bridization complex sf^3 occurring in the tetrahedral IO_4^- group, a small amount of f character would be conferred to the p orbitals of an sp^3 complex giving effectively a $sp^{3-\epsilon}f^{\epsilon}$ complex, where ϵ is supposed to be small. For a given problem ϵ could then be found by minimization of the energy eigenvalue by a variational treatment.

It thus appears that f electrons may contribute to bonding in compounds of the elements immediately preceding the rare earths, and that thereby certain chemical properties of these elements may be explained. In particular, the preferential stabilization of the higher oxidation states of these elements may be accounted for.

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Studies on the Fischer Indole Synthesis. III. Mechanism

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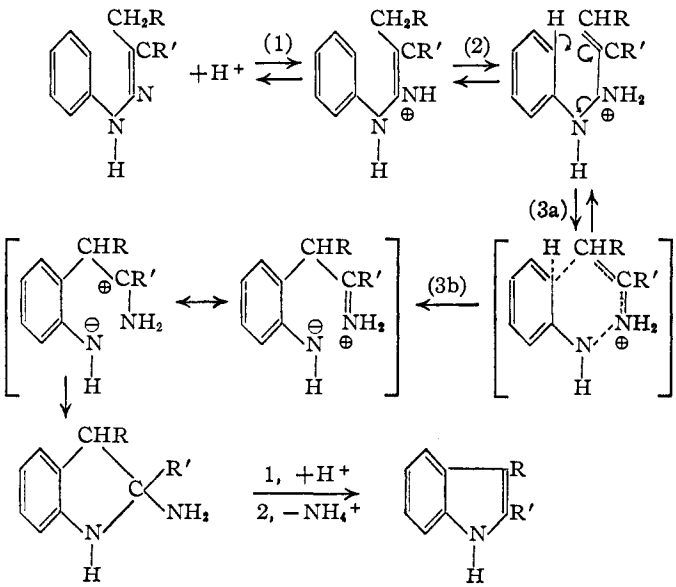
A proposed[1] mechanism for the Fischer indole synthesis has been criticized recently on the basis of a kinetics study.[2] It is the purpose of this paper to show not only that the criticism is invalid but also that a reaction sequence essentially identical with that previously proposed[1] *does* account satisfactorily for the data given by Pausacker and Schubert as well as for certain other established facts about this transformation.

The following reaction sequence appears to embody the principal features of the Robinson–



Robinson mechanism,[3] of the ring closure mechanism first suggested by Allen and Wilson,[4] and of our proposed mechanism.[1] Examination of these formulations discloses that no fundamental changes are required if the proton is accepted by the other nitrogen atom in step (1). Pausacker and Schubert argued that a similar reaction sequence[1] could not be reconciled with their rate data for the reason that the effects on the observed rate constants of introducing certain substituents into the aromatic ring of the phenylhydrazone were not those to be expected on the rates of the rearrangement step (3) in the reaction sequence above. However, the rate constants measured by Pausacker and Schubert cannot be the simple rate constants for the rearrangement step (3) alone; furthermore, there need be no relationship between changes in measured rate and changes in the rate of step (3) which result from structural alterations, as the authors implicitly assume in making their criticism. In fact, in order to account for their observed kinetics, Pausacker and Schubert assumed that the rate-determining step in the sequence is the reaction of the phenylhydrazones with a proton (step 1, above). If this assumption were to prove correct, then the observed effects of structural variations on the experimental rate constants should parallel the effects of structure on the base strengths of the phenylhydrazones; and, indeed, such a parallelism appears likely when the data of Pausacker and Schubert are examined. In any case, the effects of structure on the rate of the rearrangement step (3) should not be reflected in the experimental rate constant if this step is assumed not to be rate determining.

However, it is not necessary to assume that step 1 is rate determining in order to account for the kinetics observed by Pausacker and Schubert. If proton addition and tautomerization (steps 1 and 2) are assumed to be reversible and rapid compared to step 3, and if the succeeding steps are also rapid compared to step 3, then the following rate expression can be derived from the reaction sequence

$$\frac{dx}{dt} = \frac{k_3K_1K_2(a - x)[H^+]}{1 + K_1[H^+] + K_1K_2[H^+]}$$

in which K_1, K_2 and k_3 are the equilibrium and rate constants for the first three steps, respectively, a is the initial phenylhydrazone concentration and x is the concentration of indole at time t. If $K_1[H^+]$ and $K_1K_2[H^+]$ are small compared to 1, a likely condition, then the above expression becomes identical with the experimentally derived rate equation, where $k_{expt} = k_3K_1K_2$. Thus the experimental rate constant would be proportional to the first base constant for the phenylhydrazone and to the tautomerization equilibrium constant, as well as to the rate constant for the rearrangement step. Since the tautomeric shift (step 2) is comparatively remote structurally from the benzene ring, substitution on the latter would be expected to affect K_2 to a smaller extent than K_1 or k_3. If the introduction of the substituents selected by Pausacker and Schubert on the benzene ring causes much greater changes in K_1 than in k_3, then the fact that the relative reaction rates of cyclohexanone, phenylhydrazone and three of its aromatic

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(2) K. H. Pausacker and C. I. Schubert, *J. Chem. Soc.*, 1814 (1950).
(3) G. M. Robinson and R. Robinson, *ibid.*, **113**, 639 (1918); 827 (1924).
(4) C. F. H. Allen and C. V. Wilson, THIS JOURNAL, **65**, 611 (1943).

