Anal. Calcd. for $C_{11}H_{13}O_5N_5S$: N, 21.39. Found: N, 21.16.

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RECEIVED MARCH 4, 1948

The Chlorination of Isophthaloyl and Terephthaloyl Chloride

BY NORMAN RABJOHN

The chlorination of isophthaloyl and terephthaloyl chloride in the presence of iron leads to 5-chloroisophthaloyl chloride and 2,3,5,6-tetrachloroterephthaloyl chloride, respectively. The latter compound, due to its highly hindered structure, shows considerable stability toward reagents which are capable of attacking an acid chloride. The chlorinated phthaloyl chlorides have been converted to a number of derivatives.

Experimental

5-Chloroisophthaloyl Chloride.—A mixture of 144 g. of isophthaloyl chloride and 5 g. of iron filings was treated with chlorine at 95–100° until there was no further increase in weight. The reaction mixture was diluted with carbon tetrachloride and filtered. The filtrate was concentrated and distilled *in vacuo.* There was obtained 137 g. of material which boiled at 165–175° (22 mm.). This was redistilled through a 20″ packed column; the main fraction boiled at 126–128° (4 mm.); sapn. equiv. calcd. for $C_8H_3O_2Cl_3$, 118.8; found, 118, 120.

5-Chloroisophthalic Acid.—A mixture of 16 g. of 5-chloroisophthaloyl chloride and 100 cc. of 10% sodium hydroxide solution was warmed on a steam-bath for five hours. The solution was filtered and acidified with concentrated hydrochloric acid. The white precipitate was removed by filtration and dried, weight 11 g. After crystallization from water it melted at 278–280° (lit.[1] 279–280°).

Dimethyl 5-Chloroisophthalate.—Five grams of 5-chloroisophthaloyl chloride was dissolved in 50 cc. of methanol. The initial heat of reaction was removed by cooling and then the reaction mixture was warmed on a steam-bath for one-half hour. The excess methanol was evaporated and the residue was crystallized from dilute methanol: m. p. 80–81° (lit.[1] 79–80°).

Anal.[2] Calcd. for $C_{10}H_9O_4Cl$: C, 52.52; H, 3.94. Found: C, 52.70; H, 4.01.

5-Chloroisophthalamide.—Ten grams of 5-chloroisophthaloyl chloride was mixed with 100 cc. of aqueous ammonia and an immediate reaction occurred. The reaction mixture was allowed to cool and the precipitate removed by filtration. It was washed with water and dried, weight 8 g. After crystallization from alcohol, the fine, white crystalline solid melted at 254–255°.

Anal. Calcd. for $C_8H_7O_2N_2Cl$: C, 48.36; H, 3.53. Found: C, 48.55; H, 3.69.

2,3,5,6-Tetrachloroterephthaloyl Chloride.—A mixture of 215 g. of terephthaloyl chloride and 5 g. of iron filings was heated at 175°. Chlorine was passed into the mixture until there was no further increase in weight. The reaction mixture was dissolved in carbon tetrachloride and filtered. The filtrate was treated with Norite and cooled; a pink colored solid resulted, m. p. 133–137°. The mother liquor was concentrated and more material was obtained. The total weight of product was 223 g. Recrystallization from carbon tetrachloride yielded a white crystalline solid which melted at 144–145°. A small sample was sublimed for analysis.

Anal. Calcd. for $C_8O_2Cl_6$: C, 28.15; Cl, 62.46. Found: C, 28.40; Cl, 62.52.

2,3,5,6-Tetrachloroterephthalic Acid.—A mixture of 10 g. of 2,3,5,6-tetrachloroterephthaloyl chloride and 200 cc. of 10% sodium hydroxide solution was refluxed for twelve hours. The solution was filtered and acidified with concentrated hydrochloric acid. The white precipitate was removed by filtration and dried; weight 8.5 g. It was crystallized from water; m. p. 343–345° (dec.). Qvist and Holmberg[3] have stated that 2,3,5,6-tetrachloroterephthalic acid melts with decomposition at about 330°. Neut. equiv. calcd. for $C_8H_2O_4Cl_4$: 152. Found: 153.

