equiv., 139.7. Found: (b) C, 43.3; H, 7.3; Si, 10.1; sapon. equiv., 144.

*Ester interchange between "poly(hydroxyethoxy)silanes" and dialkyl esters.* "Poly(hydroxyethoxy)silanes" were prepared by treating diethoxydimethylsilane, methyltriethoxysilane or tetraethyl silicate with ethylene glycol. In some cases the excess glycol was distilled under vacuum; in others it was left with the reaction product to serve as a co-reactant. Diethyl oxalate, diethyl phthalate, dimethyl isophthalate, or dimethyl terephthalate were added in amounts equivalent to the total polyols present, and reesterification was carried out under the influence of a catalyst quantity of sodium methylate. Data are shown in Table III.

*Acknowledgment.* The author is indebted to Mr. E. M. Hadsell for precision distillations and to members of the Analytical Chemistry Unit of this Laboratory for ultimate analyses, molecular weights, and infrared spectra.

SCHENECTADY, N. Y.

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[CONTRIBUTION NO. 472 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

# Nuclear Substitution Derivatives of Isonicotinic Acid

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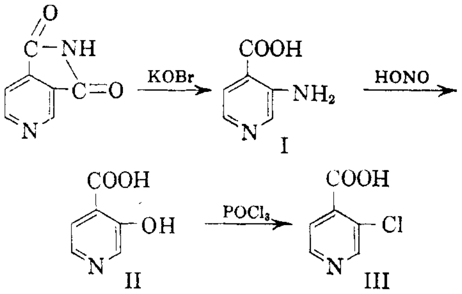
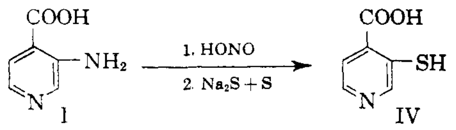
The interaction of isonicotinic acid with thionyl chloride at elevated temperatures in accordance with the Meyer and Graf procedure results in 2-chloroisonicotinic acid. None of the 3-chloroisonicotinic acid reported by Meyer and Graf was isolated.

During the course of investigations into synthetic tuberculostats, 3-hydroxyisonicotinic acid was synthesized[1] in the hope that it would demonstrate anti-tuberculous activity comparable to its benzenoid analog, P.A.S. This hope was not realized but the compound did demonstrate some activity against murine polio (MM strain). To exploit the possibilities presented by this lead, it was decided to prepare a few closely related compounds—notably other hydroxy and mercapto derivatives of isonicotinic acid. The first of these decided on was 3-mercaptoisonicotinic acid. To prepare this compound by what appeared to be the most convenient method, isonicotinic acid was chlorinated with thionyl chloride according to the method of Meyer and Graf[2] to give what they reported to be 3-chloroisonicotinic acid. On treatment of the latter with potassium hydrogen sulfide the desired 3-mercapto compound should be obtained.

This was done and a mercapto compound was isolated which analyzed correctly but which melted with decomposition at 299° (corrected) and gave no color reaction with ferric chloride. According to Sucharda and Troszkiewicz,[3] however, 3-mercaptoisonicotinic acid melts at 255° and gives a blue color with ferric chloride. To resolve this apparent discrepancy, an authentic sample of 3-aminoisonicotinic acid I prepared from chinchomeronimide by means of a Hofmann degradation[4] was diazotized and converted to the corresponding 3-hydroxy compound II which was in turn converted to 3-chloroisonicotinic acid III.



The melting points of the chloro compound obtained by the Meyer and Graf procedure[2] (235–236°) and that of the authentic 3-chloro compound III (228–229°) were too close to be useful for differentiation, but a mixture of the two gave a markedly depressed melting point at 204°. It appeared, therefore, that the chloro compound obtained by the Meyer and Graf procedure as applied in this laboratory could not be 3-chloroisonicotinic acid. This was confirmed by converting an authentic sample of 3-aminoisonicotinic acid to the corresponding 3-mercapto compound IV by the method of Sucharda and Troszkiewicz.[3] The mercapto compound so obtained melted at 265° (Sucharda and Troszkiewicz reported 255°) and gave a blue color with ferric chloride. Moreover, a mixture of the mercapto compound originating *via* the Meyer and Graf procedure and compound IV gave a depressed melting point at 216°.



