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The Synthesis of Some 3-nitroso-2-arylimidazo(1,2-a) pyrimidines

Derek T. Hurst * and John A. Saldanha

School of Chemical and Physical Sciences,
Kingston Polytechnic, Kingston upon Thames, KT1 2EE, U.K.

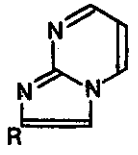
Summary

The reaction of 2-arylimidazo(1,2-a) pyrimidines in glacial acetic acid with aqueous sodium nitrite at room temperature has been shown to give good yields of the 3-nitroso-2-arylimidazo(1,2-a) pyrimidines. Reduction of these products leads to the 3-amino derivatives.

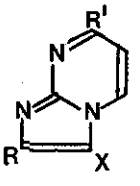
A number of imidazo(1,2-a) pyrimidines (I) have been shown to have antimicrobial[1], anti-inflammatory, antipyretic and anticonvulsant activity[2], and also 2-phenylimidazo(1,2-a) pyrimidine (I,R=Ph) (as the hydrobromide salt) has been shown[3] to be a strychnine antagonist. Thus derivatives of this ring system show considerable potential as possible pharmaceuticals.

As part of our studies on pyrimidines and related heterocycles having potential pharmacological activity we have been studying the synthesis and properties of imidazo(1,2-a) pyrimidines.

We obtained good yields of the arylimidazo(1,2-a) pyrimidines (IIa-f, X = H) by refluxing the substituted phenacyl halides with a 2-amino pyrimidine in ethanol similar to the methods of Buu-Hoi and Xuong[4] and Almirante et al[2].



I



II (a) R = Ph, R^1 = H
(b) R = Ph, R^1 = Me
(c) R = p-ClC_6H_4, R^1 = H
(d) R = p-BrC_6H_4, R^1 = H
(e) R = p-FC_6H_4, R^1 = H
(f) R = p-$C_6H_5C_6H_4$, R^1 = H

Pentimalli and Passalacqua[5] and Pentimalli and Milani[6] have carried out some studies of the reactivity of imidazo(1,2-a) pyrimidines with electrophilic reagents but only obtained two 3-nitroso derivatives IIa (X = NO) and II(R = p-$CH_3OC_6H_4$, X=NO) respectively. The only other report of 3-nitroso-2-substituted imidazo(1,2-a) pyrimidines is by La Rocca et al[7] who obtained a few such compounds whilst attempting to condense arylglyoxylhydroxamyl chlorides with 2-aminopyrimidine in order to obtain N-(2-pyrimidinyl)arylglyoxylhydroxamamides. In order to confirm the structure of the product which they believed to be the 3-nitroso derivative IIa (X = NO) these workers nitrosated IIa (X = H) by a modification of the method used for the nitrosation of some imidazopyridines[8] but they report that some difficulties were encountered.

We have found that the 2-arylimidazo(1,2-a) pyrimidines react readily in glacial acetic acid with aqueous sodium nitrite at room temperature to give good yields of the 3-nitroso derivatives and we have obtained compounds IIa-f(X = NO) without difficulty. Each of these compounds is a highly coloured, crystalline, material.

Reduction of these nitroso derivatives should give 3-aminoimidazo(1,2-a) pyrimidines, compounds which may show interesting biological activities. We have obtained 3-amino-2-p-biphenyl-imidazo(1,2-a) pyrimidine (IIf, X = NH_2) in moderate yield by reduction of IIf(X = NO) using aqueous sodium dithionite and we have also obtained some other such 3-amino derivatives in lower yield and rather less pure. However we are investigating other reduction methods as a better general route to the 3-amino derivatives.

Mass spectra (70eV) of the imidazopyrimidines showed intense molecular ions in each case, these usually being the parent ions, and significant M^{2+} ions were usually also seen. There were usually comparatively few other significant fragment ions although an initial loss of 27 (HCN) seemed to be a common feature and with the p-chloro and p-bromophenyl derivatives, the loss of halogen was significant, whilst with the phenyl and p-fluorophenyl derivatives, ions such as Ar^+, ArC^+, $ArCN^+$, etc. were significant.