Dimethyl 2,3,5,6-Tetrachloroterephthalate.—A mixture of 10 g. of 2,3,5,6-tetrachloroterephthaloyl chloride and 300 cc. of methanol was refluxed for ten hours. After standing for four days at room temperature, a white crystalline precipitate had formed; m. p. 153–155°. The mother liquor was concentrated and a total of 9.3 g. of material was obtained. After crystallization from methanol, the ester was obtained in the form of long, white needles; m. p. 154–155°.

Anal. Calcd. for $C_{10}H_6O_4Cl_4$: C, 36.15; H, 1.81. Found: C, 36.31; H, 1.74.

2,3,5,6-Tetrachloroterephthalamide.—Ten grams of 2,3,5,6-tetrachloroterephthaloyl chloride was dissolved in 500 cc. of ether and treated with 200 cc. of ether which had been saturated with anhydrous ammonia. A white solid gradually precipitated from solution. More ammonia was added and the mixture was allowed to stand overnight. The ether was removed and the residue was washed with warm water. After drying there was obtained 8 g. of a white powder. It was crystallized from acetic acid; m. p. above 400°.

Anal. Calcd. for $C_8H_4O_2N_2Cl_4$: C, 31.79; H, 1.32. Found: C, 32.15; H, 1.62.

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[1] Bradsher, Gross, Hobbs, Kittila, Rapoport, Tarrant and West, THIS JOURNAL, **70**, 1317 (1948).

[2] Semimicro analyses were carried out by W. C. Hukari.

(3) Qvist and Holmberg, *Acta Acad. Aboensis Math. et Phys.*, **6**, No. 14, 3 (1932).

CONTRIBUTION NO. 152
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AKRON, OHIO

RECEIVED MAY 27, 1948

Steroidal Sapogenins. II. New Derivatives of Kryptogenin[1]

BY G. ROSENKRANZ, ST. KAUFMANN, A. LANDA, J. J. CORONA AND A. OLALDE

At the beginning of our studies on the steroidal sapogenins very little was known about kryptogenin, so our first steps were to characterize this substance sufficiently and to prepare some functional derivatives. Some of the derivatives of kryptogenin have already been described: the diacetate, dioxime, and an amino compound which results from catalytic hydrogenation of the dioxime.[2]

Kryptogenin possesses a 1,4-diketone system and, as is known, the action of hydroxylamine leads to the formation of a dioxime. We have observed that there exists a considerable difference in the reactivity of the two carbonyl groups and that with ketonic reagents other than hydroxylamine mono derivatives are formed, in which

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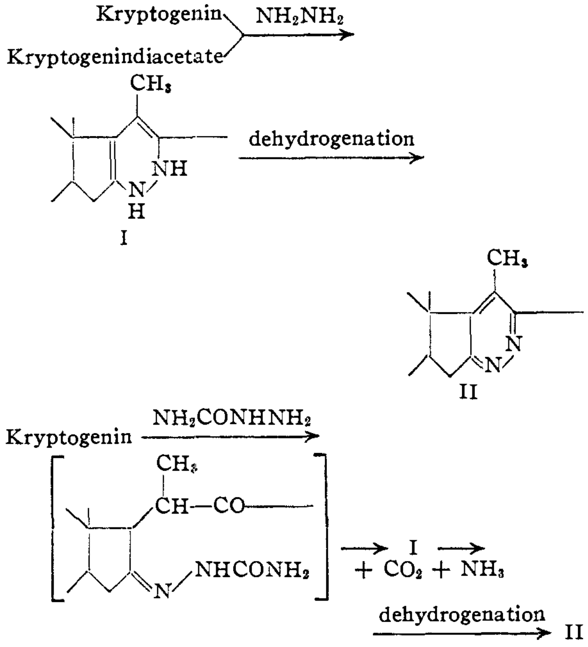
[1] For paper I in this series, see Kaufmann and Rosenkranz, THIS JOURNAL, **70**, 3502 (1948).

