A New Method of Preparation of 1*H*-1,2-Benzodiazepines by the Rearrangement of 2,4,6-Trichlorophenylhydrazones

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A new method for preparing 1*H*-1,2-benzodiazepines is described. Hydrazones of generalised structure **1** undergo base catalysed cyclisation to form 4-imidazolyl-4,5-dihydro-1*H*-1,2-benzodiazepines of general structure **2**. These compounds readily eliminate imidazole to form 1*H*-1,2-benzodiazepines of general structure **3**.

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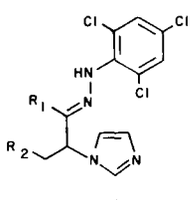
A series of hydrazones of the general structure **1** have been shown to possess interesting anti-fungal activity [1]. During the preparation of certain hydrazones we observed in addition to the desired product, a major contaminant which was subsequently found to be a 4-imidazolyl-4,5-dihydro-1*H*-1,2-benzodiazepine of generalised structure **2** arising from base rearrangement of **1**. The reaction conditions could be modified to obtain such compounds **2a-f** as the major isolated product; on further treatment compounds of general structure **2** smoothly eliminated imidazole to form the parent 1*H*-1,2-benzodiazepines of general structure **3** thus giving a new route to this class of compounds. Only a few references to previous synthesis of the 1*H*-1,2-benzodiazepine structure are to be found in the literature [2,3,4].



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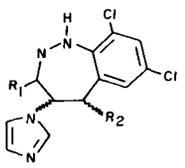

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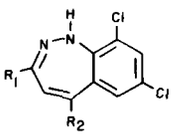

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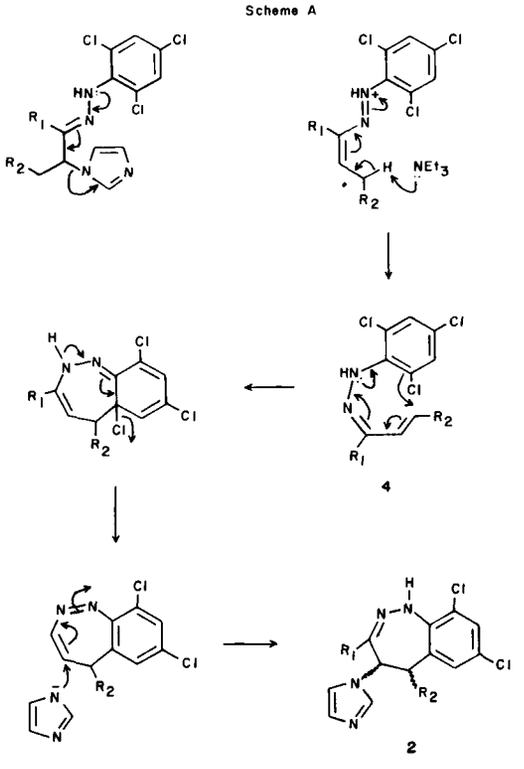
1a, 2a (S,R isomer), **3a**	$R_1 = C_6H_5$	$R_2 = CH_3$
1a, 2b	R_1 = 5-chlorothien-2-yl,	$R_2 = H$
1c, 2c	$R_1 = 3\text{-}CH_3\text{-}4\text{-}Cl\text{-}C_6H_3$,	$R_2 = H$
1d, 2d (S,R isomer)	$R_1 = CH_3(CH_2)_2$	$R_2 = CH_3$
2e (R,R isomer)	$R_1 = C_6H_5$	$R_2 = CH_3$
2f (R,R isomer)	$R_1 = CH_3(CH_2)_2$	$R_2 = CH_3$

Thus when trichlorophenylhydrazones of general structure **1** [1], [5] were refluxed in toluene with at least one equivalent of triethylamine or *N*-methylmorpholine present, rearrangement with elimination of hydrogen chloride occurred to form the 4,5-dihydro-1*H*-1,2-benzodiazepines **2,a-f**. Elucidation of the structure of one such compound **2a** and its stereochemical assignment was made with the aid of X-ray crystallographic data. This *S,R*-isomer was found to be the predominant isomer formed although approximately 30% of the *R,R*-isomer **2e** was also produced in this specific case. Unoptimised yields for the formation of compunds of structure **2** were in the range 12-58%. The rate of reaction appeared to be affected by the nature of R_2, the reaction proceeded much faster for $R_2 = CH_3$ than for $R_2 = H$.

