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Synthesis of Some Pyrimido[1,6-*a*]benzimidazole Derivatives*

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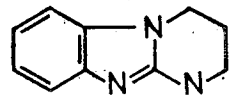
The base-catalysed condensation of 2-(β-aminoethyl)benzimidazole (V) with a variety of aldehydes, such as formaldehyde, benzaldehyde, *p*-chlorobenzaldehyde, etc., yields tetrahydropyrimido-[1,6-*a*], benzimidazoles (VI). The NMR spectral data of the products decidedly favour a cyclic structure VI as compared to the *i*someric open chain Schiff's base (VII). Condensation of carbon disulphide with V affords 3,4-dihydropyrimido[1,6-*a*]benzimidazole-1(2H)thione (XV). With piperidine and morpholine, XV yields the thiocarbamoyl derivatives (XVI) of the original amine (V).

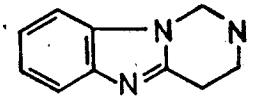
THE chemistry of pyrimido[1,2-*a*]benzimidazoles (I) has been extensively studied in the literature[1]; the isomeric pyrimido[1,6-*a*]benzimidazole (II) ring system was unknown until 1965, when a short report appeared describing the synthesis of the cyclic urea (III) and a few aminoalkyl derivatives IV[2]. The preparation of III was achieved by the treatment of the readily available 2-(β-aminoethyl)benzimidazole (V)[3] with diethyl carbonate.

In our study, the amine V was condensed with a variety of aldehydes to afford the cyclic derivatives VI in high yields.

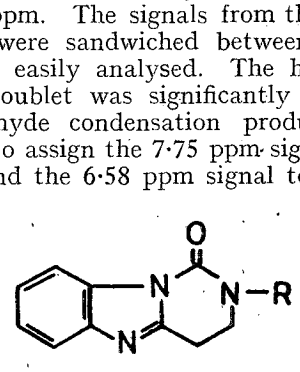
The choice between the cyclic structure VI and the isomeric open chain Schiff's base VII was readily made on the basis of NMR spectra. Thus, in the spectrum of the formaldehyde condensation product VI (R=H) in DMSO-d_6, the methylene protons at C-1 appeared as a singlet at 5·1 ppm. The methylidene proton in VII would be expected to appear at much lower fields. Likewise, in the NMR spectrum in $CDCl_3$ of the product obtained by the condensation of the amine (V) with $CHOC_6H_4Cl(p)$, the methine hydrogen at C-1 appeared as a broadened singlet at 6·05 ppm. The sharpening of this signal on D_2O treatment of the solution confirmed its adjacence to a NH function. The methine hydrogen signal of the benzaldehyde product (in $CDCl_3$) had the same location and similar shape. As a model compound for VII, *p*-chlorobenzylidenebenzylamine (VIII) was studied. In $CDCl_3$, the vinyl hydrogen had a chemical shift of 8·05 ppm, thus conclusively establishing the structures of products VI. In the NMR spectra of both the aromatic aldehyde condensation products, viz. (VI, R=C_6H_5) and (VI, R=$C_6H_4Cl(p)$, it was of interest to note that one aromatic proton appeared as a doublet with fine structure at 6·58 ppm and another as a doublet with fine structure at 7·75 ppm. The signals from the other aromatic protons were sandwiched between these two and were not easily analysed. The highfield aromatic proton doublet was significantly absent from the formaldehyde condensation product (VI, R=H). We like to assign the 7·75 ppm signal to the proton at C-6 and the 6·58 ppm signal to the one at C-9.



