

Infrared studies of hydantoin and its derivatives

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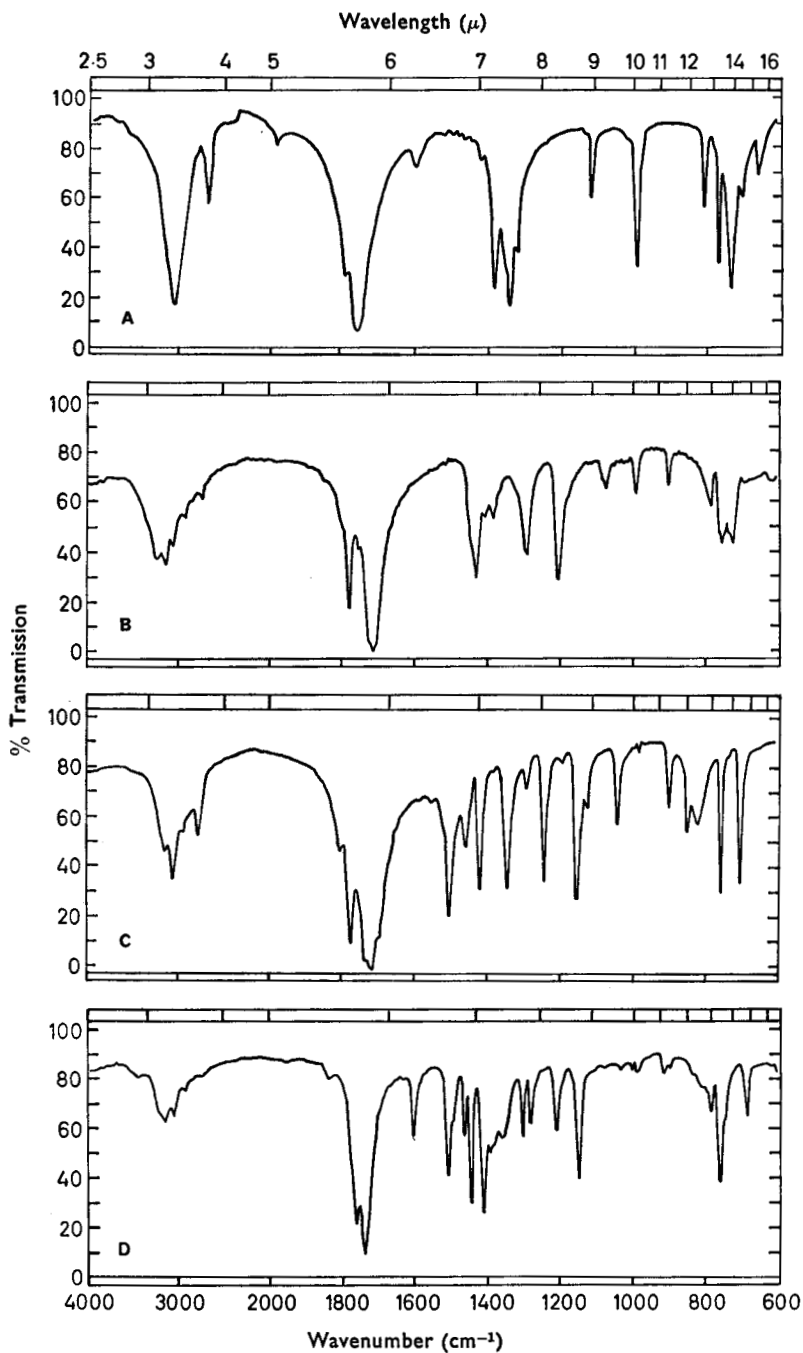
Infrared absorption spectral characteristics of hydantoin and its alkyl, aryl and aralkyl derivatives are reported. The major peaks of comparative significance are discussed in detail.