Scheme A represents the mechanism postulated for this rearrangement.

Scheme A



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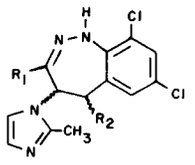
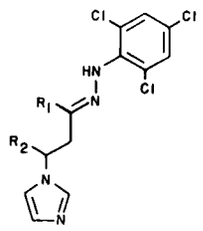
Indirect evidence for the validity of this mechanism is provided by the observations: (a) That imidazole itself acts as a catalyst to the rearrangement; (b) when 2-methyl-1*H*-imidazole is added in equimolar quantities in the rearrangement of **1a**, the alternative compound **5a** is formed,



5a, R_1 = Ph, R_2 = CH_3

and, (c) by the isolation of a byproduct **6b** from the rearrangement reaction of **1b**. Compound **6b** is presumably



6b, R_1 = 5-chlorothien-2-yl
R_2 = H

formed by the competing attack of 1,3-imidazole on species **4** in Scheme A.

Finally on refluxing in ethanol/sodium ethoxide compounds **2a-f** readily eliminate imidazole to form the corresponding 1*H*-1,2-benzodiazepines of general structure **3**.

EXPERIMENTAL

Melting points were determined with a Reichert Thermovar melting point apparatus and are uncorrected. New compounds were routinely analysed by nmr in deuteriochloroform unless otherwise indicated (Varian FT80A or Brucker 250).

7,9-Dichloro-4,5-dihydro-4*S*-(1*H*-imidazol-1-yl)-5*R*-methyl-3-phenyl-1*H*-1,2-benzodiazepine (**2a**).

1-Phenyl-2-(1*H*-imidazol-1-yl)propan-1-one 2,4,6-trichlorophenylhydrazone (**1a**) [5] (95 g, 0.233 mole), 1,3-imidazole (32.1 g, 0.472 mole) and triethylamine (70.6 g, 0.699 mole) were refluxed together in toluene (700 ml) for 4 days. The solvent was removed on the rotary evaporator and the residue partitioned between dichloromethane and water. The organic layer was isolated and the crude compound chromatographed on silica in 20:1 dichloromethane-methanol to afford a pure 3:1 mixture of the *S,R*-and *R,R*-isomers as a yellow oil 50 g (58%). A pure quantity (25 g, 29%) of compound **2a** was isolated from the first crop of crystals from dichloromethane/ether as colourless crystals mp 182-184°; nmr: δ 1.3 (3H, d, CH_3CH), 3.46 (1H, m, CH_3CH) 5.72 (1H, d, CHCHCN) 6.7-7.56 (10H, phenyl and imidazole aromatic protons) 8.72 (1H, s, NH).

Anal. Calcd. for $C_{19}H_{16}Cl_2N_4$: C, 61.46; H, 4.34; N, 15.09; Cl 19.10. Found: C, 61.43; H, 4.42; N, 15.13; Cl, 19.18.

7,9-Dichloro-4*R*-(1*H*-imidazol-1-yl)-5*R*-methyl-3-phenyl-4,5-dihydro-1*H*-1,2-benzodiazepine (**2e**).

A pure sample of **2e** was prepared by fractional crystallisation of the mother liquors from the preparation of **2a** to afford pale yellow crystals (8 g, 9%) mp 92-96°; nmr: δ 1.52 (3H, d, CH_3CH) 3.84 (1H, m, CH_3CH) 5.52 (1H, d, CHCHCN) 6.4-7.44 (10H phenyl and imidazole aromatic protons) 8.44 (1H, s, NH).

Anal. Calcd. for $C_{19}H_{16}Cl_2N_4$: C, 61.46; H, 4.34; N, 15.09; Cl, 19.10. Found: C, 61.51; H, 4.52; N, 14.93; Cl, 18.97.