I

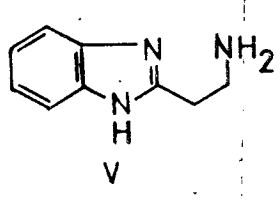


II

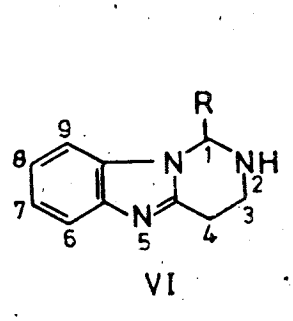


III R = H

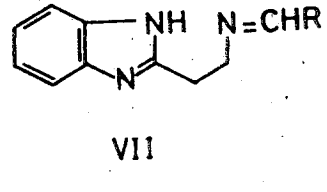
IV R = $-(CH_2)_2-N<$



V



VI



VII

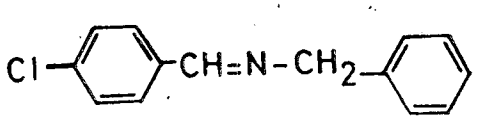
*Contribution No. 159 from the CIBA Research Centre, Goregaon, Bombay 63.

The highfield location of this signal is explicable on the basis of shielding by the 1-aryl group as shown in IX.

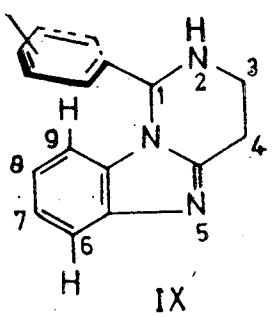
Attempts to convert the amine V into the guanidine X by using cyanamide or S-methyl-pseudothiourea sulphate were unsuccessful; likewise was an attempt to prepare a biguanide from V by reaction with dicyandiamide. It was hoped that the reaction of X with aldehydes would lead to potentially useful guanidines of the type XI.

The cyclic derivatives VI were found to be unstable to both bases and acids. The starting amine V and aldehyde were liberated. One attempt to convert the derivative VI (R= *p*-chlorophenyl) into a N-dimethylaminopropyl derivative was unsuccessful. The only product isolated was V as its dihydrochloride. However, it was possible to obtain thiocarbamoyl derivatives (XII) from VI. The unlikely possibility that VI had isomerized in this process to VII and then formed the thiourea derivatives XIII was again excluded from NMR studies. Thus, in the NMR spectrum (in $CDCl_3$) of the thiourea derived from VI (R=H) with β-phenethylisothiocyanate, the methylene hydrogens at C-1 were seen as a sharp singlet at 6·19 ppm. Their downfield movement by 1·09 ppm relative to their location in VI (R=H) would be consistent with the nitrogen at position 2 having acquired the thiocarbamoyl function.

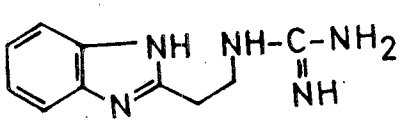
An attempted condensation of V with ethyl iminoacetate hydrochloride to form XIV was unsuccessful. On the other hand, when allowed to react with carbon disulphide and alkali, V was readily converted to the thione XV. It was hoped that XV could be alkylated with methyl iodide to yield a S-methyl compound, which could be then converted to guanidines by reaction with amines. In the event, treatment of XV with methyl iodide led to uncharacterized products. It is known that thioamides often react with primary and secondary amines to form amidines with the elimination of hydrogen sulphide. However, treatment of XV with morpholine resulted in ring opening to form the thiocarbamoyl derivative XVI of V. The formation



