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Reactions of Halogenomethanes in the Vapour Phase. Part 5.[1] The Reactions of Imidazolines, Anils, and 1-Methylimidazole with Chloroform at 550 °C, and a Comparison with their Liquid-phase Reactions with Trichloroacetate Ion or Hexachloroacetone and Base

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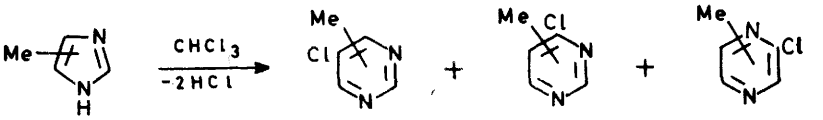
The vapour-phase reactions of imidazolines and anils with chloroform at 550 °C are compared with their liquid-phase reactions in the presence of hexachloroacetone and base or upon thermolysis with trichloroacetate ion. In the vapour-phase reactions imidazolines, unlike imidazoles, gave non-chlorinated pyrimidines, and 1-methylimidazole gave 2-cyanopyrrole and the four 3-chlorocyanopyridines.

We have shown [1] that a mixture of a *C*-methylimidazole (1) and chloroform in the vapour phase at 550 °C gives a product which contains 5-chloro- (2) and 4-chloropyrimidines (3), and chloropyrazines (4). The reaction



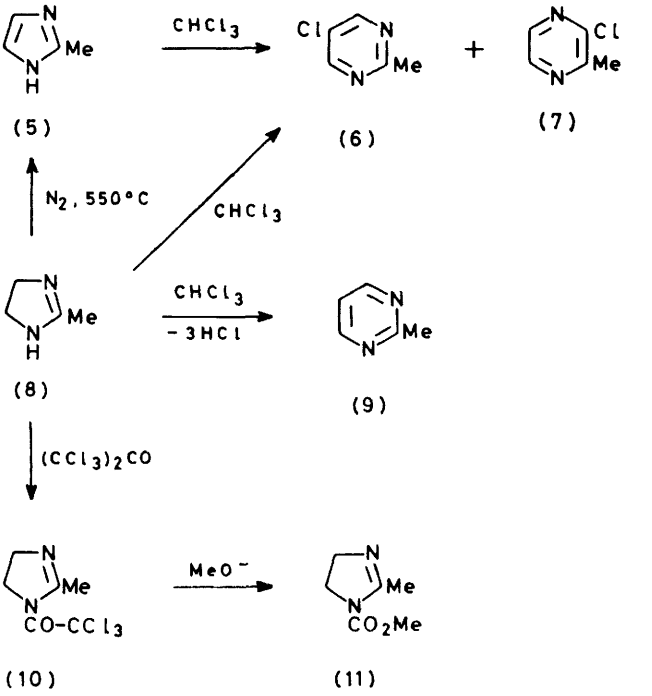
(1) (2) (3) (4)

can be considered to be insertion of the chloroform carbon atom (and bonded chlorine) into the C–C, N–C-4, and N–C-2 bonds of imidazole, respectively. In an attempt to decrease the extent of reaction at the C–C bond and to increase the proportion of chloropyrazines in the product, we investigated the vapour phase reactions of 2-methyl- (8) and 2,4-dimethyl-imidazoline (12).

RESULTS AND DISCUSSION

The major reaction product from 2-methylimidazoline was 2-methylimidazole (5), but >35% of the product consisted of diazines. Unexpectedly, the major diazine (75%) did not contain chlorine and was found to be 2-methylpyrimidine (9) (Scheme 1). The remainder comprised 5-chloro-2-methylpyrimidine (6) (16%) and 2-chloro-3-methylpyrazine (7) (9%), the latter in lower proportion than was obtained from 2-methylimidazole. It was found that 2-methylimidazoline undergoes dehydrogenation when passed through the reaction tube at 550 °C in the absence of chloroform. However, it is unlikely that significant dehydrogenation of 2-methylimidazoline occurs before reaction with chloroform, since the pyrimidine : pyrazine ratio is not the same as that from 2-methylimidazole, and non-chlorinated products are not formed from imidazoles.

