corresponding tetrahydroisoquinoline derivative, the relative activities are explicable in terms of the concentration of di-cation at physiological *p*H.

Acknowledgments.—The authors are indebted to Dr. T. B. O'Dell and his associates for the pharmacological data. Mr. D. F. Cortright and Miss Mary Unroe of these laboratories performed the ionic halogen and basic nitrogen determinations.

Experimental[6]

Intermediates.—The preparation of pure *trans*-N-methyldecahydroisoquinoline and of a *cis–trans* mixture was described earlier.[7] *trans*-Decahydroquinoline and a *cis–trans* mixture of decahydroquinolines were Eastman (White Label) Chemicals, and were methylated by the Eschweiler–Clarke method[8] to give, respectively, *trans*-*N*-methyldecahydroquinoline, b.p. 51–52° (3.5 mm.), n^{25}D 1.4787, and N-methyldecahydroquinoline (*cis–trans* mixture), b.p. 117–118° (50 mm.), n^{25}D 1.4833.

1-(3-Chloropropyl)-decahydroquinoline (XIVc).—A solution of 38 g. (0.27 mole) of decahydroquinoline (*cis–trans* mixture) and 21.4 g. (0.13 mole) of trimethylene chlorobromide in 75 ml. of benzene was allowed to stand at room temperature for three days. The precipitate was collected and washed with ether to give 19.5 g. (65%) of *trans*-decahydroquinoline hydrobromide, m.p. 280–281° (lit.[9] m.p. 277–279°). Decomposition of the salt provided *trans*-decahydroquinoline, m.p. 47–49°, no melting point depression on admixture with authentic material (lit.[9] m.p. 48°).

The filtrate and ether washings from the hydrobromide salt were combined and extracted with 10% hydrochloric acid. The acid extract was made alkaline and extracted with ether. After drying and removal of the ether the residue was distilled to yield 12.6 g. (43%) of XIVc as a colorless, relatively unstable oil, b.p. 94–96° (0.3 mm.). Presumably the *cis* isomer predominates in the product.

The hydrochloride salt of XIVc, recrystallized from isopropyl alcohol–ether, showed m.p. 162–164°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N$: C, 57.15; H, 9.19; Cl (ionic), 14.06. Found: C, 57.02; H, 9.39; Cl, 14.01.

1-Ethyldecahydroquinoline (XIVa).—To a solution of 20.0 g. (0.14 mole) of the mixture of decahydroquinoline isomers in 100 ml. of benzene was added 11.2 g. (0.07 mole) of ethyl iodide. After the initial reaction had subsided the mixture was refluxed on the steam-bath for 1 hr. The precipitate of 16.0 g. (83%) of *trans*-decahydroquinoline hydriodide (identified on the basis of the melting point of the free base) was separated and the filtrate was distilled to yield 8.0 g. (67%) of 1-ethyldecahydroquinoline, assumed to be largely the *cis* isomer, b.p. 65–67° (2.5 mm.),[10] n^{20}D 1.4830.

1-(Dimethylaminoethyl)-decahydroquinoline (XIVb).—Similarly, a solution of 30 g. (0.22 mole) of the mixed decahydroquinolines and 11.6 g. (0.11 mole) of dimethylaminoethyl chloride in 75 ml. of benzene was refluxed on the steam-bath for 80 hr. Filtering off the precipitate of 13.6 g. (72%) of *trans*-decahydroquinoline hydrochloride (identified as before) and distilling the filtrate afforded 9.0 g. (40% yield) of XIVb, probably mainly *cis*, b.p. 104–106° (1.5 mm.), n^{25}D 1.4862.

The dihydrochloride salt of XIVb, recrystallized from ethanol, melted with decomposition at 272°.

Anal. Calcd. for $C_{13}H_{28}Cl_2N_2$: C, 55.10; H, 9.96; Cl, 25.03. Found: C, 55.24; H, 10.21; Cl (ionic), 24.48.

Reaction of XIVc with Trimethylamine. Preparation of V.—Into a solution of 10.0 g. (0.04 mole) of XIVc in 75 ml. of ethanol was bubbled 12.0 g. (0.2 mole) of anhydrous trimethylamine. After being heated in a pressure bottle at 50° for 16 hr., the solution was evaporated *in vacuo* to yield 12 g. of a thick oil residue. This material rapidly liberated trimethylamine on standing. It was, therefore, redissolved in ethanol and treated with ethereal hydrogen chloride. Removal of the ethanol under reduced pressure left an oil which was crystallized and several times recrystallized from isopropyl alcohol-ether to yield 4.3 g. of V, m.p. 238–241°.

