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Quinone-imines and their derivatives as transient intermediates in cyclisation reactions[1]

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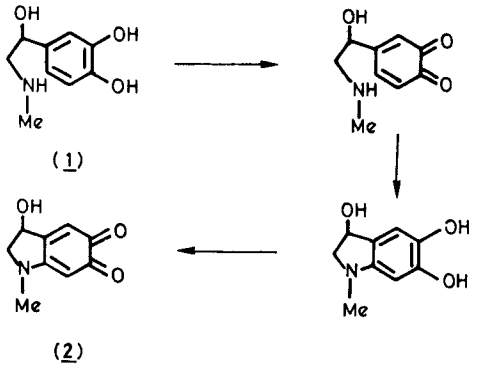
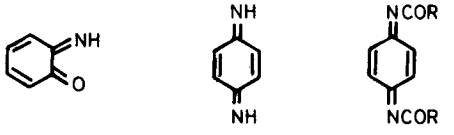
It has long been recognised that quinones may be intermediates in several cyclisation reactions (Wanzlick 1968). The ring-closure in such reactions is brought about by an intramolecular Michael addition of a suitable nucleophile located in the side chain emanating from one of the carbon atoms of the quinone. An example is the formation of adrenochrome (2) from epinephrine (1) (scheme 1). Here, the intermediate *o*-quinone, generted *in situ*, undergoes intramolecular Michael addition, followed by a further oxidation to form adrenochrome (2). Intramolecular addition of an amine to the carbonyl group of a *p*-benzoquinone intermediate may be one of the crucial steps in the Nenitzescu synthesis of 5-hydroxyindoles (Allen 1973).



(1) (2)

Scheme 1



(3) (4) (5)

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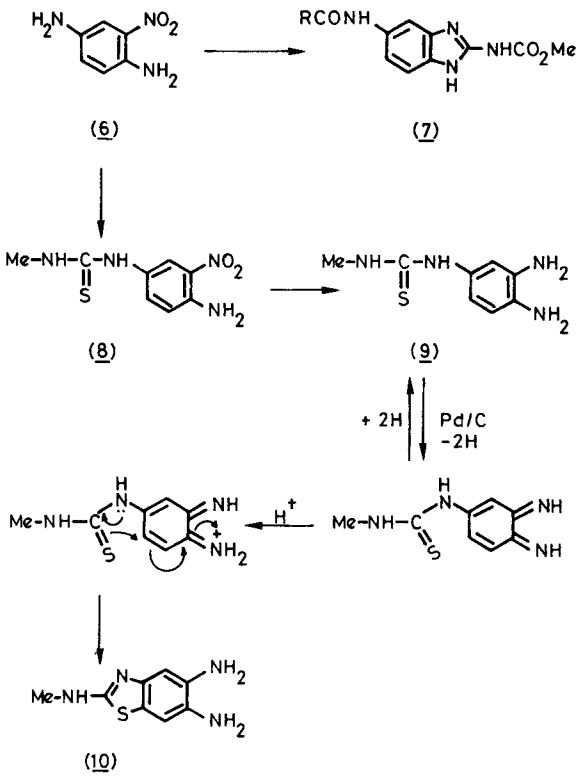
Oxidation of an *o*-aminophenol would give a quinone-monoimine (3); in such systems, it has been well-established that the first addition takes place to the C=C–C=N group. Subsequently a second nucleophile can add intramolecularly to the C=C–C=O generated by a further oxidation. Such processes have been extensively investigated in the context of actinomycins and ommochromes (Wanzlick 1968).

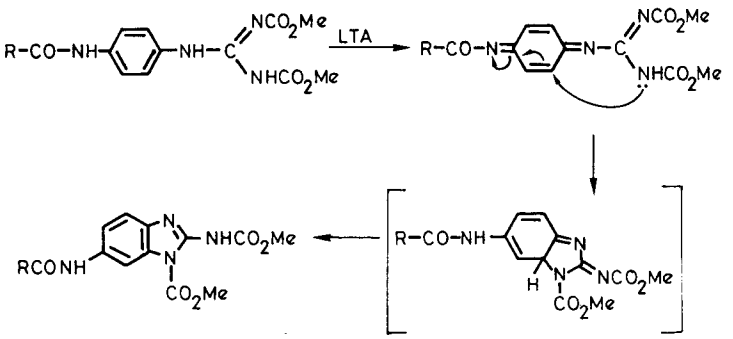
Quinone-diimines such as (4) are extremely reactive species and undergo very easy reaction with nucleophiles (Finley and Tong 1970). The disadvantage with quinone-diimines is their extreme instability. The pioneering work of Adams and his group has established that quinone-imides (5) are excellent substrates for addition reactions by virtue of their ease of preparation and relative stability compared to the quinone-diimines (Adams and Reifschneider 1958). However, intramolecular examples of addition to quinone-diimines or quinone-imides seem to be unknown.

