Reactions of 1,2-Diaminobenzene with 1,3-Diketones

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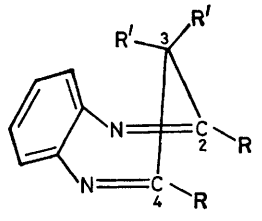
The reaction of 3-substituted derivatives of pentane-2,4-dione (acetylacetone) with 1,2-diaminobenzene has been studied. The 3-methyl, 3-prop-2-ynyl, and 3-benzyl derivatives gave 1,5-benzodiazepines, but no cyclization occurs with the 3-chloro and 3-(2,4-dinitrophenyl) derivatives. No 3,3-disubstituted benzodiazepines were obtained. 3,3-Dichloropentane-2,4-dione affords non-cyclized chloro-products. The mechanism of formation of 2,3-diaminophenazine derivatives, significant when the reactions are prolonged, is rationalized.

3*H*-1,5-BENZODIAZEPINES have been the subject of a recent review,[1] which reveals that relatively few 2,3,4-trisubstituted benzodiazepines have been prepared, and that no 2,3,3,4-tetrasubstituted benzodiazepines are known, although their synthesis has been attempted.[2,3] The latter finding agrees with the postulate of Halford and Fitch [3] that any substituent larger than H at the 3-position of a benzodiazepine will penetrate the π-electron system of the benzene ring (Figure). In a 2,3,3,4-tetrasubstituted derivative the electronic interaction would be so great that no benzodiazepine would be formed.

If the boat conformation [4] of the benzodiazepine is accepted (Figure), a single 3-substituent will tend to be directed away from the benzene ring to obviate interaction with the π-electron system. In this case the interaction between the two groups R and the 3-substituent would assume importance. In keeping with this, Halford and Fitch [3] report a 65% yield of the 2,3,4-trimethylbenzodiazepine, to be compared with an 85% yield of the corresponding 2,4-dimethyl derivative.



Conformation of 1,5-benzodiazepine

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[3] J. O. Halford and R. M. Fitch, *J. Amer. Chem. Soc.*, 1963, **85**, 3354.
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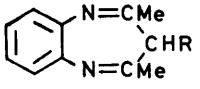
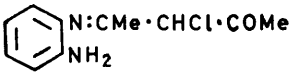
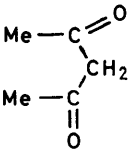
In the present study, selected 3-substituted and 3,3-disubstituted pentane-2,4-diones have been treated with 1,2-diaminobenzene (i) to determine the influence on ring closure of mono-3-substitution, and (ii) to study the steric and electronic factors which prevent formation of 3,3-disubstituted benzodiazepines. Under a set of standard conditions 3-methyl-, 3-prop-2-ynyl-, and 3-benzyl-pentane-2,4-dione gave the corresponding benzodiazepines (1)—(3) in almost quantitative yield. When the 3-substituent was strongly electron-withdrawing (chloro or 2,4-dinitrophenyl) no cyclization occurred. From the chloro-derivative the mono-imine (4) was isolated, and starting material was recovered



(1) R = Me
(2) R = $CH_2 \cdot C \equiv CH$
(3) R = CH_2Ph



(4)



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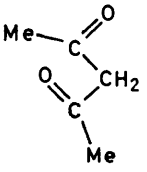

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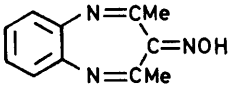

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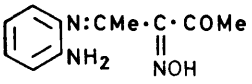

(8)

Me·CO·CRR'·COMe
(9) R = R' = Me
(10) R = Me, R' = CH_2Ph
(11) R = R' = CH_2Ph
(12) R = R' = $CH_2C \equiv CH$
(13) R = R' = Cl

quantitatively from the 3-(2,4-dinitrophenyl)pentane-2,4-dione reaction. These results suggest that the group at the 3-position of pentane-2,4-dione does not materially hinder formation of the benzodiazepine provided that it does not impede access to the two oxo-groups and that it is not strongly electron-withdrawing; however, further evidence would be required for a definitive statement.