Under normal circumstances, the evidence presented above would have sufficed to show that

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(1) H. H. Fox, *J. Org. Chem.*, **17**, 542 (1952).

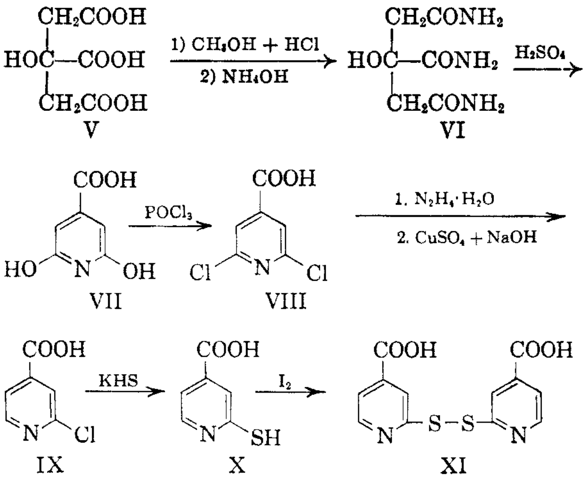
(2) H. Meyer and R. Graf, *Ber.*, **61B**, 2213 (1928).

(3) E. Sucharda and C. Troszkiewicz, *Roczniki Chem.*, 12, 493 (1932).

(4) S. Gabriel and J. Coleman. *Ber.*, **35**, 2832 (1902).

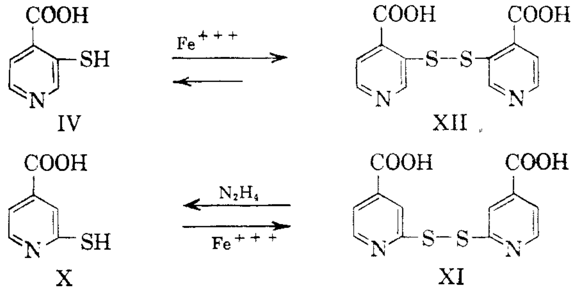
Meyer and Graf[2] had erred in assigning the 3-chloro structure to their compound and that indeed the compound they obtained was most probably 2-chloroisonicotinic acid. However, analysis of the evidence presented by Meyer and Graf for their choice of structure showed that theirs was not a casual judgment which could be lightly dismissed but was strongly based on carefully weighed experimental data which presented no obvious flaw. Certainly the situation called for more data before the issue could be resolved.

Some additional data were obtained from a parallel experiment which was designed to produce 2-mercaptoisonicotinic acid starting with citric acid. In this experiment, citric acid V was converted *via* the triamide VI to citrazinic acid VII[5] which, on treatment with phosphorus oxychloride, gave 2,6-dichloroisonicotinic acid VIII.[6] The dichloro compound was dechlorinated by means of hydrazine and copper sulfate to 2-chloroisonicotinic acid IX.[7,8] Treatment of the latter with potassium hydrogen sulfide should give the desired 2-mercaptoisonicotinic acid X.

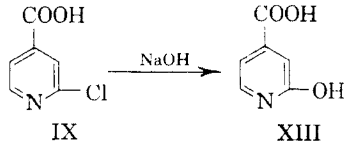


The 2-chloro compound IX thus prepared melted at 240–241° and in mixed melt with the chloro compound obtained by the Meyer and Graf procedure gave no significant depression. Similarly, the mercapto compounds derived from both chloro compounds were identical in terms of melting points, mixed melting point, and in the fact that neither of them produced a color complex with ferric chloride. Upon oxidation with iodine solution, both produced disulfides XI which melted at 277° (corr.) alone and when mixed. It is apparent therefore that chlorination of isonicotinic acid with thionyl chloride under the conditions used in this laboratory produced 2-chloroisonicotinic acid IX instead of the 3-chloro compound reported by Meyer and Graf and that the mercapto compound obtained from it was in fact the 2-mercapto derivative. This satisfactorily accounts for the absence of the typical phenolic color reaction with ferric chloride reported by Sucharda and Troszkiewicz since only hydroxy or mercapto groups in the 3 position give such reactions in this series.