THE hydantoins are a pharmaceutically important class of compounds, and the present work was undertaken primarily to provide a more certain means of characterizing those used therapeutically, and of distinguishing them from possible toxic impurities such as 5-ethyl-5-phenyl hydantoin (Nirvanol). Each of the hydantoins examined possesses a completely individual infrared spectral curve by means of which it can be readily identified. In addition, the characteristic frequencies of the imino, carbonyl, and methylene functions of hydantoin, and the influence of alkyl and aryl substituents on them, have been examined in some detail. This is because apart from the somewhat restricted original classical investigation of hydantoin and the 1-, 3- and 5-methylhydantoins by Randall, Fuson, Fowler & Dangel (1949) to assign carbonyl stretching frequencies, the similar study of hydantoin and 5-methyl- and 5-isopropyl-hydantoin by Burland & Christian (1957), and the examination of the 1,3-dihalogeno-5,5-dimethylhydantoins by Petterson, Grzeskowiak & Jules (1960), there have been no comprehensive comparative studies. Other investigations, for example by Henze & Knowles (1954), Liebermann & Kornberg (1954), Viscontini & Raschig (1959), and Fowler, Camien & Dunn (1960) have been made mainly as aids in the identification of individual compounds without the discussion of spectral details.

Experimental

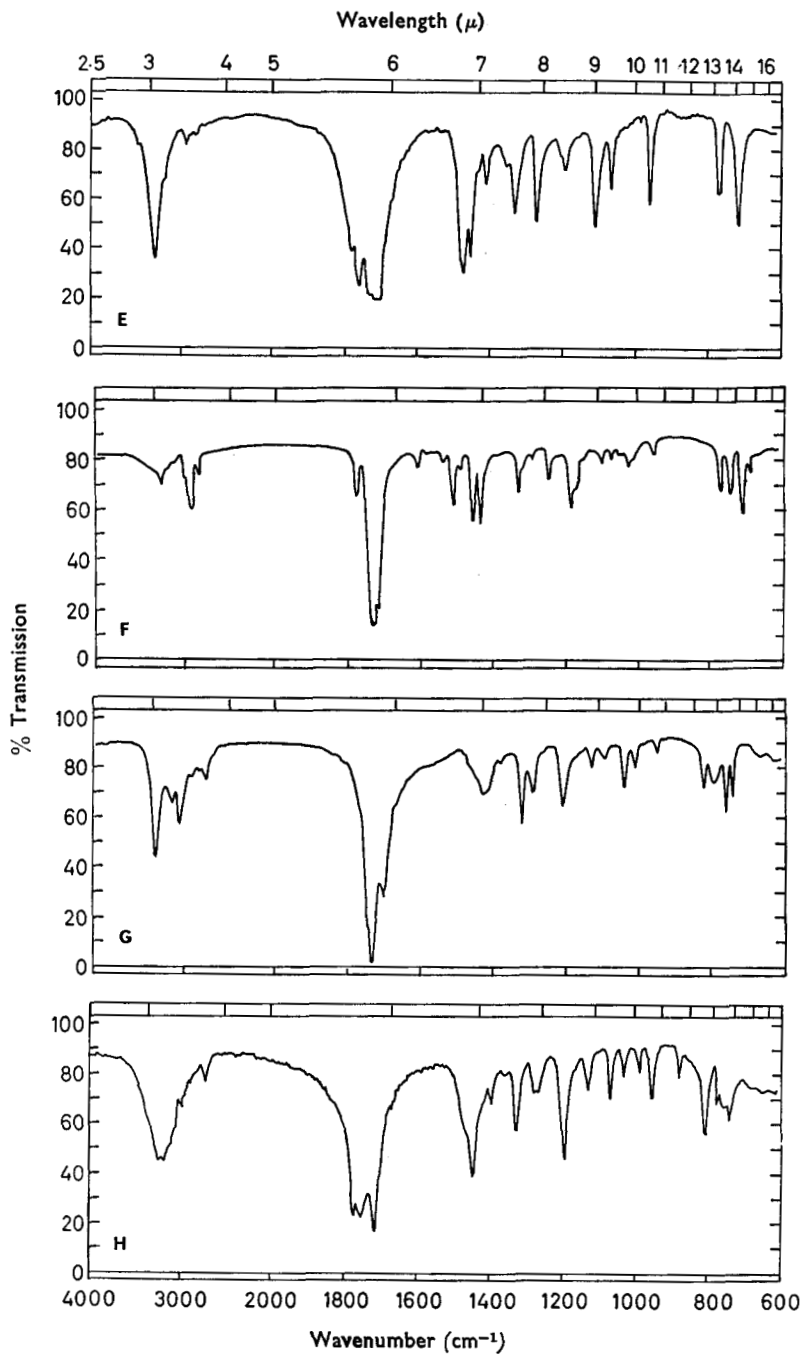
Commercially available compounds were purchased. Other derivatives were prepared by a Bucherer-Bergs synthesis (Ware, 1950) or by the condensation of the corresponding amino-acid with an alkyl or aryl isocyanate and subsequent hydrolysis and cyclization (Ware, 1950). Phenylhydantoins were crystallized from an ethanol-water mixture, and methylhydantoins from ethanol. The melting points of the compounds used agreed with those recorded in the literature. Spectra were recorded on a JASCO model IR-S double-beam spectrophotometer with sodium chloride optics. The reproducibility was 0.5 cm^{-1} and the resolution 1 cm^{-1} at $1,000\text{ cm}^{-1}$. All spectra were calibrated with a standard polystyrene film at $3,026$, $1,603$ and $1,028\text{ cm}^{-1}$ and the necessary corrections have been made. Peak absorptions in the $4,000\text{ cm}^{-1}$ to $1,250\text{ cm}^{-1}$ region were confirmed on a Perkin Elmer NIR 137G Infracord grating spectrophotometer, the accuracy of which in the $3,000\text{ cm}^{-1}$ region is better than 6 cm^{-1} .

