Intramolecular Reactions of *N*-Nitrenes: Oxidation of 3-Amino-2-(2,4-dimethoxyphenylpropyl)quinazolin-4(3*H*)-one

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Oxidation of the title compound (**3**) and its *gem*-dimethyl-substituted analogue (**10**) in methanol gave the tetracyclic products (**5**) and (**7**), respectively. A solution of compound (**5**) in methanol was converted on standing into the cyclopentane ring-containing compound (**8**) whose structure was confirmed by *X*-ray crystallography.

In the previous paper we reported that the oxidation of the quinazolone (**1**) with lead tetra-acetate (LTA) generated the *N*-nitrene which was trapped intramolecularly by the aromatic ring to give the azepine (**2**).[1]

We presumed that this reaction was initiated by attack of the nitrene on the aromatic ring *via* a six-membered transition state with the formation of spiro-dipolar intermediate species. Since we had evidence that, all other things being equal, intramolecular *N*-nitrene trapping in these systems proceeded better *via* a seven-membered transition state,[2] we synthesised the quinazolone (**3**) with a view to obtaining the corresponding azepine (**4**).[3]

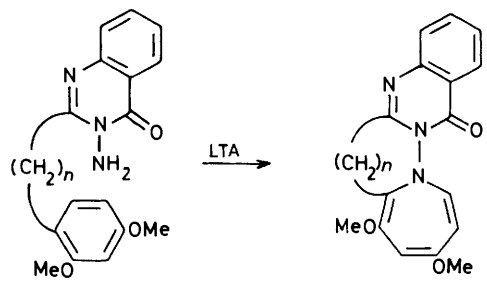
The synthesis of the 3-aminoquinazolone was accomplished by the route outlined in Scheme 1. The oxidation of compound (**3**) was carried out by intimately mixing small (equimolecular) quantities of solid (**3**) and dry LTA and adding this solid mixture in small portions to a stirred solution of benzene. The products from this reaction were exceedingly unstable to acid and a deep red colour developed within a minute on dissolution in chloroform. However, washing the benzene solution with sodium hydrogen carbonate solution and then evaporation gave an oil which crystallised in part; the crystalline material was separated by triturating the mixture with ether. An n.m.r. spectrum of this material was obtained at −23 °C in the presence of potassium carbonate and showed the presence of *three* methyl singlets at δ 3.65, 2.82, and 2.07. This, together with the i.r. spectrum, $\nu_{max.}$ 3 280, 1 737, and 1 678 cm^{-1}, suggested that a mole of acetic acid (a by-product from LTA used in the oxidation) had been incorporated into the product.

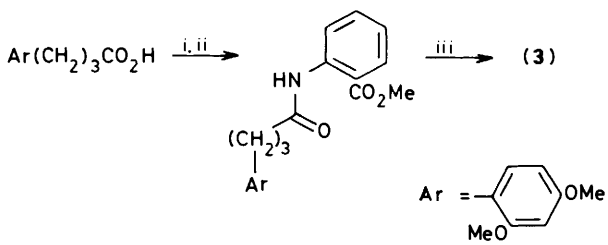
On attempted crystallisation of this acetoxy-containing material from methanol, replacement of the acetoxy group by methoxy occurred. This crystalline material, m.p. 177—180 °C, was considerably more stable than the compound from which it was derived and, on the basis of its spectroscopic properties and the transformation described below, was assigned structure (**5**).

The NH–CH–CH coupled system in compound (**5**) was evident from the signals at δ(400 MHz) 6.74 (d, *J* 5.4 Hz, NH), 4.09 (d, *J* 2.4 Hz, *H*COMe), and 3.43 (dd, *J* 5.4 and 2.4 Hz, C*H*NH) and all the protons in the linking propyl chain were non-equivalent in agreement with their proposed incorporation into a ring. A ^{13}C n.m.r. spectrum confirmed that two (sp^2) carbons which had been part of the dimethoxyphenyl ring were now sp^3 at δ 83.9 (H*C*OMe) and 58.8 (H*C*NH).

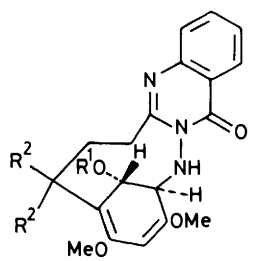
Subsequently it was found that the oxidation of compound (**3**) with LTA in methanol gave the tetracyclic compound (**5**) directly in 29% isolated yield.

