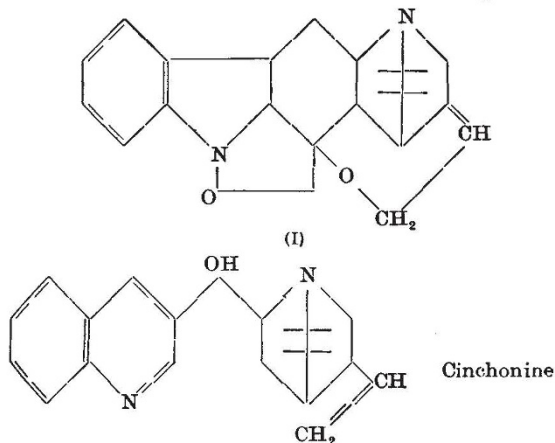


LETTERS TO THE EDITORS

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Constitution of Strychnine and its Relation to Cinchonine

THE progress of experimental studies of strychnine derivatives, especially of neostrychnine, in this Laboratory has shown that no formulation hitherto suggested is adequate. Furthermore, it has not been found possible to modify the structure in a satisfactory manner on the basis of generally accepted deductions in regard to the ring containing the amide group. The validity of the simple and direct explanations of Leuchs' degradation of the strychninolones and brucinolones has therefore become questionable, and feasible alternatives of a more complicated character have been devised. These allow the amide ring to be five-membered, and on this basis an entirely novel and very satisfactory strychnine constitution (I) can be developed. This serves to illustrate the whole chemistry of the alkaloids, including the most recent findings, and must therefore be regarded as the best working hypothesis at present available. It is free from all stereochemical difficulty, and double bonds can be accommodated where necessary.



It can be set up on the models in strainless stereoisomeric forms, of which the two most characteristic are those obtained by *cis* and *trans* disposition of the nitrogen atoms in relation to the central cyclohexane ring. The carbon skeleton can be dissected in exactly the same way as was indicated¹ in the case of another formula (with six-membered amide ring), but the relation with cinchonine is now even closer and is at once apparent on comparison of the structures. Speaking only of the carbon-nitrogen skeleton, (I) is cinchonine in which an indole nucleus replaces quinoline, and there are three additional carbon atoms in the amide ring. This is a very striking result, and nothing similar can be achieved by retaining a six-membered amide ring.

The cinchonine formula is depicted in an unusual arrangement to facilitate the comparison with (I).

A fuller discussion and description of relevant experiments will be submitted for publication elsewhere.

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Openshaw, H. T., and Robinson, R., *Nature*, 157, 438 (1946).

Influence of Tertiary Bases on the Interaction of Thionyl Chloride and Hydroxy Compounds

IN contrast to the observations of Human and Mills¹ on the use of pyridine in the interaction of thionyl chloride and the carboxylic group, we found that instead of *one* molecular proportion of tertiary base in the Darzens' procedure² for hydroxy compounds, much less than 0.1 mol. of base or its hydrochloride was sufficient. Thionyl chloride (1.0 mol.) was added to a cooled mixture of the hydroxy compound (*iso*-amyl, *n*-butyl, β -phenylethyl alcohols, or ethyl lactate) (1.0 mol.), and a few drops of base (pyridine, quinoline, or dimethylaniline) or a small amount of the corresponding hydrochloride. An excellent yield of the chloride (RCl) was distilled directly from the reaction mixture, after it had been heated for four hours at 65–80° (depending on the base). Yields approaching 95 per cent were obtained.

To account for the ease with which thionyl chloride forms pyridine hydrochloride and the sulphite (R_2SO_3), it was suggested by one of us³ that the lone pair of electrons on the nitrogen atom forms a hydrogen bond with the hydroxylic hydrogen, and this facilitates properly orientated 'broadside' collisions (I). The function of the small amount of pyridine hydrochloride in facilitating the decomposition of the intermediate chlorosulphinate ($ROSOCI$) formed in the interaction of thionyl chloride and hydroxy compound may also be due to hydrogen bonding (II), the R—O bond being thereby sufficiently weakened to increase the probability of fruitful attack along the 'end-on' direction by such groups as Cl^- or $\bar{O}SOCl$. The ion $C_5H_5NH^+$ is repeatedly regenerated. Certain structural features, such as a phenyl group attached to the reactive centre, may lead to deviations which can only be discussed in detail.