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A, parabanic acid. B, hydantoin. C, 1-methylhydantoin. D, 1-phenylhydantoin.

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E, 3-methylhydantoin. F, 3-phenylhydantoin. G, 5-methylhydantoin. H, 5-ethylhydantoin.

Results and discussion

C-H STRETCHING VIBRATIONS

The methylene group of hydantoin shows a significant peak of medium intensity at $2,910\text{ cm}^{-1}$ ascribable to in-phase stretching vibrations, and a peak of weak intensity at $2,840\text{ cm}^{-1}$ due to out-of-phase stretching vibrations. Alkyl substitution at position 5 results in an absorption band of varying intensity in the region $2,990$ to $2,960\text{ cm}^{-1}$, probably due to methyl asymmetrical stretching modes. The absorptions appearing in the $2,920\text{ cm}^{-1}$ region can be assigned to in-phase stretching vibrations of either the methylene group of the hydantoin ring or the alkyl side-chain, or of the methine group of the hydantoin ring. Out-of-phase methylene stretching vibrations in the region $2,880$ to $2,820\text{ cm}^{-1}$ are seen in all derivatives with a methylene group either in the ring or in the alkyl side-chain. The absorptions in the region $2,760$ to $2,700\text{ cm}^{-1}$ are probably overtone or combination frequencies of the deformation modes of the methyl, methylene and methine groups.

C-H DEFORMATION VIBRATIONS

Asymmetric methyl and methylene deformation frequencies in hydantoin and its derivatives occur in the region $1,476$ to $1,403\text{ cm}^{-1}$, and band intensities are proportional to the number of alkyl substituents. The broadest band, extending from $1,476$ to $1,450\text{ cm}^{-1}$ is seen in 1,3,5,5-tetramethylhydantoin (P). In 3,5,5-trimethylhydantoin (O), the band extends from $1,462$ to $1,452\text{ cm}^{-1}$, whilst 1,5,5-trimethylhydantoin (N) shows a sharp band at $1,475\text{ cm}^{-1}$. In all three compounds a further absorption of variable intensity occurs in the $1,420\text{ cm}^{-1}$ region.

