[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF MOUNT HOLYOKE COLLEGE]

THE ISOMERISM OF CERTAIN UNSATURATED ACIDS OBTAINED IN THE SYNTHESIS OF N-3-METHYL-5-TYROSYL-HYDANTOIN-N-1-PHENYLACETIC ACID

BY DOROTHY A. HAHN AND ELIZABETH DYER

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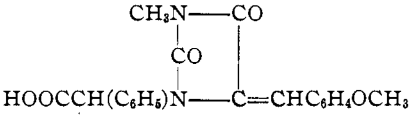
The existence of three isomeric potassium salts and of four unsaturated isomeric acids corresponding to the formula



$$\begin{array}{c}\mathrm{CH_3N{-\!-}CO}\\ \mathrm{CO}\\ \mathrm{HOOCCH(C_6H_5)N{-\!-}C{=}CHC_6H_4OCH_3}\end{array}$$

has been referred to in the preceding paper where the chemical relationships between these substances is indicated by means of arrows on an accompanying chart.[1] The description of their respective preparations and properties has been reserved for a separate paper largely because it seemed desirable to check the chemical properties against the absorption curves[2] of the respective substances.

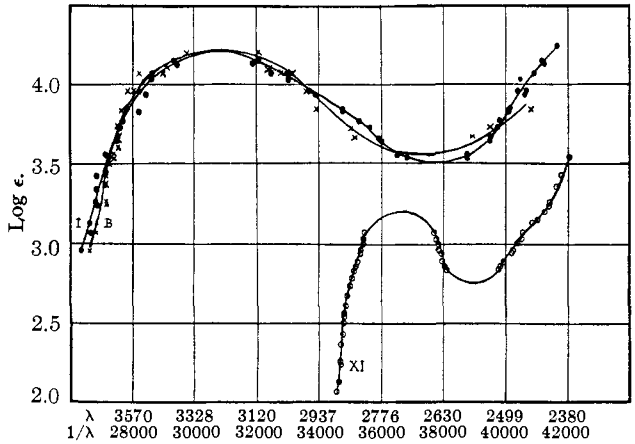


Fig. 1.—I -●-●-●- Ethyl 3-methyl-5-*p*-anisalhydantoin-1-phenylacetate, m. p. 119–120.5°. XI -O-O-O- Ethyl 3-methyl-5-*p*-anisylhydantoin-1-phenylacetate, m. p. 112–113°. B -×-×-×- 1-Methyl-5-benzalhydantoin-3-acetic acid, m. p. 198.5–199.5°.

In the first place it may be noted that Fig. 1 offers satisfactory evidence of the similarity in constitution of ethyl-3-methyl-5-anisalhydantoin-N-

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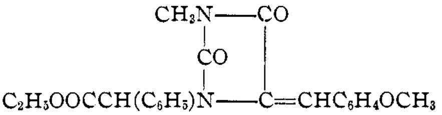
[1] Hahn and Dyer, THIS JOURNAL, **52**, 2494 (1930).

[2] Grateful acknowledgment is made to Dr. Emma P. Carr for advice and assistance in the spectrographic work.

1-phenylacetate, m. p. 119–120.5°, and N-1-methyl-5-benzalhydantoin-3-acetic acid, m. p. 198.5–199.5°[3]



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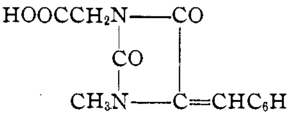

This particular acid was chosen because the absorption curve actually coincides closely with that of the ester. In general the absorption curves of acids and their corresponding esters have been found to be almost identical.[4] On the other hand, the substitution of different groups in the N-1-N-3-positions of disubstituted compounds has the effect of shifting the position of the head of the band without, however, materially changing the character of the curve.[5] And if, as it seems probable, the character of the absorption of N-1-N-3 disubstituted hydantoins is practically *independent of the nature of the substituting group*,[6] this fact is of importance in establishing the configuration of the hydantoin ring in the case of all benzal and anisal unsaturated derivatives.

The curve of the saturated ester XI, also given in Fig. 1, shows a great displacement in the position of maximum absorption toward the ultraviolet and an accompanying decrease in the persistence and width of the band produced by the reduction of the double bond.

