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Intramolecular Reactions in the Oxindole Series

In his ingenious formulation of the biogenesis of the cinchona alkaloids PRELOG[1] introduced among other things a novel structural change of an indole into a quinoline nucleus;—best illustrated by the change in position of carbon atoms 1–4 from cinchonamine (I) to cinchonine (II). While this type of rearrangement is without analogy in the chemistry of indoles, it is known with compounds of higher oxidation state, as exemplified by the transformation of 3-carboxymethyloxindole (IV) into 2-hydroxy-3,4-dihydrocinchoninic acid (V). This may be of biogenetic significance especially since quinamine (III), the only other indole-containing cinchona alkaloid, also appears in a more oxidized form.

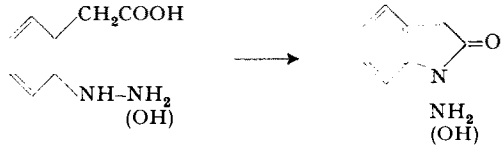
Much confusion has existed in the literature regarding the formation and stability of "oxindole-3-acetic acid" (IV) and its derivatives[2]. In fact, most structures containing the oxindole nucleus had to be revised to derivatives of 2-quinolone. Only most recently has authentic 3-carboxymethyloxindole (IV) been isolated[3]. Since all former modes of preparation of such oxindole derivatives included a hydrolytic treatment and since the six-membered lactam of o-aminophenylsuccinic acid, the hydrolysis product, is known to be more thermodynamically stable than the 5-membered cyclic amide[1,2] the rearrangement has been believed to be a consequence of a hydrolysis of the oxindole nucleus to a dibasic acid and a subsequent lactamization of the latter to a quinolone. This explanation, however, is incomplete as it ignores the relative stability of the oxindole nucleus toward hydrolysis. It thus becomes obvious that the presence of the side-chain carboxyl group is the major factor that contributes to the ease of the rearrangement. Interaction between this function and the carbonyl group of the lactam, a process well-known for γ-ketoacids, could be envisaged to yield the pseudo-acid IVa. Since the latter is also a pseudo-anhyride, it would be in equilibrium with the actual amino-anhydride which, in turn, by a similar path would form the quinolone V (as formally pictured above). The over-all equilibrium would be acid-or base-catalyzed and any of the reaction intermediates might indeed be hydrolyzed to o-aminophenylsuccinic acid under correct experimental conditions although the latter is not an essential precursor of the quinolone.

[1] R. GOUTAREL, M.-M. JANOT, V. PRELOG, and W. I. TAYLOR, Helv. chim. Acta *33*, 150 (1950).

[2] For the best review see P. L. JULIAN, E. W. MEIER, and H. C. PRINTY, in *Heterocyclic Compounds*, Vol. III (John Wiley & Sons, Inc., New York, 1952), Chapter 1, pp. 161 and 225.

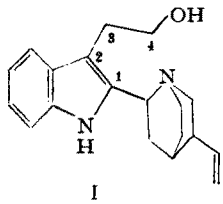
[3] P. L. JULIAN, H. C. PRINTY, R. KETCHAM, and R. DOONE, J. Amer. Chem. Soc. *75*, 5305 (1953).

[1] It is interesting to note that the cyclization of compounds containing two hetero atoms results in the formation of 5-membered lactams; e.g.:



[P. W. NEBER, Ber. dtsch. chem. Ges. *55*, 826 (1922). – P. W. NEBER and H. KEPPLER, Ber. dtsch. chem. Ges. *57*, 778 (1924). – J. MARTINET and O. DORNIER, C. r. Acad. Sci. *172*, 1415 (1921). – F. J. DI CARLO, J. Amer. Chem. Soc. *66*, 1420 (1944)].

[2] P. L. JULIAN, E. W. MEIER, and H. C. PRINTY, Note 1, p. 418.



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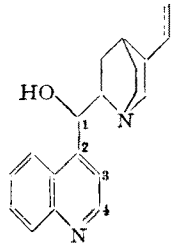

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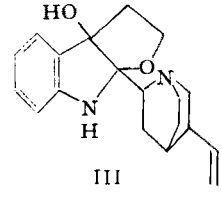

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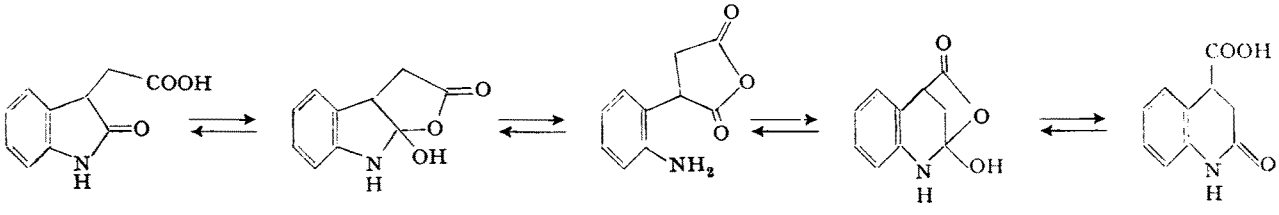
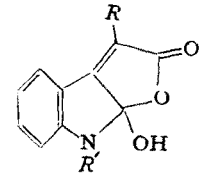


