New Route for 1-Substituted Hydantoins[1]

Alkylation reactions on hydantoins (I) lead smoothly to 3-alkyl derivatives; more rigorous conditions allow further substitution at position 1 provided the N_1–H group is activated by an aryl group or an ethylenic bond attached to the adjacent C_5[2,3]. All the hitherto available methods for the not readily accessible 3-unsubstituted-1-alkylhydantoins (IV) require placing the substituent at the appropriate nitrogen atom prior to the complete formation of the hydantoin system[2,4,5].

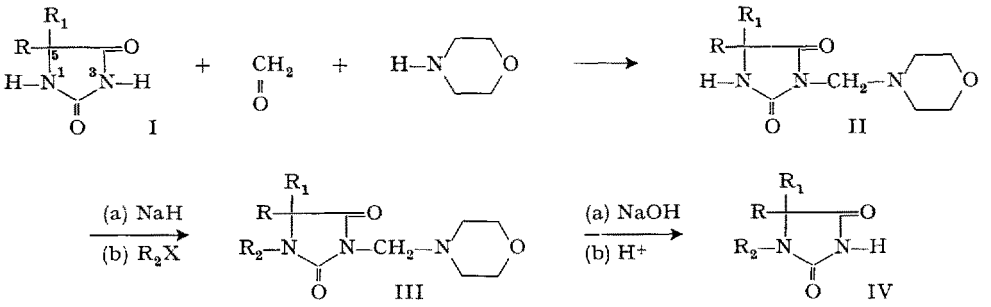
We are reporting here a new route that furnishes compounds IV through the alkylation at position 1 of the preformed hydantoin ring. This synthesis involves the following steps: (1) blockage of the more reactive position 3 by aminomethylation[6]; (2) alkylation at position 1 using a new procedure that operates under mild conditions and does not require the presence of activating groups at C_5; (3) removal of the blocking group by controlled base or acid-catalysed hydrolysis.

The entire process can be run in one operation as illustrated by the following example. Crude 3-(N-morpholinomethyl)-5,5-dimethylhydantoin (II; $R = R_1 = CH_3$), prepared from I ($R = R_1 = CH_3$; 0.001 *M*) as described earlier[6], was dried to constant weight at 56°/10^{-1} Torr and dissolved in anhydrous N,N-dimethylformamide (1.5 ml). To the solution protected from humidity, sodium hydride (0.001 *M*) as oil dispersion was added and the mixture stirred magnetically at room temperature until hydrogen evolution ceased; after addition of benzyl chloride (0.0011 *M*), the mixture was left for 24 h under the same conditions.

The solvent was evaporated under reduced pressure and the residue containing III ($R = R_1 = CH_3$; $R_2 = PhCH_2$) was washed with hexane (2 · 1 ml), dried in vacuum and then stirred 1 h at room temperature with 2 ml 3*N* aqueous sodium hydroxide. From the centrifuged solution, 1-benzyl-5,5-dimethylhydantoin (IV; $R = R_1 = CH_3$; $R_2 = PhCH_2$) was precipitated by acidification with concentrated hydrochloric acid; 45% yield, m.p. 128–129°, after recrystallization from benzene-hexane.

Alternatively, the aminomethylation step was carried out in anhydrous N,N-dimethylformamide using the calculated amount of paraformaldehyde (stirring 24 h at room temperature) instead of aqueous formaldehyde; the resulting solution was then treated directly with sodium hydride and the process followed as above. The overall yield was practically coincident.

Similar results were obtained in other experiments.



Zusammenfassung. 1,3-unsubstituierte Hydantoine (I) werden in einem 3-Stufenprozess in 1-substituierte Abkömmlinge (IV) übergeführt: Blockierung der Stellung 3 durch Aminomethylierung, gefolgt von N_1-Alkylierung mit anschliessender Entfernung der Schutzgruppe durch Hydrolyse.

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Facultad de Química y Farmacia, Universidad Nacional de La Plata (Argentine), April 2, 1965.

