The Formation of Benzimidazolones and Quinoxalines from *o*-Nitrophenyldialkylanilines: A Re-investigation

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Contrary to earlier reports, the action of acetic anhydride and zinc chloride on 2,4-dinitrodiethylaniline does not give 4-acetyl-1-ethyl-6-nitro-1,2,3,4-tetrahydroquinoxalin-3-one (IIIb) but 2-acetoxymethyl-1-ethyl-5-nitrobenzimidazole (IVb). The reaction has been extended to a variety of mono- and di-nitrophenyl-*N*-heterocycles to give good yields of benzimidazoles, and its mechanism has been examined. Spectroscopic data are presented.

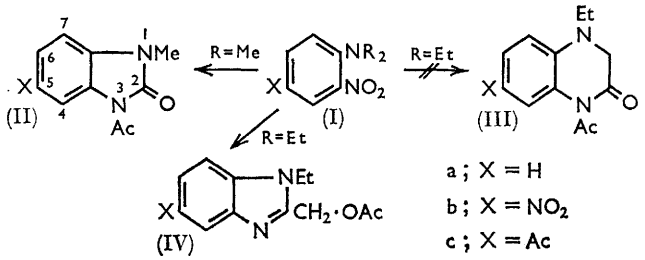
In 1926, van Romburgh and his co-workers [1] reported on their attempt to acetylate the aromatic ring of *o*-nitrodialkylanilines (I) with acetic anhydride and zinc chloride. They showed that while no ring acetylation was observed, nevertheless reaction occurred between the *o*-nitro-group and the *N*-alkyl substituent. They proposed that benzimidazolone derivatives (II) were formed from dimethylanilines (I; R = Me) and quinoxaline derivatives (III) from the diethylanilines (I; R = Et). In both cases the structure of these products was supported by synthesis, and these reactions have been commented on, though without any mechanistic explanations, in many standard texts.[2] During the course of extensive investigations into the chemistry of *ortho*-substituted dialkylanilines, we have had cause to re-investigate this reaction.

Both mono- (Ia; R = Me) and di-nitrodimethylanilines (Ib; R = Me) were found to react with acetic anhydride and zinc chloride under reflux. The product obtained from 2,4-dinitrodimethylaniline was identical with that reported by van Romburgh and his co-workers (IIb). I.r. spectroscopy showed a broad carbonyl absorption centred at 1735 cm.$^{-1}$, characteristic of a

[1] (*a*) P. van Romburgh and H. W. Huyser, *Verslag Akad. Wetenschappen Amsterdam*, 1926, **30**, 845 (*Chem. Abs.*, 1927. **21**, 382); (*b*) P. van Romburgh and H. W. Huyser, *Rec. Trav, chim.*, 1930, **49**, 165; (*c*) P. van Romburgh and W. B. Deys, *Proc. Acad. Sci. Amsterdam*, 1931, **34**, 1004 (*Chem. Abs.*, 1932, **26**, 989).

[2] (*a*) K. Hofmann, 'The Chemistry of Heterocyclic Compounds: Imidazole and its Derivatives, Part I,' Interscience, New York, 1953, p. 289; (*b*) R. C. Elderfield, 'Heterocyclic Compounds,' John Wiley, 1957, vol. 6, p. 493; (*c*) J. B. Wright, *Chem. Rev.*, 1951, **48**, 1951.

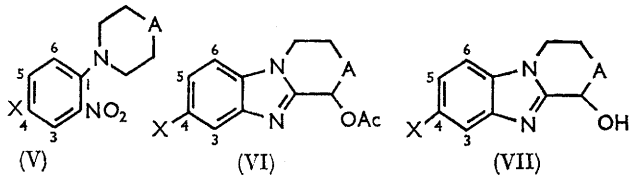
five-membered imide group,[3] while the n.mr. spectrum showed two methyl singlets at τ 7·22 (COMe) and 6·52 (N–Me) and three aromatic protons (4-H, τ 2·93 (d; J 8·9 Hz) 5-H τ 1·78 (dd, J 8·9 and 2·4 Hz) and 7-H;