Splitting of the infrared bands when more than one alkyl group is attached to a single carbon atom has been noted by Smith (1948), and by McMurry & Thornton (1952), and can be seen here in the spectrum of 5,5-dimethylhydantoin (J), where the multiple substitution of similar alkyl groups attached to the C-5 atom causes a split of the asymmetric absorption frequency, resulting in two bands at $1,440$ and $1,430\text{ cm}^{-1}$. The asymmetric C-H deformation mode of an alkyl group attached to a nitrogen atom in hydantoin derivatives is not significantly shifted. 3-Methylhydantoin (E) has two strong bands at $1,465$ and $1,448\text{ cm}^{-1}$ and a weak band at $1,408\text{ cm}^{-1}$. 1-Methylhydantoin (C) shows a medium absorption at $1,456\text{ cm}^{-1}$ and a strong absorption at $1,416\text{ cm}^{-1}$.

The C-H symmetric deformation mode of methyl and methylene groups in hydantoin and its derivatives can be assigned to the region between $1,395$ and $1,310\text{ cm}^{-1}$. Hydantoin (B) itself has a medium band at $1,386\text{ cm}^{-1}$ and 1,3,5,5-tetramethylhydantoin (P) a strong band at $1,395\text{ cm}^{-1}$. The other derivatives have usually two or sometimes more bands in this region. Multiple substitution causes, as in the asymmetric mode, a split of the symmetric deformation frequency, and alkyl substitution on a nitrogen atom is characteristic in its symmetric deformation mode; a single strong band occurs at $1,342\text{ cm}^{-1}$ for 1-methylhydantoin (C) and at $1,330\text{ cm}^{-1}$ for 3-methylhydantoin.

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LOW-FREQUENCY VIBRATIONS

Hydantoin and all its derivatives show without exception a characteristic band varying in intensity from medium to strong in the region of 768 to 755 cm^{-1} , which is probably associated with the breathing vibration of the ring. A strong benzene ring monosubstitution band at 695 cm^{-1} is seen in all 5-phenylhydantoins and this can be regarded as diagnostic. Phenyl substitution on a nitrogen alone causes a slight shift of this band to lower frequencies; for example 3-phenylhydantoin (F) shows a weak band at 684 cm^{-1} and 1-phenylhydantoin (D) a medium absorption at 688 cm^{-1} .