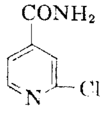
In addition to the color reaction with ferric chloride, there is another significant difference between the 2-mercaptoisonicotinic acid X and the 3-mercapto isomer IV. Both are readily oxidized to the disulfide with mild oxidants such as ferric ion or iodine but the 2-disulfide is so easily reduced that even solution in alkali causes some of it to convert spontaneously to the mercaptan—which seems to be the more stable form. The 3-disulfide XII on the other hand is extremely stable to reducing agents and cannot easily be reduced.



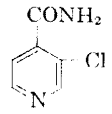
Treatment of the 2-chloro compound IX with concentrated sodium hydroxide for several hours at reflux temperature yields the corresponding hydroxy derivative XIII which gives no color test with Fe+++ and does not melt under 320°. A mixture with the 3-hydroxy compound II melted with decomposition at 284–285.5° (corr.).



The 2-chloroisonicotinic acid prepared by the dechlorination of 2,6-dichloroisonicotinic acid VIII and that prepared by the chlorination of isonicotinic acid both gave amides XIV which were identical (m.p. 201–203° corr.) and which differed from 3-chloroisonicotinamide XV; m.p. 165–167° (corr.).



XIV



XV

Similarly, methyl 2-chloroisonicotinate XVI was obtained in the form of white needles melting at 33–34° (which is reasonably in accord with the melting point of 30–31° reported by Baumler, *et*

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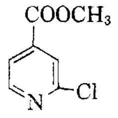
(5) A. Behrmann and A. W. Hofmann, *Ber.*, **17**, 2684 (1884).

(6) K. Bittner, *Ber.*, **35**, 2933 (1902).

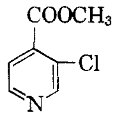
(7) E. Thielepape and O. Spreckelsen, *Ber.*, **55**, 2929 (1922).

(8) J. Buchi, P. Labhart, and L. Ragaz, *Helv. Chim. Acta*, **30**, 507 (1947).

*al.*[9]) whereas the methyl 3-chloroisonicotinate XVII occurred as an oil which would not solidify at well below room temperature. It is interesting to note that the methyl ester of the chloro compound reported by Meyer and Graf[2] melted at 32° which corresponds to the 2-chloro rather than the 3-chloro derivative. This fact and the fact that the melting point of the chloroisonicotinic acid reported by Meyer and Graf corresponds more closely with that of 2-chloroisonicotinic acid are the only intrinsic pieces of evidence presented by the German workers which suggest that they may be in error. All the rest of their evidence appears unassailable except by direct experimental investigation. In effect, therefore, the data presented above strongly indicate—but do not prove—that they may, in fact, have obtained the 2-chloro rather than the 3-chloroisonicotinic acid. What has been unequivocally established is that the interaction of isonicotinic acid and thionyl chloride in substantial accordance with the procedure of Meyer and Graf does produce a 2-chloro derivative. Since the reaction is accompanied by many side reactions it is not impossible that both monochloro derivatives are formed and that the one isolated by Meyer and Graf was indeed the 3-chloro compound.



XVI



XVII

The synthesis of the new compounds is detailed in the Experimental.

## EXPERIMENTAL

All melting points are corrected.

*3-Chloroisonicotinic acid* (III). A mixture of 1 g. of 3-hydroxyisonicotinic acid and 10 cc. of phosphorus oxychloride was heated in a sealed tube at 140° for 16 hr. The excess phosphorus oxychloride was removed under vacuum to leave a thick oily residue which was dissolved in warm water. The clear solution was evaporated to dryness under vacuum and the solid residue recrystallized from isopropyl alcohol to give the desired product in the form of white feathery crystals which melted at 228–229°. A mixture with the chloro compound obtained by chlorinating isonicotinic acid with thionyl chloride melted at 204°.