It is noteworthy that no products have been isolated which could be ascribed to attack at the methyl groups of substituted imidazoles.[1] It is possible that such compounds, which might be olefins or alkynes, would not survive the reaction and work-up procedures, but in the case where there is the largest number of methyl groups, *i.e.* 2,4,5-trimethylimidazole, the yield of the trimethyldiazines was 92%, so the extent of attack on methyl must be small. It seems unlikely, therefore, that initial attack has occurred at the methylene groups of imidazoline, and reaction at the NH group may have occurred prior to ring-expansion to give (9). Clearly, insertion at the double bond of 2-methylimidazoline does not explain the formation of 5-chloro-2-methyl- and 2-methylpyrimidine.



(5) (6) (7) (8) (9) (10) (11)

SCHEME 1

No reaction occurred between 2-methylimidazoline

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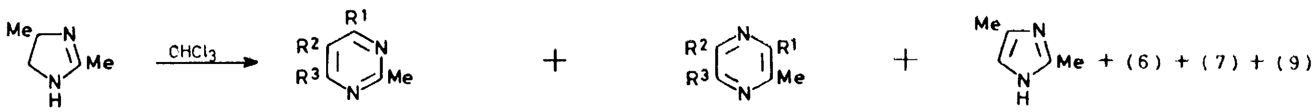
and sodium trichloroacetate [2] at elevated temperature, while sodium methoxide and hexachloroacetone [3] gave the ester (11), presumably *via* the trichloroacetyl derivative (10). No ring-expanded products were isolated.

The reaction of 2,4-dimethylimidazoline (12) with chloroform at 550 °C gave a product which comprised non-chlorinated (57%) and chlorinated pyrimidines and pyrazines (Table). A factor in the formation of a complex mixture in this case was demethylation to give methylpyrimidines, (6), (9), and (14), and 2-chloro-3-methylpyrazine (7). A slight majority (53%) of the product consisted of pyrimidine derivatives, but the proportion of non-chlorinated pyrimidines (total 8%) is markedly different from that obtained with 2-methylimidazoline. Interestingly, no change occurred when 2,4-dimethylimidazoline was pyrolysed in a stream of nitrogen only, but 2,4-dimethylimidazole (22) (7%) was present in the product from the pyrolysis with chloroform.

Composition of the diazines from imidazolines and chloroform at 550 °C

Imidazoline	Products: Methylpyrimidines		5-Chloropyrimidines		4-Chloropyrimidines		Methylpyrazines		Chloropyrazines	
(8)	(9)	75%	(6)	16%					(7)	9%
(12)	(9)	2	(6)	8	(14)	<1%	(18)	21%	(7)	5
	(13)	6	(15)	21	(16)	14	(20)	14	(19)	4
					(17)	1			(21)	3
(26)	(25)	100								



(12)

(13) R¹ = Me, R² = R³ = H
(14) R¹ = Cl, R² = R³ = H
(15) R¹ = Me, R² = Cl, R³ = H
(16) R¹ = Cl, R² = H, R³ = Me
(17) R¹ = Cl, R² = Me, R³ = H

(18) R¹ = R³ = H, R² = Me
(19) R¹ = Cl, R² = H, R³ = Me
(20) R¹ = R² = H, R³ = Me
(21) R¹ = Cl, R² = Me R³ = H

(22)

(23) (24) (25) (26)

Another marked difference in the behaviour of imidazoles and imidazolines was found with the 2-phenyl-derivatives: 2-phenylimidazole (23) was unchanged when pyrolysed with chloroform (a notable difference from the result obtained with 2-methylimidazole), while 2-phenylimidazoline (25) gave 2-phenylpyrimidine (24) but did not give the pyrazine (26). These results prompted us to investigate the reaction of acyclic systems containing the C=N group. Benzaldehyde anil (28) and chloroform at 550 °C yielded only degradation products (benzonitrile and aniline, mainly) while acetophenone anil (29) gave 1,3-diphenylbut-2-en-1-one (dypnone) (27) (Scheme 2) and 1,3,5-triphenylbenzene. It is known [4] that the anil (29) and acid yield dypnone anil on heating, and that this gives the triphenylbenzene on further heating. On treatment of benzaldehyde anil (28) with hexachloroacetone and sodium methoxide the dichloroaziridine (31) was isolated and its subsequent hydrolysis gave the chlorophenylacetanilide (33), in agreement with other findings.[5] Thermolysis of sodium trichloroacetate with (28) gave (33) directly, presumably due to hydrolysis of (31) in the work-up procedure which included chromotography on alumina. Similarly, acetophenone anil (29) and trichloroacetate gave the phenylacrylanilide (atropic acid anilide) (36), presumably by hydrolysis and dehydrochlorination of the dichloroaziridine (32), but unexpectedly no reaction occurred when (29) was treated with hexachloroacetone and base. Similarly, benzophenone anil (30) did not react with hexachloroacetone but yielded the non-chlorinated (34) upon pyrolysis with trichloroacetate; the mechanism of formation of (34) is not clear. Pyrolysis of the anil (30) with chloroform at 550 °C gave the expected chlorinated anilide (35).

