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Condensed Heterotricycles: Novel Transformation of Dibenz[*b*,*e*][1,4]diazepinones to Benzimidazole Derivatives under Vilsmeier-Haack Reaction Conditions*†‡

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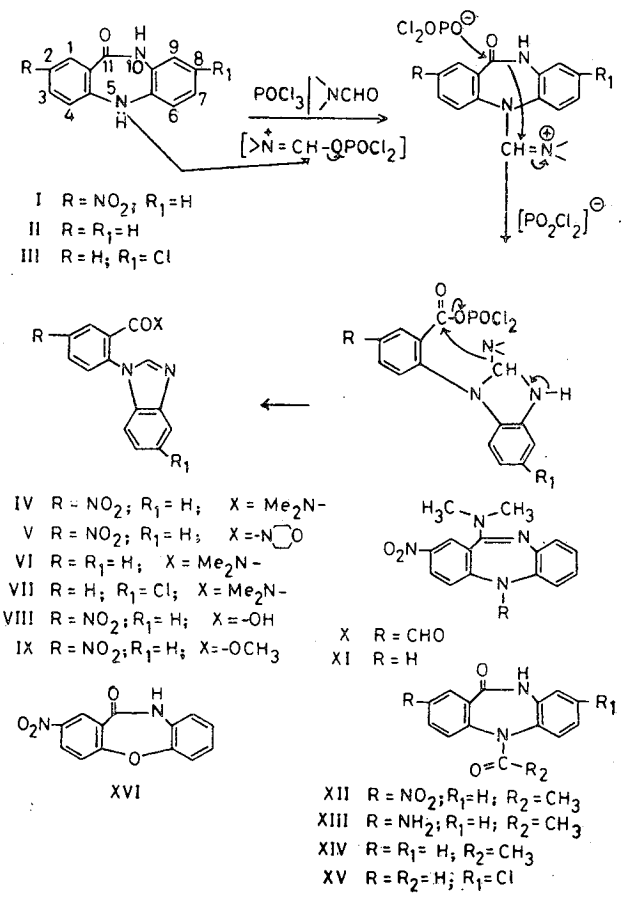
Condensation of methyl 2-chloro-5-nitrobenzoate with *o*-phenylenediamine in DMSO in the presence of triethylamine affords 2-nitrodibenz[*b*,*e*][1,4]diazepin-11(10H)-one (I) in 37% yield. Reaction of I with DMF-$POCl_3$ leads to its novel transformation to 1-(2-dimethylcarbamoyl-4-nitrophenyl)benzimidazole (IV) in high yield. Dibenz[*b*,*e*][1,4]diazepin-11(10H)-one (II) and its 8-chloro derivative (III) afford analogous products VI and VII respectively. The structure of IV is proved by acid hydrolysis to 1-(2-carboxy-4-nitrophenyl)benzimidazole (VIII), identical with a sample synthesized from benzimidazole and 2-chloro-5-nitrobenzoic acid. N-Formylmorpholine and I undergo reaction in the presence of $POCl_3$ to give the morpholide analogue V of IV. 2-Nitro-5-acetyldibenz[*b*,*e*][1,4]diazepin-11(10H)-one (XII) is formed in the reaction of I with dimethylacetamide-$POCl_3$. XII is reduced to the amine XIII, which upon diazotization and treatment with hypophosphorus acid yields known 5-acetyldibenz[*b*,*e*][1,4]diazepin-11(10H)-one (XIV). The present study constitutes the first example of ring contraction among dibenz[*b*,*e*]-diazepine derivative.

IN a previous communication[1] we had disclosed a synthesis of dibenzdiazepinone (I). We describe in this paper a similar and improved preparation of I and proof of its structure. A novel conversion of dibenzdiazepinones into benzimidazole derivatives is also reported.

Condensation of methyl 2-chloro-5-nitrobenzoate with *o*-phenylenediamine in hot dimethyl sulphoxide in the presence of triethylamine led to the formation of the red diazepinone (I) in 37% yield. An attempt to convert I into its iminochloride using excess $POCl_3$ in refluxing toluene led to recovery; reaction did occur when a little DMF was added, but an unexpected product, $C_{16}H_{14}N_4O_3$, m.p. 162-64°, was obtained in 16% yield. The yield was improved to 65% when the reaction was conducted in DMF alone at 100° for 16 hr, using 1·2 moles of $POCl_3$ per mole of I. The analytical and spectral data of the product were consistent with structure X, but heating with 6*N* HCl at 80-90° for several hours failed to convert it into XI or I. On the other hand, the available data seemed to fit the benzimidazole structure IV also. This was readily confirmed by vigorous hydrolysis of I using excess 6*N* HCl at reflux temperature. The resultant acid (VIII) was identical with the product of condensation



*Dedicated to Prof. T. R. Govindachari on the occasion of his 60th birthday.

