Cleavage of Pyrimidines and Fused Pyrimidines by Active Methylene Reagents with Closure to give Pyridine Derivatives

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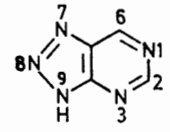
Pyrimidine and its 4-methyl derivative reacted with malononitrile to form 2-aminopyridine-3-carbonitrile and its 6-methyl derivative, respectively. Quinazoline with malononitrile gave 2-aminoquinoline-3-carbonitrile and, with dimedone, 3,4-dihydro-3,3-dimethyl-1(2*H*)-acridone (16). Similarly pyrido[3,2-*d*]pyrimidine (9) and dimedone gave 6,7-dihydro-7,7-dimethylbenzo[*b*][1,5]naphthyridin-9(8*H*)-one (18). 4-Aminopyrimido[4,5-*d*]pyrimidine (10) and malononitrile yielded 4,7-diaminopyrido[2,3-*d*]pyrimidine-6-carbonitrile (19); purine and malononitrile gave 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitrile (20). ^{1}H N.m.r. spectra are reported and the mechanisms of the reactions are discussed.

RECENTLY [1] we reported that 8-azapurine (*v*-triazolo[4,5-*d*]pyrimidine) (1) and some 2-substituted derivatives, on treatment with reagents containing strongly activated methylene groups, did not give the usual 1,6-adducts [2] [*e.g.* (2)], but products in which the pyrimidine ring had opened to form 4-(substituted amino)-5-vinyl-1,2,3-triazoles [*e.g.* (3)]. When malononitrile and dimedone (5,5-dimethylcyclohexane-1,3-dione) were the reagents, these triazoles cyclised, often spontaneously, to form the *v*-triazolo[4,5-*b*]pyridines [(4) and (5), respectively]. In the present work we show the generality of these reactions by their application to pyrimidine (6), its 4-methyl derivative (7), quinazoline (8), pyrido[3,2-*d*]-pyrimidine (9), 4-aminopyrimido[4,5-*d*]pyrimidine (10), and purine (11).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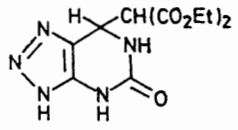
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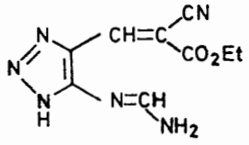
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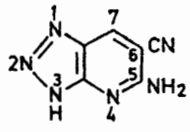
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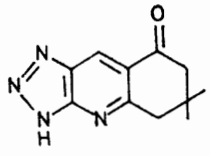
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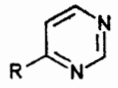
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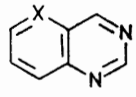
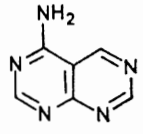
(7) R = Me

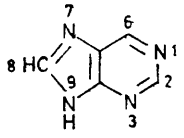

(8) X = —CH=
(9) X = —N=


(10)

Pyrimidine (6) or its 4-methyl derivative (7), when fused with malononitrile without solvent or catalyst, gave 2-amino-3-cyanopyridine (12) or its 6-methyl derivative (13), respectively, both identical with authentic specimens.[3,4] Quinazoline (8) reacted with malononitrile in neutral methanol at 20° to yield 2-aminoquinoline-3-carbonitrile (14), identical with that prepared from 2-aminobenzaldehyde and malononitrile.[5] Quinazoline formed a 3,4-adduct (15) with dimedone similar to those reported in the pteridine series.[6,7] The structure of the adduct was confirmed by elemental analysis and ^{1}H n.m.r. spectroscopy. An n.m.r. spectrum [in $(CD_3)_2SO$] showed a singlet (1H) at τ 3·81, *ca.* 3·5 p.p.m. to higher field than the pyrimidine protons of quinazoline (see Table). This is characteristic of the saturation of a carbon atom in heteroaromatic systems by addition across the neighbouring C=N bond.[8] It was expected that addition would occur across the 3,4-bond by analogy with the covalent hydration of quinazolines, which gives 3,4-dihydro-4-hydroxy-derivatives.[9,10] This was confirmed by making the dimedone adduct of 4-deuterioquinazoline;[10] the n.m.r. spectrum was closely similar to that of the adduct (15), except that the singlet at τ 3·81 was absent (Table). The n.m.r. spectra of these adducts [in $(CD_3)_2SO$] indicated that each was in equilibrium with its components, being about 30% dissociated at 33·3°. Treatment of the adduct (15) with

