

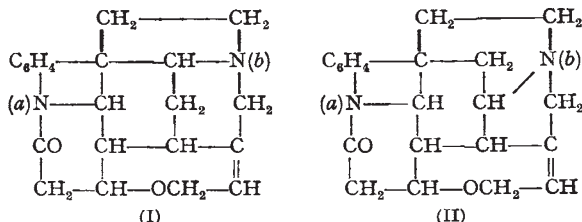
LETTERS TO THE EDITORS

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Constitution of Strychnine and the Biogenetic Relationship of Strychnine and Quinine

IN 1942 we considered the possibility that strychnine has the constitution shown in (I), but were unable to find satisfactory explanations of all the transformation products on this basis. This difficulty is no longer insuperable, and in the light of new data and a critical review we now believe that the structure interprets the whole behaviour of strychnine better than any other.

The proposed modification is derived from the current formula (II) (the skeleton of which is now assumed to be contained in dihydrostrychnidine-D) by moving N(b) from union with a carbon atom of the carbazole ring so that it becomes joined to an adjacent carbon atom. This small change affects a part of the molecule for the structure of which there was hitherto little direct evidence.



The alternative constitutions of brucine, the colubrines, and the numerous degradation products are obtained by corresponding appropriate modifications (II to I).

The expression (I) contains carbazole, tryptamine and β -collidine nuclei. It thus accommodates the formation of these substances in the decomposition of methylstrychnine, strychninolone, etc., by alkaline reagents under rather severe conditions. (II) could yield carbazole and tryptamine but has no ready-made β -collidine skeleton; this could only be provided by an intramolecular change.

Prelog and Szpilfogel¹ have suggested a different formula which contains two of the three skeletons. This is unacceptable² chiefly because it fails to illustrate the properties of pseudo-strychnine (hydroxystrychnine)³.

A very significant feature of the new formula is that it has a close relation to that of cinchonine (or β -colubrine with that of quinine). The skeletons may be dissected as follows:



The carbon chains indicated are straight; C₆ being probably originally glucose, C₅ a triose; while N.C₆.N and N.C₄.N are regarded as derived from *proto*-lysine and *proto*-ornithine respectively.

One possible interpretation of the C₄ chains was given in 1917⁴ and the main lines of that theory stand, though the hypothesis advanced for the C₆-N-C₄ moiety was speculative and is no longer advocated.

An account of new experimental work and a fuller discussion will be published elsewhere, as the matter is too complex for useful summarization.

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March 12.

¹ Prelog and Szpilfogel, *Experientia*, 1, 197 (1945).

² Robinson, R., *Experientia*, 2, 28 (1946).

³ Warnat, K., *Helv. Chim. Acta*, 14, 997 (1931). Blount, B. K., and Robinson, R., *J. Chem. Soc.*, 2305 (1932); 595 (1934). Leuchs, H., *Ber. deut. chem. Gesell.*, 70, 1543 (1937), and later papers.

⁴ Robinson, R., *J. Chem. Soc.*, 111, 885 (1917).

Isolation of Pregnane-3(a)-ol-20-one from the Hydrolysis Products of 'Sodium Pregnanediol Glucuronidate'

Astwood and Jones¹, and Talbot *et al.*², have shown that not more than about 70 per cent of the theoretical amount of pregnanediol can be obtained from sodium pregnanediol glucuronidate after hydrolysis with hydrochloric acid. Using a colorimetric method of determining pregnanediol involving the development of a yellow colour on treatment with concentrated sulphuric acid, which is essentially similar to the method employed by Talbot *et al.*, we have confirmed this finding. In the belief that the low yield of pregnanediol obtainable from the glucuronide was due to partial destruction in side-reactions during the hydrolysis, we decided to attempt the isolation and identification of the destruction products.

0.8 gm. of sodium pregnanediol glucuronidate (m.p. 270° uncorr., 280° corr.), prepared from human pregnancy urine, was heated to

boiling for 15 minutes with two litres of water and 200 c.c. of concentrated hydrochloric acid in the presence of toluene. The toluene-soluble material obtained from the hydrolysis mixture was separated into two fractions, one soluble and the other insoluble in cold *n*-hexane, and the former (0.1 gm.) after solution in hexane-benzene was adsorbed on an aluminium oxide column. By fractional elution with benzene a main fraction was obtained which after several crystallizations from *n*-hexane yielded a crystalline product, m.p. 149–150° and $[\alpha]_D^{25} = +109^\circ$. This substance gave analytical figures closely agreeing with those required for a compound of the formula C₂₁H₃₄O₂, and in the Zimmermann test it gave a brick-red colour quite unlike the pink given by 17-ketosteroids. An acetate and a semicarbazone were obtained from the substance. As the data summarized below clearly show, its identity with pregnane-3(a)-ol-20-one cannot be in doubt.