Figure 2 shows the absorption curves of two isomeric unsaturated esters (corresponding to I and II in the preceding chart) which possess bands having approximately the same width and intensity but differing slightly in position. Table I shows the wave lengths at which the intensity of absorption is a maximum and a minimum.

TABLE I

WAVE LENGTH DATA

	Log $\epsilon_{\text{max.}}$	$1/\lambda$	λ, Å.	Log $\epsilon_{\text{min.}}$	$1/\lambda$	λ, Å.
Ester I	4.22	30700	3257	3.50	37800	2646
Ester II	4.26	29100	3436	3.48	35650	2805

The curve of the higher-melting ester I is displaced toward the ultraviolet as compared with that of the lower-melting ester II, and this is in agreement with the relatively greater chemical stability of the former. Thus II is prepared from I only after prolonged heating of an alcohol

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[3] Hahn and Evans, THIS JOURNAL, **50**, 810 (1928).

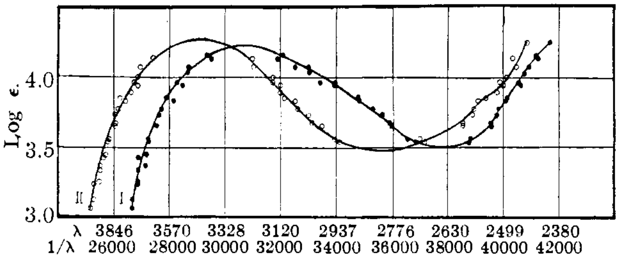
[4] Compare Figs. 2 and 3.

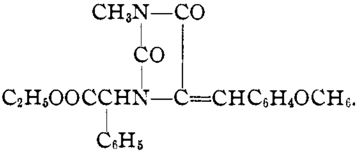
[5] Other evidence in support of this statement is to be found in unpublished spectrographic investigations of a number of different disubstituted benzal- and anisalhydantoins carried out in this Laboratory under the direction of Dr. E. P. Carr.

[6] This is interesting in view of the fact that N-3 mono-substituted hydantoins have equally characteristic and distinctly different absorption curves from N-1-N-3 disubstituted hydantoins. Compare Carr and Dobbrow, THIS JOURNAL, **47**, 2963 (1925).

solution in the presence of hydrogen chloride, and reverts to I when allowed to stand in ether solution in the sunlight. A comparison of the above absorption curves with those of the isomeric modifications of N-1-methyl-5-benzalhydantoin-N-3-acetic acid[7] reveals a very close analogy between the two pairs of isomers and is in accord with the theory that both pairs represent geometrical modifications of the same substance.

Ethyl 3-Methyl-5-*p*-anisalhydantoin-1-phenylacetates.

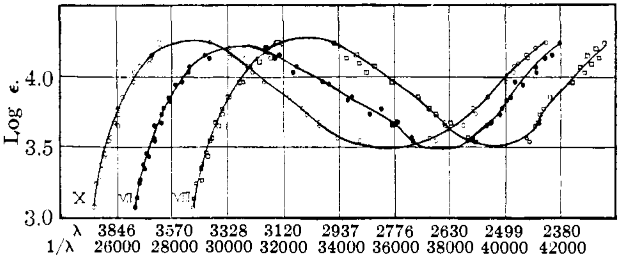


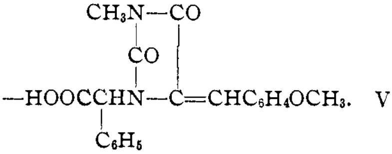


$$\begin{array}{l}\qquad\qquad\quad \mathrm{CH_3N{-}CO}\\ \qquad\qquad\quad\ \ \mathrm{CO}\qquad | \\ \text{Fig. 2.—}\mathrm{C_2H_5OOC\underset{C_6H_5}{C}HN{-}C{=}CHC_6H_4OCH_6}\end{array}$$

Fig. 2.—$C_2H_5OOCCHN-C=CHC_6H_4OCH_6$. I, m. p. 119–120.5°. II, m. p. 100.5–102°.

