H. Addition of Methylmagnesium Iodide to 2,4,5-Triphenyl-3-(4'-chlorophenyl)-cyclopenta-2,4-dien-1-one.—The product was prepared in the same manner as in F and G, using 2,4,5-triphenyl-3-(4'-chlorophenyl)-cyclopenta-2,-4-dien-1-one (1 g., 0.0024 mole), magnesium turnings (2.4 g., 0.1 mole) and methyl iodide (14.0 g., 0.1 mole) to yield 0.9 g. (86%) of off-white product, m.p. 161–163°.

Anal. Calcd. for $C_{30}H_{23}OCl$: C, 82.84; H, 5.33; Cl, 8.17. Found: C, 83.27; H, 5.47; Cl, 8.36.

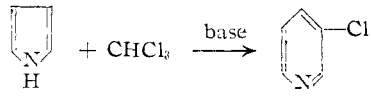
DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE
BROOKLYN, N. Y.

An Improved Synthesis for 3-Chloropyridine

BY HAROLD L. RICE AND THOMAS E. LONDERGAN

RECEIVED MARCH 24, 1955

One of the more unusual reactions of pyrrole is its conversion to 3-chloropyridine through reaction with chloroform in the presence of bases.



This ring expansion reaction, carried out in ether with sodium ethoxide as catalyst, was reported first by Ciamician[1] and was extended by Dennstedt[2] to the sodium methoxide catalyzed reaction of pyrrole with methylene iodide to give pyridine. Extension of this reaction to the indole series has been reported by several workers.[3] Substituted quinolines were the reported products in yields as high as 50%. Recently Alexander and co-workers[4] made a study of catalysts for the pyrrole–chloroform reaction. Their best yield of 3-chloropyridine (12.8%) was obtained using pyrryllithium as a reactant. Reactions described in these references were carried out in the liquid phase, mostly in anhydrous media.

The chloroform–pyrrole reaction has been reexamined in our laboratory according to the directions given in the literature. Sodium hydroxide, sodium ethoxide and sodium methoxide were used as catalysts in liquid phase experiments. Results were erratic with low yields and the 3-chloropyridine was difficult to isolate from the mass of polymeric by-products. In attempts to improve yields and inhibit side reactions, a study of the vapor phase reactions of pyrrole and chloroform was initiated. Using alumina or molybdena on alumina as catalysts at 440–510°, only tars were formed. However, when chloroform and pyrrole vapors were passed through an empty glass reaction tube at 550°, 3-chloropyridine was formed in yields up to 33% of theory. In runs at 500°, yields of 20–25% were obtained. Increasing amounts of starting materials were recovered as temperatures were reduced below 500°, while increasing amounts of tars were produced above 600°. The best results were obtained when the chloroform to pyrrole ratio was about five to one. About one-third volume of nitrogen per volume of reactant mixture was passed into the reaction zone with the reactants. The contact time in the hot zone was about three seconds.

The preparation of 3-chloropyridine to the exclusion of the other isomeric monochloropyridines under such extreme conditions would seem unusual. In fact, 2-chloropyridine was produced in yields of 2 to 5%. Evidence that rearrangement of the 3-chloropyridine was not taking place was found in our unsuccessful attempts to interconvert 3-chloropyridine and 2-chloropyridine under the conditions of the reaction. The third isomer, 4-chloropyridine probably would not be recovered, even if formed, because it would not be stable at such high temperatures.[5]

The consideration of a mechanism for this high-temperature synthesis leads to the suggestion that it may be in part base-catalyzed by the glass of the tube. A recent report by Parham and Reiff[6] may indicate the reaction path. In their work, the synthesis of chloronaphthalene from chloroform and indenylsodium is described. These authors isolated the intermediate dichlorocyclopropane resulting from the attack on indene by the dichlorocarbene anion. The 3-chloropyridine synthesis may well proceed by such a mechanism.

