Isomerism of Disubstituted Tricycloquinazolines

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CERTAIN disubstituted tricycloquinazolines exhibit a structural isomerism of an unusual type which originates from the modification of the three-fold rotational symmetry of tricycloquinazoline by appropriate disubstitution. For example, substitution at positions 3 and 8 by X and Y and Y and X respectively yields two isomers (I) and (II), which are remarkable for their structural similarity. The isomers are not mirror images of one another nor superimposable. The structural difference is made evident in the graphic formulae; whichever way the formulae are oriented (I), (Ia), and (II), (IIa), the substituents 3-X, 8-Y (I), (Ia) and 3-Y, 8-X (II) (IIa) are in reversed order around the formulae for the two isomers. These features are true for X, Y and Y, X substituents in any two of the groups of the equivalent positions 1, 6, 11; 2, 7, 12; 3, 8, 13; 4, 9, 14.

In the course of a detailed study of structural features controlling carcinogenic activity in tricycloquinazoline, we have synthesised pairs of isomers of the foregoing type having the following substituents:

2-bromo-7-methyl; 7-bromo-2-methyl

3-bromo-8-methyl; 8-bromo-3-methyl

2-fluoro-7-methyl; 7-fluoro-2-methyl

3-fluoro-8-methyl; 8-fluoro-3-methyl.

For comparison, the following pairs of isomers with substituents in non-equivalent positions have also been synthesised:

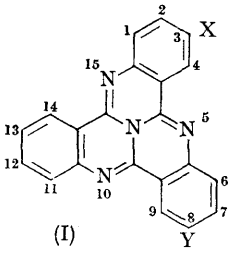
3-bromo-7-methyl; 7-bromo-3-methyl

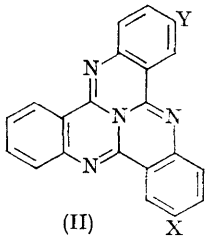
2-bromo-8-methyl; 8-bromo-2-methyl.

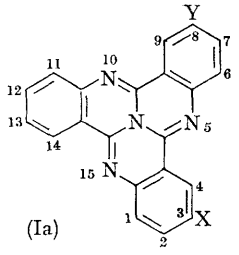
The compounds were purified until shown to be homogeneous by thin-layer chromatography.

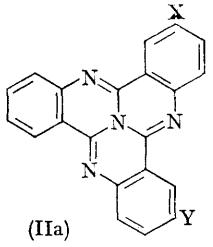
It was expected that pairs of isomers would be practically indistinguishable in their properties. However, certain differences were observed. Their melting points were all within the range 291 to 315°; the lower melting point of a mixture of a pair of equivalent 2,7 and 7,2 isomers was that of the lower melting isomer, whereas pairs of equivalent 3,8 and 8,3 or of non-equivalent 3,7 and 7,3 or 2,8 and 8,2 isomers showed depressed mixed melting-points.

The low solubility of these tricycloquinazoline derivatives in useful solvents restricted study of their spectra. In chloroform, there were seven absorption bands between 282 and 459 mμ in the spectra of all the foregoing isomers, but with small bathochromic or hypsochromic shifts in the maxima or inflexions compared with tricycloquinazoline. For pairs of equivalent and non-equivalent isomers the wavelengths of absorption maxima appeared to be identical, However, for both types of pairs of isomers, considerable differences in intensities of absorption were observed. Likewise in the fluorescence spectra, produced from a constant activation wavelength, the greatest differences were in the relative intensities of absorption.









Infrared spectra were examined in potassium bromide discs. Those of pairs of non-equivalent isomers were clearly distinguishable in both the frequencies and relative intensities of the bands. In pairs of equivalent isomers, some differences in the relative intensities of bands were evident. Differences in band frequencies were difficult to detect convincingly. For example, in the superimposed curves for the pair, 7-bromo-2-methyl- and 2-bromo-7-methyl-tricycloquinazoline, there was possibly one additional, low-intensity band present at 680 cm.$^{-1}$ in the spectrum of the latter compound and thirty six bands common to the spectra of both compounds between 670 and 1640 cm.$^{-1}$

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