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of benzimidazole with 2-chloro-5-nitrobenzoic acid in amyl alcohol under basic conditions. The strong similarity of the UV spectrum of IV with that of VIII rendered it unlikely that the product of reaction of I with DMF-$POCl_3$ was indeed X, which underwent acid-catalysed rearrangement to IV.

The reaction of DMF-$POCl_3$ with similar dibenzdiazepinones II[2] and III[3] led to the benzimidazole derivatives VI and VII respectively in 50 and 73% yields. In the latter case, a small amount of the N-formyldiazepinone (XV) was also obtained. Similarly, reaction of I with N-formylmorpholine and $POCl_3$ afforded the benzimidazole derivative V in 57% yield. This was identical with the morpholide of VIII prepared through its acid chloride by treatment with morpholine. This provided conclusive evidence for the structures of products IV-VII.

Lactam (I) was recovered unchanged after reaction with DMF-sulphuric acid. The benzoxazepinone analogue XVI[1] of I was also largely unaffected by DMF-$POCl_3$.

Reaction of I with dimethylacetamide and $POCl_3$ interestingly enough led only to the formation of the N-acetyl derivative XII. That N-5 rather than N-10 bore the acetyl group was evident from its colourless appearance and UV spectrum (λ_{max} 267 nm) whereas I was red and had λ_{max} at 285 and 360 nm. Catalytic reduction to XIII, followed by diazotization and treatment with hypophosphorus acid led to the known acetyl derivative XIV[4], thus simultaneously confirming the site of acetylation and the validity of structure I for the condensation product of methyl 2-chloro-5-nitrobenzoate and *o*-phenylenediamine.

Dibenzdiazepinones carrying a methyl group at N-5 have been converted into the iminochlorides using PCl_5 in $CHCl_3$; compounds lacking a substituent at N-5 present problems, presumably because the chlorinating agent attacks the diphenylamine NH to give side reactions[5]. A plausible mechanism for the transformation of I to IV is indicated in the chart. This explains the role of DMF, which contributes C-2 of the benzimidazole ring of product IV.

The Vilsmeirer-Haack reaction is generally a straight-forward reaction and gives the expected products in high yields. There are, however, some unusual instances where other products are formed as a result of secondary reactions[6]. Lactams like 2,3,4,5-tetrahydro-1,4-benzoxazepin-5-one are known to undergo N-formylation with DMF-$POCl_3$ complex[6]. Hence the formation of XII and XV under Vilsmeier-Haack conditions has parallels in the literature. But the conversion of I into IV under these conditions is unprecedented and provides a new facet to this synthetically useful reaction[6].

Ring contraction of benz[1,5]diazepinones to benzimidazoles has been reported under different conditions[7]; but to our knowledge, the present study constitutes the first encounter of such a transformation among dibenz[*b*,*e*][1,4]diazepine derivative.

Experimental Procedure

M.ps. are uncorrected. IR spectra (ν_{max} in cm^{-1}) were generally run on a Perkin-Elmer 337 infracord spectrometer. UV spectra (λ_{max} in nm, log ϵ in parentheses) were recorded on a Beckman DK2A spectrophotometer; mass spectra were taken on a Varian Mat CH-7 spectrometer and NMR spectra on Varian A60 spectrometer. Chemical shifts are quoted in δ (ppm) downfield from TMS internal standard.

2-Nitrodibenz[b,e][1,4]diazepin-11(10H)-one (I)— Methyl 2-chloro-5-nitrobenzoate (21·6 g, 0·1 mole), *o*-phenylenediamine (10·8 g, 0·1 mole) and triethylamine (10·1 g, 0·1 mole) were heated together in DMSO (50 ml) for 4 hr. The solution was diluted with water and the red precipitate filtered. Washing with methanol afforded I[1] (9·5 g, 37%), m.p. >300°.

Action of DMF-$POCl_3$ on I: Formation of benzimidazole (IV)— A solution of I (1·3 g, 5 mmoles) in DMF (10 ml) and $POCl_3$ (0·9 g, 6 mmoles) was heated at 100° for 16 hr. DMF was removed *in vacuo* and ice-water added to the residue. The resultant clear solution was made basic with ammonia and the gummy product extracted with chloroform. The chloroform layer was dried, concentrated to a small volume and treated with ether. The gummy precipitate was discarded and the supernatant concentrated to give IV (1·0 g, 65%), m.p. 158-60°, which recrystallized from EtOH, m.p. 162-64° (Found: C, 61·81; H, 4·79; N, 18·39. $C_{16}H_{14}N_4O_3$ requires C, 61·93; H, 4·55; N, 18·06%); IR (nujol): 1640 (C=O); UV (EtOH): 245, 270 (inflex), 310 (4·22, 3·99, 3·85); NMR ($CDCl_3$): 2·53 (N—CH_3, *s*), 2·87 (N—CH_3, *s*), 7·25-7·60 (3 aromatic H, *m*), 7·80 (C_6—H, *m*), 7·83 (C_4—H, *d*, J=9·5 Hz), 8·48 (C_1—H, *d*, J=2·5 Hz) and 8·50 (C_3—H, *q*, J=9·5, 2·5 Hz); *m/e*: 310 (M^+), 266, 239, 238, 221, 220, 208, 193, 192, 191, 165, 164.