Reaction of 2-Methyldecahydroisoquinoline (*cis–trans* **Mixture) with 3-Bromopropyl-N-methylpyrrolidinium Bromide. Preparation of VII and VIII.**—A solution of 11.0 g. (0.07 mole) of the N-methyldecahydroisoquinoline mixture and 20.7 g. (0.07 mole) of 3-bromopropyl-N-methylpyrrolidinium bromide[11] in 50 ml. of acetonitrile was refluxed on the steam-bath for 7 hr. The solid which precipitated from the cooled solution was recrystallized from isopropyl alcohol to give 9.6 g. of white powder, m.p. 188–193°. Two further recrystallizations afforded 2.0 g. of VII, m.p. 218–220°.

Recrystallization of a mother liquor fraction from isopropyl alcohol provided VIII, m.p. 188–189°.

DECATUR, ILL.

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[6] Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill.

[7] A. P. Gray and D. E. Heitmeier, THIS JOURNAL, **80**, 6274 (1958).

[8] M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1728 (1934).

[9] I. M. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

[10] Y. Sawa, K. Inouye and T. Kitamura, *J. Pharm. Soc. Japan*, **63**, 401 (1943); *C. A.*, **44**, 7323^{g} (1950), report b.p. 71–75° (3.5 mm.) for 1-ethyldecahydroquinoline of unspecified configuration, prepared in another way.

[11] A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3648 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

2,4,6-Tri-*p*-chlorophenylpyridine—a By-product of a Fischer Indole Transformation[1]

BY ROBERT B. CARLIN AND LUIS AMOROS-MARIN[2]

RECEIVED JULY 3, 1958

A by-product previously isolated from the Fischer reaction of *p*-chloroacetophenone 2,6-dichlorophenylhydrazone with molten stannous chloride at 260° has now been shown to be 2,4,6-tri-*p*-chlorophenylpyridine. The chief product of this reaction was 2-*p*-chlorophenyl-7-chloroindole, but a small amount of 2-*p*-chlorophenyl-5,7-dichloroindole has also been isolated. A relatively larger amount of the latter compound and a better conversion of the hydrazone to products was observed when stannous chloride–hydrogen chloride replaced stannous chloride as the promoter and when the reaction temperature was 160°, but no triarylpyridine was formed under these conditions. 2,4,6-Tri-*p*-chlorophenylpyridine was also formed, along with 2-*p*-chlorophenyl-7-chloroindole, when *p*-chloroacetophenone *o*-chlorophenylhydrazone was fused with stannous chloride at 300°. The same hydrazone, when heated to 300° with zinc chloride, gave 2-phenylindole as the only crystalline product. *p*-Chloroacetophenone phenylhydrazone gave only 2-*p*-chlorophenylindole and no triarylpyridine when fused with stannous chloride at 260°. An unexpected stability of *p*-chloroacetophenone *o*-chlorophenylhydrazone was demonstrated when 33% of it was recovered unchanged after an hour's treatment with stannous chloride at 260°.

An investigation of the action of molten stannous chloride on the 2,6-dichlorophenylhydrazones of five ketones disclosed that each reaction yielded a 7-chloroindole but that a by-product could be isolated in only one instance; *p*-chloroacetophenone

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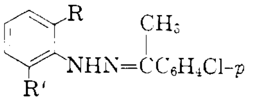
[1] Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology.

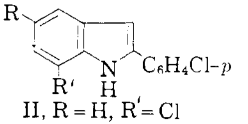
[2] American Viscose Corp. Fellow, 1954–1955.

2,6-dichlorophenylhydrazone gave 2-*p*-chlorophenyl-7-chloroindole in 6% yield plus an 11% yield of a crystalline substance (A), m.p. 262°, whose analytical values corresponded to the empirical formula $C_{24}H_{18}NCl_3$.[3] At that time this by-product was observed to give a negative Ehrlich test,[4] but no effort was made to establish its structure. The investigation described here was undertaken in an effort to prove the structure of the by-product (A) and if possible to show how it was formed. Some incidental observations on Fischer reactions of several *p*-chloroacetophenone arylhydrazones under various conditions are also recorded.