*Anal.* Calcd. for $C_6H_4NO_2Cl$: C, 45.7; H, 2.5. Found: C, 46.2; H, 2.3.

*3-Chloroisonicotinamide* (IV). A mixture of 2 g. of 3-hydroxyisonicotinic acid and 10 cc. of phosphorus oxychloride was allowed to react as described above except that concentrated ammonium hydroxide was carefully added to the oily residue left after the removal of the phosphorus oxychloride. The resulting precipitate was recrystallized successively from water, ethyl acetate-benzene mixture and from water again to yield yellow spires which melted at 165–168°.

Anal. Calcd. for $C_6H_5N_2OCl$: C, 46.0; H, 3.2. Found: C, 45.7; H, 3.1.

*Methyl 3-chloroisonicotinate* (XVII). A mixture of 7 g. of 3-hydroxyisonicotinic acid and 25 cc. of phosphorus oxychloride was heated at 140° for about 20 hr. The residue left on removal of the phosphorus oxychloride was treated with methanol and the methanol then removed. The resulting residuum was dissolved in a little water and the solution was saturated with anhydrous potassium carbonate. The oily layer was extracted with ether; the ether solution was dried over potassium carbonate (anhyd.), treated with decolorizing carbon, filtered, and distilled to yield a colorless oil which distilled at 70–75°/0.1 mm. $n_D^{20}$ 1.53425.

Anal. Calcd. for $C_7H_6NO_2Cl$: C, 49.0; H, 3.5. Found: C, 48.7; H, 3.9.

The oil solidified in the cold but melted well below room temperature.

*2-Mercaptoisonicotinic acid* (X). To a pressure tube containing 14 g. of potassium hydrogen sulfide (solid) and 75 cc. of ethanol, was added portionwise, 10 g. of 2-chloroisonicotinic acid; $H_2S$ was evolved. The mixture was warmed until most of the $H_2S$ was removed, the tube was sealed and then heated at 150° for 24 hr. The reaction mixture was evaporated to dryness and the residue dissolved in water and acidified with HCl to *p*H 2. On cooling strongly, an orange precipitate was obtained which was dissolved in hot methanol and filtered to remove a small quantity of insoluble yellow material. A further quantity of the yellow material which settled out of the methanol solution on cooling was removed and the solution was evaporated to dryness to yield an orange residue which on recrystallization from water was obtained in the form of orange diamonds; m.p. (dec.) 299°.

*Anal.* Calcd. for $C_6H_5NO_2S$: C, 46.4; H, 3.2; S, 20.6. Found: C, 46.5; H, 3.3; S, 20.4.

*2,2'-Dithiodiisonicotinic acid* (XI). To a solution of 2-mercaptoisonicotinic acid (X) in hot water was added iodine in potassium iodide solution until a faint iodine color remains. As the iodine was added the disulfide precipitated as a white microcrystalline solid which was insoluble in all solvents except alkali. The product was filtered off, washed with hot water, and dried to give a fine white powder which decomposed at 277°.

*Anal.* Calcd. for $C_{12}H_8N_2O_4S_2$: C, 46.7; H, 2.6. Found: C, 46.9; H, 2.9.

*2-Chloroisonicotinamide* (XIV). A mixture of 1 g. of 2-chloroisonicotinic acid and 10 cc. of thionyl chloride was refluxed for 0.5 hr. The excess thionyl chloride was removed under vacuum and the residue was treated carefully with concentrated ammonium hydroxide to give the desired product. Upon recrystallization from methanol using decolorizing carbon, it was obtained in the form of fine white needles; m.p. 201–203°.

*Anal.* Calcd. for $C_6H_5N_2OCl$: C, 46.1; H, 3.2. Found: C, 46.2; H, 3.2.

*Acknowledgment.* The authors are indebted to Dr. A. Steyermark and his staff for the microanalysis and to Mr. M. Stefaniw for technical assistance.

NUTLEY, N. J.

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(9) J. Baumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 496 (1951).