A solution of compound (**5**) in methanol was slowly converted on standing into a different crystalline product, m.p. 210—215 °C. Both the i.r. and the n.m.r. spectra of this material indicated that the quinazolone ring had been modified with the formation of a second N–H bond and the n.m.r. spectrum also showed that one of the methyl groups in the starting compound





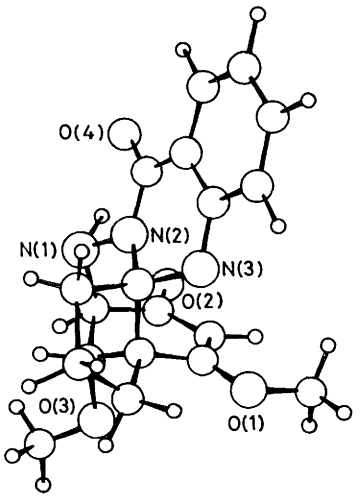
Scheme 1. *Reagents:* i, $(COCl)_2$ + Na^+ salt; ii, methyl anthranilate; iii, NH_2NH_2–EtOH

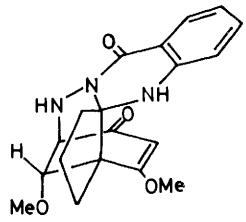


(**5**) R^1 = Me, R^2 = H
(**6**) R^1 = COMe, R^2 = H
(**7**) R^1 = Me, R^2 = Me

(**5**) had been lost. The structure (**8**) which accommodates all the spectroscopic data was confirmed by an *X*-ray crystallographic determination (Figure 1).

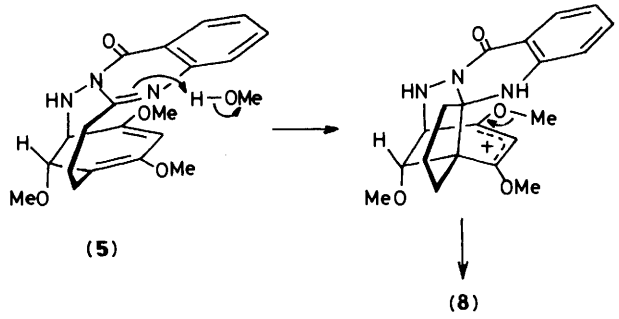
This easy conversion of compound (**5**) into compound (**8**) is presumably assisted by the stability of the 1,3-dimethoxyallyl cation and relief of the strain in the nine-membered ring (Scheme 2). Since the sp^3-hybridised methoxy-bearing carbon is





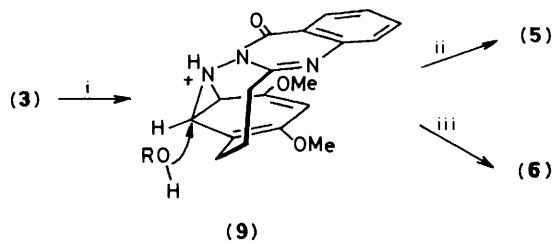
(8)

Figure 1. A view of the molecular structure of compound (**8**). Unlabelled atoms are carbon (larger circles) or hydrogen (small circles). All hydrogen atoms are shown apart from the one attached to N(3) which could not be located unambiguously



(5) (8)

Scheme 2.

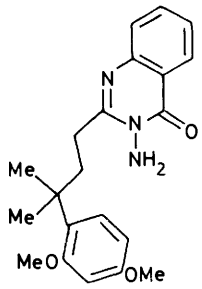


(3) (9) (5) (6)

Scheme 3. *Reagents:* i, LTA; ii, MeOH; iii, AcOH (benzene)

not disturbed in this cyclisation, it is reasonable to assume that the configuration at this carbon is the same in compounds (**5**) and (**8**) (an examination of models suggests that the magnitude of the vicinal coupling constant between the two hydrogens in MeOC*H*–C*H*–N does not define this configuration). Consequently it seems that the mechanism of formation of compound (**5**) involves the ring-opening of the intermediate aziridine (**9**) by methanol (Scheme 3). In benzene, the aziridine is attacked in a similar fashion by acetic acid and so the acetoxy-containing compound referred to earlier would have structure (**6**): transformation of compound (**6**) into (**5**) by treatment with methanol with retention of the configuration can be ascribed to the intervention of the aziridinium ion (**9**).