Our entry into the area of intramolecular nucleophilic addition to quinone-diimines and quinone-imides came about partly through serendipity. A few years back, we were interested in the synthesis of derivatives of 5-amino-benzimidazole-2-carbamates (7). We achieved this by selective functionalisation of the amine *meta* to the nitro group in 2-nitro-*p*-phenylene diamine (6), followed by reduction and cyclisation (Rajappa and Sreenivasan 1980a). The functionality in these examples was an amide, urea or urethane (R in 7 was alkyl, aryl, alkylamino or alkoxy). When the functional group was a thiourea, however, the reduction step provided an unexpected result. Catalytic reduction in neutral solution (10% Pd-C, methanol, 29°, 1 atm. pressure) of the 4-thioureido-2-nitroaniline (8) gave both the expected diamine (9) and the cyclised product (10). The structure of the latter was proved by its mass spectrum (MW 194) and ^{1}H NMR spectrum (two singlets in the aromatic region). Catalytic reduction of 8 in acid solution gave only the hydrochloride of 5,6-diamino-2-methylaminobenzthiazole (10). The thioureidophenylene diamine (9) could be converted to the benzthiazole (10) by stirring in ethanolic HCl with Pd/C catalyst in the presence of atmospheric oxygen. Omission of the catalyst resulted in recovery of 9 as its hydrochloride. These results led to the postulation of the following mechanism (Rajappa and Sreenivasan 1980b). In neutral solution, in the presence of catalyst, an oxidation-reduction equilibrium is set up between 9 and the corresponding quinone-diimine. Protonation of the latter leads to a rapid, irreversible cyclisation, with the ideally located sulphur atom acting as the nucleophile. A subsequent prototropic shift results in the formation of the benzthiazole (10) (scheme 2).

This chance encounter with a presumed transient quinone-diimine set us wondering about the possible use of such intramolecular nucleophilic attack on deliberately generated quinone-imides as a route to the synthesis of novel heterocycles. We anticipated the following difficulty: quinone-imides are normally made by lead tetraacetate (LTA) oxidation of 1,4-*bis* acylaminobenzene derivatives. The prospective side-chain nucleophile should be stable under these conditions, and yet be reactive enough to attack the newly formed quinone-imide before the latter embarked on other unwanted reaction pathways. The nucleophile-bearing side-chain can be attached either to a carbon atom of the quinone-imide as in the case of the quinones mentioned earlier, or to one of the nitrogen atoms of the potential quinone-imide system. In the latter event, it should also serve the function of a stabilising group on the quinone-imine, *i.e.*, it should be a surrogate for the acylamine normally employed as substrates in LTA oxidations. Consideration of all these factors suggested that the ideal group would be a biscarbomethoxyguanidine (scheme 3). In this projected scheme, the substrate is



