (**XVI**).

was found to be exclusively the thermodynamically less stable *cis*-nitron (**XXI**).



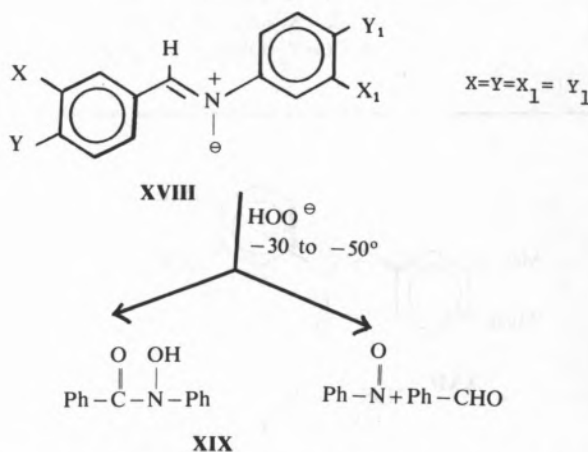
Since hydroxamic acids have thus been shown to be useful substrates for constructing condensed heterocycles, a new method for the preparation of the former was sought. Generally, aromatic hydroxamic acids are synthesized by condensing acid chlorides or esters with aromatic hydroxylamines.



However, arylhydroxylamines are obtained by controlled reduction of the corresponding nitro compounds and the reaction is often capricious and the yield is at best modest.

C, N-diarylnitrones could in principle be converted into hydroxamic acid by either nucleophilic or electrophilic substitution at the α -carbon atom of the nitron group. The canonical forms **XVIIa** or **XVIIb** explain the chemical reactivity in a simple way without recourse to a more sophisticated treatment.

On treatment with alkaline hydrogen peroxide *C, N*-diphenylnitron (**XVIII**) yielded rapidly the hydroxamic acid (**XIX**), the major products being nitrosobenzene and benzaldehyde:

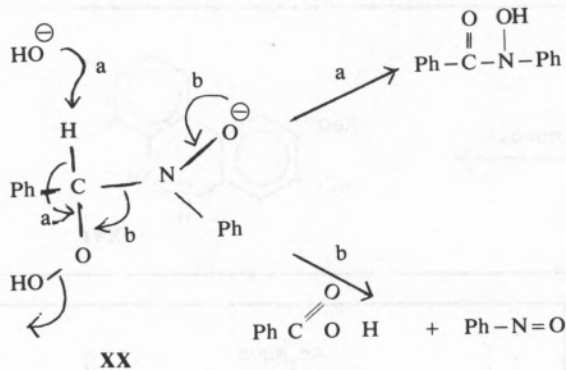


The formation of the products could be explained on the basis of two concurrent reactions (path a and b) involving the common intermediate (**XX**): When NBS is treated with the nitron (**XVIIa**) in the presence of DABCO a relatively slow reaction occurred and the product, after aqueous work-up,

The tetramethoxynitron (**XXII**), similarly, yielded initially the *cis*-nitron (**XXIII**) which on heating isomerised to the *trans*-compound (**XXIV**) the structure of which was confirmed by X-ray analysis.

The various α -succinimidyl nitrones prepared by the above method, as well as their physical properties are collected (Table 2).