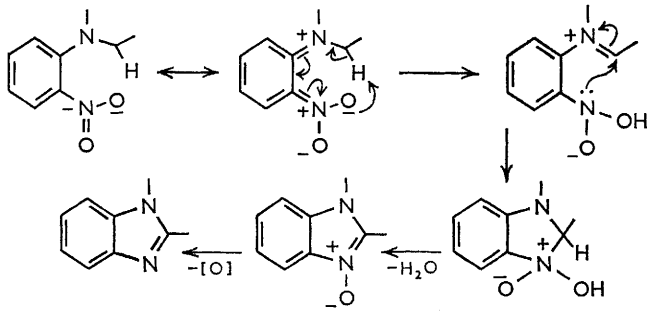
τ 1·01 (d, J 2·4 Hz)), thus supporting the benzimidazolone structure proposed by the Dutch workers. From *o*-nitrodimethylaniline the primary product obtained by treatment with zinc chloride and acetic anhydride was the benzimidazolone (IIc) in which acetylation of the aromatic ring had also occurred. Thus the i.r. spectrum showed the broad imide carbonyl group (*ca.* 1730 cm.$^{-1}$), the ketone carbonyl (1705 cm.$^{-1}$), and an amide carbonyl absorption (1670 cm.$^{-1}$), while the n.m.r. spectrum showed three methyl signals [τ 7·37 (Ar·COMe), 7·22 (N·COMe), and 6·56 (N–Me)] and three aromatic protons [4-H; τ 2·98 (d, J 8·1 c./sec.), 5-H; 2·09 (dd J 8·1 and 1·3 c./sec.), and 7-H; 1·27 (d, J 1·3 c./sec.). The u.v. spectrum (Table 4) was very similar to that of the nitrobenzimidazolone (IIb).

However, when the 2,4-dinitrodiethylaniline (Ib; R = Et) was similarly treated, spectroscopy of the product was not compatible with its proposed structure (IIIb). Thus the i.r. spectrum showed an ester carbonyl ($\nu_{max.}$ (Nujol) 1720 cm.$^{-1}$) and not the expected amide carbonyl absorption (*ca.* 1650 cm.$^{-1}$). The u.v. spectrum was characteristic of a benzimidazole (Table 4), while the n.m.r. spectrum confirmed the presence of an acetate methyl group (τ 7·81) rather than an acetamide [τ 7·22 in (IIb)] and a low-field methylene group (τ 4·59) compatible with that of an acetoxymethylbenzimidazole, rather than that of the quinoxaline (IIIa). The compound gave empirical analysis in agreement with that of van Romburgh and Huyser and we thus conclude that the structure should be 2-acetoxymethyl-1-ethyl-5-nitrobenzimidazole (IVb), despite the synthesis described by the Dutch workers.* Furthermore, Joseph and Julca [4] have synthesised 1-ethyl-2-hydroxymethyl-5-nitrobenzimidazole (IVb; Ac = H), m.p. 162°, identical to the hydrolysis product of the above (m.p. 158°; van Romburgh and his co-workers reported m.p. 157°).

In order to ascertain the scope of the reaction we examined the action of refluxing acetic anhydride and zinc chloride on a variety of cyclic tertiary anilines (V). By this means we have prepared, generally in high yield, a variety of benzimidazoles [(VI) and (VII)]



related to the product from the diethylaniline (I; R = Et). With the mono-nitroanilines (Va) a zinc salt of the product was obtained, which was most effectively dissociated by passing hydrogen sulphide through an aqueous acid solution of the salt. By this means the hydroxyalkylbenzimidazole (VIIa) was obtained. Optimum yields of benzimidazoles from the dinitro-compounds were realised with a 2 : 1 molar ratio of zinc chloride to substrate. Nevertheless, some starting material generally accompanied the reaction of the dinitroanilines (Vb), which was readily removed by chromatography, by which means the benzimidazole was obtained in a high state of purity. The progress of the reaction was readily monitored by t.l.c.