[2] F. C. Uhle and W. H. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945); R. E. Marker, *et al.*, THIS JOURNAL, **69**, 2197 (1947).

presumably the ketonic group in position 16 is involved. Thus we were able to prepare the 16-mono-2,4-dinitrophenylhydrazones of kryptogenin, kryptogenin acetate and kryptogenin benzoate.

During our attempts to obtain the hydrazones and the semicarbazones of kryptogenin and its esters, we could observe that the main reactions consisted in the formation of 16-mono derivatives immediately followed in virtually all cases by condensation, resulting finally in the formation of the same compound containing a pyridazine ring (II). The reaction can be illustrated by the formulas



As we planned some oxidation degradation studies of kryptogenin, we also prepared the hydrogen chloride addition product of kryptogenin diacetate with the purpose of temporarily protecting the double bond in the 5,6-position. It was possible to carry out the dehalogenation of this product with acetic acid and potassium acetate with the formation of kryptogenin acetate in good yields. An attempt to prepare ketonic derivatives of the 5-chloro compound[3] failed because simultaneous dehalogenation took place with formation of the dioxime of kryptogenin diacetate. The removal of the acetyl group by saponification also proved unsuccessful, as hydrolysis was always accompanied by simultaneous dehalogenation.

Experimental[4,5]

Kryptogenin Dibenzoate.—This compound is prepared with benzoyl chloride in pyridine. After recrystallization from chloroform–methanol it melts at 184–186°. *Anal.* Calcd. for $C_{41}H_{50}O_6$: C, 77.08; H, 7.89. Found: C, 77.02; H, 8.08.

Kryptogenin 2,4-Dinitrophenylhydrazone.—Five grams of kryptogenin is dissolved in just the necessary amount of ethanol, to which a mixture of 5 g. of 2,4-dinitrophenylhydrazine, 25 cc. of ethanol and 10 cc. of concentrated sulfuric acid is added. An abundant red precipitate settles down immediately, which is filtered and recrystallized from chloroform–benzene, m.p. 263–265°. *Anal.* Calcd. for $C_{33}H_{46}O_7N_4$: C, 64.89; H, 7.59; N, 9.17. Found: C, 64.59; H, 7.44; N, 9.05.

2,4-Dinitrophenylhydrazone of Kryptogenin Diacetate.—This substance is prepared in the same manner as the foregoing dinitrophenylhydrazone; recrystallized from chloroform–methanol, m.p. 189–190°. *Anal.* Calcd. for $C_{37}H_{50}O_9N_4$: C, 63.96; H, 7.26; N, 8.07. Found: C, 63.97; H, 7.44; N, 8.04.

2,4-Dinitrophenylhydrazone of Kryptogenin Dibenzoate.—Prepared as before; recrystallized from chloroform–methanol, m.p. 251.5–252.5°. *Anal.* Calcd. for $C_{47}H_{54}O_9N_4$: C, 68.93; H, 6.65; N, 6.83. Found: C, 69.09; H, 6.79; N, 6.96.

Pyridazine from Kryptogenin.—Ten grams of kryptogenin, 25 cc. of hydrazine hydrate (85% in water) and 125 cc. of carbitol are refluxed for two hours. The reaction vessel is left standing overnight in the ice box. The product, which precipitates, is filtered: m.p. of the crude product 140–153°. A chromatogram over aluminum oxide gives two fractions: (a) eluted with benzene–ether 10:1, m.p. 154–155° and (b) eluted with benzene–ether 1:1, m.p. 215°.

Recrystallization of (b) from ethyl acetate yields a product of melting point 222–223.5°, which, according to the analysis, is the pyridazine of kryptogenin. *Anal.* Calcd. for $C_{27}H_{40}O_2N_2$: C, 76.37; H, 9.49. Found: C, 76.50; H, 9.23.