The imidazoles and imidazolines employed in the vapour phase reactions up to this stage contained the NH group. This function is absent in the anils and we therefore investigated the reaction of an *N*-substituted imidazole. 1-Methylimidazole (41) and chloroform at 550 °C gave a complex mixture including the expected chloropyrimidine (37) and chloropyrazine (39). An *N*-methyl substituent on imidazole is known [6] to migrate at

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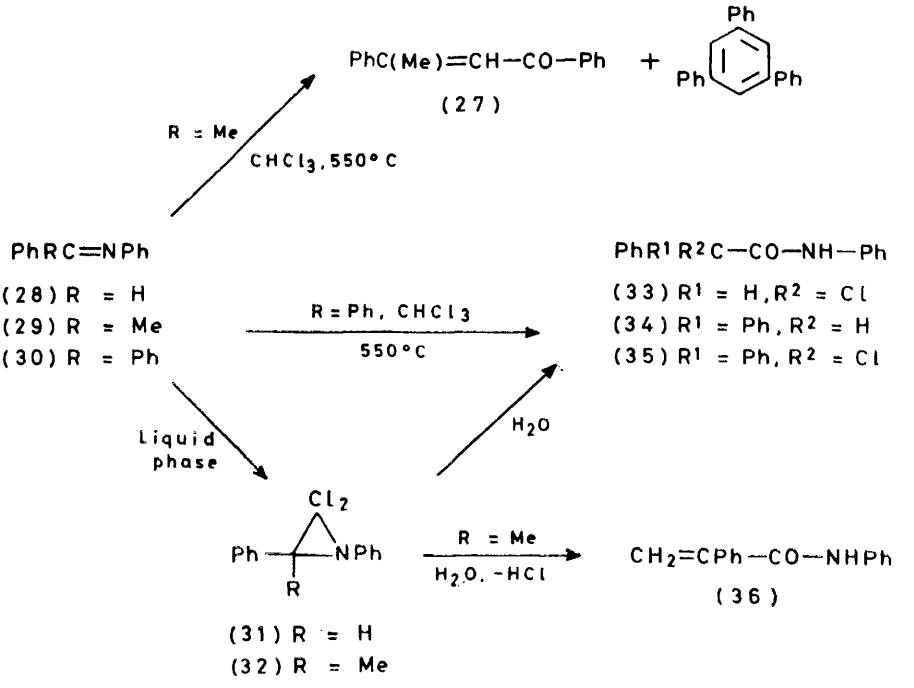
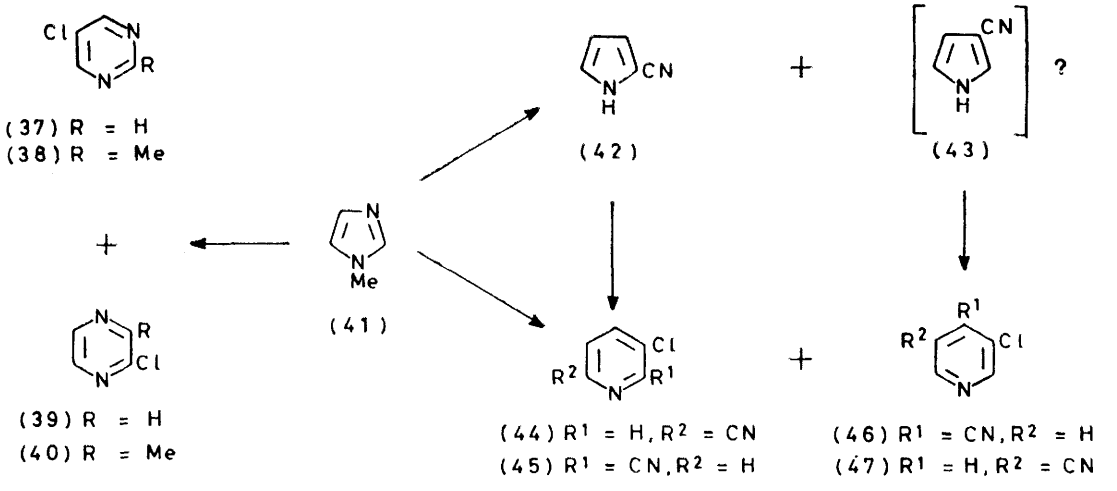
high temperature and the traces of 5-chloro-2-methylpyrimidine (38) and 2-chloro-3-methylpyrazine (40) are, presumably, formed from the 2-methylimidazole produced in a thermal rearrangement. More interestingly, to give chlorocyanopyridines. Photo-isomerisation of 2-cyanopyrrole (42) to (43) is known,[7] but (42) was recovered in high yield after passage through the reactor in the absence of chloroform. Thus, 3-cyanopyr-