Repetition of the original experiment in which the hydrazone I was heated at 240–260° with molten stannous chloride produced chiefly intractable tars; however, small amounts of three crystalline solids could be separated and purified by fractional crystallization and chromatography. Two of the products, the indole II and the by-product (A), had been isolated during the earlier investigation,[3] but the third, 2-*p*-chlorophenyl-5,7-dichloroindole (III), had not been isolated before from the products of this reaction. The structures of the two indoles II and III were established by mixed melting point determinations with authentic samples.[3,5]



I, R = R' = Cl
IV, R = H, R' = Cl
V, R = R' = H



II, R = H, R' = Cl
III, R = R' = Cl
VI, R = R' = H

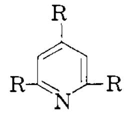
In the hope that a successful Fischer transformation of I at lower temperatures might produce more crystalline product and less tar and that hydrogen chloride–stannous chloride might promote the reaction at lower temperatures than those required when stannous chloride alone was employed, we treated I with the acid complex. Reaction occurred at 160°, but the crystalline product, obtained in 20% yield, comprised II and III in about 3:1 ratio, and no by-product (A) could be isolated. It is curious that in the presence of hydrogen chloride, which with stannous chloride constitutes a source of hydrogen for reduction, compound I gave relatively more halogen migration product III and relatively less reduction product II than were formed in the presence of stannous chloride alone.

Careful purification of A yielded a sample melting at 269–270°. Analysis of this sample accorded with the formula $C_{23}H_{14}NCl_3$ rather than with the one derived in the earlier work.[3] However, either formula suggested the possibility that only the ketone portion of I took part in the formation of A. This possibility was tested by heating *p*-chloroacetophenone *o*-chlorophenylhydrazone (IV) with stannous chloride at 300°, and the venture was rewarded when 2.2 g. of A, along with a 20% yield of the anticipated indole II, was isolated from 64 g. of IV. Analysis of a purified specimen of A derived from this source confirmed the formula $C_{23}H_{14}NCl_3$. Incidentally, the quite unexpected stability of the hydrazone IV was demonstrated in one experiment in which it was recovered unchanged in 33% yield after an hour's heating with stannous chloride at 260°. An attempt also to form A by heating *p*-chloroacetophenone phenylhydrazone (V) with stannous chloride at 300° failed; the only detectable product was 2-*p*-chlorophenylindole (VI), obtained in 65% yield.

In an attempt to discover whether zinc chloride could replace stannous chloride as the promoter of the formation of A, the hydrazone IV, which had produced the largest amount of A when heated with stannous chloride, was heated to 300° with zinc chloride. The appearance of the resulting reaction mixture was uncommonly forbidding; indeed, charcoal was the chief product. Nevertheless, a crystalline product was isolated in 4% yield which was proved by its analytical values and by its melting and mixed melting point behavior to be 2-phenylindole. The means employed by the hydrazone IV to rid itself of both of its chlorine atoms while undergoing this transformation remains obscure.

The ultraviolet and infrared absorption spectra of A were altogether different from those of known[3,6] halogenated 2-phenylindoles. The infrared spectrum, measured in chloroform solution, showed no sharp band at about 2.90 μ, so characteristic of N–H stretching in the halogenated 2-phenylindoles; in fact, there were no absorption bands of any significance at wave lengths below 6 μ. The number and character of the bands in the 6-7.5 μ region bore some resemblance to those of some simple derivatives of pyridine.

Riehm[7] had observed that boiling acetophenone reacts with ammonia in the presence of phosphorus pentoxide to form 2,4,6-triphenylpyridine and 1,3,5-triphenylbenzene. Inasmuch as the evidence suggested that A was formed from the *p*-chloroacetophenone portion of I and IV, since ammonia was certainly being introduced into the reaction mixture as a result of the Fischer reactions that always accompanied the formation of A and because an acidic reagent was also present when A was formed, the formation of 2,4,6-tri-*p*-chlorophenylpyridine (VII) from either I or IV during their Fischer reactions then appeared to be quite possible. The fact that the analytical values obtained from samples of A derived from I and from IV agreed unusually well with those calculated for VII left little doubt that A had that structure. The final proof was supplied by an independent synthesis of VII and the identification of the synthetic product with A by their melting and mixed melting points and by the essential identity of their infrared absorption spectra.[8]



VII, R = *p*-C_6H_4Cl

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[3] R. B. Carlin, J. G. Wallace and E. E. Fisher, THIS JOURNAL, **74**, 990 (1952).