3-Methyl-5-*p*-anisalhydantoin-1-phenylacetic Acids.





$$\begin{array}{l}\qquad\qquad\ \mathrm{CH_3N{-}CO}\\ \qquad\qquad\ \ \ \mathrm{CO}\qquad | \\ \text{Fig. 3.—}\mathrm{HOOC\underset{C_6H_5}{C}HN{-}C{=}CHC_6H_4OCH_3}\end{array}$$

Fig. 3.—$HOOCCHN-C=CHC_6H_4OCH_3$. VII, m. p. 203–204°. VIII, m. p. 227–229°. X, m. p. 178.5–180.5°.

The curves for the three isomeric acids (Fig. 3) corresponding to X, VII and VIII in the preceding chart also show bands having similar width and intensity but differing in position. The wave lengths for maximum and minimum absorption are given in Table II.

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[7] Hahn and Evans, This Journal, **50**, 810 (1928).

TABLE II

WAVE LENGTH DATA

	Log $\epsilon_{max.}$	$1/\lambda$	λ, Å.	Log $\epsilon_{min.}$	$1/\lambda$	λ, Å
X	4.26	28800	3472	3.49	35700	2800
VII	4.22	30550	3274	3.49	37700	2653
VIII	4.27	32900	3039	3.51	39650	2523

Similarity in the shape of the curves would indicate that these acids are closely related isomeric forms. It is, moreover, to be noted that the progressive displacement of the absorption band toward the ultraviolet from X to VII to VIII corresponds to a progressive rise in melting points accompanied by an increase in the chemical stability of the substances. The relations here are similar to those presented by the isomeric esters. For example, the acid, m. p. 178.5–180.5°, is transformed into the acid of m. p. 203–204° by the action of hydrogen chloride and the latter by a similar process into the acid of m. p. 227–229°. Reversion of the higher- to the lower-melting modifications has, however, not been observed.

In comparing the absorption curves of the esters with those of the acids it is interesting to find that the curve of II (Fig. 2) corresponds closely to the curve of X (Fig. 3) in the positions of the maximum and minimum intensities of absorption and that similarly the curve of I (Fig. 2) corresponds to the curve of VII (Fig. 3). These relationships are confirmed by the chemical data since the ester II hydrolyzes to give the acid X which in turn is readily esterified to the former, and similar transformations take place in the case of the ester I and the acid VII.

The fact that there are three acids instead of the two geometrical isomers which would normally be expected may possibly be interpreted as bringing the chemistry of the unsaturated hydantoins into line with the chemistry of the *cis* and *trans* geometrical modifications of cinnamic acid.

Experimental

N-3-methyl-5-anisalhydantoin-1-phenylacetic Acids

A. Acids Derived from the Ester I by Acid or Alkaline Hydrolysis.—VII, m. p. 203–204°, and VIII, m. p. 227–229°.—The ester melting at 119–120.5° gives on both acid and alkaline hydrolysis an acid melting at 203–204°. In both cases the yield is low, averaging 33 and 40%, respectively, of the theoretical. This may be accounted for by the tendency of all of these substances to isomerize. However, in spite of the side reactions which undoubtedly take place, clear relationships have been established between the ester I, the corresponding acid VII, and the salt III, as shown in the chart (p. 2496).

(1) **Acid Hydrolysis.**—Seven grams of the ester, m. p. 119–120.5°, was suspended in 30 cc. of boiling concd. hydrochloric acid and just enough boiling glacial acetic acid added to dissolve the oil. After heating for one hour the mixture was cooled and diluted with water, when 1.7 g. of a yellow powdery precipitate, m. p. 198–203°, separated. When the filtrates from this product were evaporated to dryness under a stream of air and the resulting gum was treated with ether, an additional 0.6 g. of the same acid

was obtained. The product was purified by recrystallization from alcohol, from which it separates as clusters of long yellow needles, m. p. 203–204°.

Anal. Calcd. for $C_{20}H_{18}O_5N_2$: N, 7.65. Found: N, 7.54, 7.46.

The acid is also formed as one of the products of acid hydrolysis of the ester II. The acid is fairly soluble in hot acetone (1 g. in 35 cc.), and in hot alcohol (1 g. in 20 cc.), and is less soluble in cold alcohol (1 g. in 80 cc.). It is transformed into the ester I in 90% yield when its alcohol solution is saturated with hydrogen chloride. The acid passes quickly and quantitatively into the corresponding potassium salt III when its hot alcoholic solution is treated with one equivalent of potassium hydroxide.