SCHEME 1

Sutton and Suschitzky [5] have recently shown that pyrolysis of the nitro-compounds (V) results in good yields of the benzimidazoles (VII; OH = H) and have suggested that the reaction involves the formation of the corresponding benzimidazole *N*-oxide in the manner indicated in Scheme 1. We believe that the present reaction basically follows a similar course, but that the *N*-oxide (or a derivative of it) is trapped by the acetic anhydride to give the above products in accord with the known properties of benzimidazole *N*-oxides. Thus, 1-methylbenzimidazole 3-oxide has been shown to yield 1-methylbenzimidazolone by action of acetic anhydride,[3b] while under the same conditions, 1,2-dimethylbenzimidazole 3-oxide gives 2-acetoxymethyl-1-methylbenzimidazole.[6] In order to test this hypothesis we have endeavoured to isolate the *N*-oxide by

* In fact, they were not able to synthesis the compound (IIIb), and instead reduced the nitro-group of the unknown product, deaminated it and compared this by mixed m.p. with the synthetic quinoxaline (IIIa).

[3] (*a*) K. Nakanishi, 'Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1962, p. 47; (*b*) S. Takahashi and H. Kano, *Chem. Pharm. Bull. Japan*, 1964, **12**, 783.

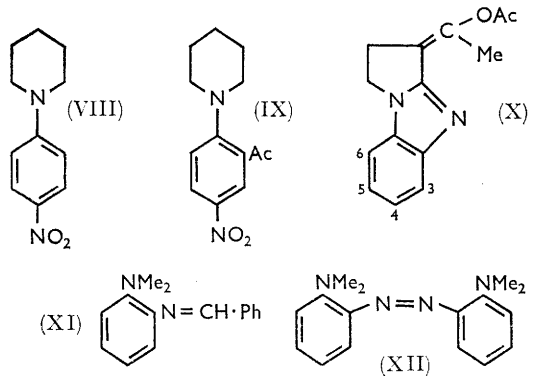
[4] L. Joseph and J. Julca, *J. Org. Chem.*, 1962, **27**, 1101.

[5] M. Sutton and H. Suschitzky, *Tetrahedron Letters*, 1967, **40**, 3933.

[6] S. Takahashi and H. Kano, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1219.

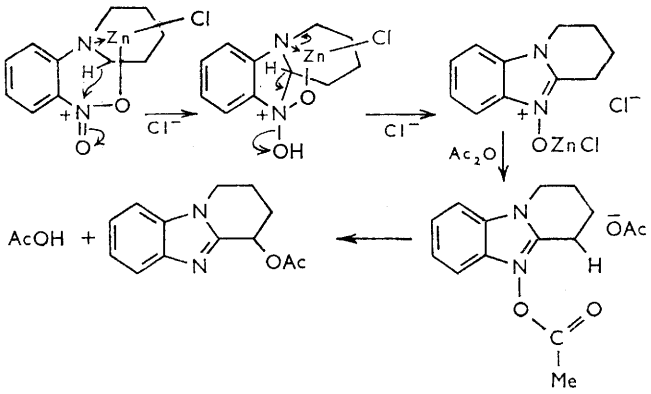
performing the reaction with zinc chloride in an inert solvent. However, after treatment at similar reaction times and temperatures we were unable to isolate the *N*-oxide in diglyme, acetic acid, xylene, anisole, dimethylformamide, dimethyl sulphoxide, or with zinc acetate in acetic acid. Since the starting compound and tar were recovered, it would appear that if the *N*-oxide was formed, it was unstable under the reaction conditions. Takahashi and Kano have reported * on the heat sensitivity of benzimidazole *N*-oxides.[3b] Attempts to trap the *N*-oxide by use of zinc chloride with reagents other than acetic anhydride (*e.g.* benzonitrile, maleic anhydride, dimethyl maleate and methyl acetylenedicarboxylate in diglyme), resulted in the formation of much tar. From the reactions carried out in diglyme solution a white crystalline solid was isolated, (identical to that obtained from the action of hot diglyme on zinc chloride alone) which from analytical and n.m.r. evidence appeared to be a stable diglyme–zinc chloride complex (1 : 1).

The action of zinc chloride and acetic anhydride on *p*-nitrophenylpiperidine (VIII) gave only 2-acetyl-4-nitrophenylpiperidine (IX) and the starting compound. Furthermore, the use of polyphosphoric acid and acetic anhydride with *o*-nitrophenylpiperidine (Va, ii) gave no benzimidazole derivative but instead 4-acetyl-2-nitrophenylpiperidine (Vc, ii) together with unchanged starting material. Migration of the nitro-group was also observed in this reaction, since *p*-nitrophenylpiperidine (VIII) was isolated. The use of zinc acetate in place of zinc chloride or the use of acetic anhydride alone was without effect on *o*-nitrophenylpiperidine. It would thus appear that both reagents play a vital role in the reaction sequence.