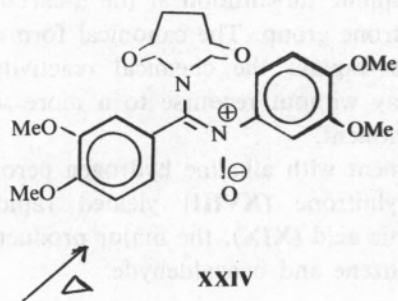
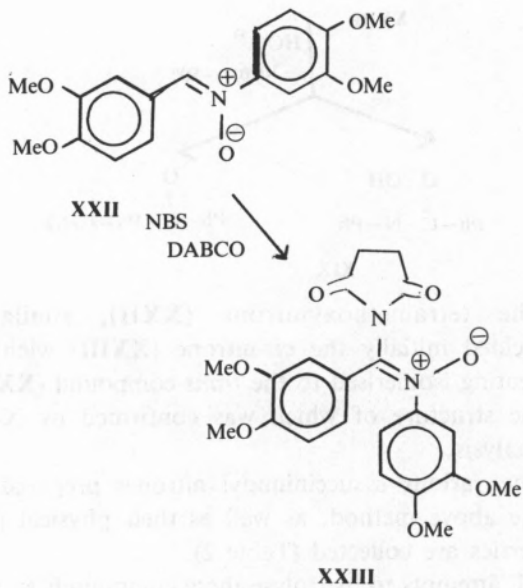
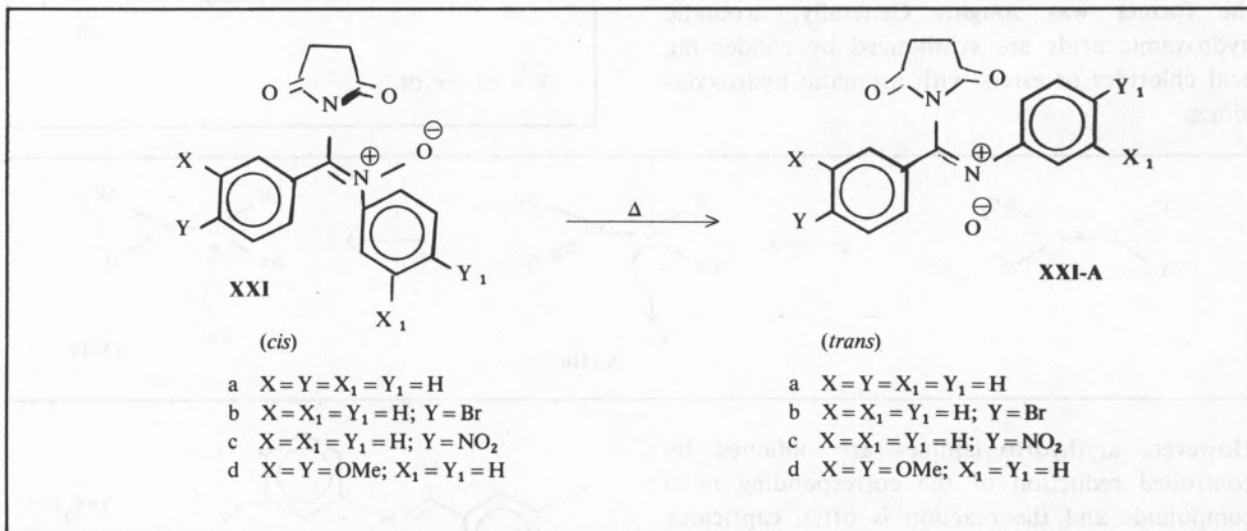
All attempts to hydrolyse these compounds to give



of the type (XXI):

Mechanism A

It is proposed * that after *O-Br* formation, the succinimidyl anion adds to the double bond in such a manner that it assumes an antiperiplanar geometry with respect to the nitrogen lone pair (intermediate **XXV**). *Cis*-Elimination of *HBr* involving a 5-membered transition state would lead to the observed product.



* The thermodynamically more stable *trans* nitron (XVIII) is assumed to be reactive species.