3-(5-Chlorothien-2-yl)-7,9-dichloro-4-(1*H*-imidazol-1-yl)-4,5-dihydro-1*H*-1,2-benzodiazepine (**2b**).

A mixture of **1b** [5] (20 g. 0.046 mole), *N*-methylmorpholine (7.9 g, 0.078 mole) and 1,3-imidazole (10 g, 0.147 mole) was refluxed in toluene (300 ml) for 7 days. Compound **2b** was isolated by a similar process to **2a** as a pale yellow powder 2.5 g (12%) mp 188-190°; nmr: δ 3.16 and 3.56 (2H, d and dd, CH_2CH) 5.8 (1H, d, CH_2CHCN) 6.48-7.26 (7H phenyl, thiophene and imidazole protons) 8.3 (1H, s, NH).

Anal. Calcd. for $C_{16}H_{11}Cl_3N_4S$: C, 48.33; H, 2.79; N, 14.08. Found: C, 48.24; H, 2.76; N, 14.05.

A separate product (yellow oil) was isolated from the reaction mixture which formed a crystalline hydrochloride salt with ethereal hydrogen chloride. This was identified as the monohydrochloride of 1-(5-chlorothien-2-yl)-3-(1*H*-imidazol-1-yl)ethanone, 2,4,6-trichlorophenylhydrazone (**6b**), mp 88-100°; nmr (D_6-DMSO): δ 3.46 (2H, t, CH_2CH_2-N) 4.48 (2H, t, $NCCH_2CH_2$) 7.0-7.95 (6H phenyl, thiophene and imidazole aromatic protons) 9.08-9.24 (1H aromatic and 1H NH).

Anal. Calcd. for $C_{16}H_{13}Cl_5N_4S.0.5H_2O$: C, 40.08; H, 2.94; N, 11.67. Found: C, 40.16; H, 3.05; N, 11.38.

3-(1*H*-Imidazol-1-yl)heptan-4-one 2,4,6-Trichlorophenylhydrazone (**1d**).

A mixture of 3-bromo-4-heptanone [6] (35 g, 0.18 mole) and 1,3-imidazole (14.8 g, 0.22 mole) was refluxed overnight in 200 ml of methanol. After cooling, the *p*H of the solution was adjusted to 2 with concentrated hydrochloric acid and the mixture was rotary-evaporated, the last traces of water being removed by azeotroping with toluene and ethanol. The residue and 2,4,6-trichlorophenylhydrazine (42.3 g, 0.2 mole) were refluxed in 200 ml of ethanol for 2 hours. The crude product was purified by chromatography on silica in ethyl acetate to yield compound **1d** as a yellow oil (40 g, 56%); nmr: δ 0.87 (3H, t, $CH_3CH_2CH_2$) 0.97 (3H, t, CH_3CH_2CH) 1.24 (2H, m, $CH_3CH_2CH_2$) 1.98-2.34 (4H, CH_3CH_2CH and CH_2CH_2CN) 4.52 (1H, t, CH_2CH) 6.95-7.58 (5H phenyl and imidazole aromatic protons).

Anal. Calcd. for $C_{16}H_{19}Cl_3N_4$: C, 51.42; H, 5.12; N, 14.99. Found: C, 51.07; H, 5.29; N, 14.69.

7,9-Dichloro-4-(*R,S*)(1*H*-imidazol-1-yl)-5-(*R,S*)methyl-3-(1-propyl)-4,5-dihydro-1*H*-1,2-benzodiazepine (**2d,2f**).