(2) **Alkaline Hydrolysis.**—While the above acid, VII, m. p. 203–204°, may be obtained as the principal product resulting from the alkaline hydrolysis of the ester I, two side reactions have been observed which indicate that the transformations are somewhat complicated. These are (a) the formation of a second isomeric acid, VIII, m. p. 227–229°, and (b) decomposition of the salt accompanied by the formation of methylanisalhydantoin and anisaldehyde. The latter (by varying the conditions) may be controlled and even eliminated.

The most convenient method for preparing the acid VII was to acidity an aqueous solution of the corresponding potassium salt III. Ten grams of ester I, m. p. 118–120°, was dissolved in 70 cc. of boiling 95% alcohol to which was added 1 equivalent of potassium hydroxide dissolved in 30 cc. of boiling alcohol. The solution changed color immediately from a pale yellow to a deep red; this was followed in about three minutes by a complete disappearance of color and the precipitation of a white solid. After boiling for fifteen minutes the mixture was iced and filtered. The product consisted of 4.1 g. of a salt III, m. p. 208–210° with decomposition.

Anal. Calcd. for $C_{20}H_{17}O_5N_2K$: N, 6.93. Found: N, 6.67, 6.60.

The salt, when dissolved in warm water and acidified with hydrochloric acid, passed quantitatively into the acid VII. The salt was transformed into the ester I by dissolving it in absolute alcohol and saturating the solution with hydrogen chloride, or by heating an alcohol solution with ethyl iodide. In neither case, however, was the yield more than 10% of the theoretical, due to the presence of an oily residue which would not crystallize.

Although the main product which was obtained on alkaline hydrolysis of the ester I consisted of the salt III, which was transformed into the acid VII, a second isomeric acid VIII was obtained by acidifying the alkaline filtrates (representing the combined mother liquor and washings from the salt precipitate). Under these conditions 4 g. of a white crystalline precipitate separated, m. p. 215–229°. By extracting this mixture with hot alcohol or acetone traces of the above-mentioned acid VII were removed, and the residue was found to consist of a new acid VIII, melting at 227–229° The latter was purified by recrystallization from boiling acetic acid and analyzed.

Anal. Calcd. for $C_{20}H_{18}O_5N_2$: N, 7.65. Found: N, 7.63. 7.57.

The same acid was found in small quantities among the products of alkaline hydrolysis of the ester II. It was also obtained by isomerizing the acid VII in acetic acid solution under the action of dry hydrogen chloride. This acid is soluble in boiling acetic acid (1 g. in 15 cc.) from which it separates almost completely on cooling in the form of small hard white plates. It is slightly soluble in boiling alcohol (1 g. in 100 cc.) from which it separates almost completely in the form of regular cubes. Negative results were obtained in all attempts at esterification whether by suspending the salt or acid, respectively, in alcohol and saturating the mixture with hydrogen chloride, or by heating the salt with ethyl iodide, or by application of the Schotten–Baumann reaction.

The acid VIII was transformed quantitatively into the salt IV by boiling the acid suspended in alcohol with alcoholic potassium hydroxide. After heating for twenty minutes the acid dissolved, and the solution when cooled deposited the salt in the form of clusters of colorless prisms which melted at 212° with decomposition. The salt was purified by one recrystallization from alcohol and analyzed.

Anal. Calcd. for $C_{20}H_{17}O_5N_2K$: N, 6.93. Found: N, 6.72, 6.68.

The salt was completely soluble in water and its aqueous solution when acidified passed quantitatively into the acid VIII.