	Substance isolated	Authentic pregnane-3(a)-ol-20-one	Mixture
Hydroxy-ketone Acetate Semi-carbazone	m.p. 149–150° ; [α] _D + 109° m.p. 98–99°	m.p. 147–149° ; [α] _D + 107° m.p. 98–100.5°	m.p. 147°–149° m.p. 98–100.5°
	m.p. 246–249° (slight decomp.)	m.p. 248–251° (slight decomp.)	m.p. 248–251° (slight decomp.)

(All melting points are corrected.)

Since it seemed unlikely that the pregnanone could be formed from pregnanediol during acid hydrolysis, we considered the possibility that the original 'sodium pregnanediol glucuronidate' might have contained a water-soluble derivative of pregnane-3(a)-ol-20-one as an impurity. That this explanation is almost certainly the correct one was shown by the fact that six different preparations of sodium pregnanediol glucuronidate, all of which had been carefully purified, were found to give positive Zimmermann reactions with a brick-red tint on 4–5 mgm. quantities.

The usual methods for purifying sodium pregnanediol glucuronidate seem to be ineffective in removing this pregnanone derivative, since the intensity of the Zimmermann reaction given by one preparation was not noticeably diminished even after two crystallizations from 90 per cent ethanol and two precipitations from aqueous acetone by acetone. Furthermore, a fractionation with Girard's reagent *T* of the toluene-soluble material obtained from this sample after acid hydrolysis showed that about 20 per cent was ketonic. Our findings therefore suggest that 'sodium pregnanediol glucuronidate' prepared from human pregnancy urine and purified by the usual methods may contain as much as about 20 per cent of a water-soluble derivative—presumably the sodium salt of the glucuronide, of pregnane-3(a)-ol-20-one. It is possible that sodium pregnanediol glucuronidate has not so far been obtained by anyone free from this contaminant.

We have found that pregnane-3(a)-ol-20-one, in the quantities likely to be present, is completely eliminated by the water-ethanol precipitation process employed by Astwood and Jones and by Talbot *et al.* in their methods for determining pregnanediol. We have, furthermore, found that it is only feebly chromogenic in the sulphuric acid reaction. These facts lead us to suggest that the low yields of pregnanediol obtained from 'sodium pregnanediol glucuronidate' after acid hydrolysis by these workers and by ourselves may be partly accounted for by the presence as an impurity in the latter substance of sodium pregnane-3(a)-ol-20-one glucuronidate. We would not suggest, however, that destruction of pregnanediol during acid hydrolysis of the glucuronide does not occur at all.

Full experimental details of this work will be published elsewhere.
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Jan. 22.

¹ Astwood, E. B., and Jones, G. E. S., *J. Biol. Chem.*, 137, 397 (1941).
² Talbot, N. B., Berman, R. A., MacLachlan, E. A., and Wolfe, J. K., *J. Clin. Endocrin.*, 1, 668 (1941).

Reactions of Organic Halides in Solution

REACTIONS of organic halides in solution which involve substitution by a nucleophilic reagent at a saturated carbon atom have been extensively studied by Hughes, Ingold and co-workers¹. These authors conclude that reactions of this type may occur by two possible mechanisms, a unimolecular mechanism S_N1, or a bimolecular mechanism S_N2. The increase in the unimolecular S_N1 reaction-rate of the halide R-X as R varies along the series methyl, ethyl, *sec*-propyl, *tert*-butyl, is attributed by these authors to the increase in electron accession to the reaction centre². The decrease in the bimolecular S_N2 reaction-rate along this series³ is also attributed to the increase in electron accession to the reaction centre; this electron accession is assumed to inhibit the approach of the nucleophilic reagent.

We have calculated the activation energies of the reactions of R-X for the series methyl, ethyl, *sec*-propyl, *tert*-butyl, and conclude that the experimental results for the S_N2 reactions can be satisfactorily interpreted in terms of the quantities (a) carbon-halogen bond strength, (b) ionization potential of the radical R and the electron affinity of the halogen X, (c) heats of solution of the ions R⁺ and X⁻; and that the results for the S_N1 reactions can be interpreted in terms of (a) carbon-halogen bond strength, and (d) steric hindrance.

The unimolecular S_N1 reaction has been discussed previously for aqueous solutions in terms of the quantities (a), (b) and (c)^{4,5}. From a more detailed examination of these quantities, we find that along the sequence MeX to *tert*-BuX the decrease in carbon-halogen bond strength is of the same order as the decrease in the heat of solution