Scheme 2

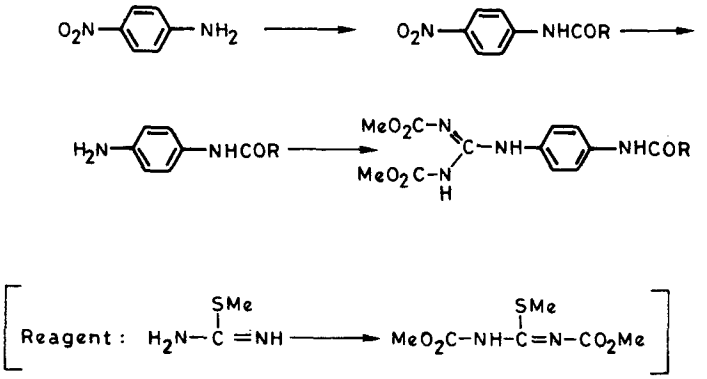


Scheme 3

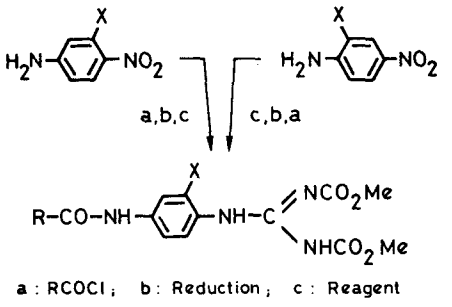
an N′,N″-biscarbomethoxy-N-(4-acylamino) phenylguanidine; LTA oxidation of this would hopefully produce the corresponding quinone-imide derivative in which either of the nitrogen atoms bearing a carbomethoxy group would be poised to attack the C=C–C=N system. The product after cyclisation would be a 6-acylamino-1-carbomethoxybenzimidazole-2-carbamate.

The precursor itself could be easily synthesised from 4-nitroaniline by acylation and reduction, followed by reaction with N,N′-biscarbomethoxy-S-methyl thiourea (scheme 4). Similar 4-acylaminophenyl guanidines with an extra substituent at either position 2 or 3 of the benzene ring have also been prepared. The synthetic route adopted depends upon the availability of the starting materials. If the substituent were to be at position 2 (adjacent to the guanidine), then in principle, either of the two sequences shown in scheme 5 can be used. In practice, however, it turned out that an NH_2 *para* to NO_2 does not react with the reagent (step 'c'). Hence the alternate route shown in scheme 6 had to be used.

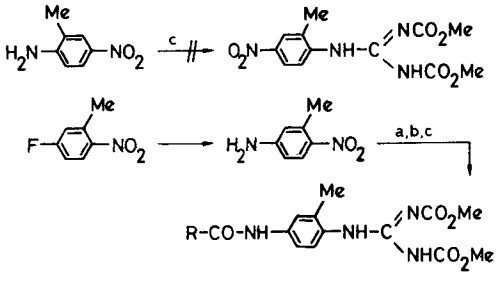
Substrates with the substituent (Me, OMe or Cl) adjacent to the acylamino group could be easily prepared from the corresponding readily available *p*-nitroanilines.



Scheme 4

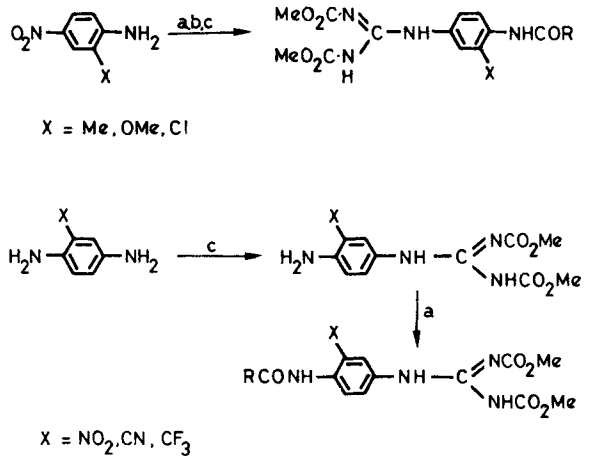


Scheme 5



Scheme 6

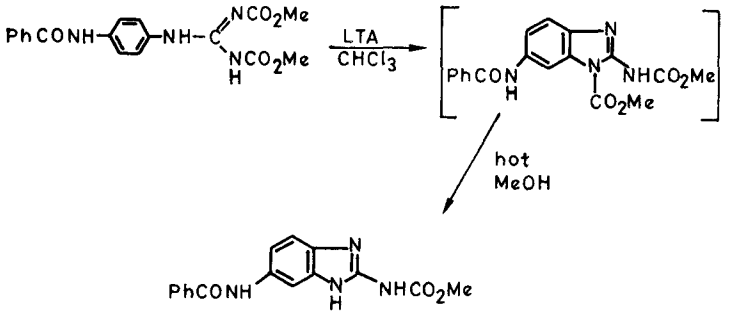
However, if the substituent was strongly electron-withdrawing (NO_2, CN, CF_3), the best route was to start from the corresponding *p*-phenylene diamine as shown in Scheme 7. Initial reaction with the reagent (step 'c') took place exclusively on the NH_2 *meta* to the deactivating substituent; subsequent acylation gave the required 4-acylamino-3-substituted-phenylguanidine.