[1] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, 1620.
[2] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, 457.
[3] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, 1954, **19**, 1633.
[4] T. Matsukawa and T. Matsuno, *J. Pharm. Soc. Japan*, 1944, **64**, 145.
[5] B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Amer. Chem. Soc.*, 1958, **80**, 2806.
[6] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117.
[7] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1968, 63.
[8] T. J. Batterham, *J. Chem. Soc.* (*C*), 1966, 999; J. Clark, *ibid.*, 1967, 1543; J. Clark and W. Pendergast, *ibid.*, 1968, 1124.
[9] W. L. F. Armarego, *J. Chem. Soc.*, 1962, 561.
[10] W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.* (*B*), 1967, 449.

aqueous alkali yielded 3,4-dihydro-3,3-dimethyl-1(2*H*)-acridone (16), identical with a sample obtained by condensation of 2-aminobenzaldehyde with dimedone in ethanolic potassium hydroxide.[11] Similarly pyrido-[3,2-*d*]pyrimidine (9) afforded 3,4-dihydro-4-(4,4-dimethyl-2-hydroxy-6-oxocyclohex-1-enyl)pyrido[3,2-*d*]-pyrimidine (17), which on treatment with aqueous alkali gave 7,8-dihydro-7,7-dimethylbenzo[*b*][1,5]naphthyridin-9(6*H*)-one (18). The n.m.r. spectra of both these products resembled those of the corresponding products



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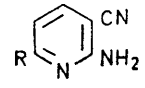
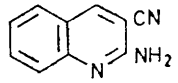


(12) R = H

(13) R = Me



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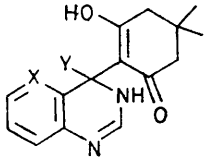
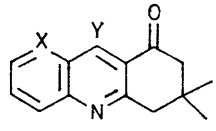


(15) X = –CH=, Y = H

(17) X = –N=, Y = H

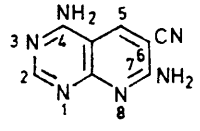
(21) X = –CH=, Y = D



(16) X = –CH=, Y = H

(18) X = –N=, Y = H

(22) X = –CH=, Y = D



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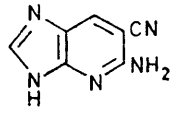

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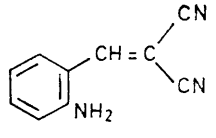


(23)

(15) and (16) from quinazoline (Table). 4-Aminopyrimido[4,5-*d*]pyrimidine (10)[12] gave 4,7-diaminopyrido-[2,3-*d*]pyrimidine-6-carbonitrile (19) when condensed with malononitrile in glacial acetic acid. Purine (11) yielded 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitrile (20) with malononitrile in water. The 2- and 7-protons of the latter had the same chemical shift [in $(CD_3)_2SO$], and were observed as a two-proton singlet at τ 1·83. The signal was resolved into two one-proton singlets (τ 1·85 and 2·03) in NaOD–D_2O. The upfield signal was assigned to H-2 (likely to be more strongly affected by the negative charge in the imidazole ring).