Benzimidazole (V)— Diazepinone (I, 1·3 g, 5 mmoles) was treated with N-formylmorpholine (15 ml) and $POCl_3$ (0·9 g, 6 mmoles) at 100° overnight to give V (1 g, 57%), m.p. 224-26° (from ethanol) (Found: C, 61·09; H, 4·76; N, 15·95. $C_{18}H_{16}N_4O_4$ requires C, 61·36; H, 4·58; N, 15·90%; IR (nujol): 1640 (C=O); UV (EtOH): 243, 270 (inflex), 307 (4·22, 3·94, 3·85), identical with a sample prepared from acid VIII (*vide infra*).

Benzimidazole (VI)— Diazepinone[2] (II, 1·05 g, 5 mmoles) was treated with dimethyl formamide (7 ml) and $POCl_3$ (0·9 g, 6 mmoles) at 100° overnight to give VI (0·65 g, 50%), m.p. 120-22° (from ether) (Found: C, 72·83; H, 6·01; N, 15·92. $C_{16}H_{15}N_3O$ requires C, 72·43; H, 5·70; N, 15·84%); IR (nujol): 1622 cm^{-1} (C=O); UV (EtOH): 245, 272 (inflex), 280 (inflex) (4·15, 3·67, 3·58); NMR ($CDCl_3$): 2·45 (N—CH_3, *s*), 2·77 (N—CH_3, *s*), 8·12 (N=CH, *s*); nitrate salt, m.p. 158-60° (from ethanol) (Found: C, 58·85; H, 5·11; N, 17·04. $C_{16}H_{16}N_4O_4$ requires C, 58·53; H, 4·91; N, 17·07%).

Benzimidazole (VII)— Diazepinone[3] (III, 1·2 g, 5 mmoles) was treated with dimethyl formamide (10 ml) and $POCl_3$ (0·9 g, 6 mmoles) to give a gummy product which deposited crystals on rubbing with ether. Recrystallization from aq. ethanol afforded the N-formyldiazepinone (XV, ~100 mg), m.p. 199-200° (Found: C, 61·60; H, 3·57; N, 9·73. $C_{14}H_9ClN_2O_2$ requires C, 61·64; H, 3·32; N, 10·28%); IR (KBr): 1660, 1620 (C=O); M^+ 272, 274. The

ethereal filtrate on evaporation gave VII as a gum; IR (CH_2Cl_2): 1620, 1640 (C=O); NMR ($CDCl_3$): 2·53 (N—CH_3, *s*), 2·80 (N—CH_3, *s*), 8·15 ppm (N=CH); M^+ 299, 301. It formed a crystalline picrate, m.p. 217-18° (from MeOH) (Found: C, 50·15; H, 3·50; N, 15·52. $C_{22}H_{17}ClN_6O_8$ requires C, 49·96; H, 3·24; N, 15·89%).

Action of dimethylacetamide — $POCl_3$ on I: Formation of N-acetyl derivative (XII)— I (3·9 g, 15 mmoles), dimethylacetamide (40 ml) and $POCl_3$ (3·1 g, 20 mmoles) were heated at 100° for 16 hr. The solvents were removed *in vacuo* and ice chips added to the residue. The solid was filtered off and dissolved in MeOH. The solution was filtered from insolubles and concentrated to give crystals which recrystallized from acetone-EtOH to give XII (3·1 g, 70%), m.p. 273-75° (Found: C, 60·75; H, 3·92; N, 14·35. $C_{15}H_{11}N_3O_4$ requires C, 60·60; H, 3·73; N, 14·14%); IR (nujol): 1700, 1680 (C=O); UV (EtOH): 267 (4·09); NMR ($CDCl_3$): 2·17 ($COCH_3$, *s*), 8·50 (C_3—H, *q*, *J*=10, 2·5 Hz), 8·58 (C_1—H, *d*, *J*=2·5 Hz), 11·40 (NH, *s*); *m/e* 297 (M^+), 269, 255, 238, 209, 208, 181, 180, 179, 169, 168.