Scheme 7

We now turn to the results of oxidative cyclisation of the various substrates discussed above.

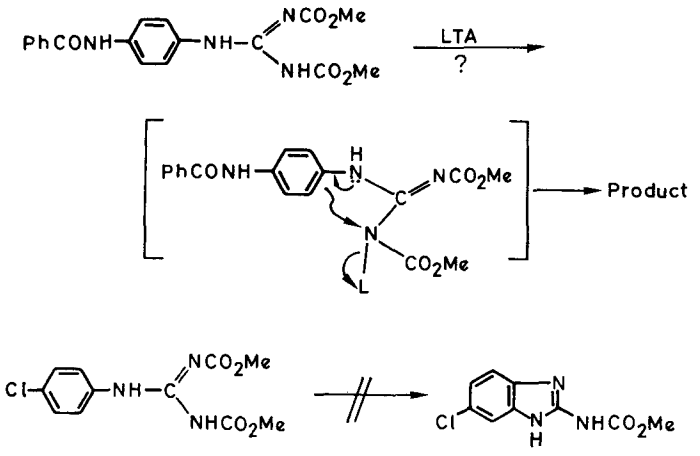
The simple 4-benzamidophenylguanidine was treated with LTA in refluxing chloroform. After filtering off the lead salts, the chloroform was evaporated and the product isolated. The compound at this stage appeared to be the required one; but it was still contaminated with small quantities of lead salts. In order to remove these, it was digested for a few minutes in boiling methanol and filtered. This procedure removed the lead salts; but at the same time, it also achieved 1-decarbomethoxylation! So the final product obtained was 5-benzamido-benzimidazole-2-carbamate. We had earlier synthesised the same compound (7: R = Ph) from 2-nitro-*p*-phenylenediamine (6) by selective monobenzoylation, reduction and cyclisation. The two products were identical, thus establishing the validity of the oxidative cyclisation route (scheme 8).



Scheme 8

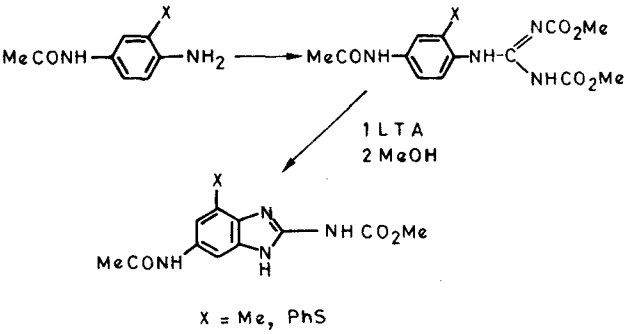
That 6-acylamino-1-carbomethoxybenzimidazole-2-carbamates are indeed the initial cyclisation products in such LTA oxidation reactions, was established by determining the ^{1}H NMR spectra of the compounds before treatment with methanol. Thus the 6-acetamido derivative showed the presence of two distinct OMe groups (3·89, 4·17 ppm in $CDCl_3$) at this stage; the benzimidazole obtained on methanolysis of this compound has only one OMe group (4·07 ppm in TFA).

We have assumed in the above discussion that the cyclisation proceeds *via* a quinone-imide. However, an alternate mechanism would involve nucleophilic attack by the *ortho*-carbon on the nitrogen atom which now carries a leaving group L[this could be $Pb(OAc)_3$ or OAc) (scheme 9). However, N′,N″-biscarbomethoxy-N-(4-chlorophenyl)guanidine was recovered unchanged after treatment with LTA under the above conditions. It is clear therefore that a *p*-acylamino group is necessary for the cyclisation; this strongly implicates the intermediacy of a quinone-imide. Further confirmation of this is provided by the substituent effect on the site of cyclisation as discussed below.