The effect of the bulky 2,4-dinitrophenyl group can be demonstrated with a space-filling model by assuming that the 1,3-diketone favours those conformations [(5) or (6)] which involve minimum dipole–dipole interaction.[5] Failure of the 3-chloropentane-2,4-dione to give a benzodiazepine is not readily explained, since the carbonyl groups should be very susceptible to nucleophilic attack. The literature contains little information on benzodiazepines with electron-withdrawing groups at the 3-position. A related example, 3-hydroxyimino-2,4-dimethyl-1,5-benzodiazepine (7), is unstable and is readily converted into a quinoxaline with an acylhydrazine and acid.[6-8] It has been suggested [6-8] that this reaction could proceed *via* partial hydrolysis of the benzodiazepine to the non-cyclic intermediate (8), although this compound was not isolated. If the above mechanism operates, our product (4) would then represent an analogous intermediate. Compound (4) proved difficult to isolate: during concentration of the solution a vigorous, exothermic reaction was initiated, which frequently left only a charred residue.

Five 3,3-disubstituted pentane-2,4-diones [(9)—(13)] were examined. Under our standard conditions no benzodiazepines were formed. From the derivatives (9)—(12) starting material was always recovered [quantitatively for (10) and (11)], and was accompanied by a trace of fluorescent material. In the case of (13), five products were isolated. These were compounds (14) (35%) and (15) (9%), 1,2-diacetamidobenzene (11%), the 2,3-diaminophenazine derivative (16) (1%), and 2-methylbenzimidazole (trace). Halford and Fitch [3] have suggested that the reaction between 1,2-diaminobenzene and 1,3-diketones can follow two pathways. One leads to the benzodiazepine, the other to the benzimidazole. The latter pathway becomes dominant if factors opposing ring closure (*e.g.* steric ones) are present in the diketone. We have found small amounts of 2-methylbenzimidazole after the standard reaction time (5 h). This becomes a major product (up to 35%) after prolonged (18 h) reaction. With 3,3-dichloropentane-2,4-dione the benzimidazole route is also followed, but the main pathway is different. This is probably the result of the electron-withdrawing nature of the two chloro-groups. A suggested mode of formation of the products is shown in Scheme 1. The products resulting from pathway (C) follow directly from the loss of keten, initiated by the electronegative nature of the chloro-substituents. The products (14) and (15) darken rapidly at room temperature [particularly (14)], but can be kept unchanged for several weeks at 0 °C. The main product from pathway (D) (16), is analogous to ' Vaisman's base,' obtained from 1,2-diaminobenzene and 3,3-dimethylpentane-2,4-dione. The 2,3-diaminophenazine structure for this base was established recently.[9] It is suggested that the 2,3-diaminophenazine shown in this pathway is formed by the known aerial oxidation of 1,2-diaminobenzene.[6]

In all the above reactions, the major products were always accompanied by traces of bright yellow 2,3-diaminophenazine derivatives. In an attempt to examine the formation of these substances in more detail, the condensation between 1,2-diaminobenzene and 3-benzyl-3-methylpentane-2,4-dione was allowed to proceed for 18 h. From such a preparation were isolated 2-methylbenzimidazole (35%), 2-amino-3-(2-benzyl-1-