^{1}H N.m.r. data (33·3°)

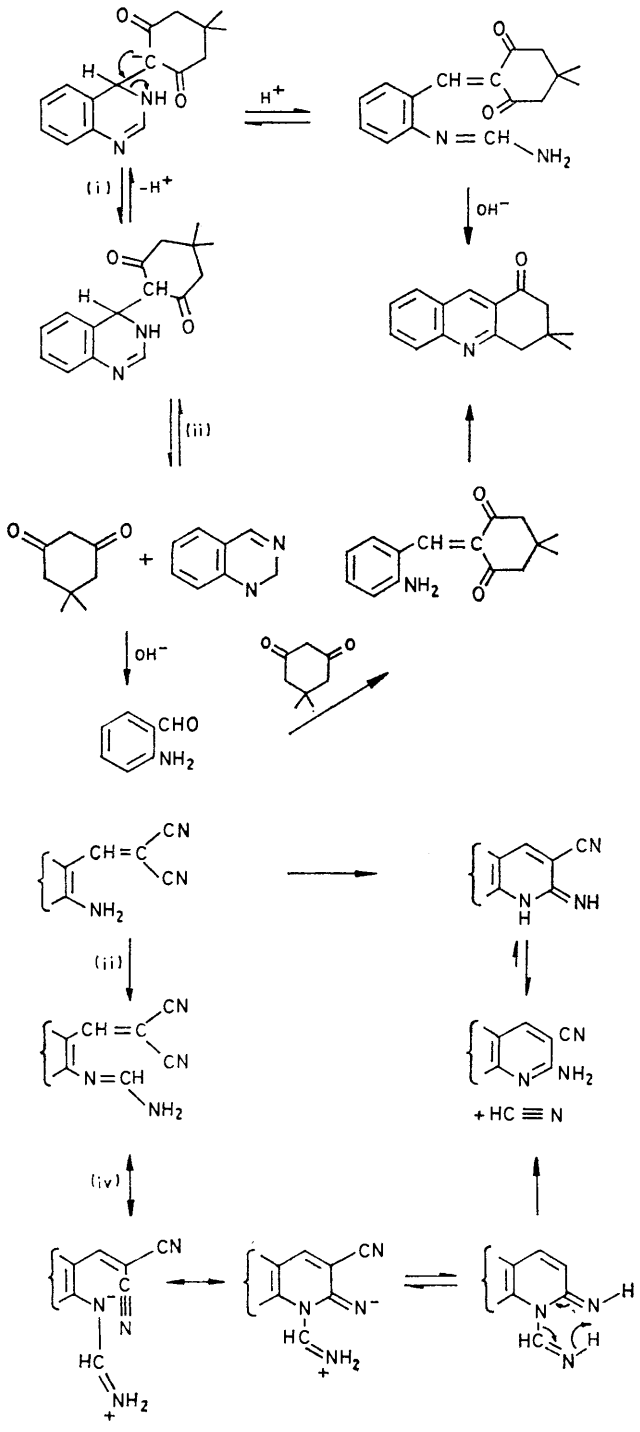
Compound	τ [b]	Assignment	Solvent [a]
(15) [c]	1·84	H-2	$(CD_3)_2SO$
	2·94 (m) (4)	H-5,6,7,8	
	3·81	H-4	
	8·02 (4)	CH_2 (dimedone)	
	9·06 (6)	CH_3 (dimedone)	
(21) [c]	1·99	H-2	$(CD_3)_2SO$
	3·07 (m) (4)	H-5,6,7,8	
	8·07 (4)	CH_2 (dimedone)	
	9·09 (6)	CH_3 (dimedone)	
(8) [d]	0·30	H-4	$(CD_3)_2SO$
	0·59, 0·58 [e]	H-2	
(16)	0·98	H-9	$(CD_3)_2SO$
	1·96 (m) (4)	H-5,6,7,8	
	6·79 (2)	2-CH_2 [f]	
	7·28 (2)	4-CH_2 [f]	
	8·90 (6)	3-CH_3	
(22)	1·96 (m) (4)	H-5,6,7,8	$(CD_3)_2SO$
	6·83 (2)	2-CH_2 [f]	
	7·32 (2)	4-CH_2 [f]	
	8·93 (6)	3-CH_3	
(17)	2·20	H-2	0·5N-NaOD–D_2O
	2·99 (m) (3)	H-6,7,8	
	4·18	H-4	
	7·90 (4)	CH_2 (dimedone)	
	9·03 (6)	CH_3 (dimedone)	
(9) [d]	0·35	H-4	$(CD_3)_2SO$
	0·60	H-2	
(18)	1·16	H-10	CCl_4
	1·8—2·6 (m) (3)	H-2,3,4	
	6·84 (2)	8-CH_2 [f]	
	7·41 (2)	6-CH_2 [f]	
	9·00 (6)	7-CH_3	
(20) (neutral species)	1·83 (2)	H-2,7	$(CD_3)_2SO$
	3·52(2) [g]	NH	
anion	1·85	H-7	0·5N-NaOD–D_2O
	2·03	H-2	
(4) [h]	1·19	H-7	$(CD_3)_2SO$
	2·76 (2) [g]	NH	