[1] This paper represents Part V of the series *Substitution in the Hydantoin Ring*; preceding Part, L. TRIPPETTA, O. O. ORAZI, and R. A. CORRAL, An. Asoc. quím. argent., in press.

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[3] However, A. NOVELLI, Z. M. LUGONES, and P. VELASCO [An. Asoc. quím. argent. *30*, 225 (1942)] converted (60% yield) the 3-methyl-5,5-(2'-isopropyl-5'-methyl-pentamethylene)hydantoin into its 1-methyl derivative by means of dimethyl sulphate and sodium hydroxide in ethanol.

[4] E. CATTELAIN and P. CHABRIER, Bull. Soc. chim. Fr. *1947*, 639, reported the preparation of 1-methyl-5,5-diphenylhydantoin (and other 1-alkyl derivatives) from 5,5-diphenyl-2-thiohydantoin, but other workers[5] identified the product as the 3-methyl-5,5-diphenylhydantoin.

[5] H. C. CARRINGTON and W. S. WARING, J. chem. Soc. *1950*, 354, transformed 5,5-diphenylhydantoin into 2-keto-4-methylthio-5,5-diphenyl-2,5-dihydro-glyoxaline, which by methylation and subsequent hydrolysis of the product led to 1-methyl-5,5-diphenylhydantoin.

[6] O. O. ORAZI and R. A. CORRAL, Tetrahedron *15*, 93 (1961).

A Uniform Numbering System for Indole Alkaloids[1]

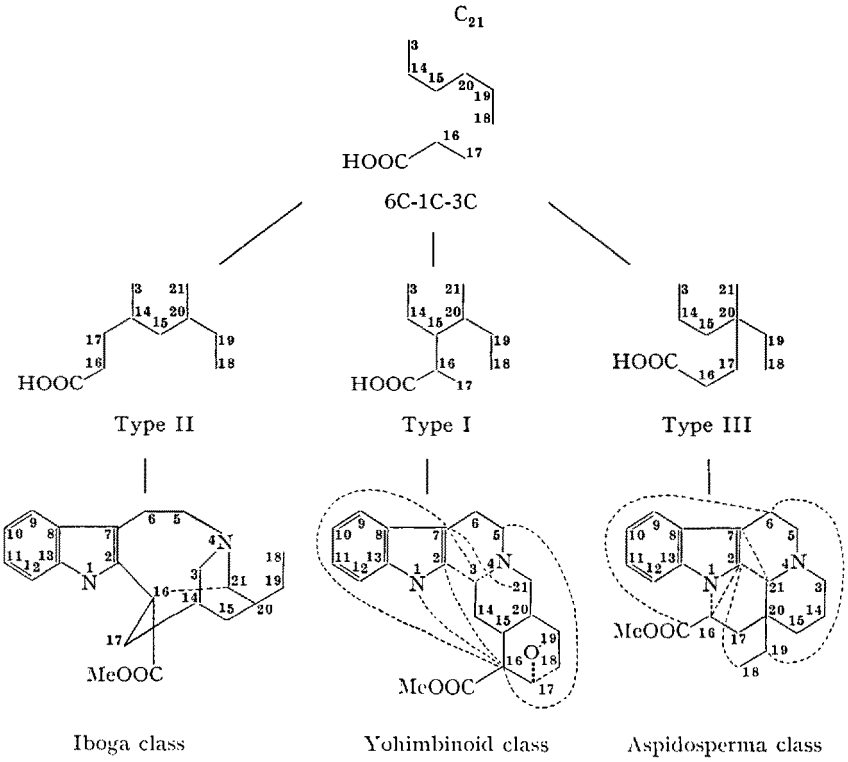
It is a remarkable fact that the occurrence of complex alkaloids (some 350 of known structure[2]) containing indole or equivalent moieties is largely restricted to a few plant families, viz. *Apocynaceae*, *Loganiaceae*, and *Rubiaceae*. It is worth remembering that these families stand close together in the phylogenetic charts of the taxonimists[3].