Experimental

The vapor phase reactions were carried out in a 1.5 in. × 48 in. Pyrex glass tube. The tube was made up in two sections; the upper section was packed with Berl Saddles and used as a preheater, while the lower unpacked section served as the reactor. The sections of the tube were heated separately using a 12-in. (preheater) combustion furnace and an 18-in. (reactor) combustion furnace. Above the preheater was mounted a water-cooled dropping funnel. A mixture of 30 g. (0.45 mole) of pyrrole and 270 g. (2.25 moles) of chloroform was added to the preheater through the dropping funnel at the rate of 2–3 drops per second. A continuous flow of nitrogen through the preheater and reactor (600 ml./min.) was maintained. Products from the reaction were collected in a 2-liter flask which was cooled in an ice-bath. Hydrogen chloride was removed in a second trap by passing through a caustic solution, and any further condensable vapors were collected in a series of two Dry Ice-cooled traps. Temperatures during the reaction were measured with thermocouples inserted into a thermowell in the reactor. After the addition of reactants was complete the receivers were removed and the chloroform layers from the receiver and traps were combined and extracted with 6% hydrochloric acid. The acid extract was made alkaline with 30% sodium hydroxide solution and steam distilled. The distillate was extracted with four 30-ml. portions of methylene chloride and the product was recovered by distilling off the methylene chloride. The residue, 17.9 g., consisted of from 13 to 16.5 g. (25 to 33%) of 3-chloropyridine and from 1.0 to 2.5 g. (2 to 5%) of 2-chloropyridine.

The products from several such reactions were combined and fractionally distilled to separate the two products. The 3-chloropyridine distilled at 77–78° (62 mm.), while the 2-chloropyridine distilled at 81–85° (62 mm.). Redistillation of the 3-chloropyridine was carried out for analysis.

Anal. Calcd. for C_5H_4NCl: N, 12.34. Found: N, 12.22.

The picrate, recrystallized from ethanol, melted at 146–147°.[4]

A sample of 2-chloropyridine was added to a solution of picric acid in ethanol and the resulting picrate was recrystallized from ethanol; m.p. 92–93.5°. A mixed melting

(1) G. L. Ciamician and M. Dennstedt, *Ber.*, **14**, 1153 (1881); G. L. Ciamician and P. Silber, *ibid.*, **18**, 721 (1885); **20**, 191 (1887).

(2) M. Dennstedt and J. Zimmerman, *ibid.*, **18**, 3316 (1885).

(3) P. C. Madnanini, *ibid.*, **20**, 2608 (1887); A. Ellinger, *ibid.*, **39**, 2515 (1906); A. Ellinger and C. Flamand, *ibid.*, **39**, 4388 (1906).

(4) E. R. Alexander, A. B. Herrick and T. M. Roder, THIS JOURNAL, **72**, 2760 (1950).

(5) J. P. Wibaut and F. W. Brookman, *Rec. trav. chim.*, **58**, 885 (1939).

(6) Parham and Reiff, Abstracts of Papers, Cincinnati Meeting of the A.C.S., March 29 to April 7, 1955, p. 20N.

point with an authentic 2-chloropyridine picrate gave no depression.

Anal. Calcd. for $C_{11}H_7N_4O_7Cl$: N, 16.36. Found: N, 16.53.

ELECTROCHEMICALS DEPT.
E. I. DU PONT DE NEMOURS AND CO., INC.
WILMINGTON 98, DELAWARE

The Biosynthesis of Valine in *Aerobacter Aerogenes*[1]

BY MAX E. RAFELSON, JR.

RECEIVED APRIL 9, 1955

Strassman, *et al.*,[2] have shown by isotopic studies in *Torulopsis utilis* that pyruvic acid was apparently the sole source of the carbon chain of valine. The distribution of the carbon atoms of glycine and acetate as well as carbon 1 of glucose was in accord with their prior conversion to pyruvate *via* known biochemical processes.

As a result of experiments designed to study the biosynthesis of tryptophan,[3,4] various radioactive valine samples were isolated from *Aerobacter aerogenes* grown on acetate-1-C^{14}, glucose-1-C^{14} and glucose-3,4-C^{14}. These valine samples were subjected to degradation in order to determine the intramolecular distribution of the isotope. The results are presented in Table I and are identical with those obtained by Strassman, *et al.*,[2] in *T. utilis*. This may be interpreted as indicating that the biosynthetic pathways for valine in these two organisms are very similar, if not identical. The present data are in accord with the proposed mechanism for valine biosynthesis.[2] This visualized the prior conversion of glucose and acetate to pyruvate and the subsequent condensation of pyruvate and acetaldehyde (derived from pyruvate by decarboxylation) to yield α-acetolactate which undergoes a pinacol-like rearrangement to form the keto analog of valine.