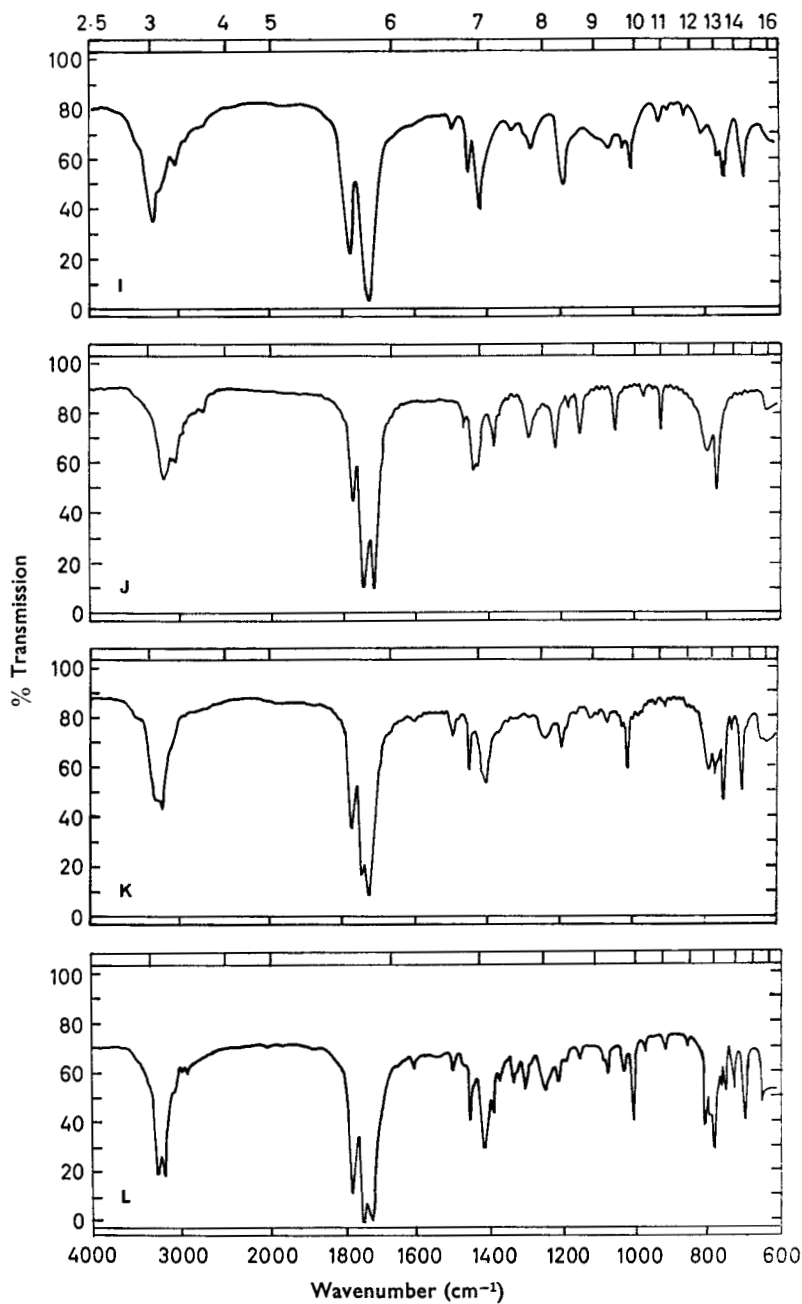
Randall & others (1949), from a consideration of the spectra of hydantoin (B), 1-methylhydantoin (C), 3-methylhydantoin (E) and 5-methylhydantoin (G), have assigned the bands occurring in the region 1,776 to 1,730 cm^{-1} to the stretching frequency of the carbonyl group in position 4 and the bands occurring in the region 1,712 to 1,695 cm^{-1} to the stretching frequency of the carbonyl group in position 2. The values recorded in this work for a more extended range of hydantoin derivatives in potassium bromide discs generally correspond with those reported by Randall & others (1949) for Nujol mull preparations. The significant difference, however, is the occurrence of a third carbonyl stretching absorption in hydantoin and all its derivatives in the region 1,756 to 1,730 cm^{-1} , which was also observed in Nujol mull preparations provided that the concentration of the hydantoin was not excessive. In relatively thick preparations, only two peaks were noted. Whether this third peak was due to polymorphism of samples in the solid state is difficult to determine, as most of the derivatives of hydantoin are insoluble in the common spectroscopic solvents. However, in those derivatives that were sufficiently soluble in chloroform for liquid spectra to be measured, viz. 1,3,5,5-tetramethyl- (P), 1,5,5- (N) and 3,5,5-trimethyl (O), 3-methyl- (E) and 3-phenylhydantoin (F) a third peak could be seen in the 1,740 cm^{-1} region and the spectra were virtually identical with those observed in potassium bromide disc preparations.

N-H STRETCHING FREQUENCY

Three absorption bands in the region of 3,390 to 3,220 cm^{-1} , 3200 to 3,120 cm^{-1} , and 3,080 to 3,040 cm^{-1} are seen in hydantoin and most of its derivatives. Substitution on both the nitrogen atoms, as in 1,3,5,5-tetramethylhydantoin (P), results in the total disappearance of these bands. A single absorption band occurs in the region of 3,280 to 3,220 cm^{-1} in the case of 3-methyl- (E), 3-phenyl- (F) and 3,5,5-trimethylhydantoin (O), all of which bear a substituent in position 3. This leads to a reasonable assignment of the absorption frequency in this region to the N-H stretching mode of the imino-group in position 1. Substitution of the imino-group in position 3 results in the disappearance of the absorption band in the 3,080 to 3,040 cm^{-1} region. Parabanic acid (A), in which both the amino-groups are situated similarly to that in position 3 in hydantoin,