On the assumption that the poor yield of product (**5**) or (**6**) might be the result of competitive attack by the nitrene to give



(10)

the azepine (**4**) (or products derived from it), we also synthesised the 3,3-dimethyl-substituted analogue of compound (**3**), namely (**10**), by a route identical with that shown in Scheme 1.

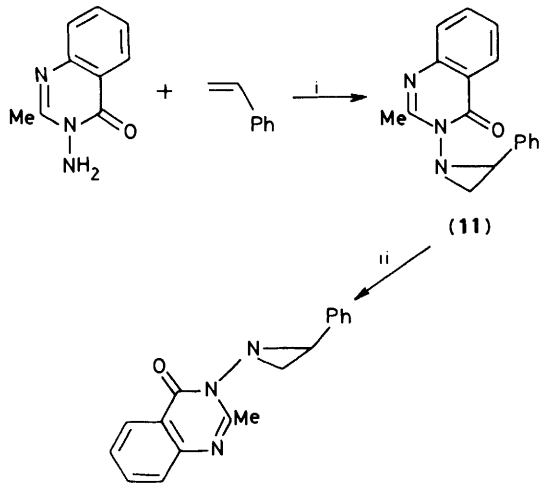
It was expected that the *gem*-dimethyl bulk would inhibit attack by the nitrene at the adjacent dimethoxyphenyl-ring carbon but would also, as a result of the *gem*-dimethyl effect,[4] encourage the alternative ring formation as occurs in compound (**5**). In the event, the oxidation of compound (**10**) in methanol gave the product (**7**) in 55% yield, the spectroscopic properties of which left no doubt that it was the *gem*-dimethyl analogue of compound (**5**). Two additional crystalline products were isolated from the oxidation of (**10**) in methanol; their structures are currently being investigated. It could be shown in a separate experiment that one of these two oxidation products was also obtained by treatment of compound (**5**) with LTA, *i.e.* compound (**7**) is actually produced in greater than 55% yield in the oxidation of (**10**), but is probably further oxidised by LTA.

As we have not isolated the azepine (**4**) we cannot exclude the possibility that its rearrangement or decomposition products may account for the major part of the products from the oxidation of compound (**3**). Nevertheless, the competitivve formation of compound (**5**) by addition to a more distant double bond is of particular interest. A peculiar feature in the *inter*molecular additions of these nitrenes to double bonds is the preference for a *syn* relationship between the quinazolone ring and the substituent on the double bond in the kinetically formed aziridine, particularly when the substituent contains π-electrons conjugated with the double bond.[5] Thus oxidation of 3-amino-2-methylquinazolone with LTA in the presence of styrene at −20 °C has been shown[6,*] to give initially the aziridine (**11**) which inverts at nitrogen to give the more stable compound (**12**) when the temperature is raised above −5 °C (Scheme 4).

Evidently, for addition of the nitrene to the styrene double bond to occur, there must be an attractive interaction between the quinazolone and phenyl rings in the transition state. We propose that a similar interaction between the double bond(s) of the dimethoxyphenyl ring which are not attacked by the nitrene and the quinazolone is responsible for the addition of the nitrene to the β double bond as shown in Figure 2 (such an interaction is not possible in an addition to the α double bond).

The conversion of an aromatic system regiospecifically into a relatively stable dihydroaromatic derivative as is the case in the transformations (**3**)→(**5**) and (**10**)→(**7**) is uncommon and potentially useful: both these products contain reactive diene functions in which only one face is likely to be attacked by a dienophile. The stability of compounds (**5**) and (**7**) towards re-aromatisation can be attributed in part to the strain in the *meta*-cyclophane which would thereby result.[7]

* The measurable rate of inversion at the aziridine ring nitrogen in compound (**11**) even at −20 °C makes it difficult to show that this compound is formed *stereospecifically* at nitrogen (as is the case with other heterocycles; ref. 5) although we believe this is the case.



Scheme 4. *Reagents:* i, LTA, −22 °C; ii, above −5 °C

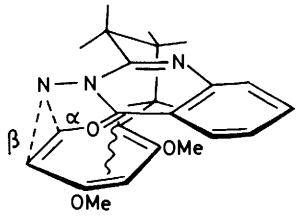


Figure 2.