[4] L. H. Chernoff, *Ind. Eng. Chem., Anal. Ed.*, **12**, 273 (1940).

[5] R. B. Carlin and E. E. Fisher, THIS JOURNAL, **70**, 3421 (1948).

[6] R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).

[7] P. Riehm, *Ann.*, 1 (1887).

[8] L. Amoros-Marin and R. B. Carlin, THIS JOURNAL, **81**, 733 (1959).

Although the conditions that led to the formation of VII from I or IV were similar to those used by Riehm[7] to convert acetophenone into 2,4,6-triphenylpyridine, the fact that Riehm also isolated 1,3,5-triphenylbenzene whereas we detected none of this substance suggests that different mechanisms may be operative. The observation that stannous chloride apparently is required for the formation of VII from I or IV must also be explained by any satisfactory mechanism. At least three different mechanisms may now be written which accord with the currently available information; however, a detailed search of the reaction mixtures to discover whether (a) methane and/or ammonia are evolved, (b) *p*-chlorobenzaldehyde is formed and (c) dypnone and/or dihydrodypnone derivatives are present must be carried out before any suggested mechanism can be based on more than speculation.

Experimental[9]

2,4,6-Tri-*p*-chlorophenylpyridine. A. From *p*-Chloroacetophenone 2,6-Dichlorophenylhydrazone (I).—In portions, 28 g. of I[5] was added to 140 g. of molten stannous chloride, and the mixture was then heated for 30 minutes at 240–260°. The cooled mixture was digested for 3 hours with 1 l. of 2% hydrochloric acid on the steam-bath, and the acid-insoluble material was collected by filtration and dissolved in benzene. The dried (Drierite) benzene solution was allowed to trickle through a 2-in. column of activated alumina (80–200 mesh), the benzene was removed and the residue was dissolved in boiling ether. When cooled the ether solution deposited 0.52 g. of a white crystalline solid, m.p. 258–262°. Repeated recrystallizations from acetone afforded a sample of **2,4,6-tri-*p*-chlorophenylpyridine (VII)**, m.p. 269–270°. Its identity with a synthetic specimen is established in the accompanying paper.[8]

Anal. Calcd. for $C_{23}H_{14}NCl_3$: C, 67.25; H, 3.44; N, 3.41; Cl, 25.90. Found: C, 67.27; H, 3.59; N, 3.49; Cl, 25.95.

The ether filtrate from the triarylpyridine was concentrated, and the residue was sublimed at 1 μ. The sublimate comprised 5.8 g. of a yellow crystalline solid from which 0.77 g. of **7-chloro-2-*p*-chlorophenylindole (II)**, m.p. 125–126°, was obtained by repeated recrystallizations from ethanol. A sample failed to depress the m.p. of an authentic specimen[3] when the two were mixed. The mother liquors from II were concentrated, and the residue was dissolved in benzene to make a 2% solution, which was chromatographed onto a 25-cm. column of activated alumina, and the chromatogram was developed with more benzene. The first 500 ml. of eluate, after evaporation of the benzene, yielded a solid, m.p. 115–122°, but the second fraction similarly treated gave 0.06 g. of crystalline material, m.p. 147–150°. Recrystallization from mixed heptanes afforded white needles, m.p. 164–165°, undepressed when mixed with authentic[5] **5,7-dichloro-2-*p*-chlorophenylindole** (III).

B. From *p*-Chloroacetophenone *o*-Chlorophenylhydrazone (IV).—A mixture of 64 g. of IV[5] and 300 g. of anhydrous stannous chloride was heated for 2 hours at 300°. Treatment of the reaction mixture in accordance with the procedure described in part A gave 2.7 g. of a white crystalline solid, m.p. 260–264°, and recrystallization from acetone afforded white needles, m.p. 269–270°. Mixed melting point determinations with a sample prepared as described in part A and with a synthetic specimen[8] of **2,4,6-tri-*p*-chlorophenylpyridine (VII)** revealed no depressions.

Anal. Calcd. for $C_{23}H_{14}NCl_3$: C, 67.25; H, 3.44; N, 3.41; Cl, 25.90. Found: C, 67.38; H, 3.61; N, 3.41; Cl, 25.55.

The dark, oily residue that remained after evaporation of the ether from the filtrate from the triarylpyridine was dissolved in hot chloroform. This solution when cooled deposited 13.1 g. (20%) of a crystalline material which, after recrystallization from chloroform, melted at 122–125°, undepressed when a sample was mixed with authentic[3] **2-*p*-chlorophenyl-7-chloroindole** (II).