ring substitution products are in the same order as their probable base strengths is readily understandable. Also subject to interpretation on the basis of the above development is the observation recorded by Robinson and Robinson[3] that, of a series of phenylhydrazones derived from structurally similar carbonyl compounds, those phenylhydrazones which are derived from the most readily enolizable aldehydes or ketones give the most facile Fischer reactions. If the tautomeric shift represented in step 2 is closely analogous to the keto–enol change, then the most readily enolizable ketone of a related series should give a phenylhydrazone whose K_2 value should be greatest of the series. Since K_1 and k_3 values would not be expected to vary much throughout a series of phenylhydrazones of related aldehydes or ketones, the changes in k_{expt} should be functions mainly of changes in K_2. In this connection it should be stressed, however, that quantitative data permitting comparisons of degrees of enolization of carbonyl compounds on the one hand with rates of Fischer reactions of their phenylhydrazones on the other are not available. A study of this problem will be carried out in this Laboratory.

Finally, the latter part of the proposed reaction sequence is not fundamentally different from the ring-closure mechanism proposed by Allen and Wilson[4]; it therefore gives a satisfactory accounting for the fact demonstrated by them that the phenylhydrazone nitrogen atom bound to the benzene ring is that which remains in the indole ultimately formed.

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The Preparation of C^{14}-Chain Labeled Choline Chloride

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The role of choline in transmethylation reactions and in phospholipid biochemistry has been widely investigated. For the former type of study, choline labeled in the methyl groups with either deuterium or C^{14} has been employed.[1,2] Such a labeled compound is of questionable use, however, in phospholipid investigations or in the determination of the metabolic fate of choline itself. In order to pursue problems of the latter type, choline labeled in the chain with C^{14} is most desirable. Recently, Fields and his collaborators[3] reported the preparation of such a labeled material starting with barium carbide and progressing through acetylene and ethylene bromohydrin. Choline, so prepared, is labeled in both carbon atoms of the chain. We wish to report an alternate synthetic route which starts with the more readily available and more easily manipulated acetic acid and also allows for specific labeling of the individual carbon atoms.

$$ClCH_2C^*OOH \xrightarrow{CH_3CHN_2} ClCH_2C^*OOC_2H_5 \xrightarrow{(CH_3)_2NH}$$
$$(CH_3)_2NCH_2C^*OOC_2H_5 \xrightarrow{LiAlH_4} (CH_3)_2NCH_2C^*H_2OH$$
$$\xrightarrow{CH_3I} (CH_3)_3NCH_2C^*H_2OH\ I^- \xrightarrow[HCl]{Ag_2O} (CH_3)_3NCH_2C^*H_2OH\ Cl^-$$

Carboxyl-labeled sodium acetate was converted into chloroacetic acid in the standard fashion[4] and this acid was esterified with diazoethane. The resulting ethyl chloroacetate was then allowed to react with dimethylamine and the product reduced to N,N-dimethylaminoethanol with lithium aluminum hydride. The substituted ethanol was further methylated with methyl iodide and the choline iodide so formed converted into choline chloride.

During this preparation, it was found that when methyl chloroacetate was subjected to aminolysis, not only was the chlorine atom displaced but the ester was also transformed in a large part into a substituted amide. The ethyl ester, however, was found to be sufficiently less reactive[5] so that this latter side-reaction occurred only to a minor amount. The usual mode of preparation of choline from ethylene chlorohydrin could not be used in this synthesis since it is known that when chloroacetic acid is reduced with lithium aluminum hydride, ethanol is the major product.[6]

Experimental

Diazoethane.—N-Nitrosoethylurea was prepared in the manner described for the methyl derivative[7] except 33% aqueous ethylamine was substituted for methylamine; yield 38%. An ethereal solution of diazoethane was prepared by adding 15.0 g. of N-nitrosoethylurea to a chilled mixture of 150 ml. of ether and 45 ml. of 50% aqueous potassium hydroxide. After standing for 20 minutes, the ether was decanted and the solution used directly in the next reaction.

Carboxyl-labeled Ethyl Chloroacetate.—Carboxyl-labeled acetic acid, generated from carboxyl-labeled sodium acetate (0.596 g., 7.3 mmoles) containing approximately 4.2 millicuries of C^{14}, was diluted with 0.329 g. (4.2 mmoles) of inactive acetyl chloride. The resulting mixture was allowed to react with iodine, phosphorus pentachloride and chlorine as described by Hughes and Tolbert[4] and the reaction diluted first with 1 ml. of water and then with ether. The resulting ethereal solution was added to the chilled solution of diazoethane prepared above. The excess reagent was removed by distillation and the residual ethereal solution of the ester dried over anhydrous potassium carbonate. The radioactive ester was not distilled but in inactive experiments the ester was isolated in yields of 75–90% (based upon acetic acid moieties), b.p. 144° (lit. 144°).

Ethyl N,N-Dimethylaminoacetate.—The crude ester prepared above was allowed to react for 12 hours at room temperature with 1.2 g. (26 mmoles) of dimethylamine in 5 ml. of dry benzene in a flask fitted with a Dry Ice condenser.[8] The reaction mixture was filtered and the salt washed with small portions of dry ether. After removal of the solvents, the amino ester was distilled through a micro fractionation column[9] in order to separate the ester from any amide which might have been formed. The product boils at 144–149°. The over-all yield of pure material was 55% based on acetic acid moieties.

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