SCHEME 2

the product contained chlorocyanopyridines (44)—(47), and 2-cyanopyrrole (42) as major components (74% of the total yield) (Scheme 3). Thus, the absence of the NH group markedly affects the nature of the reaction role, if it is present as an intermediate, must be formed either directly from the 1-methylimidazole, or from 2-cyanopyrrole by the action of chloroform or HCl (a by-product of the reaction). In the presence of chloroform,



SCHEME 3

and leads to ring-expansion with, probably, either the incorporation of both the *N*-methyl and chloroform carbon atoms into the pyridine ring, or the rapid formation of cyanopyrrole intermediate(s) and subsequent reaction with chloroform in a ring-enlargement process 2-cyanopyrrole gave low yields of 3-chloro-6-cyanopyridine (44) and 3-chloro-2-cyanopyridine (45) only, both of which are minor products from 1-methylimidazole. It seems unlikely that the major pyridine derivatives from (41), *i.e.* (46) and (47), are formed from 2-cyano-

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pyrrole. It is possible that 3-cyanopyrrole (43) is more reactive under the pyrolysis conditions than the 2-cyano-isomer, and (43) is a potential intermediate in the formation of (46) and (47). However, if (43) is an intermediate, it must be formed directly from 1-methylimidazole. We are investigating the details of these processes.

The assignment of structures to the isomeric 3-chlorocyanopyridines was based on the following evidence. Two isomers (46) and (47) were isolated from the pyrolysis reaction product and their structures were deduced from the evidence of molecular formula (mass spectrum) and the presence of a CN group and a pyridine ring (i.r. spectrum). The substitution pattern was determined from the ^{1}H n.m.r. spectrum. The other two isomers (44) and (45) were not isolated, but their mass spectra were almost identical, and also very similar to those of the previous compounds. Further quantities of (44) and (45) were obtained from the reaction of chloroform with 2-cyanopyrrole and this provided further evidence in support of their structure as 3-chloro-2- and -6-cyanopyridines, since these are the expected major products from the reaction.

EXPERIMENTAL

Spectroscopic data were obtained with the instruments previously described.[8] The pyrolysis experiments were conducted in the manner indicated [8,9] and the basic fraction of the products were removed from the aqueous phase by separate extraction with ether and either chloroform or dichloromethane. The difference in polarity of these solvents provided a useful separation of azoles and azines in some cases. The analytical g.l.c. was performed on the instruments described [8] with either 10% Apiezon L (column 1) or 3% OV17 (column 2) stationary phases on silanised Chromosorb G. Preparative g.l.c. used 15% OV17 (column A) or 20% OV17 (column B) stationary phases.