Experimental

For general experimental details see ref. 1.

Methyl N-[3-(2,4-Dimethoxyphenyl)butanoyl]anthranilates.—These were prepared by the general method given in ref. 1. *Methyl* N-[4-(2,4-*dimethoxyphenyl*)*butanoyl*]*anthranilate* was obtained as a colourless solid (65%), m.p. 72—73 °C (from ethanol) (Found: C, 67.0; H, 6.5; N, 3.9. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%); δ 10.95br (s, NH), 8.66 (d, *J* 8 Hz, H *ortho* to NH), 7.91 (dd, *J* 7 and 2 Hz, H *ortho* to CO_2Me), 7.5 (ddd, *J* 8, 8, and 2 Hz, H *meta* to NH), 7.0 (m, H *meta* to CO_2Me, Ar 6-H), 6.45—6.35 (m, Ar 3-, and 5-H), 3.9—3.75 (2 × s, OMe, CO_2Me), 2.65 (t, *J* 7 Hz, 2 × 4-H), 2.45 (t, *J* 7 Hz, 2 × 2-H), and 2.15—1.85 (m, 2 × 3-H); $\nu_{max.}$ 3 300w, 1 685s, and 1 600m cm^{-1}. *Methyl* N-[4-(2,4-*dimethoxyphenyl*)-4,4-*dimethylbutanoyl*]*anthranilate* was obtained from the corresponding acid (prepared by the method given below) as a colourless solid (80%), m.p. 115—116 °C (from methanol) (Found: C, 68.25; H, 7.0; N, 3.55. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.05; N, 3.65%); δ 10.92br (s, NH), 8.62 (dd, *J* 8 and 1 Hz, H *ortho* to NH), 7.92 (dd, *J* 7 and 2 Hz, H *ortho* to CO_2Me), 7.45 (ddd, *J* 8, 8, and 2 Hz, H *meta* to NH), 7.1—6.85 (m, H *meta* to CO_2Me, Ar 6-H), 6.4—6.25 (m, Ar 3- and Ar 5-H), 3.85, 3.75, 3.7 (2 × s, 2 × OMe, CO_2Me), 2.32—1.9 (m, 2 × 2-H, 2 × 3-H), and 1.32 (s, 2 × Me); $\nu_{max.}$ 3 270w, 1 690s, and 1 595s cm^{-1}.

4-(2,4-Dimethoxyphenyl)-4,4-dimethylbutyric acid was prepared by dissolving equimolar quantities of γ,γ-dimethylbutyrolactone[8] (18 g) and 1,3-dimethoxybenzene (22 g) in dry nitrobenzene (130 ml), cooling the mixture to 0 °C, and then adding anhydrous aluminium chloride (21 g) in portions with stirring while maintaining the temperature in the range 0—5 °C. After 48 h at 5 °C the mixture was poured into ice-cold hydrochloric acid (150 ml) and the nitrobenzene removed by steam distillation. The residue was extracted with ether, and the ether layer dried and evaporated to give a dark oil which solidified on standing. Crystallisation from ethanol–water gave colourless crystals, m.p. 68—69 °C (82%); δ 9.3br (s, CO_2H), 7.03 (d, *J* 9 Hz, Ar 6-H), 6.41—6.28 (m, Ar 3- and 5-H), 3.73 (s, 2 × OMe), 2.3—1.8 (m, CH_2CH_2), and 1.33 (s, 2 × Me); $\nu_{max.}$ 2 800—2 500m and 1 705s cm^{-1}.