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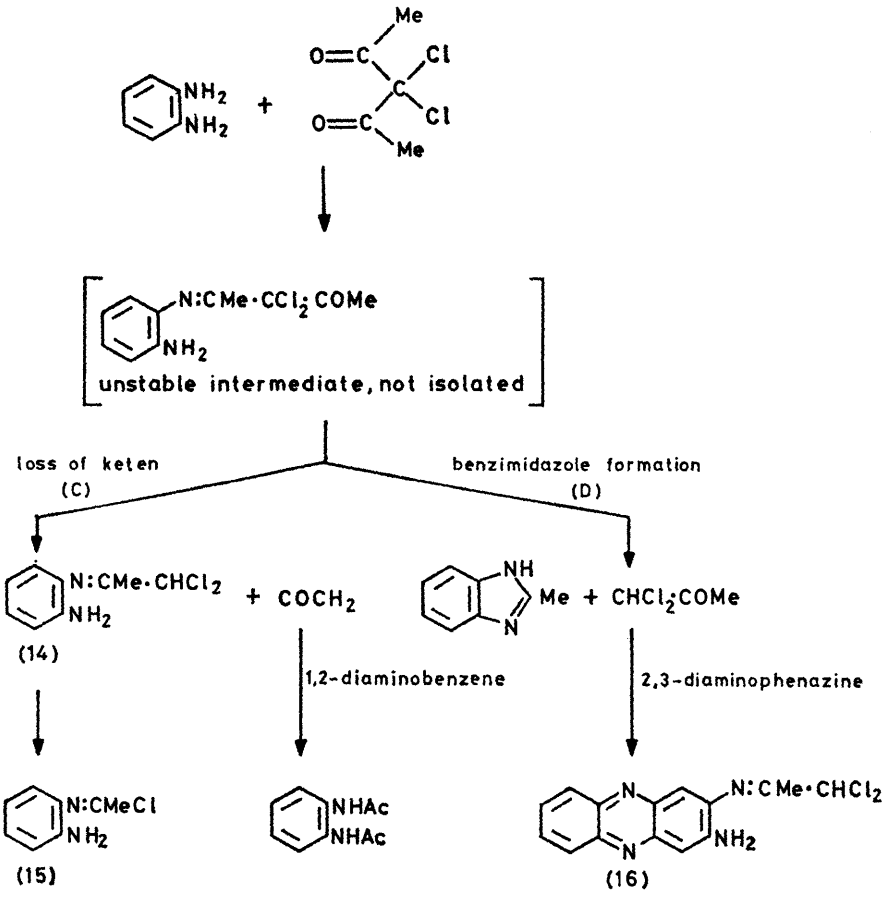
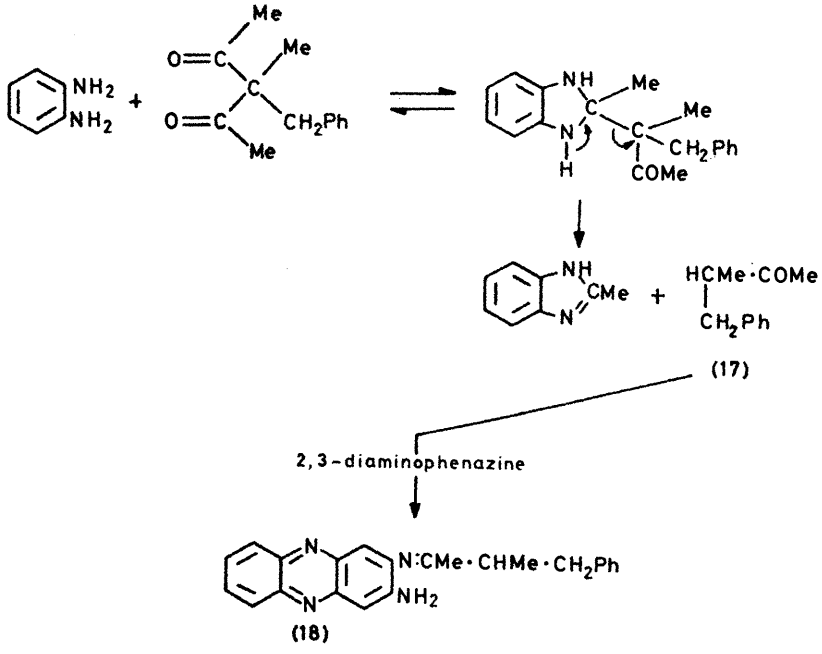


SCHEME 1



SCHEME 2

methylpropylideneamino)phenazine (18) (3%), and 3-methyl-4-phenylbutan-2-one (17) (18%). The reaction mixture was separated by dry column chromatography.[10] It is suggested that the ketone (17), as well as the 2-methylbenzimidazole, originates from fission of the mono-Schiff's base shown in Scheme 2. Whereas formation of the benzimidazole is well documented, the formation of the ketone and its subsequent reactions has so far been ignored. It is now suggested that the ketone (17) can react further with the 2,3-diaminophenazine formed by oxidation of 1,2-diaminobenzene,[6] to afford the 2,3-diaminophenazine derivative (18) (Scheme 2). Proof for the structure of (18) came from its independent synthesis from the ketone (17) [11] and 1,2-diaminobenzene by the 'direct' method reported recently.[12]

EXPERIMENTAL

Mass spectra were obtained with a Varian CH7 spectrometer at 70 eV and n.m.r. spectra with a Varian T60 instrument.

Preparation of 3-Substituted Pentane-2,4-diones.—3-Methyl-, 3-prop-2-ynyl-, and 3-benzyl-pentane-2,4-dione were prepared from acetylacetone by the method of Johnson *et al.*[13] The 3-benzyl derivative contained *ca.* 30% of 3,3-dibenzylpentane-2,4-dione (11); [14] separation was achieved by distillation. 3,3-Dimethyl- (9) and 3,3-di-prop-2-ynyl-pentane-2,4-dione (12) [15] were obtained from acetylacetone with the appropriate halide in dimethyl sulphoxide with sodium hydride as base.[16] For 3-benzyl-3-methylpentane-2,4-dione (10) [17] potassium t-butoxide was used as base. Treatment of acetylacetone with sulphuryl chloride readily yielded the mono- and dichloro-derivatives (13).[18] 3-(2,4-Dinitrophenyl)pentane-2,4-dione [19] was obtained as yellow needles from the reaction at room temperature (16 h) between acetylacetone (0.025 mol) and 1-fluoro-2,4-dinitrobenzene (0.025 mol) in the presence of sodium methoxide (0.04 mol).

Conditions for Preparation of Benzodiazepines.—Various solvents, acid concentrations, and reaction times were employed to determine conditions which would give the best yield of 2,3,4-trimethyl-3*H*-1,5-benzodiazepine (1) [3] from 1,2-diaminobenzene and 3-methylpentane-2,4-dione. Final conditions were as follows. To 1,2-diaminobenzene (2.5 g, 0.023 mol) in benzene (100 ml) and acetic acid (1 ml) the 1,3-diketone (0.023 mol) was added, and the solution was stirred at 43 °C for 5 h. Concentration of the mixture *in vacuo* and dilution with water, followed by extraction with ether, afforded the benzodiazepine in 95% yield. 2-Methylbenzimidazole was obtained from the aqueous layer.

2,4-*Dimethyl*-3-*prop*-2-*ynyl*-3H-1,5-*benzodiazepine* (2). Under the above conditions, reaction between 1,2-diaminobenzene and 3-prop-2-ynylpentane-2,4-dione gave yellow *prisms* (100%), m.p. 133° (from ethanol) (Found: C, 80.0; H, 6.9. $C_{14}H_{14}N_2$ requires C, 80.0; H, 6.7%), δ ($CDCl_3$) 2.03 (1 H, t, CH≡C), 2.26 (1 H, t, CH), 2.30 (6 H, s, 2 × Me), 2.96 (2 H, q, CH_2), and 7.14—7.53 (4 H, m, ArH), *m/e* 210 (M^+, 77%), 195, 171, 168, and 154.

3-*Benzyl*-2,4-*dimethyl*-3H-1,5-*benzodiazepine* (3). From 1,2-diaminobenzene and 3-benzylpentane-2,4-dione, white *prisms* (100%), m.p. 111—112°, were obtained (from ethanol) (Found: C, 82.6; H, 6.6. $C_{18}H_{18}N_2$ requires C, 82.7; H, 6.55%), δ ($CDCl_3$) 2.13 (6 H, d, 2 × Me), 2.33 (1 H, t, CH), 3.39 (2 H, d, CH_2), and 6.83—7.54 (9 H, m, ArH), *m/e* 262 (M^+, 88%), 247, 171, 148, 131, 105, and 91.

Reactions of 1,2-diaminobenzene with 3,3-disubstituted diketones (9)—(13) under the standard conditions were worked up as before. All the above reactions could be followed conveniently by t.l.c. [ethyl acetate–ethanol (97 : 3) as solvent]. Typical R_F values were: 1,3-diketone (0.9), 1,2-diaminobenzene (0.7), 2-methylbenzimidazole (0.3).

4-(2-*Aminophenylimino*)-3-*chloropentan*-2-*one* (4).—The products from the reaction of 1,2-diaminobenzene and 3-chloropentane-2,4-dione were concentrated *in vacuo*. Addition of ethyl acetate afforded buff-coloured *needles* (33%), m.p. 84° (from ethanol) (Found: C, 58.8; H, 6.05. $C_{11}H_{13}ClN_2O$ requires C, 58.8; H, 5.85%), δ ($CDCl_3$) 2.68 (3 H, s, COMe), 2.72 (3 H, s, Me), 3.90 (2 H, s, NH_2), 6.66—7.18 (4 H, m, ArH), and 12.48 (1 H, s, enolic OH), *m/e* 226 (M^+, 12%), 224 (M^+, 28%), 209, 188, 146, 133, 108, and 92.

Reaction of 1,2-Diaminobenzene with 3,3-Dichloropentane-2,4-dione.—The reaction products, after concentration *in vacuo* were diluted with a small quantity of ethanol. This gave shiny buff-coloured plates of 2-(2-*aminophenylimino*)-1,1-*dichloropropane* (14) (35%), m.p. 102° (from ethanol). After melting, needles were formed with m.p. 235—238° (Found: C, 50.1; H, 5.0%; M^+, 216.0220. $C_9H_{10}Cl_2N_2$ requires C, 49.8; H, 4.65%; *M*, 216.0223), δ ($CDCl_3$) 1.69 (3 H, s, Me), 4.15 (2 H, s, NH_2), 5.65 (1 H, s, CH), and 6.39—6.73 (4 H, m, ArH), *m/e* 218 (M^+, 3%), 216 (M^+, 4%), 144, 133 (100%), 117, and 92. Concentration of the mother liquor yielded 1,2-diacetamidobenzene (11%), m.p. 187° (lit.,[20] 185—186°), identical with an authentic sample.

During the reaction of 3,3-dichloropentane-2,4-dione with the diamine, a heavy oil separated from the benzene solution. This oil, dissolved in the minimum of ethanol, when diluted with a large volume of ethyl acetate, deposited a shiny grey solid (9%). This contained traces of 2-methylbenzimidazole. Vacuum sublimation gave fine white needles of 1-*amino*-2-(1-*chloroethylideneamino*)*benzene* (15), m.p. 260° (after change of shape of needles at 180°) (Found: C, 57.1; H, 5.4; Cl, 20.4; N, 16.5. $C_8H_9ClN_2$ requires C, 57.0; H, 5.4; Cl, 21.0; N, 16.6%), δ (CD_3OD) 2.47 (3 H, s, Me) and 6.95—7.30 (4 H, m, ArH), *m/e* 132, 104, and 92; the *acetate* had m.p. 215°, *m/e* 174 (132 + 42), confirming the presence of an amino-group. The mother liquor from the oil above exhibited an intense fluorescent yellow colour. It was concentrated to dryness *in vacuo* and diluted with ethanol, and the insoluble residue was filtered off. This proved to be 2-*amino*-3-(2,2-*dichloro*-1-*methylethylidene-amino*)*phenazine* (16) (1%), m.p. >300° (from ethanol) (Found: C, 56.5; H, 4.2. $C_{15}H_{12}Cl_2N_4$ requires C, 56.4; H, 3.8%), δ (CD_3OD–CF_3CO_2H) 1.47 (3 H, s, Me), 5.74

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(1 H, s, CH), 6.26 (2 H, s, ArH), and 7.17—7.57 (4 H, m, ArH), *m/e* 320 (M^+, <1%), 318 (M^+, 2%), 246 (M^+ — 2HCl), 235 (M^+ — $CHCl_2$), 219, 178, 151, and 118.

Prolonged Reaction of 1,2-*Diaminobenzene and* 3-*Benzyl*-3-*methylpentane*-2,4-*dione*.—To 1,2-diaminobenzene (2.5 g, 0.023 mol) in ethanol (10 ml) and acetic acid (3.98 ml), 3-benzyl3-m-ethylpentane-2,4-dione (4.7 g, 0.023 mol) was added, and the mixture was stirred at 43 °C for 18 h. The solution was concentrated *in vacuo*, diluted with water, and extracted with ether. From the aqueous layer 2-methylbenzimidazole (35%) was isolated. The products in the ether layer were separated on a dry alumina column,[10] with ethyl acetate as eluant to give (in order of elution) (i) 3-methyl-4-phenylbutan-2-one (17) (18%), b.p. 90° at 5 mmHg (lit.,[21] 127—130° at 12 mmHg), identical with the product synthesized from propionic acid by the method of Normant and Angelo,[11] δ ($CDCl_3$) 1.01 (3 H, d, Me), 2.00 (3 H, s, COMe), 2.43—3.03 (1 H, m, CH), 2.70 (2 H, d, CH_2), and 7.11 (5 H, s, ArH), *m/e* 162 (M^+, 43%), 147, 119, and 91; (ii) (from an intense yellow band) 2-*amino*-3-(2-*benzyl*-1-*methylpropylideneamino*)*phenazine* (18) (3%), m.p. 210° (from ethanol) (after the initial melting, needles were formed with m.p. 240°) (Found: C, 77.8; H, 6.6. $C_{23}H_{22}N_4$ requires C, 77.9; H, 6.25%), δ [$(CD_3)_2SO$–CF_3CO_2H] 0.80 (3 H, d, Me), 1.60 (3 H, s, COMe), 2.10—2.93 (3 H, m, CH_2 and CH), 6.47 (2 H, s, ArH), 7.13 (5 H, s, ArH), and 7.46—7.90 (4 H, m, ArH), *m/e* 354 (M^+, 2%), 261, 247, 235 (M^+ — CHMe·CH_2Ph), 194, 167, 117, and 91; and (iii) traces of 1,2-diaminobenzene and 2-methylbenzimidazole.

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