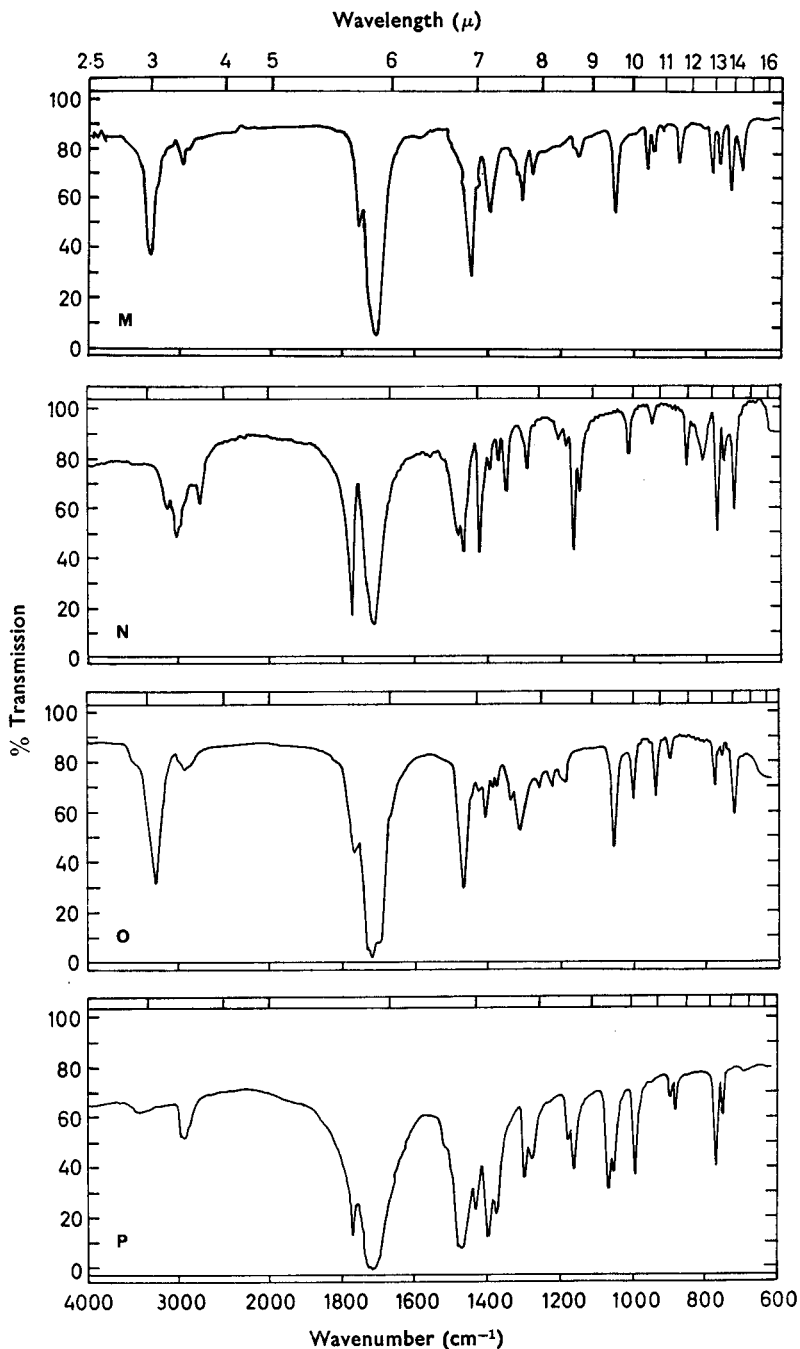
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Wavelength (μ)



I, 5-phenylhydantoin. J, 5,5-dimethylhydantoin. K, 5,5-diphenylhydantoin (Phenytoin). L, 5,5-phenylethylhydantoin (Nirvanol).

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M, 5,5-phenylethyl-3-methylhydantoin (Mesantoin). N, 1,5,5-trimethylhydantoin. O, 3,5,5-trimethylhydantoin. P, 1,3,5,5-tetramethylhydantoin.

shows a single strong band at $3,040\text{ cm}^{-1}$. On the basis of these observations, it seems reasonable to assume that the absorption band in the region of $3,080$ to $3,040\text{ cm}^{-1}$ is due to the N-H stretching mode in position 3 and is possibly characteristic of the grouping CO-NH-CO in cyclic systems. The third band in the $3,200$ to $3,120\text{ cm}^{-1}$ region could be attributed to either of the two imino-functions, though it follows more closely the pattern of the absorption band in the region of $3,080$ to $3,040\text{ cm}^{-1}$.

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