3-*Amino*-2-[3-(2,4-*dimethoxyphenyl*)*propyl*]*quinazol*-4(3H)-*ones.*—These were prepared from the corresponding amides above by the method given in ref. 1. 3-*Amino*-2-[3-(2,4-*dimethoxyphenyl*)*propyl*]*quinazol*-4(3H)-*one* (**3**) was obtained as a colourless solid (89%), m.p. 120—122 °C (from methanol–dichloromethane) (Found: C, 66.85; H, 6.3; N, 12.15. $C_{19}H_{21}N_3O_3$ requires C, 67.25; H, 6.25; N, 12.4%); δ 8.14 (d, *J* 8 Hz, quinaz. 5-H), 7.65—7.15 (quinaz. 6-, 7-, and 8-H), 6.98 (d, *J* 8 Hz, Ar 6-H), 6.38 (s, Ar 3-H), 6.33 (d, *J* 8 Hz Ar 5-H), 4.8 (s, NH_2), 3.7 (s, 2 × OMe), 2.98 (t, *J* 7.5 Hz, 3-CH_2), 2.7 (t, *J* 7.5 Hz, 1-CH_2), and 2.13 (m, 2-CH_2); $\nu_{max.}$ 3 315w, 3 258w, 1 665s, and 1 610m cm^{-1}. 3-*Amino*-2-[3-(2,4-*dimethoxyphenyl*)-3,3-*dimethylpropyl*]*quinazol*-4(3H)-*one* (**10**) was obtained as a colourless solid monohydrate (70%), m.p. 54—55 °C (from methanol–water) (Found: C, 65.0; H, 6.6; N, 10.8. $C_{21}H_{25}N_3O_3H_2O$ requires C, 65.5; H, 7.0; N, 10.9%); δ 8.2 (d, *J* 8 Hz, quinaz. 5-H), 7.7—7.0 (m, quinaz. 6-, 7-, and 8-H, Ar 6-H), 6.5—6.25 (m, Ar 3-and 5-H), 4.76br (s, NH_2), 3.70, 3.73 (2 × s, 2 × OMe), 2.70 (t, *J* 5 Hz, 1-CH_2), 2.35 (t, *J* 5 Hz, 2-CH_2), and 1.4 (s, 2 × Me); $\nu_{max.}$ 3 315w, 3 265w, 1 650s, and 1 600s cm^{-1}.

Oxidation of the Quinazolone (**3**) *in Benzene.*—The *N*-aminoquinazolone (**4**) (100 mg) and dry lead tetra-acetate (130 mg, 1 mol equiv.) were powdered together in a small sample tube (**CAUTION:** this experiment has not been carried out on more than 500 mg total solid) and added continuously during 5 min in small quantities to stirred benzene (50 ml). After being stirred for an additional 5 min, the insoluble lead diacetate was separated and the benzene solution washed with sodium hydrogen carbonate solution, dried and evaporated under reduced pressure to give an oil which crystallised in part. The crystalline material (37 mg) was separated by trituration with ether. Crystallisation from chloroform–light petroleum (with minimum contact time with neat chloroform) gave the acetate (**6**), m.p. 138—140 °C; δ ($CDCl_3$, −23 °C in the presence of solid K_2CO_3) 8.08 (d, *J* 7 Hz, quinaz. H *ortho* to C=O), 7.8—7.2 (m, 3 × quinaz. H), 6.7 (d, *J* 6 Hz, NH), 5.65 (d, *J* 2 Hz, C*H*OAc), 4.83 (CH=C, s), 3.65 [s, OMe + NHC*H* (obscured)], 2.82 (s, OMe), 2.9—1.9 [m, $(CH_2)_3$], and 2.07 (s, $OCOCH_3$); $\nu_{max.}$ 3 280w, 1 737s, 1 648sh, 1 678s, and 1 658s cm^{-1}. In chloroform solution at room temperature, this material rapidly decomposed with a red colouration.

Oxidation of Compound (**3**) *in Methanol.*—The procedure above was followed but using dry methanol (60 ml) containing suspended potassium carbonate (1 g) instead of benzene. After it had been stirred for an additional 5 min as above, the solution was evaporated under reduced pressure to *ca.* one-third of its bulk, chloroform was added to the residue, and the solution was filtered and then evaporated under reduced pressure. Trituration of the residue with ether gave 1,2,7,8-*tetrahydro*-3,5,17-*trimethoxy*-2,6-*methano*[1,2]*diazacycloundecino*[3,2-b]-*quinazolin*-15(9H)-*one* (**5**) as a colourless solid (29%), m.p. 179—180 °C (from methanol) (Found: C, 64.8; H, 6.3; N. 11.3. $C_{20}H_{23}N_3O_4$ requires C, 65.05; H, 6.3; N, 11.4%); δ 8.12 (dd, *J* 8.0 and 1.4 Hz, quinaz. H *ortho* to C=O), 7.67 (ddd, *J* 7.0, 8.2 and 1.4 Hz, quinaz. H *meta* to N), 7.56 (d, *J* 8.2 Hz, quinaz. H *ortho* to N), 7.36 (ddd, *J* 7.0, 8.0, and 1.2 Hz, quinaz. H *meta* to C=O), 6.74 (d, *J* 5.4 Hz, NH), 4.73 (s, CH=C), 4.09 (d, *J* 2.4 Hz, C*H*OMe), 3.43 (dd, *J* 5.4 and 2.4 Hz, NHC*H*), 3.50, 3.35,