Pyrolysis with Chloroform in a Flow System at 550 °C.—2-Methylimidazoline (10 g) yielded an oil (3.8 g, 44%) from the ether extract, and 2-methylimidazole (5.2 g) from the chloroform extract. The oil was separated into three components by preparative g.l.c. on column A at 80 °C: 2-methylpyrimidine (75%); 5-chloro-2-methylpyrimidine (16%); and 2-chloro-3-methylpyrazine (9%).

2,4-Dimethylimidazoline (14.4 g) gave an oily residue (5.5 g) from the ether extract and a mixture (1.2 g) of 2,4-dimethylimidazole and 2-methylimidazole in a ratio of 2 : 1 respectively, from the dichloromethane extract. The oil was analysed on column 1 and separated by preparative g.l.c. on column B at 125 °C into seven fractions, five of which proved to be pure compounds: 2-methylpyrimidine (2%); fraction 2; 4-chloro-2-methylpyrimidine [1] (<1%); 2-chloro-3-methylpyrazine (5%); 5-chloro-2,4-dimethylpyrimidine [1] (21%); 4-chloro-2,6-dimethylpyrimidine [1] (14%); and fraction 7.

Analysis of fraction 2 by n.m.r. spectroscopy showed it to be composed of 2,4-dimethylpyrimidine (6% of the total diazines), 2,5-dimethylpyrazine (21%), 2,6-dimethylpyrazine (14%), and 5-chloro-2-methylpyrimidine (8%). Similarly, fraction 7 was shown to contain 2-chloro-3,5-dimethylpyrazine [1] (4%), 3-chloro-2,5-dimethylpyrazine [1] (3%), and 4-chloro-2,5-dimethylpyrimidine [1] (1%).

2-Phenylimidazoline (16 g) yielded a brown oil (14 g) from the chloroform extract. Fractional distillation (at 0.01 mmHg) yielded two products: 2-phenylpyrimidine (1.4 g), b.p. 100—110 °C, and 2-phenylimidazoline (6.1 g), b.p. 120—140 °C. The residue solidified and was crystallised from benzene as 2-phenylimidazole (5.1 g).

N-Benzylideneaniline (benzaldehyde anil) (28) (10 g) yielded aniline hydrochloride (3 g), and benzonitrile (2.5 g), together with traces of benzene and benzaldehyde.

N-(Methylphenylmethylene)aniline (acetophenone anil) (29) (34 g) gave aniline hydrochloride (6.8 g) and an ether-soluble fraction which yielded acetophenone (4.5 g) and a mixture (10.6 g) of 1,3-diphenylbut-2-en-1-one, 1,3,5-triphenylbenzene, benzonitrile, and benzene.

N-(Diphenylmethylene)aniline (benzophenone anil) (30) (10 g) gave aniline hydrochloride (3.6 g), benzophenone (5.1 g), benzonitrile (0.3 g), 1,1-diphenyl-1-chloroacetanilide (0.3 g), m.p. 205—206 °C (from diethyl ether) (Found: C, 75.1; H, 5.2; N, 4.5; Cl, 10.7. $C_{20}H_{16}ClNO$ requires C, 74.8; H, 5.0; N, 4.4; Cl, 11.1%); $\nu_{max.}$ (KBr) 3 330 (NH) and 1 655 cm^{-1} (CO); τ [$(CD_3)_2SO$] −0.6 (1 H, s, NH) and 2.2—3.0 (15 H, m, 3 × Ph). An intensely fluorescent yellow compound (0.8 g), m.p. 216—219 °C, was isolated but not identified.

1-Methylimidazole (16 g) gave a product which afforded an oil (4.8 g) from the ether extract and 1-methylimidazole (3.2 g) from the dichloromethane extract. The oil was analysed by g.l.c. on column 2 at 110 and 140 °C and separated on column B at 120 °C into nine components: 5-chloropyrimidine (24%): 3-*chloro*-5-*cyanopyridine* (39%) (Found: M^+, 137.9987. $C_6H_3{}^{35}ClN$ requires M, 137.9985); τ ($CDCl_3$) 1.64 (1 H, q, J 2.5 and 1.5 Hz, 4-H), 1.53 (1 H, d, J 1.5 Hz, 6-H), and 1.41 (1 H, d, J 2.5 Hz, 2-H): chloropyrazine (2%): 5-chloro-2-methylpyrimidine (traces): 2-chloro-3-methylpyrazine (traces): 3-*chloro*-4-*cyanopyridine* (20%) (Found: M^+, 137.9985. $C_6H_3{}^{35}ClN_2$ requires M, 137.9985); $\nu_{max.}$ (film) 3 082 (aromatic CH) and 2 234 cm^{-1} (CN); τ ($CDCl_3$) 2.46 (1 H, d, J 5.0 Hz, 5-H), 1.35 (1 H, d, J 5.0 Hz, 6-H), and 1.20 (1 H, s, 2-H): 2-cyanopyrrole [10] (10%): 5-*chloro*-2-*cyanopyridine* (4%) (Found: M^+, 137.9989. $C_6H_3{}^{35}ClN_2$ requires M, 137.9985): and 3-*chloro*-2-*cyanopyridine* (<1%) (Found: M, 137.998 5).