[a] For spectra in $(CD_3)_2SO$ and in CCl_4, tetramethylsilane as internal standard; for measurements in D_2O, sodium 3-trimethylsilylpropane-1-sulphonate as internal standard. [b] No. of protons (if more than 1) in parentheses. [c] From spectrum of equilibrium mixture. Signal ratios indicate dissociation (*ca.* 30 mol %) of the adduct into quinazoline (*q.v.*) and dimedone [τ 7·86 (4H) and 8·99 (6H)]. The sharpness of the singlet due to the 4-proton of the adduct suggests the absence of any adjacent proton on the dimedone system (*i.e.* that the latter is enolic). The equivalence of the signals due to the 2- and 6-H of the dimedone suggests that there is rapid equilibration of the two possible enolic tautomers. [d] All values from W. L. F. Armarego and T. J. Batterham, *J. Chem. Soc.* (*B*), 1966, 750. [e] 2-Proton of 4-deuterioquinazoline. [f] These assignments interchangeable. [g] Exchanged by D_2O. [h] All values from ref. 1.

[11] B. H. Iyer and G. C. Chakravarti, *J. Indian Inst. Sci., Ser. A*, 1932, **14**, 157.

[12] E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Amer. Chem. Soc.*, 1960, **82**, 5711.

Mechanism of the Reactions.—The fact that 8-azapurines are capable of forming, with active methylene reagents, compounds of type (2) [2] or (3),[1] indicated that



dihydro-compounds, *e.g.* (2), were likely to be the precursors of the ring-opened products (3). The latter would thus be produced when the methylene proton was sufficiently acidic to form the carbanion as in the Scheme (i). The intermediacy of these dihydro-compounds is supported by the isolation of the adduct (15) from the reaction of quinazoline with dimedone, and its subsequent conversion by alkali into the acridone (16). That the mechanism is a true ring-opening reaction of the carbanion [Scheme (i)] and not a mere dissociation of the adduct into its constituents, followed by alkaline ring-opening [13] of quinazoline to give 2-aminobenzaldehyde and subsequent recombination of the latter with dimedone (ii) was shown as follows. The adduct (21), prepared from 4-deuterioquinazoline [10] and dimedone, was ground with an equimolar quantity of quinazoline, and the mixture was dissolved in alkali. The acridone (22), isolated by acidification of the mixture with acetic acid, contained deuterium only in the 9-position, as evidenced by (*a*) the mass spectrum (M^+ 226), and (*b*) the n.m.r. spectrum (Table), which resembled closely that of the acridone (16) except for the absence of the 9-proton absorption. If the reaction had involved dissociation of the adduct into 4-deuterioquinazoline and dimedone (ii), isotopic scrambling would have occurred in the presence of unlabelled quinazoline.