The fraction (a) of the chromatogram is unstable in air and can be readily oxidized to (b). 0.500 mg. of (a) and 20 cc. of nitrobenzene are refluxed for three hours. The reaction product is next steam-distilled until free of nitrobenzene. A dark brown powder precipitates, which is decolorized with Norit "A" and activated alumina. The resulting product melts at 222–223° and gives no depression with (b). The same pyridazine can be obtained from kryptogenin diacetate and hydrazine hydrate under the same conditions as above.

Pyridazine from Kryptogenin Diacetate.—7.8 g. of semicarbazide hydrochloride and 5.75 g. of sodium acetate are finely ground with 100 cc. of ethanol. The mixture is filtered and the filtrate is added to a solution of 5 g. of kryptogenin diacetate in 100 cc. of ethanol. The mixture is refluxed for a period of twelve to fourteen hours. The reaction product is poured into water and the white precipitate filtered. Chromatography of this product over aluminum oxide in benzene–ether 10:1 gives a substance which, recrystallized from ethyl acetate, melts at 194–195°. The same product is obtained by the acetylation of the diazine from kryptogenin. *Anal.* Calcd. for $C_{31}H_{44}O_4N_2$: C, 73.19; H, 8.72; N, 5.51. Found: C, 73.23; H, 8.72; N, 5.45.

Hydrogen Chloride Addition Product of Kryptogenin Diacetate.—To a solution of 25 g. of kryptogenin diacetate in 50 cc. of pure chloroform is added 50 cc. of glacial acetic acid. The vessel is cooled in a salt-and-ice-bath. Through the cold mixture (0°) a stream of dry gaseous hydrogen chloride is bubbled for two hours. The temperature should be kept at 0°. Next the vessel is firmly closed and is placed in the ice-box for a period of ten days, after which period the excess hydrochloric acid is eliminated *in vacuo* at room temperature. When almost all the hydrochloric acid has disappeared, the reaction mass is poured into water and extracted with chloroform. The extract is first washed with water, then with a 5% solution of sodium bicarbonate and finally with water again to neutrality. The neutral chloroform solution is dried over anhydrous sodium sulfate and distilled to dryness. To the residue pure isopropyl ether is added. Ten grams of deli-

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(3) The position of the chlorine atom is not proved, but in analogy to similar addition reactions it can be assumed to be attached to carbon atom 5.

(4) Microanalysis by Dra. L. Norymberska of the Instituto Politécnico Nacional, México, D. F.

(5) All the melting points are determined on the Kofler micromelting point apparatus.

cate needles is obtained, m.p. 165–168°. After recrystallization from ether–chloroform the m.p. is 172–174°. *Anal.* Calcd. for $C_{31}H_{47}O_6Cl$: C, 67.55; H, 8.59. Found: C 67.53; H, 8.80.

Dehalogenation.—A solution of 500 mg. of 5-chlorokryptogenin diacetate in 5 cc. of glacial acetic acid and 500 mg. of anhydrous potassium acetate is refluxed for one hour. After cooling, the reaction product is poured into water and extracted with ether. The residue left by evaporation of the ethereal solution is crystallized from ethanol, m.p. 147–150°. This product gave no depression with an authentic sample of kryptogenin diacetate.

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MÉXICO, D. F.
RECEIVED JANUARY 30, 1948

Separation of Radium from Barium by the Use of an Ion-exchange Column Procedure[1]

BY EDWARD R. TOMPKINS[2]

In current radium production processes, the radium and barium are separated by fractional crystallization, the method originally developed by the Curie's. This is a very tedious process, which requires many recrystallizations and extensive recycling of the various fractions to obtain a clean separation without excessive losses. To carry out this procedure without endangering the safety of the operating personnel requires considerable remote control equipment, and, because of the large number of operations, contributes appreciably to the present cost of radium.