2-Cyanopyrrole [10] (2.75 g) afforded an oil (1.1 g) from the dichloromethane extract which was analysed by g.l.c. on column 2 at 140 °C to be: 2-cyanopyrrole (76%); 5-chloro-2-cyanopyridine (19%); and 3-chloro-2-cyanopyridine (5%).

1-*Methoxycarbonyl*-2-*methylimidazoline* (11).—2-Methylimidazoline (3 g), sodium methoxide (8 g), hexachloroacetone (20 g), and methylene chloride (100 cm^3) gave, after the usual procedure,[3] a residue from the methylene chloride. Distillation of this gave an oil (b.p. 68—70 °C at 0.07 mmHg) which crystallised as 1-*methoxycarbonyl*-2-*methylimidazoline* (3.98 g, 80%), m.p. 46—48 °C (from diethyl ether) (Found: C, 50.8; H, 7.2; N, 19.6; M, 142. $C_6H_{10}N_2O_2$ requires C, 50.7; H, 7.1; N, 19.7%, M, 142); $\nu_{max.}$ (KBr) 1 720 cm^{-1} (CO); τ ($CDCl_3$) 6.24 (7 H, m, Me + 2 × CH_2), and 7.7 (3 H, s, 2-Me).

1-*Phenyl*-1-*chloroacetanilide* (35).—A mixture of benzaldehyde anil (9 g), sodium methoxide (10.8 g), hexachloroacetone (26 g), and dry light petroleum (b.p. 40—60 °C) (150 cm^3) gave 1,3-diphenyl-2,2-dichloroaziridine (11.4 g, 86%), m.p. 96—98 °C (lit.,[11] m.p. 99 °C). Hydrolysis of the aziridine in boiling water for 0.5 h yielded 1-phenyl-1-chloroacetanilide (60%), m.p. 144—146 °C (lit.,[11] m.p. 147—148 °C).

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The same compound was obtained (56%) from benzaldehyde anil (4.5 g) and sodium trichloroacetate (13.8 g) after refluxing in dimethoxyethane (70 cm^3) for 18 h, and chromatography of the product on alumina.

α-*Phenylacrylanilide* (36).—A mixture of acetophenone anil (8 g), sodium trichloroacetate, and 1,2-dimethoxyethane (70 cm^3) was refluxed for 14 h. After evaporation of the solvent under vacuum, the residue was extracted with ether and the solution evaporated. The product was chromatographed on neutral alumina with ether and the solid crystallised to give α-phenylacrylanilide (3.8 g, 41%), m.p. 134—136 °C (from ethanol) (lit.,[12] m.p. 134 °C).

1,1-*Diphenylacetanilide* (35).—Benzophenone anil (6 g) and sodium trichloroacetate (11.9 g), gave, in a similar way to that described previously, 1,1-diphenylacetanilide (1.2 g, 18%), m.p. 184—186 °C (from aqueous ethanol) (lit.,[13] 180 °C) (Found: C, 83.4; H, 5.8; N, 4.9. Calculated for $C_{20}H_{17}NO$: C, 83.6; H, 5.9; N, 4.8%); $\nu_{max.}$ (KBr) 3 300 (NH) and 1 650 cm^{-1} (CO); τ [$(CD_3)_2SO$] −0.6 (1 H, s, exchanged in D_2O, NH), 2.2—3.1 (15 H, complex m, 3 × Ph), and 4.8 (1 H, s, CH).

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