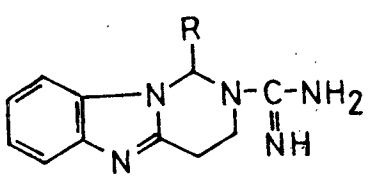
VIII



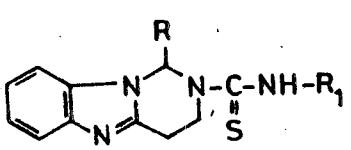
IX



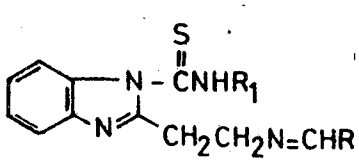
X



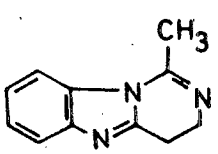
XI



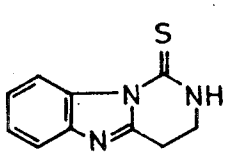
XII



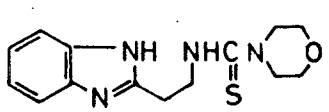
XIII



XIV



XV



XVI

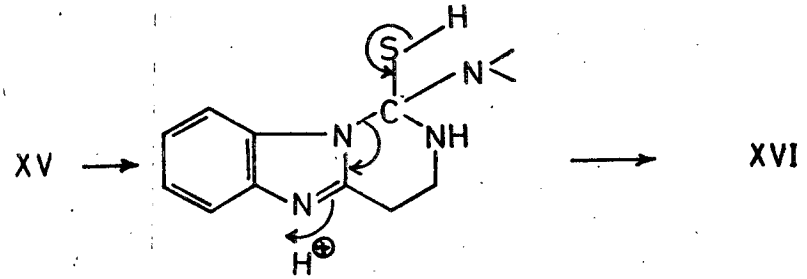
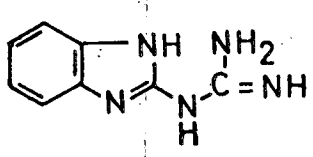
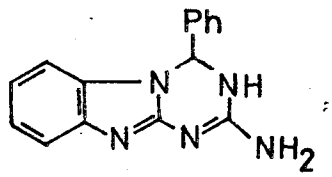


Chart 1 — Mechanism of formation of compound (XVI) from (XV)



XVII



XVIII

of XVI can be rationalized by the initial addition of morpholine to the thiocarbamoyl group, followed by expulsion of the highly stable benzimidazolyl anion (Chart 1). Similar products were obtained with other bases.

2-Guanidinobenzimidazole (XVII)[4] has a correctly disposed 1,5-diamine system which could be expected to be readily bridged by aldehydes, carbon disulphide, etc. Among a number of reagents tried, only benzaldehyde afforded a well-characterized product formulated as XVIII.

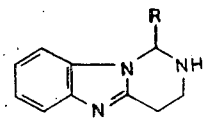
Experimental Procedure

All melting points are uncorrected. NMR spectra were run on a Varian A-60 spectrometer. Chemical shifts are quoted in ppm downfield from internal TMS standard.

Preparation of 1,2,3,4-*tetrahydropyrimido*[1,6-*a*]*benzimidazoles* — A solution of 2-(β-aminoethyl)benzimidazole dihydrochloride (4·6 g, 20 mmoles) in 1*N* aq. sodium hydroxide (40 ml) was warmed with benzaldehyde (2·2 g, 20 mmoles) at 80-90° and with shaking for 15 min. The precipitate was collected and crystallized from aq. methanol; yield 4·6 g (92%). Other derivatives were similarly prepared and are listed in Table 1.

2-*Thiocarbamoyl*-1,2,3,4-*tetrahydropyrimido*[1,6-*a*]-*benzimidazoles* — A solution of 1-(*p*-chlorophenyl)-1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazole (VI, R = *p*-chlorophenyl) (4·2 g) in benzene (120 ml) containing methyl isothiocyanate (1·1 g) was refluxed for 12 hr. Evaporation of benzene and crystallization of the residue from ethanol gave the methylthiourea (5 g), m.p. 197-200° (Found: C, 60·88; H, 4·89; N, 15·41. $C_{18}H_{17}ClN_4S$ requires C, 60·59; H, 4·80; N, 15·70%). Likewise were prepared 1-(*p*-chlorophenyl)-2-phenylthiocarbamoyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazole (from ethanol),