In order to exclude the possibility that the products from the action of zinc chloride and acetic anhydride on the nitroanilines, arose from the action of the anhydride on the benzimidazoles (VII; OH = H) we subjected pyrrolidino[1,2-*a*]benzimidazole (VIIa; OH = H) to the above reaction conditions. The only product isolated was the enol ester (X) the formation of which is in accord with the expectations based on the analogous reaction of benzoyl chloride and pyridine with the same compound.[7]

It would thus appear that the ring-closure requires the formation of a complex involving the tertiary amino- and the nitro-groups with zinc chloride (Scheme 2) thus



SCHEME 2

facilitating cyclisation. Similar complexes have been isolated using the anils (XI)[8] and the azo-compounds (XII).[9] In the latter case, the action of heat on the complex gave a benzimidazole by a mechanism similar to that described here. The observation that 2 mol. of zinc chloride were necessary for the high yield conversion of the dinitro- compounds to the benzimidazoles is possibly explained by some interaction with the second nitro-group. Nitro- groups are known as ligands for complex formations.[10]

Further work on this reaction is being carried out.

EXPERIMENTAL

I.r. spectra were recorded on a Unicam SP 200 spectrophotometer, generally as Nujol mulls. N.m.r. spectra were conducted on a Varian A60A spectrometer in deuteriochloroform solution (unless otherwise indicated) with tetramethylsilane as an internal reference. M.p.'s are uncorrected. Empirical analyses were carried out by Weiler and Strauss of Oxford.

Nitro-compounds.—These were all prepared by standard literature methods.[11]

Formation of Benzimidazoles.—The appropriate nitro-compound (0·01 mole), zinc chloride (0·01 mole for mononitro-compounds and 0·02 mole for dinitro-compounds) and acetic anhydride (10 ml.) were heated under reflux for periods of 3—5 hr. until the starting nitro-compound was absent or minimal, as indicated by t.l.c. The reaction mixture was poured onto water (100 ml.) and worked up by one of the following methods:

(A) *For mononitro-compounds.* The precipitated solid was warmed with conc. hydrochloric acid (*ca.* 20 ml., 36%) and then diluted with an equal volume of water. Hydrogen sulphide was passed through this solution for 5 min. and the solution was boiled for a further 5 min. Basification (dilute sodium hydroxide) precipitated a mixture of zinc

* They observed that 1-methylbenzimidazole 3-oxide at 130° for 5 hr. gave much tar and low yields of dimeric materials.

[7] O. Meth-Cohn, *J. Chem. Soc.*, 1964, 5245.
[8] P. Bamfield, *J. Chem. Soc.*, 1967, 804; *ibid.*, 1968, 81.
[9] R. Price, *J. Chem. Soc.*, 1967, 521 and 2048.
[10] (*a*) R. F. Grossman, *J. Org. Chem.*, 1957, **22**, 581; (*b*) N. A. Pushin, L. Nikolic, A. Radojcin, and T. Voronopova, *Annalen*, 1942, **551**, 259.
[11] O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, 1963, 1666.

sulphide and the product, which was extracted with chloroform (3 × 50 ml.); the extracts were dried ($MgSO_4$) and evaporated. The residue was recrystallised (ethyl acetate) in the presence of active charcoal.

(B) *For dinitro-compounds.* The precipitated product was extracted with chloroform (3 × 50 ml.), dried, and evaporated; the residue was chromatographed on a column of silica gel (Merck). Residual starting material was eluted with benzene and the product with chloroform. Crystallisation of the eluate was accomplished from ethyl acetate–light petroleum (b.p. 60—80°) to give the products as white needles.

The reaction conditions, yields, and physical properties of these compounds are recorded in Table 1 and the spectral data in Tables 2, 3, and 4.