In the course of extensive investigations of ion-exchange separation methods for the preparation of pure fission products,[3] it was noted that microgram quantities of strontium and barium (two of the fission elements) could be separated readily by this method. The separation, which depends chiefly upon the differences in the dissociation constants of the barium and strontium citrate complexes, was made by first adsorbing the mixture at the top of a bed of synthetic ion-exchange resin, Amberlite IR-1, 100 cm. in length, and subsequently eluting the elements preferentially from this column by the use of complexing agents at carefully adjusted values of *p*H. By exercising considerable care it was possible to effect nearly complete separation of the barium and strontium in these low concentrations, although the separation was much poorer when milligram quantities of these elements were present. The apparatus was simple and was thus easily adaptable to remote control procedures.

Recently samples of several new organic exchangers have been obtained.[4] One of these, Dowex 50, has a much higher combining capacity than any exchanger tested here previously. Because of this it is much more applicable to the separation of ponderable quantities of materials. Extensive studies of this resin for rare earth separations[5,6,7] had shown the importance of using small particle sizes and/or elevated temperature to obtain optimum results. A special sample of colloidal agglomerates of Dowex 50 had proved especially effective for rare earth separations, a column of this resin 10 cm. in length giving a better separation than had been obtained with a 100-cm. column of Amberlite resin under similar conditions.[6]

From these results and the earlier observations regarding the behavior of strontium and barium when eluted from Amberlite resin columns, it appeared that a good separation of barium from radium should be possible by the use of a short column of the new resin. Because of the much greater affinity of Dowex 50 resin for cations (as compared to IR-1), it was necessary to determine the correct conditions for the elution of the alkaline earths from this resin. Whereas the separation with IR-1 had been made by eluting strontium and barium with 0.23 *M* citrate at *p*H 4.75, preliminary experiments with strontium showed that it was necessary to use 0.5 *M* citrate at *p*H 7.5 to 8.0 to remove it from Dowex 50 at a convenient rate. It was also shown that barium and strontium in trace concentrations could be separated by elution from a column of colloidal agglomerates of Dowex 50, 1 sq. cm. × 15 cm.

This column of colloidal agglomerates was next employed to test the separation of barium from radium. The starting solution containing 20μc (20 μg) of radium, 20 mg. of barium with Ba^{140} tracer (and La^{140} daughter) and 20 mg. of strontium with $Sr^{89,90}$ tracer, was first slowly passed through the column, causing the solute mixture to be adsorbed at the top. Ammonium citrate solution, 0.5 *M* (*p*H 7.8), was then passed through the column at a rate of 0.3 ml. per minute, the effluent being monitored by means of a special apparatus consisting of a thin-windowed flow cell facing a mica-windowed Geiger–Mueller counter tube which was attached to a counting rate meter and recorder. By means of this apparatus it was possible to obtain a continuous record of the concentration of the β- and γ-emitters in the effluent from the column. A reproduction of this recorded curve is shown by the solid, curved line in Fig. 1.

Fractions of the effluent solution were collected as indicated on this curve (I to XVIII), and aliquots were counted for α, β and γ activity. Aluminum absorption and decay curves of these radioactivities were taken, as a method of determining the composition of each fraction. From these results the approximate composition of the various fractions and the percentage of each element

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[1] This work was done at Clinton Laboratories (renamed Oak Ridge National Laboratory), a part of the Plutonium Project, during June, 1947, and was done under Contract W-35-058-eng-71 for the Atomic Energy Project.

[2] Present address: 1834 University Ave., Berkeley, Calif.

[3] E. R. Tompkins, J. X. Khym and W. E. Cohn, THIS JOURNAL, 69, 2769 (1947).

[4] Through the courtesy of W. C. Baumann, The Dow Chemical Company, Midland, Michigan.

[5] D. H. Harris and E. R. Tompkins, THIS JOURNAL, 69, 2792 (1947).

[6] S. W. Mayer and E. R. Tompkins, *ibid.*, 69, 2859, 2866 (1947).

[7] B. H. Ketelle and G. E. Boyd, *ibid.*, 69, 2800 (1947).