The Fischer reaction of *p*-Chloroacetophenone 2,6-Dichlorophenylhydrazone (I) Promoted by Stannous Chloride–Hydrogen Chloride.—A stirred slurry of 152 g. of anhydrous stannous chloride in 800 ml. of anhydrous ether was treated for 3 hours with dry hydrogen chloride; then 40 g. of I was added, and the mixture was stirred overnight. An Ehrlich test[4] was negative. The ether was removed, and the residue was heated at 150–160° for 10 minutes. The dark, tarry mixture was digested with hydrochloric acid and the acid-insoluble portion dissolved in benzene in accordance with the procedure described above. The benzene extract was allowed to pass through a 2-in. alumina column, the benzene was removed from the filtrate, and the residue was subjected to sublimation at 1 μ. The sublimate, a crystalline solid weighing 8 g., was recrystallized from mixed heptanes, from which it appeared as a yellowish solid, m.p. 115–121°. Both the crystalline material and mother liquor were subjected to chromatography on alumina. The substance to be chromatographed was first dissolved in a mixture of mixed heptanes and benzene (4:1 to 6:1), and the solution was allowed to run through the column; then development was carried out with mixed heptane–benzene mixtures increasingly rich in benzene and finally with benzene–methanol. This procedure separated the mixtures into fractions melting in the range 121–128°, which could readily be recrystallized from ethanol to yield pure **2-*p*-chlorophenyl-chloroindole (II)**, m.p. and mixed m.p. 125–126°; and fractions that were more highly adsorbed on alumina, melting in the range 156–165°, from which pure **2-*p*-chlorophenyl-5,7-dichloroindole (III)**, m.p. and mixed m.p. 164–165°, could be obtained by recrystallization from mixed heptanes. The chromatograms gave II and III in about 3:1 molar ratio. No triarylpyridine was discovered either in the chromatographic work or by treating the residue from the original benzene extracts with ether.

Recovery of *p*-Chloroacetophenone *o*-Chlorophenylhydrazone (IV) after Exposure to Molten Stannous Chloride.—In portions 62 g. of IV was added to 300 g. of molten stannous chloride at 260°. Treatment of the cooled mixture in accordance with the standard procedure described above gave 22 g. (33%) of an ether-insoluble fraction, from which long, white needles, m.p. 80–82°, were obtained after recrystallization from petroleum ether (b.p. 60–110°). A mixture of this material and IV showed no m.p. depression. The ether-soluble material from the fusion reaction gave a positive Ehrlich test, but no effort was made to isolate an indole.

2-Phenylindole from the Reaction of *p*-Chloroacetophenone *o*-Chlorophenylhydrazone (IV) with Zinc Chloride.—An intimate mixture of 25 g. of IV with 125 g. of anhydrous zinc chloride was heated at 300° for 15 minutes. The cooled product, which resembled charcoal, was given the usual hydrochloric acid digestion and benzene extraction. The residue remaining after evaporation of the benzene was subjected to sublimation at 1 μ, and the sublimate (1 g.) was recrystallized from petroleum ether (b.p. 60–110°). The product formed white prisms, m.p. 186–187°, alone or when mixed with an authentic sample.[10]

Anal. Calcd. for $C_{14}H_{11}N$: C, 87.05; H, 5.69; N, 7.25. Found: C, 86.74; H, 5.75; N, 7.43.

Absorption Spectra.—The ultraviolet absorption spectrum of **2,4,6-tri-*p*-chlorophenylpyridine**, measured in ethanol solution by means of a Beckman model DU spectrophotometer, showed maxima at 260 and 320 mμ (ϵ 55,000 and 11,300, respectively) and minima at 230 and 303 mμ (ϵ 18,500 and 9,100, respectively). Its infrared absorption spectrum, measured in chloroform solution at about 20 mg./ml. concentration by means of a Perkin–Elmer model 21 double beam infrared spectrophotometer equipped with sodium chloride optics, showed the following bands (in microns): 6.23i, 6.33m, 6.47i, 6.70i, 7.05m, 7.23m, 8.88w, 9.15i, 9.86i, 11.33w, 12.17i.

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(9) Melting points are corrected.

(10) R. L. Shriner, W. C. Ashley and E. Welch, "Organic Syntheses," Coll. Vol. 111, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 725.