Acetylation of Nitrophenylpiperidines.—(*a*) *N*-(*o*-Nitrophenyl)piperidine (2·1 g.), acetic anhydride (5·0 g.), and polyphosphoric acid (2·0 g.) were heated under reflux for 4 hr. after which time the mixture was poured into water. Extraction with chloroform gave a brown solution which was dried and evaporated; the residue was chromatographed on a dry silica column prepared in a nylon tube.[12] Development with benzene gave three bands consisting of (1) starting material (1·5 g.), (2) *p*-nitrophenylpiperidine (0·15 g., 7%), m.p. 105° (lit.,[13] 105·5°), and (3) *N*-(2-nitro-4-acetylphenyl)piperidine (Vc, ii) (0·05 g., 2%), m.p. 90° (lit.,[14] 90·5—91·5°), $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$ ($COCH_3$), n.m.r. (CCl_4); τ 8·3 (br, $CH_2{\cdot}CH_2{\cdot}CH_2$), 7·50 ($COCH_3$), 6·84 (br, t, $CH_2{\cdot}N{\cdot}CH_2$), 2·95 (d, *J* 9·0 Hz, 6-H), 2·05 (dd, *J* 9·0 and 2·0 Hz, 5-H), and 1·75 (d, *J* 2·0 Hz, 3-H).

(b) *N*-(*p*-Nitrophenyl)piperidine (2·5 g.), zinc chloride (1·4 g.), and acetic anhydride (10 ml.) were heated under

Table 1

Benzimidazolones (II) and benzimidazoles (IV), (VI) and (VII)

Compound	Time (hr.)	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Requires (%) C	Requires (%) H	Requires (%) N	M.p.
(IIb)	4									174·5—175·5° [1]
(IIc)	4	48	62·0	5·5	12·35	$C_{12}H_{12}N_2O_3$	62·1	5·2	12·05	169—170
(IVa; Ac = H)	5	0								
(IVb)	4	65	54·7	4·9	16·2	$C_{12}H_{13}N_3O_4$	54·75	5·0	16·0	167
(VIb, i)	4	68	54·9	4·1	15·95	$C_{12}H_{11}N_3O_4$	55·2	4·2	16·1	148
(VIb, ii)	4	85	56·7	4·7	15·2	$C_{13}H_{13}N_3O_4$	56·7	4·8	15·3	160
(VIb, iii)	2½	87	58·0	5·0	14·5	$C_{14}H_{15}N_3O_4$	58·1	5·2	14·5	205
(VIb, iv)	4	15	52·0	3·9	15·1	$C_{12}H_{11}N_3O_5$	52·0	4·0	15·1	196
(VIIa, i)	3	67	68·45	5·7	15·9	$C_{10}H_{10}N_2O$	68·9	5·8	16·1	190
(VIIa, ii)	4	73	69·7	6·4	14·4	$C_{11}H_{12}N_2O$	70·2	6·4	14·85	170
(VIIa, iii)	3	70	71·2	7·3	13·6	$C_{12}H_{14}N_2O$	71·2	7·0	13·8	182
(VIIa, iv)	5	0								

Table 2

Chemical shifts (τ) and coupling constants [*J* (Hz)] of compounds (IV)

Compound	CH_3	CH_2–N	–CH_2–O	CH_3CO	4-H	6-H	7-H
(IVb)	8·48t, *J* 7·5	5·62q, *J* 7·5	4·59	7·84	1·38d, *J* 2·0	1·76dd, *J* 9·1, 2·0	2·50d, *J* 9·1
(IVa) *	8·49t, *J* 7·5	5·56q, *J* 7·5	5·07		1·40d, *J* 2·0	1·78dd, *J* 9·0, 2·0	2·53d, *J* 9·0

* In deuteriochloroform with two drops of hexadeuteriodimethylsulphoxide. d = Doublet, dd = double doublet, q = quartet, t = triplet.