IV IVa V

The presence of steric factors which may restrict the rotation of the side-chain carboxyl group and hold it rigidly in close proximity to the lactam linkage would diminish the stability of the oxindole nucleus. Such is the case with substituted carboxymethyleneoxindoles[1]. The base-or acid-catalyzed condensation products of isatin with malonic acid derivatives (after hydrolysis), malonic acid itself, or phenylacetic acid, and the REFORMATSKY reaction products of variously N-substituted isatins have been proved to possess the 1- and/or 3-



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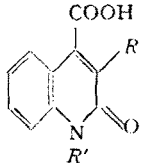

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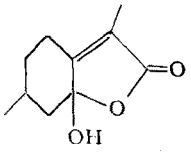
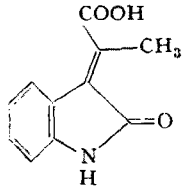


VIII



IX

substituted 2-hydroxycinchoninic acid structure (VII). The short-lived intermediate carboxymethylene compounds would be expected to exist exclusively in their pseudo-acid form (VI). The latter has an excellent analogue in the recently assigned structure of the autoxidation product of menthofuran (VIII)[2]. Internal interaction as illustrated in VI can be expected only in stereoisomers whose carboxyl and amide groups are cis toward each other, i.e. in compounds whose *R* group is equal to or larger than the carboxyl group. Thus the stability of the carboxymethylene compound most recently obtained by the base-catalyzed reaction of oxindole and pyruvic acid or its acetimino derivative[3] is not surprising. The position of the carboxyl group in this product must be in a trans relationship to the lactam function (*vide* IX).

[1] P. L. JULIAN, E. W. MEIER, and H. C. PRINTY in *Heterocyclic Compounds*, Vol. III (John Wiley & Sons, Inc., New York, 1952), Chapter 1.

[2] R. B. WOODWARD and R. H. EASTMAN, J. Amer. Chem. Soc. *72*, 399 (1950).

[3] P. L. JULIAN, H. C. PRINTY, R. KETCHAM, and R. DOONE, J. Amer. Chem. Soc. *75*, 5305 (1953).

Intramolecular reactions between a hetero atom at the end of a C_3-situated two-carbon sidechain and the lactam or imine functions of oxindoles or indolenines, respectively, are quite common. Hence the formation of tetrahydrofuro- and tetrahydropyrrolo-indoles through such reactions as peracid oxidation of indoles, e.g. WITKOPS's conversion of cinchonamine (I) to quinamine (III)[1], alkylation of tryptamine- or tryptophol-Grignard complexes[2], and chemical reduction of substituted oxytryptamines, e.g. JULIAN's synthesis of physostigmine[3], indicate the generality of this interaction. An interesting similar case involves the conversion of 3-phenylacetyloxindole oxime (X) to 3-phenylethylindole (XII) on catalytic hydrogenation[4]. Acid-induced cyclization to an isoxazole followed by hydrogenolysis could be envisaged to yield 3-phenylacetylindole oxime (XI), which in turn would undergo hydrogenation and hydrogenolysis producing the indole (XI)[5]. (Form. X, XI, XII).

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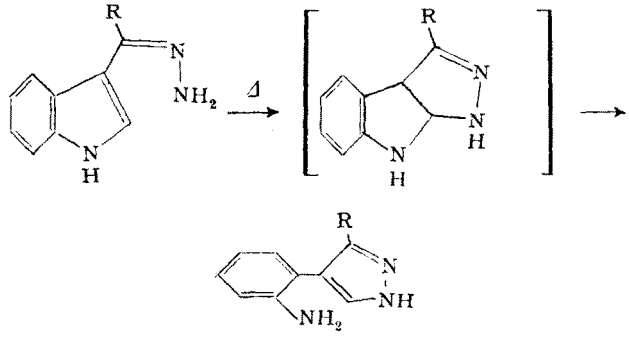
Department of Chemistry, Iowa State College, Ames, Iowa, December 21, 1953.

Zusammenfassung

Es werden verschiedene Reaktionen in der Oxindolreihe diskutiert. Man kann sie sich als ähnliche Mechanismen vorstellen, da alle über intramolekular gebildete Zwischenprodukte bzw. Endprodukte laufen.



[1] B. WITKOP, J. Amer. Chem. Soc. *72*, 2311 (1950).

[2] T. HOSHINO *et al.*, Ann. Chem. *500*, 42 (1932); *520*, 19 (1935).

[3] P. L. JULIAN and J. PIKL, J. Amer. Chem. Soc. *57*, 539 (1935).

[4] R. B. WOODWARD and E. WENKERT, unpublished results. The authors express their thanks to Professor WOODWARD for permission to include the above data in this article.

[5] As a sidelight to the above discussion, the interesting thermal rearrangement of 3-acylindole hydrazones should be noted [C. ALBERTI, Gazz. Chim. ital. *77*, 398 (1947)]. This reaction may be postulated to proceed via an internally interacted intermediate which breaks up into the more thermodynamically stable aminophenylpyrazole: