(I^{131}) in day-old white leghorn chicks[6] fed a low-iodine starter mash,[7] a modification of that described by Shellabarger.[8] The minimally effective dose of the U.S.P. standard by this method is 10 milliunits. Assays were carried out using 2 dose levels of unknowns with 2 or 3 dose levels of the U.S.P. standard, 5 to 8 chicks per group.

Once purified, TSH can be readsorbed providing the excess cations are removed by dialysis, and by this means the specific activity of the final preparation can be further enhanced. The system also has been found to operate in batch preparation and is capable of removing TSH activity from other purified anterior pituitary hormone preparations. The finer mesh carboxylic cation exchange resin XE-64 also has been used but found to possess no apparent advantages over IRC-50 with respect to capacity for TSH activity.

Other investigators[9] working independently have recently reported to us that they have obtained similar reversible adsorption of TSH activity with IRC-50.

[6] White leghorn chicks were obtained from the Hall Bros. Hatchery Inc., of Wallingford, Conn.

[7] Low-iodine starter mash was furnished by the Wirthmore Feeds through the courtesy of Dr. W. A. Glista.

[8] C. J. Shellabarger, *J. Applied Physiol.*, **6**, 721 (1954).

[9] R. W. Bates and P. G. Condliffe, personal communication.

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The Mode of Hydrolysis of Tetraalkyl Titanates

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It was of interest to determine the mode of hydrolysis of the tetraalkyl titanates. The hydrolysis may occur either by cleavage of the C–O– bond by S$_N$1 or S$_N$2 attack or by cleavage of the Ti–O– bond by attack of water along the coördinate axis of titanium.

That S$_N$1 attack does not occur has been shown by Cullinane and co-workers[1] who obtained isobutyl alcohol on hydrolysis of tetraisobutyl titanate. If S$_N$1 attack has occurred, isomerization of the primary carbonium ion would have led to the isolation of *sec*-butyl alcohol.

Due to the nature of the neopentyl system[2] it was felt that investigation of hydrolysis of tetraneopentyl titanate would distinguish between cleavage of the C–O– bond and cleavage of the Ti–O– bond by attack along the coördinate axis of titanium. If the attack of water is along the coördinate axis of titanium, with subsequent breaking of the Ti–O– bond, then the alcohol produced will be neopentyl alcohol. However, if the C–O– bond is broken, then a rearrangement of the carbon skeleton will occur with the formation of isoamyl alcohol.

Accordingly, tetraneopentyl titanate was triturated with water and the alcohol produced separated from the resulting titanium dioxide. The solid alcohol gave an infrared curve identical with that of an authentic sample of neopentyl alcohol. Thus the attack of hydrolytic reagents on titanium alkylates must proceed along the coördinate axis of titanium with subsequent cleavage of the titanium–oxygen bond.

Experimental

Materials.—The trimethylacetic acid was obtained from Eastman Kodak Co. and the tetraisopropyl titanate from E. I. du Pont Co.

Neopentyl Alcohol.—Trimethylacetic acid was reduced to neopentyl alcohol with $LiAlH_4$,[3] m.p. 51–53°, in 85% yield.

Tetraneopentyl Titanate.—Neopentyl alcohol (88.15 g., 1.0 mole) and titanium tetraisopropylate (71.0 g., 0.25 mole) were mixed together and allowed to stand overnight. The mixture was fractionally distilled and a fraction boiling at 130–132° at 1 mm. was collected. This material solidified immediately in the collecting flask. It weighed 62 g. and melted at 58–60°.

Anal. Calcd. for $C_{20}H_{44}O_4Ti$: Ti, 12.1. Found: Ti, 12.7.

Hydrolysis of Tetraneopentyl Titanate.—Tetraneopentyl titanate (7.93 g., 0.02 mole) was triturated with 25 ml. of water for one hour. The mixture was extracted with ether and the ether layer dried over anhydrous sodium sulfate.

After filtering from the sodium sulfate the ether solution was fractionally distilled. On removal of the ether and cooling of the residue, a solid weighing 5.2 g. and melting at 51–53° precipitated out.

Comparison of the infrared curve of this material with the infrared curve of an authentic sample of neopentyl alcohol showed that the two are identical.

Acknowledgment.—The authors are indebted to Mrs. Celia M. Jorgensen for the infrared spectra and Drs. Jason Salsbury and John T. Shaw for their interest in this problem.

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[1] N. Cullinane, *et al.*, *J. Soc. Chem. Ind.*, **69**, S 38–40 (1950).

[2] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 317–318.

[3] R. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947).

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Nature of the Organic Base in Reissert Compounds[1]

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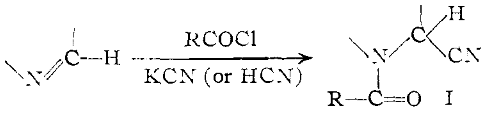
Reissert compounds (I) result from the addition of an acyl and a cyano group to the azomethine linkage of certain N-heterocyclics.[2] However, Gassman and Rupe[3] found that among a variety of



I

quinoline derivatives there was no easily discernible relation between the electronic nature of the substituent and the ability to form a Reissert compound. The series of quinoline bases studied by Rupe is more noteworthy for the examples of failure than success.[4] In addition to quinoline itself, 6-methoxyquinoline[3] and 7-methoxyquinoline[5] have been

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[1] Supported in part by a Cottrell grant from the Research Corporation.

[2] (a) A. Reissert, *Ber.*, **38**, 1603; 3415 (1905); (b) for a complete discussion of "Reissert Compounds" see W. E. McEwen and R. L. Cobb, *Chem. Rev.*, in press.

[3] A. Gassman and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

[4] Quinolines with the following substituents did not give the Reissert compound by the method of Rupe: 2-methyl-, 5-nitro-, 5-amino-, 6-dimethylamino-, 7-nitro-, 8-hydroxy-, 8-methoxy-, 8-benzoyloxy- and 8-acetoxy-.

[5] E. Späth and O. Brunner, *Ber.*, **57**, 1234 (1924).

shown to yield Reissert compounds. Very little work has been reported on the substituted isoquinolines.[2b]

Three new Reissert compounds have been prepared from six heterocyclic bases studied here. They are 1-benzoyl-6-chloro-1,2-dihydroquinaldonitrile (II) from 6-chloroquinoline, 1-benzoyl-6-methyl-1,2-dihydroquinaldonitrile (III) from 6-methylquinoline and 2-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (IV) from 3-methylisoquinoline. When 6-nitroquinoline, 8-nitroquinoline or β-carboline was used no Reissert compound was obtained; the original base was recovered, and an oil, presumed to be phenylglyoxylonitrile dimer, was isolated. Even with these additional examples, other than to point out an obvious steric effect resulting from a substituent in the 2- or 8-position of the quinoline ring, it does not appear possible to generalize on the electronic effects that result in a favorable reaction.

In the three cases where Reissert compounds were obtained they were hydrolyzed in acid solution to give benzaldehyde.[2] The yields of benzaldehyde were found to be as follows: from II (98%), from III (91%), and from IV (95%).

One corollary to the mechanism proposed[2b] for the hydrolysis in which aldehydes are formed from Reissert compounds is the possibility that an acyl group on a nitrogen which is not part of a heterocyclic ring can undergo the same type of cleavage to produce aldehydes. The basic requirement appears to be the juxtaposition of the nitrile group and the amide carbonyl (I). Using this hypothesis the synthesis of an "aliphatic analog" of the Reissert compounds was undertaken. Aniline was cyanomethylated by glycolonitrile and, without attempting to purify the phenylglycinonitrile formed, it was benzoylated by the Schotten–Baumann procedure to give N-benzoyl-N-phenylglycinonitrile (V). Interestingly, V had an ultraviolet absorption spectrum very much like that of 1-benzoyl-1,2-dihydroquinaldonitrile and 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile.[6] There were no definite maxima or minima over the range studied, but compared to the Reissert compound and its dihydro derivative the curve had a considerable hypsochromic shift (of 20 to 35 mμ). The infrared spectrum of V shows an amide carbonyl band at 1660 cm.$^{-1}$, and, again like the Reissert compounds,[2b] it exhibits no absorption for a nitrile group in the region 2100 to 2400 cm.$^{-1}$.

Despite the expectations from the hypothesis and the similarities of V to Reissert compounds in its absorption spectra, the hydrolysis of V in acid solution did not give benzaldehyde; instead benzoic acid was obtained. The reason for the failure of V to yield benzaldehyde is not apparent.