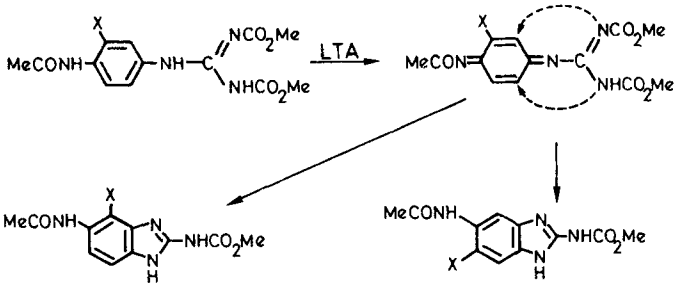
Scheme 9

In scheme 6 we had illustrated the preparation of 4-acylaminophenylguanidines with a methyl group adjacent to the guanidine. In such compounds there is only one *ortho*-position available for cyclisation and so there is no ambiguity. The resulting benzimidazoles have the substituent at position 7 and the acylamino group at position 5 (scheme 10).



Scheme 10

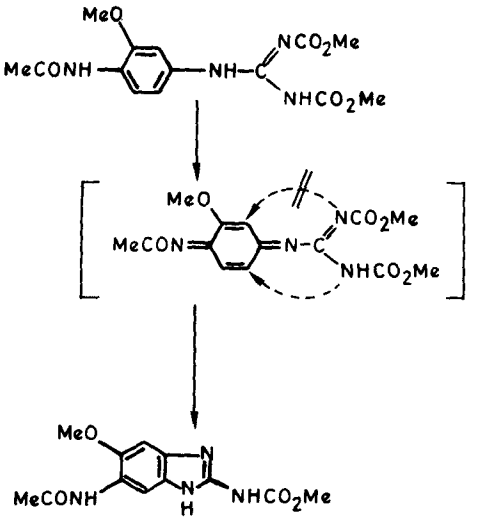
On the other hand, if the substituent is next to the acetamide, the guanidine has both *ortho*-positions free; attack by the nucleophile can take place in either direction (scheme 11). The two possible isomers can be distinguished by ^{1}H NMR (two singlets *vs* an AB quartet in the aromatic region).

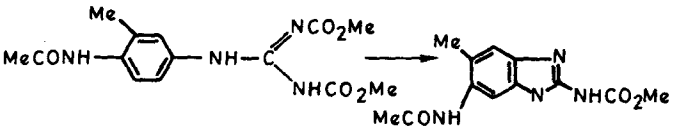


Scheme 11

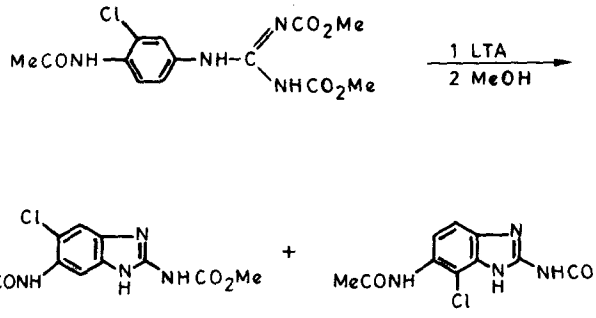
Consider the LTA oxidation of the 3-methoxy-4-acetamidophenylguanidine (scheme 12). Of the two possible loci for nucleophilic addition in the quinone-imide, the enol-ether terminus is electron-rich. Addition therefore is expected to take place at the other locus. This is exactly what happens in practice. Only one isomer is formed in 24% yield (^{1}H NMR in TFA: singlets at 7·33 and 8·50 ppm). The other isomer, if present, is below the detectable limit. A similar situation prevails with the methyl substituent.

When the substituent is chlorine, its (−I + M) effect comes into operation and so both isomers are formed (ratio 5:3; total yield 47%) (scheme 13). Thus the ^{1}H NMR shows two singlets (7·83 and 8·37) and two doublets (7·63 and 7·90 ppm).



