

## Novel Condensed Isoquinolines with an Enamine System\*

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Manuscript received 2 May 1970

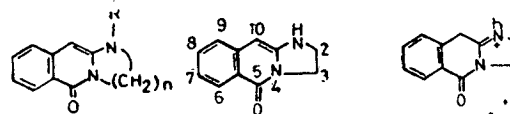
Novel condensed imidazo-, pyrimido- and azepino-[1,2-*b*]isoquinolines having interesting enaminic properties have been obtained by pyrolysis of 1,2-, 1,3- and 1,4-diamine salts of homophthalic acid in boiling *o*-dichlorobenzene. The structures assigned to the condensation products have been supported by NMR data.

A RECENT publication<sup>1</sup> on the synthesis of condensed isoquinolines by reaction of *o*-cyano-methylbenzoic acid with ethylene- and propylene-diamines encourages us to summarize our extensive work in the area of novel imidazo-, pyrimido- and azepino[1,2-*b*]isoquinolines having interesting enaminic properties. The only earlier relevant report<sup>2</sup> appeared in 1968 and was concerned with the synthesis of a pyrimido[1,2-*b*]isoquinoline derivative by intramolecular alkylation of 3-( $\beta$ -chloropropion-amido)-isoquinoline.

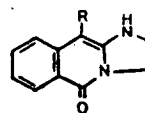
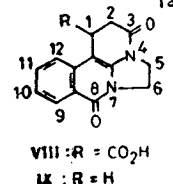
Pyrolysis of the ethylenediamine salt of homophthalic acid in boiling *o*-dichlorobenzene, cooling and precipitation with hexane gave 5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*b*]isoquinoline (I)†, m.p. 217-18°, in 90-95% yield. Similar condensation with other appropriate 1,2- and 1,3-diamines afforded products II to VI in high yields. With 1,4-diaminobutane, it was possible to obtain a 20% yield of the azepino-isoquinoline (VII), while the isolable product from the reaction of homophthalic acid with 1,5-diaminopentane was only 1,5-pentamethylene-bis-homophthalimide.

Structure I was supported by analysis, IR [as nujol mull: 3220 (NH), 1680 (C=O), 1630 cm<sup>-1</sup> (C=C)] and UV spectrum in EtOH,  $\lambda_{\max}$  231, 292 (inflex.), 300, 368 nm (log  $\epsilon$  4.48, 4.18, 4.26, 3.60) changing in 2*N* HCl to species Ia with  $\lambda_{\max}$  233, 240, 264 nm (log  $\epsilon$  3.99, 3.97, 4.08). The NMR spectrum of I in DMSO-*d*<sub>6</sub> at 60 Mc showed the following signals [chemical shifts ( $\delta$ -scale) downfield from TMS internal standard]: C-2 protons, triplet with fine structure at 3.58; C-3 protons, similar triplet at 4.13; C-10H, singlet at 5.55; C-7, C-8, C-9 protons and NH, multiplet at 6.50-7.60 and C-6 proton, broadened doublet at 8.0 ppm ( $J = 8$  cps). The signals due to NH and C-10 protons were washed out by D<sub>2</sub>O in 17 hr. Trifluoroacetic acid (TFA) protonated I at C-10 to form the salt Ia as revealed by the NMR spectrum: C-2 and C-3 protons, 4.50; C-10 protons, 4.67; C-7, C-8 and C-9 protons, 7.4-8.0; C-6 proton, broadened doublet at 8.23 ( $J = 7$  cps) and  $\overset{\oplus}{N}-H$  at 10.42 ppm.

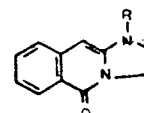
The marked enaminic properties of I became apparent when an attempted salt formation with maleic acid in hot ethanol led, with loss of the



- I: R = H; n = 2  
II: R = CH<sub>3</sub>; n = 2  
III: R = H; n = 3  
IV: R = CH<sub>3</sub>; n = 3  
V: R = Cyclohexyl; n = 3  
VI: R = H<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>; n = 3  
VII: R = H; n = 4



- X: R = -CH<sub>2</sub>CH<sub>2</sub>CN  
XI: R = -CH<sub>2</sub>Ph  
XII: R = -CH<sub>2</sub>CH=CH<sub>2</sub>  
XIII: R = -C<sub>6</sub>H<sub>4</sub>NHPh



- XIV: R = -COCH<sub>3</sub>  
XV: R = -COPh  
XVI: R = -SO<sub>2</sub>CH<sub>3</sub>  
XVII: R = -C<sub>6</sub>H<sub>4</sub>NHCH<sub>3</sub>  
XVIII: R = -C<sub>6</sub>H<sub>4</sub>Cl

elements of water, to product VIII (70% yield), m.p. >320° (IR as nujol mull: 1740, 1720, 1695, 1630 and 1610 cm<sup>-1</sup>). With acrylic acid, lactam IX, m.p. 293.4°, resulted [NMR (in TFA): C-1, C-2 protons, 3.22; C-5 protons, 4.5; C-6 protons, 4.65; C-10, C-11 and C-12 protons, 7.40-8.15 and C-9 proton, broadened doublet at 8.52 ppm]. Acrylonitrile likewise attacked C-10 to give the 10- $\beta$ -cyanoethyl derivative (X), m.p. 231-2°. Benzyl and allyl bromides afforded the C-alkylated products, XI, m.p. 255° and XII, m.p. 202.5° respectively. C-10 in I was likewise the target of attack by phenyl isothiocyanate. The product XIII, m.p. 226-7°, as well as XI and XII lacked the signal of an enamine proton at C-10 in the NMR spectrum.

Towards acylating agents, e.g. acetic anhydride, benzoyl chloride, methanesulphonyl chloride and methyl- and *p*-chlorophenylisocyanates, the nitrogen atom in I was vulnerable. The products, XIV, m.p. 241-2°; XV, m.p. 162.4°; XVI, m.p. 176-8°; XVII, m.p. 234-8° and XVIII, m.p. 247-8°, all showed the C-10 proton signal in the NMR spectrum at 6.4-7.0 ppm. [A sharp singlet for 3 protons in the NMR spectrum at 3.08 ppm ruled out a thietane dioxide structure for the compound (XVI)].

1-Alkyl derivatives like II and IV were unreactive towards maleic acid and acid chlorides. However, they underwent C-alkylation readily, and C-acylation with *p*-chlorophenyl isocyanate under forcing conditions. Further reactions of enamines I-VII are under study.

We thank Prof. T. R. Govindachari, Director, CIBA Research Centre, for his interest in this work and Dr S. Selvavinayakam and his associates for physical data.

### References

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\*Contribution No. 192 from CIBA Research Centre, Bombay 63.

†All the new compounds reported correctly analysed for C, H and N.