No ring-opened product resembling the amidine (3) was isolated in the present work. However the close parallel between these reactions and those of 8-azapurines [1] suggests that such vinyl compounds are formed as unstable intermediates. Cyclisation could then proceed either by (*a*) degradation of the amidino-group to a primary amino-group, followed by cyclisation [Scheme, (iii)] or (*b*) cyclisation involving simultaneous addition of the 4-NH group across the C≡N (or C=O) group and elimination of the amidine side-chain [Scheme, (iv)]. Although possibility (*a*) could be envisaged in basic aqueous solution (*e.g.* in the quinazoline–dimedone reaction), it is difficult to reconcile this path with cyclisation of the cyano-compounds under neutral conditions or in organic solvents. Also 2-amino-α-cyanocinnamonitrile (23) requires a basic catalyst for cyclisation to 2-aminoquinoline-3-carbonitrile (14),[5] whereas quinazoline gives (14) directly on treatment with malononitrile in neutral methanol. Furthermore, copious evolution of hydrogen cyanide (detected as Prussian Blue after trapping in N-NaOH [14]) took place during the reactions of pyrimidine, 4-methylpyrimidine, and quinazoline with malononitrile. This supports the concerted mechanism indicated in the Scheme (iv).

EXPERIMENTAL

Samples for microanalysis were dried at 100° and 0·1 mmHg unless otherwise stated. ^{1}H N.m.r. spectra were determined with a Perkin-Elmer R10 instrument operating at 33·3° and 60 MHz, and i.r. spectra (Nujol mulls) with a Unicam SP 200 instrument. Identity of samples was determined by mixed m.p. where practicable, and by i.r. spectroscopy.

[13] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 1944.
[14] M. Ishidate, 'Qualitative Microanalysis,' Nanzando and Co., Tokyo, 1960, p. 270.

Reactions with Malononitrile.—Pyrimidine (0·08 g, 0·001 mol) and malononitrile (0·066 g, 0·001 mol) were fused, heated momentarily to boiling, and set aside for 2 days. The crystalline mass, pressed on a filter and washed with a little ice-cold methanol, yielded 2-aminopyridine-3-carbonitrile (12) (46%), m.p. 130°, identical with an authentic specimen [3] (lit.,[3] m.p. 131—133°). Similarly 4-methylpyrimidine (0·095 g, 0·001 mol) and malononitrile (0·066 g, 0·001 mol), heated to boiling for 2 min, gave 2-amino-6-methylpyrimidine-3-carbonitrile (48%), m.p. 184°, identical with an authentic specimen [4] (lit.,[4] m.p. 186°). In both cases, heating the reaction mixture for longer periods resulted in lower yields. Quinazoline (8) (0·065 g, 0·0005 mol) and malononitrile (0·033 g, 0·0005 mol) in methanol (0·25 ml), set aside overnight, deposited yellow crystals (52%), m.p. 223°, identical with an authentic specimen of 2-aminoquinoline-3-carbonitrile [5] (14) (lit.,[5] m.p. 225°). This compound (26%) was also prepared by heating quinazoline (0·065 g, 0·0005 mol), malononitrile (0·066 g, 0·001 mol), and potassium carbonate (0·1 g) in water (0·5 ml) at 90° for 2 min, and cooling the solution for 1 h at 0°. A solution of 4-aminopyrimido[4,5-*d*]pyrimidine [12] (10) (0·073 g, 0·0005 mol) in glacial acetic acid (0·5 ml) was stirred with malononitrile (0·033 g, 0·0005 mol) at 50° until the latter dissolved (*ca.* 5 min) and set aside for 2 days. The deposited solid was heated under reflux with methanol (0·75 ml) for 1 h; the mixture was cooled and filtered to yield 4,7-*diaminopyrido*[2,3-d]*pyrimidine*-6-*carbonitrile* (19) (49%), which gradually decomposed above 200° (Found: C, 51·5; H, 3·2; N, 45·3. $C_8H_6N_6$ requires C, 51·6; H, 3·25; N, 45·15%), ν_{CN} 2200m cm^{-1}. Purine (0·06 g, 0·0005 mol) and malononitrile (0·033 g, 0·0005 mol) in water (0·5 ml) were set aside at 20° overnight, heated at 90° for 90 min, then cooled in ice to yield greenish crystals of 5-*aminoimidazo*[4,5-b]*pyridine*-6-*carbonitrile* (20) (50%), m.p. 280° (Found: C, 49·6; H, 3·4; N, 41·8. $C_7H_5N_5$,0·5H_2O requires C, 50·0; H, 3·6; N, 41·7%), ν_{CN} 2200m cm^{-1}.