Aminodibenzdiazepinone (XIII)— XII (3 g) was hydrogenated in methanol (300 ml) at atmospheric pressure and room temperature using platinum oxide catalyst (0·2 g) to give XIII (2·6 g) (from methanol), m.p. >300° (Found: C, 67·47; H, 5·20; N, 15·84. $C_{15}H_{13}N_3O_2$ requires C, 67·40; H, 5·20; N, 15·84%); IR (nujol): 3480, 3360 (NH_2), 1650, 1670 (C=O).

Deamination of XIII: *Formation of dibenzdiazepinone* (XIV)— XII (1·07 g) was dissolved in conc. H_2SO_4 (3 ml) and conc. HCl (2 ml) in water (5 ml); the solution was cooled to 0° and treated with sodium nitrite (0·3 g) in water (2 ml). After ½ hr, hypophosphorus acid (32% solution, 8 ml) was added, and the mixture stirred at 0° for 1 hr and then at room temperature overnight. The precipitate was filtered off, washed with water and recrystallized from ethanol to give XIV (0·45 g), m.p. 256-58° (Found: C, 71·24; H, 5·34; N, 11·15. $C_{15}H_{12}N_2O_2$ requires C, 71·41; H, 4·80; N, 11·11%); IR (nujol): 1670, 1650 (C=O). This was identical with a sample prepared by acetylation of II (0·5 g) with acetic anhydride (5 ml) and conc. H_2SO_4 (5 drops) at 100° for 1 hr (ref. 4).

1-(*2-Carboxy-4-nitrophenyl*)*benzimidazole* (VIII): (a) *From amide* (IV) *by hydrolysis* — IV (0·6 g) in 6*N* HCl (10 ml) was heated under reflux for 16 hr. The solution was evaporated to dryness. The residue was dissolved in a small volume of water and carefully treated with sodium bicarbonate until precipitation of VIII was complete. The acid was filtered off and recrystallized from MeOH (0·3 g); m.p. 292° (d) (Found: C, 59·09; H, 3·47; N, 14·40. $C_{14}H_9N_3O_4$ requires C, 59·36; H, 3·20; N, 14·84%); IR (nujol): 1710 (C=O); UV (EtOH): 246, 270 (inflex), 317 (4·21, 3·98; 3·82), *m/e* 283 (M^+), 253, 239, 235, 219, 207, 193, 192. The acid was identical with the one prepared below.

(b) *From benzimidazole and 2-chloro-5-nitrobenzoic acid* — Benzimidazole (11·8 g, 0·1 mole), 2-chloro-5-nitrobenzoic acid (20·2 g, 0·1 mole) and anhydrous potassium carbonate (13·8 g, 0·1 mole) were heated together in amyl alcohol (100 ml) and a trace of copper powder with stirring under reflux for 6 hr. The solvent was then evaporated off *in vacuo*. The residue was treated with aq. sodium bicarbonate and ether and the mixture filtered from insolubles. The aqueous layer from the filtrate was separated and carefully neutralized (*p*H 6-7) with conc. HCl. The precipitated solid was filtered off and crystallized from MeOH to give VIII (4·8 g), m.p. 292° (d) (Found: C, 59·05; H, 3·44; N, 14·27. $C_{14}H_9N_3O_4$ requires C, 59·36; H, 3·20; N, 14·84%).

1-(*2-Carbomethoxy-4-nitrophenyl*)*benzimidazole* (IX) — To a solution of benzimidazole (3·54 g, 30 mmoles) in dimethyl formamide (30 ml) at 60°, was added sodium hydride (1·45 g of 50% suspension in mineral oil). The mixture was stirred at 60° for ½ hr, treated with methyl 2-chloro-5-nitrobenzoate (6·48 g, 30 mmoles) and heated under reflux for 2 hr. It was then filtered and dimethyl formamide removed *in vacuo* from the filtrate. The residue was treated with water and extracted with chloroform. The extract was washed with water, dried and evaporated. The gummy product was digested with ether and the ether solution concentrated to give IX (1·8 g), m.p. 154-58°. Recrystallization from MeOH gave 1·3 g, m.p. 156-58° (Found: C, 60·77; H, 3·82; N, 14·20. $C_{15}H_{11}N_3O_4$ requires C, 60·60; H, 3·73; N, 14·14%); IR (nujol): 1735 (C=O); UV (EtOH); 247, 275 (inflex), 317 (4·22, 3·90, 3·77).

Morpholide V *of benzimidazole acid* (VIII)— VIII (0·5 g), thionyl chloride (2 ml) and benzene (20 ml) were heated together under reflux for 2 hr. Solvents were evaporated off and morpholine (2 ml) and benzene (20 ml) were added. The mixture was again heated under reflux for 2 hr. After removal of solvents, water and aq. NaOH were added to the residue. The precipitate was collected and crystallized from ethanol to give V (0·45 g), m.p. 222-24° (Found: C, 61·54; H, 4·86. $C_{18}H_{16}N_6O_4$ requires C, 61·36; H, 4·58%).

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