On the chemical side there has been discerned an apparent uniformity in the building blocks of these substances which is not always obvious upon casual examination[4]. For a number of alkaloids tryptophan or its equivalent has been proved to be one of the precursors; but the source of the remaining portion, a ten (or nine)

carbon fragment divisible[5] into linear six carbon (6 C), one carbon (1 C) and three carbon (3 C) units, connected as defined in Chart I, remains obscure. The nine carbon fragment is considered to be formed by the loss at some stage of one of the carbons from the 3 C unit, and there are also a few indole bases which appear to have ended up without the 3 C or the 1 C units, e.g. flavopereirine[6] and gelsemicine[7], as well as examples where the 3 C has lost C-17 and the carboxyl group, e.g. aspidospermatidine[8]. It is not known at this time whether there is any biochemical reality to be attached to the formal residues, 6 C, 1 C and 3 C, let alone the three hypothetical building blocks, Types I, II and III. It is nevertheless a useful way of dividing indole alkaloids into groups based on their sub-architecture. Since Type I alkaloids are by far the most numerous, they may be the source of Type II and III bases, but there is not yet any experimental basis for this assumption.

For a number of years it has become customary to assign to the atoms of Type I alkaloids the numbers given to their presumed equivalents in yohimbine. This has had a pedagogic value in serving to accentuate common features of structure and chemistry and has been an aid in remembering degradations and interconversions. We would like to suggest that this convention be extended to cover Type II and III alkaloids (Figure).

For those bases which retain the carboxyl group at C-16[9] there is an ambiguity for Type III bases since the linear three carbon unit, C-17 + C-16 + COOH is on paper equivalent to C-15 + C-14 + C-3; in this possible equivalency may lie the reason for the isolation of optical antipodes and racemates among the aspidosperma-



[1] This is a precis of a suggestion discussed at the fifth annual meeting, American Society of Pharmacognosy, Symposium on the Chemistry and Biological Activity of Catharanthus, Vinca and Related Indole Alkaloids, Pittsburgh (Pennsylvania), June, 1964.

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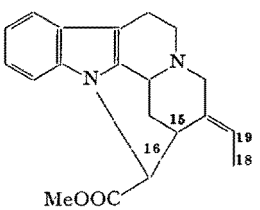
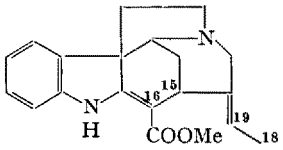
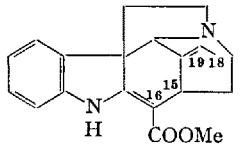
[9] There is another possible ambiguity, as illustrated by the cases of pleiocarpamine [M. Hesse, W. v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, Helv. chim. Acta *47*, 878 (1964)], akuammicine [K. Aghoramurthy and R. Robinson, Tetrahedron *1*, 172 (1957)], and condylocarpine [K. Biemann, A. C. Burlingame, and D. Stauffacher, Tetrahedron Letters *1962*, 527]. Each of these Type I bases has a carboxyl group (present as a methylester) but subtraction of the tryptamine unit yields a 9 C rather than a 10 C residue. Although we assume this carboxyl group has the same derivation as the other Type I bases, it could conceivably have been derived from C-17.



pleiocarpamine



akuammicine



condylocarpine

vincamine alkaloids[10]. We suggest for the present the convention that the carbon to which the carboxyl group is attached be C-16.

When an alkaloid lacks a carboxyl group the numbering should be the same as its carboxyl containing homologue. This convention is necessary because in the line drawings of the Figure, carbons 16 and 17 become equivalent to C-14 and C-3 in Type I bases, to C-19 and C-18 in Type II, and to C-19 and C-18 in Type III bases, respectively. This is not regarded as an ambiguity in deciding the numbering since the biogenesis of the almost ubiquitous two carbon side chain (C-19 and C-18) is probably the same for all types and also in the specific case of Type I alkaloids the absolute stereochemistry at C-15[10,11] has so far been proved to be invariant.