Reactions with Dimedone.—Quinazoline (0·065 g, 0·0005 mol) and dimedone (0·07 g, 0·0005 mol) in methanol (0·5 ml) were set aside overnight. The deposited crystals, filtered off and washed with cold methanol, yielded 3,4-*dihydro*-4-(4,4-*dimethyl*-2-*hydroxy*-6-*oxocyclohex*-1-*enyl*)*quinazoline* (15) (63%), m.p. 144° (Found: C, 64·8; H, 7·1; N, 9·4. $C_{16}H_{18}N_2O_2$,1·5H_2O requires C, 64·6; H, 7·1; N, 9·4%). This compound (52%) was also prepared by shaking quinazoline (0·065 g, 0·0005 mol) with a solution of dimedone (0·07 g, 0·0005 mol) and potassium hydrogen carbonate (0·1 g) in water (1 ml). The foregoing product (0·05 g, 0·00017 mol) was set aside overnight in 4N-NaOH (0·25 ml), then the pH was adjusted to 5 with acetic acid. The deposited solid, on crystallisation from aqueous methanol, yielded 3,4-dihydro-3,3-dimethyl-1(2*H*)-acridone (16) (92%), m.p. 116°, identical with an authentic specimen [11] (lit.,[11] m.p. 117°). Similarly pyrido[3,2-*d*]pyrimidine (0·013 g, 0·0001 mol) and dimedone (0·014 g, 0·0001 mol) in methanol (0·25 ml) gave 3,4-*dihydro*-4-(4,4-*dimethyl*-2-*hydroxy*-6-*oxocyclohex*-1-*enyl*)*pyrido*[3,2-d]-*pyrimidine* (17) (58%), m.p. 228° (Found: C, 65·8; H, 6·7; N, 15·2. $C_{15}H_{17}N_3O_2$,0·25H_2O requires C, 65·3; H, 6·4; N, 15·2%). Heating the foregoing compound (0·01 g) with 4N-NaOH (0·1 ml) at 90° for 20 min, and isolating the product as for that from quinazoline, yielded 7,8-*dihydro*-7,7-*dimethylbenzo*[b][1,5]*naphthyridin*-9(6H)-*one* (18) (49%), m.p. 131° (Found: C, 74·0; H, 6·6; N, 12·5. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·2; N, 12·4%).

Deuteriation Studies.—4-Deuterioquinazoline (0·033 g, 0·00025 mol) was condensed with dimedone (0·035 g, 0·00025 mol) in methanol (0·25 ml). The product (isolated as for the corresponding adduct of quinazoline) yielded 4-*deuterio*-3,4-*dihydro*-(4,4-*dimethyl*-2-*hydroxy*-6-*oxocyclohex*-1-*enyl*)*quinazoline* (21) (56%), m.p. 132° [Found: C, 64·4; H(D), 7·1; N, 9·4. $C_{16}H_{17}DN_2O_2$,1·5H_2O requires C, 64·6; H(D) 7·1; N, 9·4%]. N.m.r. spectroscopy (Table) indicated complete deuteriation at position 4. This adduct (0·01 g) was ground with quinazoline (0·05 g); the mixture was dissolved in 4N-NaOH (0·1 ml) and set aside overnight. The solution was extracted with a little ether to remove excess of quinazoline, then the pH was adjusted to 5 with acetic acid. Crystallisation of the deposited solid from aqueous methanol gave 9-*deuterio*-3,4-*dihydro*-3,3-*dimethyl*-1(2H)-*acridone* (22) (66%), m.p. 115° (Found: M^+, 226. $C_{15}H_{14}DNO$ requires M, 226). N.m.r. spectroscopy indicated complete deuteriation at position 9.

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