2.81 (3 × s, 3 × OMe), 3.41 2.85, 2.53, 1.90 (ddd, *J* 12.4, 14.0, and 1.4 Hz; ddd, *J* 8.0, 13.4, and 1.2 Hz; ddd, *J* 7, 14.0, and 1.8 Hz; ddd, *J* 13.4, 8.0, and 11.0 Hz, respectively; each 1 H, $CH_2CH_2CH_2$), and 2.69, 2.24 (2 × m, $CH_2CH_2CH_2$); δ_C 161.2(s), 160.6(s), 157.6(s), 153.2(s), 146.6(s), 134(d), 126.4(d), 126.2(d), 125.8(d), 119.8(s), 104.5(s), 91.3(d), 83.9(d), 58.8(d), 56.3(s), 55.4(s), 54.9(s) 29.6(t), 29.0(t), and 27.2(t); $\nu_{max.}$ 3 246w, 1 677, and 1 650s cm^{-1}.

An identical product with that above was obtained by heating the acetate (**6**) (15 mg) to boiling in methanol (0.5 ml) containing sodium acetate (5 mg) then immediately cooling the solution in ice and inducing crystallisation (8 mg) by scratching.

Oxidation of Compound (**10**) in Methanol.—The procedure described above was followed using compound (**9**) (200 mg), LTA (241 mg), and methanol (100 ml) to give 1,2,7,8-*tetrahydro* 3,5,17-*trimethoxy*-7,7-*dimethyl*-2,6-*methano*[1,2]*diazocycloundecino*[3,2-b]*quinazolin*-15(9H)-*one* (**7**) (55%), m.p. 198—201 °C (from methanol–dichloromethane) (Found: C, 66.25; H, 6.8; N, 10.55. $C_{22}H_{27}N_3O_4$ requires C, 66.5; H, 6.85; N, 10.55%); δ 8.1 (d, *J* 8 Hz, quinaz. H *ortho* to C=O), 7.7—7.2 (m, 3 × quinaz. H), 6.65 (d, *J* 5.4 Hz, NH), 4.7 (s, CH=C), 4.21 (d, *J* 2.4 Hz, C*H*OMe), 3.57 (dd, *J* 5.4 and 2.4 Hz, NHC*H*), 3.45, 3.32, 2.79 (3 × s, 3 × OMe), 2.68—1.65 (m, CH_2CH_2), and 1.39, 1.25 (2 × s, 2 × Me); $\nu_{max.}$ 3 279w and 1 677s cm^{-1}.

Cyclisation of the Methyl Ether (**5**) *into Compound* (**8**) .—When the methyl ether (**5**) (30 mg) was set aside in methanol overnight or heated in methanol for 15 min and conversion into (**8**) took place in quantitative yield. Crystallisation gave the *product* (**8**) as a colourless solid (from methanol–dichloromethan), m.p. 210—215 °C (Found: C, 64.05; H, 6.0; N, 11.8. $C_{19}H_{21}N_3O_4$ requires C, 64.2; H, 5.95; N, 11.8%); δ 7.97 (dd, *J* 7.7 and 1.5 Hz, quinaz. H *ortho* to C=O), 7.25 (ddd, *J* 7.5, 7.9, and 1.6 Hz, quinaz. H *meta* to N), 7.06 (d, *J* 2.6 Hz,* N–N*H*), 6.83 (ddd, *J* 7.7, 7.5, and 1 Hz, quinaz. H *meta* to C=O), 6.57 (d, *J* 7.9 Hz, quinaz. H *ortho* to N), 5.56 (s, CH=C), 4.25 (s, CNH), 3.74 (s, OMe), 3.73—3.67 (m, C*HCH*NH), 3.46 (s, OMe), 2.62—2.41 (m, CH_2), 2.17—2.07 (m, CH_2), and 2.00—1.92 (m, CH_2).

* This value was incorrectly given as 6.6 Hz in ref. 3.

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