Résumé. Nous proposons un mode uniforme de numérotation pour le squelette des alcaloïdes indoliques complexes. Il est basé sur le fait que tous ces composés sont susceptibles d'être coupés en éléments identiques.

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École Nationale de Médicine et de Pharmacie de Reims (Marne, France) and Research Division, CIBA Pharmaceutical Company, Summit (New Jersey USA), June 21, 1965.

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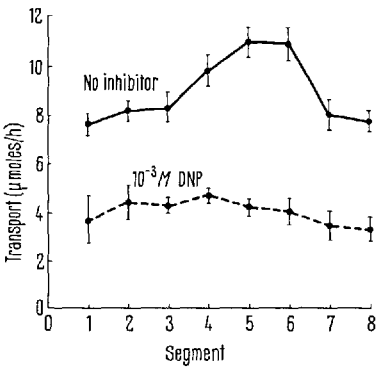
Effect of Dinitrophenol on the Pattern of Methionine Transport Along the Small Intestine of the Rat

It is well known that metabolic inhibitors such as 2,4-dinitrophenol reduce the intestinal transport of amino acids[1]. It is also known that in the case of glucose transport, metabolic inhibitors have a much greater effect on those portions of intestine which transport the best[2]. By virtue of this effect fluoride is able to abolish the gradation along the rat intestine for glucose absorption in vitro[2]. The purpose of the present study was to determine if a similar effect of a metabolic inhibitor could be shown on the pattern along the intestine for amino acid transport.

Methods. The everted small intestine from 24 h-fasted male albino rats (Holtzman; body weight 281–408 g) was divided into eight segments of nearly equal length and transport was studied using the in vitro technique of CRANE and WILSON[3]. Procedural details may be found in a previous publication[2]. Initially, both mucosal and serosal solutions (8.0 ml and 1.0 ml respectively) contained D-glucose at 5.55 μmoles/ml; the mucosal solution contained L-methionine at a concentration of 12.0 μmoles per ml; no methionine was present in the initial serosal solution. In some experiments $10^{-3}M$ 2,4-dinitrophenol (DNP) was present on both sides. Incubation was at 37°C for 1 h. Methionine concentrations were determined on samples of the serosal solution by a modification of the RUDRA and CHOUDHURY revision[4] of the MCCARTHY and SULLIVAN method[5].

When intestinal segments were incubated in the absence of added methionine, small amounts of endogenous methionine appeared in the serosal solution; in 16 segments 0.45 $\pm$ 0.17 μmoles appeared per segment. This amount was considered to be negligible compared to the amounts transported in the presence of mucosal methionine. When methionine was initially placed on both sides of the intestine, uphill transport into the serosal solution was readily observed, thereby reaffirming the viability of this preparation.

Results and discussion. The results are shown in the Figure. Transport is expressed as μmoles of L-methionine which appeared in the serosal solution of each segment during the 1 h incubation period. In the absence of DNP maximum transport was observed in segments 5 and 6 (upper ileum). This pattern is quite similar to the patterns reported by LIN and WILSON for L-tyrosine[6], SPENCER and SAMIY for L-tryptophan and L-phenylalanine[7,8], and SPENCER and BRODY for L-proline[9]. This pattern is not at all similar to the patterns reported by NEIL for L-cystine[10], NATHANS et al. for monoiodo-L-tyrosine[11], and SCHEDL and CLIFTON for L-methionine[12]. These discrepancies cannot at present be explained.



Transport of L-methionine into the serosal solution by 8 levels of rat small intestine. Segment 1 is duodenum, segment 8 is terminal ileum. Each point is mean from 10 animals in experiments without inhibitor, and 6 animals in presence of $10^{-3}M$ 2,4-dinitrophenol (DNP). Standard error of mean is indicated for each point.

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