TABLE 1 — ANALYTICAL DATA AND THE PHYSICAL CHARACTERISTICS OF PYRIMIDOBENZIMIDAZOLES



R	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
			C	H	N	C	H	N
H	197-9	$C_{10}H_{11}N_3$	69·34	6·40	24·26	69·54	6·56	23·90
Phenyl	156-7	$C_{16}H_{15}N_3$	77·08	6·06	16·86	76·86	6·12	16·82
p-Chlorophenyl	190-91	$C_{16}H_{14}ClN_3$	67·72	4·97	14·81	67·71	4·93	14·67
m-Nitrophenyl	189-90	$C_{16}H_{14}N_4O_2$	65·29	4·80	19·04	65·26	5·19	19·21
p-Bromophenyl	221-2	$C_{16}H_{14}BrN_3$	58·55	4·30	12·80	58·56	4·37	13·32
p-Dimethylaminophenyl	225-6	$C_{18}H_{20}N_4$	73·94	6·90	19·16	74·12	7·16	18·55
2-Furyl	184(d)	$C_{14}H_{13}N_3O$	70·27	5·48	17·56	70·21	5·55	17·73
2-Thienyl	224-5	$C_{14}H_{13}N_3S$	65·87	5·13	16·46	65·58	4·97	16·34
4-Pyridyl	160-61 (transition at 115°)	$C_{15}H_{14}N_4$	71·97	5·64	22·39	71·65	5·82	21·92

m.p. 154-5° (Found: C, 65·76; H, 4·38; N, 13·03. $C_{23}H_{19}ClN_4S$ requires C, 65·95; H, 4·57; N, 13·38%) and 2-(β-phenethyl)thiocarbamoyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]benzimidazole (from ethanol), m.p. 178-80° (Found: C, 67·51; H, 6·22; N, 16·35. $C_{19}H_{20}N_4S$ requires C, 67·84; H, 5·99; N, 16·66%).

3,4-*Dihydropyrimido*[1,6-*a*]*benzimidazole*-1(2*H*)-*thione* (XV) — 2-(β-Aminoethyl)benzimidazole dihydrochloride (11·2 g, 0·05 mole) was heated under reflux with NaOH (4 g, 0·1 mole), carbon disulphide (10 ml), ethanol (75 ml) and water (50 ml) for 20 hr. Most of the ethanol was removed *in vacuo*. The water-insoluble material was collected, dissolved in hot 2% aq. NaOH and filtered. The filtrate was acidified and the precipitate collected. The product (6·8 g) was recrystallized from dimethylformamide; m.p. 216° (decomp.) (Found: C, 59·30; H, 4·30. $C_{10}H_9N_3S$ requires C, 59·10; H, 4·46%).

Action of bases on (XV) — A mixture of the thione (XV, 2 g) and piperidine (5 ml) was heated at 120° for 6 hr. Excess piperidine was removed under reduced pressure and the residue triturated with water and filtered. Crystallization from aq. ethanol gave N-β-(2-benzimidazolylethyl)thiocarbamoylpiperidine (1·8 g), m.p. 183-4° (Found: C, 62·56; H, 7·35; N, 19·15. $C_{15}H_{20}N_4S$ requires C, 62·48; H, 6·99; N, 19·43%). Similar treatment of the thione with morpholine gave N-β-(2-benzimidazolylethyl)thiocarbamoylmorpholine (from ethanol); m.p. 210-11° (decomp.) (Found: C, 57·89; H, 6·62; N, 19·25. $C_{14}H_{18}N_4OS$ requires C, 57·92; H, 6·25; N, 19·30%). With hydrazine hydrate the thione yielded 4-β-[2-benzimidazolyl]ethylthiosemicarbazide (from methanol); m.p. 194-5° (Found: C, 51·42; H, 5·90; N, 29·64. $C_{10}H_{13}N_5S$ requires C, 51·05; H, 5·57; N, 29·77%).

2-*Amino*-3,4-*dihydro*-4-*phenyl*-*s*-*triazolo*[1,2-*a*]*benzimidazole* (XVIII) — A mixture of 2-guanidinobenzimidazole (10·5 g), benzaldehyde (6·3 g) and potassium hydroxide (4 g) in ethanol (150 ml) was heated under reflux for 5 hr. The resultant solution was diluted with water and filtered. The product (15 g) was recrystallized twice from dimethylformamide; m.p. 294-5° (Found: C, 68·57; H, 5·20; N, 26·86. $C_{15}H_{13}N_5$ requires C, 68·42; H, 4·98; N, 26·60%).

Acknowledgement

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