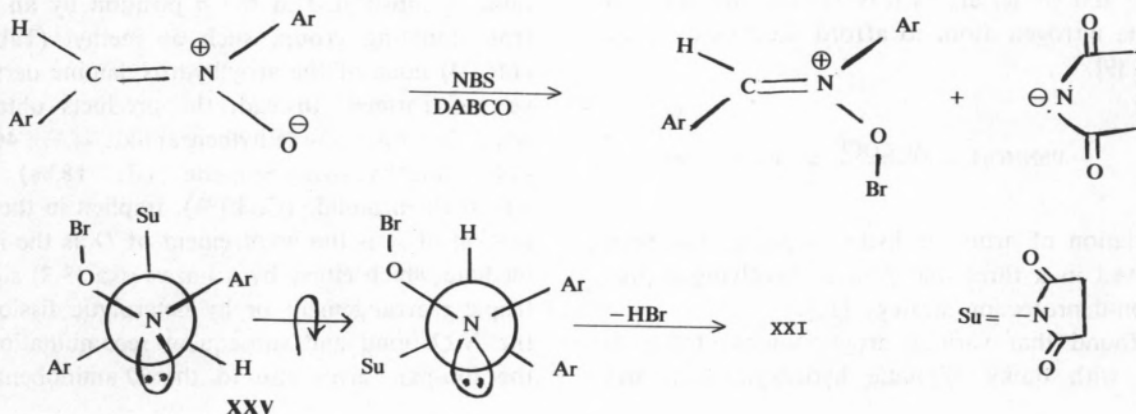
Table 2
Physical Properties of the C-Succinimidyl Nitrones XXI and XXI-A

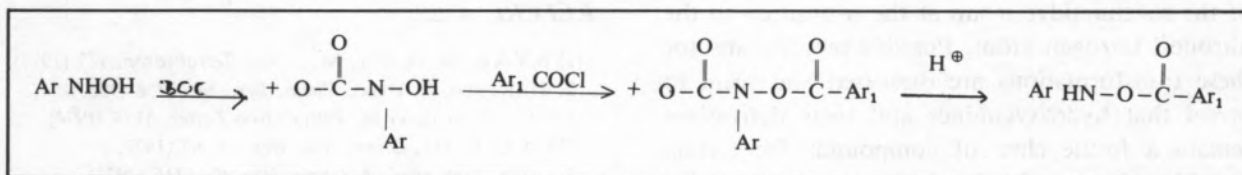
Compound		Yield (XXI + XXI-A) ^(c) (%)	m.p. (°C)	I.R. (KBr) (cm ⁻¹)	¹ H NMR (CDCl ₃) δ (ppm)	m/e ^(d) (M ⁺) (M ⁺ -O) (M ⁺ -C ₄ H ₄ NO ₂) (M ⁺ -C ₄ H ₄ NO ₂ -O)			
X	Y								
H	H	56	≈130 ^(a)	1785, 1725	7.36-7.17 (10H, m, ArH) 3.17-2.81 (4H, m, -CH ₂ -CH ₂ -)	294	278	196	180
			170-172	1785, 1725	8.46-7.88 (2H, m, ArH) 7.50-7.41 (8H, m, ArH) 2.98-2.18 (4H, m, -CH ₂ -CH ₂ -)	"	"	"	"
H	Br	60	92-102 ^(a)	1785, 1720	7.36-6.95 (9H, m, ArH) 3.11-2.78 (4H, m, -CH ₂ -CH ₂ -)	373	357	275	259
			102-104	1792, 1723	7.43-7.29 (8H, m, ArH) 7.00 (1H, d, J 3Hz, ArH) 3.09-2.86 (4H, m, -CH ₂ -CH ₂ -)	"	"	"	"
H	NO ₂	83	(a)	1788, 1723	8.07 (2H, d, J 8Hz, ArH) 7.42-7.36 (7H, m, ArH) 3.19-2.86 (4H, m, -CH ₂ -CH ₂ -)	339	323	241	225
			187 (dec.)	1790, 1726	8.34 (4H, d, J 2.4Hz, ArH) 7.44 (5H, s, ArH) 2.91-2.29 (4H, m, -CH ₂ -CH ₂ -)	"	"	"	"
OMe	OMe	40	(b)						
			186 (dec.)	1785, 1730	8.78 (1H, d, J _m 2.1Hz, 2-H) 7.43 (5H, s, ArH) 7.12 (1H, dd, J _o 8.7Hz, J _m 2.1Hz, 6-H) 6.89 (1H, d, J _o 8.7Hz, 5-H) 3.98 (3H, s, CH ₃ O) 3.94 (3H, s, CH ₃ O) 2.94-2.19 (4H, m, -CH ₂ -CH ₂ -)	354	338	256	240
OMe	OMe	64	(b)						
			185-190 (dec.)	1785, 1730	8.77 (1H, d, J _m 2.2Hz, 2-H) 7.14-6.75 (5H, m, ArH) 3.96-3.93-3.90-3.86 (4 × 3H, 4s, 4 × CH ₃ O) 2.95-2.29 (4H, m, -CH ₂ -CH ₂ -)	414	398	316	300