The statement has been made that under certain conditions alkaline hydrolysis of the ester I is accompanied by decomposition with the formation of methylanisalhydantoin and anisaldehyde. For example, in a few experiments where the hydrolysis was carried out in 25 or 50% aqueous alcoholic mixtures, it was observed that after the salt III had separated as described above, the alkaline filtrate behaved in a curious way. Thus, when concentrated to one-third its volume to remove the alcohol, and then diluted with water to the original volume, precipitation of a neutral product, m. p. 212–215°, took place. This was fully identified as methylanisalhydantoin. The filtrate from this precipitate when acidified yielded the usual quantity of the acid VIII. Decomposition could be eliminated by carrying out the hydrolysis in 95% alcohol and acidifying immediately without concentrating to remove the alcohol. The same decomposition was brought about when the pure salt III was heated for six days in a 95% alcohol solution containing 0.1 equivalent of alkali or for three hours in a weakly alkaline aqueous solution. In both cases about 10% of the salt was decomposed into methylanisalhydantoin and at the same time a secondary decomposition with the splitting off of anisaldehyde took place. The anisaldehyde was separated from the alkaline mixture by steam distillation, and its identity was established by its odor, its reaction with Tollens' reagent, and its conversion into anisic acid, which was compared with a pure laboratory specimen.

B. Acids Derived from the Ester II by Acid or Alkaline Hydrolysis.—VII, m. p. 203–204°; IX, m. p. 58–62°; and X, m. p. 178.5–180.5°.

(1) Acid Hydrolysis.—The products obtained by acid hydrolysis of the ester II consisted of a new acid, X, along with small quantities of the acid VII. For example, 2 g. of the ester II, m. p. 100.5–101.5°, was suspended in 25 cc. of hydrochloric acid and about 20 cc. of acetic acid was added gradually accompanied by boiling and shaking. After the material had dissolved completely, the solution was boiled for one hour and then cooled. The product (which separated as an oil) was precipitated completely by the addition of water, the acid solution decanted, the oil washed with water and finally taken up with alcohol. This solution on dilution with water yielded 1.7 g. of a somewhat granular precipitate, m. p. 75–145°. The acids composing this mixture were separated by extraction with small quantities of ether. The insoluble residue consisted of an acid, m. p. 199–202°, which when pure was identified as the acid VII. The ether extract on evaporation deposited a hard yellow gum which after recrystallization from alcohol yielded a crystalline acid, m. p. 178.5–180.5° (X).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: N, 7.65. Found: N, 7.54, 7.71.

This acid is soluble in boiling alcohol (1 g. in 15 cc.) and less soluble in cold alcohol (1 g. in 50 cc.), from which it crystallizes in the form of hard bright yellow plates. Its aqueous solution neutralizes the theoretical quantity of standard base. When dissolved in alcohol previously saturated with hydrogen chloride and boiled for one hour, it is transformed into the ester II (yield 84% of the theoretical). Esterification is accompanied also by isomerization, since a small quantity of the ester I is also always formed. The acid X is partially changed into the isomeric acid VII on prolonged boiling of its acetic acid solution with concentrated hydrochloric acid.

(2) Alkaline Hydrolysis.—The potassium and sodium salts V and VI were prepared, respectively, by boiling an alcohol solution of the ester II with 1.2 equivalents of alcoholic potassium hydroxide or with a corresponding amount of sodium alcoholate. In each case the reaction was accompanied by a color change first to dark red and then to light yellow and was complete after boiling from fifteen to twenty minutes. Quantitative amounts of salt were precipitated from their respective solutions upon cooling, and after recrystallization from water the potassium salt melted at 192–194° with decomposition and the sodium salt at 128–132° with decomposition.

Anal. Calcd. for $C_{20}H_{17}O_5N_2K{\cdot}2H_2O$: N, 6.36. Found: N, 6.26, 6.22. Calcd. for $C_{20}H_{17}O_5N_2Na{\cdot}H_2O$: N, 6.90. Found: N, 6.83, 6.73.

When an aqueous solution of either of the above salts was acidified with hydrochloric acid, a yellow granular precipitate was formed. This, when washed with water and dried in the air, yielded a pale yellow powder which melted at 58–62°. On further heating it solidified completely at 130° and then remelted to a clear liquid at 178–180°. A sample when heated in an oven at 50° did not change in weight but was then observed to melt at 88–178°. Since it was impossible to purify the substance by recrystallization, analyses were made using freshly precipitated samples both before and after heating at 50°.

Anal. Calcd. for $C_{20}H_{18}O_5N_2$: N, 7.65. Found: N, 7.54, 7.46, 7.42.