TABLE I

INTRAMOLECULAR DISTRIBUTION OF GLUCOSE AND ACETATE CARBON IN VALINE

Valine carbon atom	Total activity in valine, % Glucose C-1	Glucose C-3,4	Acetate C-1
1	2	100	99
2	4	0	0
3	4	0	0
4,4[1]	90	0	0

Experimental

The cultivations of the organism on acetate-1-C^{14} and on glucose-3,4-C^{14} have been described in previous publications.[3,4] The details of the glucose-1-C^{14} cultivation[5] were very similar to those of the cultivation on glucose-3,4-C^{14}. The procedures for the assay of radioactivity have also been presented in detail.[3,4,6]

Following the removal of tryptophan, tyrosine and phenylalanine from the hydrolysates,[3,6] glutamic and aspartic acids were separated from the hydrolysate according to Cannan.[7] The remaining amino acids were separated on a column of Dowex-50.[8] The fractions containing valine were treated as described by Ehrensvärd, *et al.*[9] The identity and purity of the valine samples were determined by filter paper chromatography and radioautography.

The methods for the degradation of valine were essentially those of Strassman, *et al.*,[2] the differences being minor.

(1) Supported in part by a grant (G-4175) from the National Institutes of Health, United States Public Health Service.

(2) M. Strassman, A. J. Thomas and S. Weinhouse, THIS JOURNAL, **77**, 1261 (1955).

(3) M. E. Rafelson, G. Ehrensvärd, M. Bashford, E. Saluste and C. G. Hedin, *J. Biol. Chem.*, **211**, 725 (1954).

(4) M. E. Rafelson, *ibid.*, **213**, 479 (1955).

(5) M. E. Rafelson, to be published.

(6) M. E. Rafelson, G. Ehrensvärd and L. Reio, *Exptl. Cell Research*, in press (1955).

(7) R. K. Cannan, *J. Biol. Chem.*, **152**, 401 (1944).

(8) W. H. Stein and S. Moore, *Cold Spring Harbor Symposia Quant. Biol.*, **14**, 179 (1950).

(9) G. Ehrensvärd, L. Reio, E. Saluste and R. Stjernholm, *J. Biol. Chem.*, **189**, 93 (1951).

DEPARTMENT OF BIOLOGICAL CHEMISTRY
UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE
CHICAGO, ILLINOIS

Steric Effects on Migration Aptitudes. Reaction of Some *o*-Substituted Benzophenones with Peroxyacetic Acid

BY WILLIAM H. SAUNDERS, JR.

RECEIVED FEBRUARY 16, 1955

It has been known for some time that the migration aptitude of a *p*-substituted phenyl group in the pinacol and allied rearrangements depends upon the electron-releasing ability of the substituent. The abnormally low migration aptitudes of *o*-substituted phenyl groups have been explained on the basis of a steric effect,[1] and recently the nature of this steric effect has been discussed in some detail.[2] According to this viewpoint the migrating aryl group must adopt a rotational conformation such that the π-electrons of the ring may effectively overlap the vacant (or partially vacant) *p*-orbital left by the departing group on the migration terminus. An *o*-substituent interferes with this process and thus lowers the mobility of the group.

The data on the pinacol rearrangement give no indication as to whether the major source of interference with the *o*-substituent lies in other groups on the migration origin or in groups on the migration terminus. An answer to this question would be of considerable assistance in formulating a more precise picture of the transition state for the rearrangement. One possible approach is the selection of a system in which there are no interfering substituents on the migration terminus. Kharasch[3] found that in the treatment of tertiary aromatic alcohols with hydrogen peroxide under acidic conditions, which leads to phenols and ketones, both *o*-anisyl and *o*-tolyl migrated better than phenyl, in contrast to behavior of these groups in the pinacol rearrangement. Here there is no possibility of interference by groups on the migration terminus, since the only such group in the protonated hydroperoxide intermediate is the departing $-OH_2^+$, which must be *trans* to the migrating group. Unfortunately there was not a sufficient variety of substituents employed to permit a decision concerning the degree of similarity between this reaction and the pinacol rearrangement. Another recent study of the *ortho* effect, in which Smith[4] deter-

(1) C. H. Beale and H. H. Hatt, THIS JOURNAL, **54**, 2405 (1932).

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 478.

(3) M. S. Kharasch, A. Fono, W. Nudenberg and A. C. Poshkus, *J. Org. Chem.*, **15**, 775 (1950).

(4) P. A. S. Smith, THIS JOURNAL, **76**, 431 (1954).