(a) On heating compounds (XXI) isomerise slowly to (XXI-A).

(b) Detected only on t.l.c. of the reaction mixture, but on attempted crystallisation isomerised to XXI-A.

(c) Crude yield.



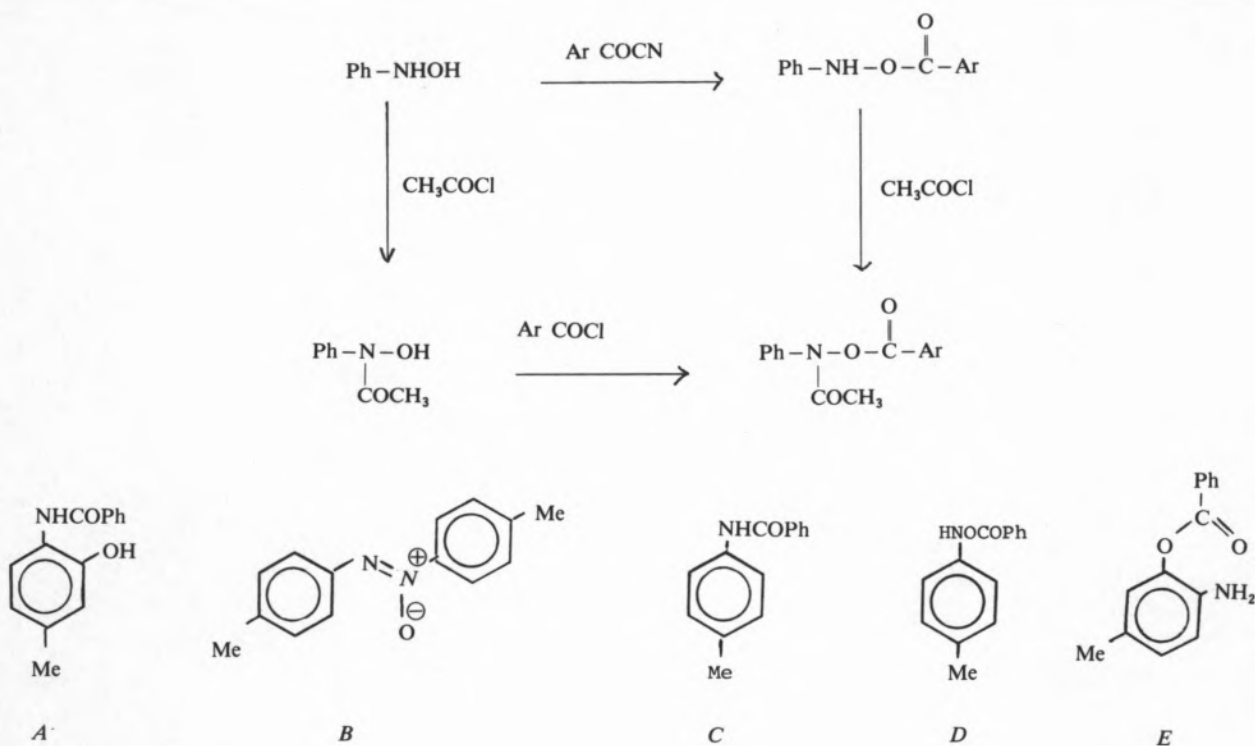


(*E*). *O* to *N* transfer of benzoyl group generates *A*. However, hydroxylamine and its *N*-methyl derivative yielded with the above acyl transfer reagent only the corresponding hydroxamic acids. The formation of these acids appears not to involve initial *O*-acylation followed by a rapid *O* to *N* rearrangement. Thus when *N*-methylhydroxylamine is allowed to react with benzoyl cyanide in CDCl_3 at -40° and the reaction monitored by n.m.r. only the *N*-methyl signal (δ 3.41 s) of the corresponding hydroxamic acid is observed. Further studies are underway to explain the profound difference in reactivity between aroyl cyanides and aroyl chlorides towards hydroxylamines and the differing ambident properties of the latter.

Concluding remarks

Although hydroxylamines and hydroxamic acids have been studied for over a century, there is still

scope for discovering new and interesting reactions that they might undergo. Thus the ability of the latter to form stable boron complexes could be exploited for the construction of heterocyclic systems present in pharmacologically active compounds. The general assumption that hydroxylamines lead to hydroxamic acids on acylation is shown to be erroneous. Instead it is found that the nature of the product formed (*O* versus *N*) acylation) is subject profoundly to the type of acylating agent used. Whereas aroyl hydroxylamines form the corresponding aroyl hydroxamic acids with aroyl chloride, the use of aroyl cyanide, as a transacylating agent, leads, almost always, to the thermodynamically *less stable O*-acylated compound. *C*, *N*-Diarylnitrones were tested as potential starting materials for *C*, *N*-diarylhydroxamic acids. Treatment of the former with NBS-DABCO was found to yield, not the acids, but to substitution



of the succinimidyl group at the α -position to the nitrones' nitrogen atom. Possible mechanisms for these transformations are discussed and seem to reveal that hydroxylamines and their derivatives remain a fertile class of compounds for testing new ideas in organic chemistry.

Received 12. December. 1983.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge my sincere appreciation to my collaborators, A.M. Lobo, M.R. Tavares and M.M. Marques for their efforts in exploring the chemistry outlined in the review. My thanks are also due to NATO (Grant No. 1971), Gulbenkian Foundation and Junta Nacional de Investigação Científica e Tecnológica for financial support without which realization of the work would not have been possible.

REFERENCES

- [1] S.V. KESSAR, D. PAL, M. SINGH, *Tetrahedron*, 177 (1973).
- [2] H. KONDO, S. UYEO, *Chem. Ber.*, **68**, 1756 (1935).
- [3a] M. NATSUME *et al*, *Tetrahedron Letter*, 1179 (1974).
- [3b] A.C. PRATT, *Chem. Soc. Rev.*, **1**, 63 (1977).
- [3c] D.H. HEY *et al*, *J. Chem. Soc. (C)*, 116 (1971).
- [4] A. MONDON, K. KROHN, *Chem. Ber.*, **105**, 3726 (1972).
- [5] F. UMLAND *et al*, *Chem. Ber.*, **106**, 1973 (1973).
- [6] S. PRABHAKAR, A.M. LOBO, M.R. TAVARES, *J.C.S. Chem. Comm.*, 884 (1978).
- [7] S. PRABHAKAR, A.M. LOBO, M.R. TAVARES, 2nd Portuguese National Meeting of Chemistry, Coom. 5E32, Oporto, 1979.
- [8] A.M. LOBO, S. PRABHAKAR, H.S. RZEPA, A.C. SKAPSKI, M.R. TAVARES, D.A. WIDDOWSON, *Tetrahedron*, 3833 (1983).
- [9] P.A. SMITH in "Open Chain Nitrogen Compounds", Vol. 2, p. 10, W.A. Benjamin, 1966.
- [10] L.A. CARPINO *et al*, *J. Am. Chem. Soc.*, **81**, 955 (1959).
- [11] S. PRABHAKAR, A.M. LOBO, M.M. MARQUES, *Tetrahedron Letters*, 1931 (1982).