Table 3

Chemical shifts (τ) and coupling constants (*J* (Hz)] of compounds (VI) and (VII)

Compound	–CH	OAc/OH	A	N–CH_2–	–CH_2–A	3-H	4-H	5-H	6-H
(VIb, i)	3·72q, *J* 7·7 and 4·0	7·83s		5·63c	6·4—7·5c	1·40d, *J* 2·1		1·81dd, *J* 2·1, 9·1	2·52d, *J* 9·1
(VIb, ii)	3·74br	7·81s	7·65br	5·72br	7·65br	1·44d, *J* 2·3		1·84dd, *J* 2·3, 9·1	2·57d, *J* 9·1
(VIb, iii)	3·67br	7·80s	7·96br	5·59br,t	7·96br	1·39d, *J* 2·2		1·78dd, *J* 2·2, 9·1	2·54d, *J* 9·1
(VIb, iv)	2·77s	7·81s		5·4	5·8c	1·35d, *J* 2·2		1·72dd, *J* 2·2, 9·1	2·47d, *J* 9·1
(VIIa, i)	4·57q, *J* 7·0, 4·0	2·2br		5·4—6·2c	6·65—7·5c	2·2c	———	2·6—2·9c	———
(VIIa, ii)	4·85br,t	2·7br	7·79br	5·99br,t	7·79br	2·2c	———	2·6—2·9c	———
(VIIa, iii)	4·92br,t	4·68br	8·1br	5·4—6·5c	8·1br	2·33c	———	2·6—3·1c	———

br = Broad, c = complex, d = doublet, dd = double doublet, q = quartet, s = singlet, t = triplet.

Table 4

U.v. spectra of benzimidazolones (II) and benzimidazoles (IV), (VI), and (VII)

Compound	$\lambda_{max.}$ (mμ), [ε]
(II; X = H)	222 [6950], 287 [5260]
(II; X = NO_2)	199 [13,700], 222 [11,900], 280 [12,300]
(IV); X = NO_2)	242 [33,200], 303 [13,240]
(VIb, iii)	240 [37,920], 307 [13,840]
(VIIa, iii)	216 [8650], 254 [9580], 269 [7290], 276 [8650], 283 [7720]

[12] B. Loev and M. M. Goodman, *Chem. and Ind.*, 1967, 2026.
[13] E. Lellman and E. Geller, *Ber.*, 1888, **21**, 2281.
[14] W. Borsche, L. Stackmann, and J. Makaroff-Semijanski, *Ber.*, 1916, **49**, 2238.

reflux for 4 hr. after which time the mixture was poured into water and extracted with chloroform; the extract was dried and evaporated to give a brown residue. Chromatography on silica gel gave first startling material (1·4 g.) [25% benzene–light petroleum (b.p. 40–60°)] then *N*-(2-acetyl-4-nitrophenyl)piperidine (0·9 g., 33%) [25% benzene–light petroleum (b.p. 40—60°)], m.p. 62° as yellow plates from light petroleum (b.p. 40—60°); $\nu_{max.}$ (Nujol), 1670 cm.$^{-1}$ (CO·CH_3); n.m.r. ($CDCl_3$) τ 8·29 (br, CH_2·CH_2·CH_2), 7·40 ($COCH_3$), 6·80 (br, t, CH_2–N–CH_2), 2·93 (d, *J* 8·9 Hz, 6-H), 1·75 (overlapping signals due to 3-H and 5-H); (C_6D_6) 3·64 (d, *J* 9·0 Hz, 6-H), 3·02 (dd, *J* 9·0 and 2·6 Hz, 5-H, and 1·64 (d, *J* 2·6 Hz, 3-H).

Acetylation of Pyrrolidino[1,2-a]*benzimidazole*.—Pyrrolidino[1,2-*a*]benzimidazole (2·5 g.), zinc chloride (1·4 g.), and acetic anhydride (10 ml.) were heated under reflux for 3 hr., ethanol was added (5 ml.) and the mixture was poured onto water. The mixture was extracted with chloroform to give, after the extract had been dried and evaporated, an oil which precipitated a crystalline solid (1·8 g.) on addition of ether. The solid crystallised as white *needles* from light petroleum (b.p. 80—100°), m.p. 125—126·5° (Found: C, 69·6; H, 6·0; N, 11·4. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·6%); $\nu_{max.}$ (Nujol) 1750 (CH_3CO) and 1700 cm.$^{-1}$ (C=C); n.m.r. ($CDCl_3$) τ 7·82 (s, $COCH_3$), 7·42 (t, *J* 2·0 Hz, CH_3–C=), 6·83 (complex t, CH_2–C=), 5·97 (t, *J* 7·0 Hz, –CH_2–N), 2·55–3·0 (4-H, 5-H, and 6-H), and 2·2 (complex, 3-H).

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