Since these results agree very closely with those calculated, it may be assumed that the substance represents an unstable isomeric modification of the acid X into which it gradually tends to rearrange. This is confirmed by the fact that an acid, m. p. 178.5–180.5°, which was fully identified as X is formed (a) when the acid, m. p. 58–62°, is heated, (b) when it is allowed to stand at room temperature for several days and (c) when it is dissolved in cold solvents such as alcohol, chloroform, ether or acetic acid. In every case the substance dissolved readily to give a clear solution which in a few minutes became cloudy and then yielded a fine crystalline powder which was found to consist of the acid X in pure condition. A spectrographic analysis, conducted as rapidly as possible with a specimen of the substance melting at 58–62°, gave an absorption curve which was identical in all respects with that of the acid X, m. p. 178.5–180.5°.

Spectrographic measurements were made with a Hilger quartz spectrograph (E 36) according to the quantitative method of Henri.[8] The substances to be examined, having been purified by repeated crystallization from absolute alcohol, were dissolved in specially purified absolute alcohol.[9] Solutions of 0.0001 and 0.0002 *M* concentration were placed in Baly quartz tubes and exposed to a spark from iron electrodes for periods of forty to sixty seconds, the thickness of the solution varying from 6 to 60 mm. For purposes of comparison the same thicknesses of solvent were exposed for periods of ten seconds each. Lumière and Jougla photographic plates were used. The extinction coefficients were calculated from the expression

$$\epsilon = \frac{n}{cd} \log \frac{t_{\text{solution}}}{t_{\text{solvent}}}$$

where ϵ equals the molecular extinction coefficient, n is a constant depending on the photographic plates (*i. e.*, 0.9), c is molar concentration, d is thickness in centimeters and t is period of exposure in seconds.[10]

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[8] Henri, "Études de Photochemie," Gauthier-Villars, Paris, **1919**, p. 5.

[9] Castille and Henri, *Bull. soc. chim. biol.*, **6**, 299 (1924).

[10] Acknowledgment must be made to Miss Katherine M. Haring for assistance in making some of these measurements.

Summary

The fact that N-1-N-3-disubstituted unsaturated hydantoins with different groups in union with the nitrogen show practically the same absorption spectra may be applied in determining the configuration of the molecule.

A strikingly close analogy has been observed between the relationship indicated by a comparison of absorption curves and the chemical properties of the substances studied.

Three closely related isomers have been discovered where only two might normally be predicted on the basis of geometrical isomerism.

SOUTH HADLEY, MASSACHUSETTS

[A COMMUNICATION FROM THE LABORATORIES OF ORGANIC AND AGRICULTURAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE PREPARATION AND ANTIRACHITIC ACTIVATION OF SOME DERIVATIVES OF ERGOSTEROL AND CHOLESTEROL

BY D. W. MACCORQUODALE, HARRY STEENBOCK AND HOMER ADKINS

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Inasmuch as biochemical tests revealed that extraction of yeast and plant materials with alcohol, or even with concentrated solutions of potassium hydroxide in alcohol, failed to free them of substances capable of antirachitic activation (unpublished work) it occurred to us that ergosterol was probably present therein in the form of derivatives. Speculation concerning the possible nature of such derivatives led us to attempt the synthesis of the *d*-glucoside of ergosterol and N-ergosterol glycine, as representatives of carbohydrate and protein substances, respectively. We were successful in our attempt to synthesize the carbohydrate compound, but failed with the latter. In order to avoid waste of ergosterol, preliminary experiments were always carried out with cholesterol.

The glucoside of cholesterol was first described by Salway[1] who obtained it by the condensation of the sterol with tetra-acetylbromoglucose by means of dry silver oxide, and subsequent saponification of the acetyl derivative. This method was found to be entirely satisfactory for the preparation of the glucoside of ergosterol, the only precaution necessary being the rigid exclusion of moisture.

A large number of experiments were made in an unsuccessful attempt to obtain an ergosteryl halide which, it was hoped, might be condensed with the amino acids to produce secondary amines. Darzens' method[2] for the preparation of halides by treatment of the appropriate alcohol with thionyl chloride in the presence of pyridine or other tertiary base when applied to

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[1] Salway, *J. Chem. Soc.*, **103**, 1026 (1913).

[2] Darzens, *Compt. rend.*, **152**, 1314 (1911).