Experimental[7]

1-Benzoyl-6-chloro-1,2-dihydroquinaldonitrile (II).—Powdered 6-chloroquinoline (30 g.), 45 g. of potassium cyanide in 250 ml. of water, and 70 g. of benzoyl chloride reacted by the method of Rupe.[3] The residue, after washing with water, dilute sodium hydroxide and dilute hydrochloric acid, was dissolved in ethanol, and the solution deposited 26 g. (48%) of II as colorless prisms, m.p. 142–143°.

Anal. Calcd. for $C_{17}H_{11}N_2ClO$: C, 69.27; H, 3.76; N, 9.51; Cl, 12.03. Found: C, 69.41; H, 3.73; N, 9.81; Cl, 12.02.

An alternative method for preparing this and several other Reissert compounds was tried, using a solution of 67% dimethylformamide–33% water which dissolved both the heterocyclic base and potassium cyanide. The results in this solvent mixture were inferior to the preparations in water alone.

Hydrolysis of II in concentrated hydrochloric acid gave 98% yield of benzaldehyde, isolated as the 2,4-dinitrophenylhydrazone.[6]

1-Benzoyl-6-methyl-1,2-dihydroquinaldonitrile (III).—This compound was prepared in the manner described for II; III was isolated in 60% yield as colorless prisms, m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.80; H, 5.14; N, 10.22. Found: C, 79.02; H, 5.14; N, 10.52.

The yield of benzaldehyde 2,4-dinitrophenylhydrazone from the hydrolysis of III was 91%.

2-Benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (IV).—Compound IV was prepared like II and was isolated in 66% yield as colorless prisms, m.p. 127–128°.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.80; H, 5.14; N, 10.22. Found: C, 78.78; H, 4.97; N, 10.37.

Hydrolysis of IV yielded 95% of benzaldehyde 2,4-dinitrophenylhydrazone.

Attempted Reaction with 6-Nitroquinoline, 8-Nitroquinoline and β-Carboline.—When each of these compounds was used as the heterocyclic base for the Reissert compound by the method outlined for II, the semi-solid residue obtained gave no product that could be identified with the expected Reissert compound. Treatment of the oily substance with concentrated phosphoric or hydrochloric acid over a period of several days produced no evidence of benzaldehyde. Neutralization of the hydrochloric acid washings in each case yielded considerable amount of the starting quinoline or β-carboline.

The β-carboline Reissert reaction also was run in dimethylformamide with the minimum amount of water added to dissolve the potassium cyanide, but no Reissert compound was obtained.

N-Benzoyl-N-phenylglycinonitrile[8] (V).—To 105 g. of aniline was added 100 ml. of water and 20 ml. of ethanol, and the mixture was heated on the steam-bath with stirring; to this mixture was added 120 g. of a 50% solution of glycolonitrile over a period of 1 hour. The solution was refluxed at 95° for 4 hours longer, and the water was removed by distillation under reduced pressure, leaving a clear red liquid. On cooling overnight the mixture solidified to a crystalline mass, but attempts to recrystallize the N-phenylglycinonitrile from ethanol gave only oils. Portions of the crude phenylglycinonitrile were treated with benzoyl chloride and sodium hydroxide to yield V, which was obtained after several crystallizations from ethanol as colorless crystals, m.p. 101–102°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.08; N, 11.86. Found: C, 76.47; H, 5.17; N, 11.97.

The infrared spectrum of V shows an amide carbonyl band at 1660 cm.$^{-1}$, but no nitrile absorption in the region 2400–2100 cm.$^{-1}$. The ultraviolet absorption spectrum has no characteristic maxima or minima, but in this respect it resembled the spectra of known Reissert compounds,[6] with the expected modification of a strong hypsochromatic shift of the curve of V compared to 1-benzoyl-1,2-dihydroquinaldonitrile.

When N-benzoyl-N-phenylglycinonitrile was warmed with a solution of 2,4-dinitrophenylhydrazine in concentrated hydrochloric acid, benzoic acid was formed but no benzaldehyde.

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(6) W. E. McEwen, R. H. Terss and I. W. Elliott, THIS JOURNAL, **74**, 3605 (1952).

(7) Melting points are uncorrected. Analyses are by Schwarzkopf Microanalytical Laboratory, 56-19 37th Ave., Woodside 77, N. Y.

(8) The directions for the preparation of N-phenylglycinonitrile as well as a sample of glycolonitrile were kindly provided by Dr. V. C. Meunier of Rohm and Haas Co., Philadelphia, Penna.