A mixture of **1d** (13.4 g, 0.036 mole), 1,3-imidazole (7 g, 0.103 mole) and *N*-methylmorpholine (7.9 g, 0.079 mole) was refluxed together in toluene (200 ml) for 3 days. The mixture was worked up and purified as in previous examples to afford 1.5 g (12%) of a yellow oil which proved to be a 2:1 mixture of the *S,R* and *R,R* isomers (**2d** and **2f** respectively). This mixture (1.5 g, 0.00445 mole) was dissolved in ethyl acetate (10 ml) and 5.5 ml of 1*N* ethereal hydrogen chloride was added followed by hexane (100 ml). The product was collected as yellow crystals of the monohydrochloride of the isomer mixture, mp 110-120°; nmr (D_6-DMSO): where possible values corresponding to the *S,R* isomer are given first in the pair; δ 0.90 and 0.82 (3H, t, CH_3CH_2) 1.20 and 1.29 (3H, d, CH_3CH) 1.32-1.67 (2H, m, CH_3CH_2) 2.29 and 1.98 (2H, t, CH_2CH_2) 3.60 and 3.84 (1H, m, CH_3CH) 5.69 and 5.64 (1H, d, CHCHCN) 6.8-7.65 (4H, phenyl and imidazole aromatic protons) 9.0 and 8.95 (1H phenyl or imidazole aromatic proton) 9.61 and 9.16 (1H, s, NH).

Anal. Calcd. for $C_{16}H_{19}Cl_3N_4.0.7H_2O$: C, 49.75; H, 5.32; N, 14.50. Found: C, 49.86; H, 5.04; N, 14.27.

7,9-Dichloro-4-(1*H*-imidazol-1-yl)-3-(3-methyl-4-chlorophenyl)-4,5-dihydro-1*H*-1,2-benzodiazepine (**2c**).

Compound **2c** was prepared from **1c** [5] in 14% yield as for previous examples, pale yellow crystals mp 82-84°; nmr: δ 2.36 (3H, s, CH_3-Ar) 3.24 and 3.58 (2H dd and d, $CHCH_2C$) 5.88 (1H, d, $CHCH_2$) 6.74-7.44 (8H phenyl and imidazole aromatic protons) 8.48 (1H, s, NH).

Anal. Calcd. for $C_{19}H_{15}Cl_3N_4$: C, 56.25; H, 3.73; N, 13.80; Cl, 26.22. Found: C, 56.17; H, 3.91; N, 13.57; Cl, 25.89.

7,9-Dichloro-5-methyl-3-phenyl-1*H*-1,2-benzodiazepine (**3a**).

Ethanol (100 ml) was treated with sodium (3 g, 0.13 mole) to prepare a solution of sodium ethoxide; **2a** (7.5 g, 0.02 mole) was refluxed overnight with this solution. The solvent was removed on the rotary evaporator and the residue partitioned between water and ethyl acetate. The organic layer was isolated and the crude product was purified by chromatography on silica in ethyl acetate to afford bright yellow crystals of **3a** (4g 66%), mp 112-115°; nmr: δ 2.27 (3H, s, C*H*$_3$C) 6.66 (1H, s, CC*H*CN) 7.12-7.72 (7H phenyl aromatic protons).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_2$: C, 63.39; H, 3.99; N, 9.23; Cl, 23.38. Found: C, 63.64; H, 4.14; N, 9.12; Cl, 23.12.

7,9-Dichloro-4-(1*H*-2-methylimidazol-1-yl)-5-methyl-3-phenyl-4,5-dihydro-1*H*-1,2-benzodiazepine (**5a**).

Compound **1a** [5] (1.5 g, 0.0037 mole), 2-methyl-1,3-imidazole (0.3 g, 0.0043 mole) and triethylamine (0.4 g, 0.0040 mole) were refluxed in toluene (10 ml) for 2 days. A sample of the mixture was subjected to preparative thin layer chromatography to afford two pure products; one product was identified by nmr and mass spectral studies to be compound **2a** and the other to be compound **5a**; nmr: δ 1.32 (3H, d, C*H*$_3$CH) 2.25 (3H, s, C*H*$_3$C) 3.3 (1H, m, CH$_3$C*H*) 5.5 (1H, d, CHC*H*CN) 6.2-7.4 (9H phenyl and imidazole aromatic protons) 9.4 (1H, s, N*H*).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_4$: C, 62.35; H, 4.71; N, 14.54. Found: C, 62.26; H, 4.83; N, 14.14.

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