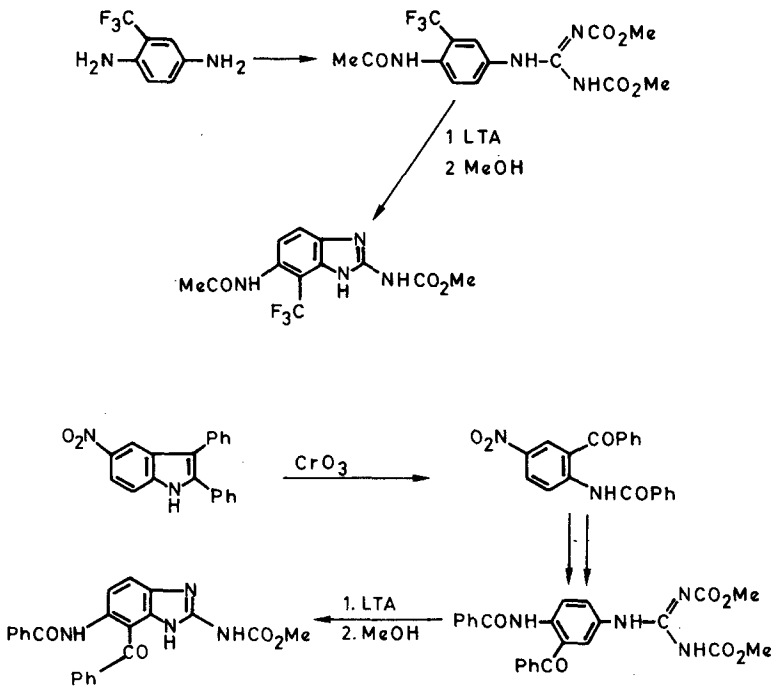


Scheme 12



Scheme 13

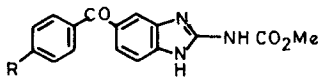
Our hypothesis that the regioselectivity of these cyclisations is largely controlled by the electronic factors associated with the substituent can be considered proven only if the sterically disfavoured vicinal cyclisation takes place exclusively when the substituent is electron-withdrawing. For this purpose, the CF_3 substituted derivative was ideal. To our delight, LTA oxidation of this gave exclusively the vicinal cyclised product (yield 20%) as shown by the AB quartet in the ^1H NMR spectrum at 7·70 and 8·03 ppm. The carbonyl substituent exerts a similar effect as shown by the oxidative cyclisation of the phenyl ketone (scheme 14).



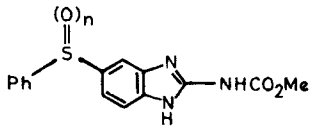
Scheme 14

More powerful electron-attracting groups like NO_2 or CN deplete the nucleus of so much of its electron-density that the oxidation step itself fails; the substrates are recovered. At the other extreme, when there is an excess of electron-release into the ring, oxidative polymerisation predominates; quinone-imine intermediates thus fail to yield cyclised products in contrast to quinone-imides. However, within the range of substituents discussed above, a wide variety of substrates undergo the regioselective oxidative cyclisation. The position *para* to the guanidine can be occupied by an NHCOR, $NHCO_2R$, $NHSO_2R$ or $NHSO_2NR_2$. Further a C=C or C=N can be interposed in some cases between the CO or SO_2 and the NH at that position.

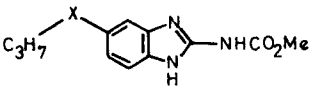
Apart from the chemical novelty of the synthesis we have described above, it has also great relevance to our quest for more efficient drugs against parasitic diseases. Benzimidazole-2-carbamates with specific substituents at the 5-position are known to be active against hookworms and roundworms (scheme 15). These are invariably



R = H: Mebendazole
R = F: Flubendazole

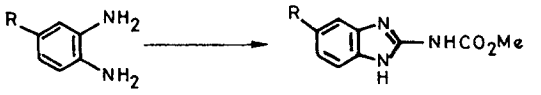


n = 0: Fenbendazole
n = 1: Oxfendazole



X = O: Oxibendazole
X = S: Albendazole

Synthesis:



Scheme 15

synthesised from an appropriately substituted *o*-phenylenediamine. The route we have described above opens up the possibility of preparing benzimidazole-2-carbamates with novel substitution patterns, inaccessible by conventional methods.

The oxidative cyclisation to benzimidazole-2-carbamates was first disclosed at the 48th Annual General Meeting of the Indian Academy of Sciences at Nainital on 10 October, 1982. A preliminary communication has subsequently been published (Rajappa *et al* 1983). It is appropriate that the present elaboration of the theme should find a place in the Golden Jubilee Issue of the Proceedings of the Academy.

The author wishes to thank his colleagues, Mr R Sreenivasan and Miss A V Rane for their excellent contribution to the work reported here.

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