The mass spectra of the 3-nitroso derivatives showed that these compounds underwent ready fragmentation to give many ions. In no case was the molecular ion the parent ion and the different substituents caused varying effects. In each case losses of 16 (O) and 17 (OH) were noted, usually the M-16 ion being very intense, but the loss of 40 (NO) was not found to be significant. The loss of NO from nitroso compounds is usually

an important fragmentation. Further discussion of the fragmentation of such nitroso compounds will be carried out elsewhere as will discussion of the n.m.r. spectra of the imidazopyrimidines.

Experimental

2-Arylimidazo (1,2-a)pyrimidines were prepared by refluxing the substituted phenacyl halide and 2-aminopyrimidine together in absolute ethanol for an appropriate time according to the method of Buu-Hoi[4] and Almirante[2].

2-p-biphenylimidazo(1,2-a)pyrimidine(IIf,X=H) was obtained as buff-coloured crystals, m.p. 260° (ex benzene).

Analysis: C,79.4; H,4.8; N,15.0%. $C_{18}H_{13}N_3$ requires: C,79.8; H,4.8; N,15.5%. M^+ 271.

3-Nitroso-2-arylimidazo(1,2-a)pyrimidines. The 2-arylimidazo (1,2-a) pyrimidine was dissolved in glacial acetic acid and an aqueous solution of sodium nitrite was added with stirring. The crystalline product was collected and recrystallised from ethanol (see Table).

3-Amino-2-p-biphenylimidazo(1,2-a)pyrimidine.

3-Nitroso-2-p-biphenylimidazo(1,2-a)pyrimidine (1.0g) was suspended in water (35 ml) and heated to ≃ 97° on a steam-bath. The mixture was stirred whilst sodium dithionite (5.0g) was added, portionwise. The nitroso derivative slowly dissolved during the addition then a yellow precipitate formed. This product was collected from the cooled mixture and recrystallised from ethanol as pale yellow crystals (0.4g) m.p. 205-207°.

Analysis: C,75.3; H,4.8; N,18.7%. $C_{18}H_{14}N_4$ requires: C,75.6; H,4.9; N,19.5%.

TABLE

3-Nitroso-2-arylimidazo(1,2-a)pyrimidines

Compound II,X=NO	Yield %	m.p.	Analysis	M^+
a	96	225° (lit.[7] 224°)	-	224
b	50	176-177°	Found:C,65.5;H,4.3;N,22.8% Required:C,65.6;H,4.2;N,23.5%	238
c	80	220° (lit.[7] 228°)	-	258(^{35}Cl)
d	55	224-226°	Found:C,47.5;H,2.3;N,18.7% Required:C,47.5;H,2.3;N,18.5%	302(^{79}Br)
e	45	202°	Found:C,59.3;H,2.7;N,23.2% Required:C,59.5;H,2.9;N,23.1%	242
f	75	245-247°	Found:C,71.7;H,3.9;N,18.0% Required:C,72.0;H,4.0;N,18.7%	300

References

1. G.R. Revankar, T.R. Matthews and R.K. Robins, J.Medicin.Chem., 1975,18, 1253.
2. (a) L. Almirante, L.Polo, A.Mugnaini, E.Provinciali, P.Rugarli, A. Gamba, A. Oliri and W. Murmann, J.Medicin.Chem., 1966, 9, 29.
   (b) L. Almirante et al., J.Medicin.Chem., 1965, 8, 304.
3. R.J. Collins, A.H. Tang and H.H. Keasling, J.Pharm.Exp.Ther., 1967, 158, 428.
4. N.P. Buu-Hoi and N.D. Xuong, Compt.rend., 1956, 243, 2090.
5. L.Pentimalli and V. Passalacqua, Gazz.Chim.Ital., 1970, 100,110.
6. L. Pentimalli and G. Milani, Gazz,Chim.Ital., 1970, 100, 1106.
7. J. P.LaRocca, C.A. Gibson and B. Blackburn Thompson, J.Pharm.Sci.,1971, 60, 74.
8. L. Pentimalli and S. Bozzini, Boll.Sci.Fac.Chim.Ind.Bologna,1965, 23, 181.
9. E. Ochiai and M. Yanai, J. Pharm.Soc.Japan, 1939, 59, 97.

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