STUDIES ON THE STRUCTURE OF STRYCHNINE. III.
STRYCHNINOLONE AND ITS DERIVATIVES.

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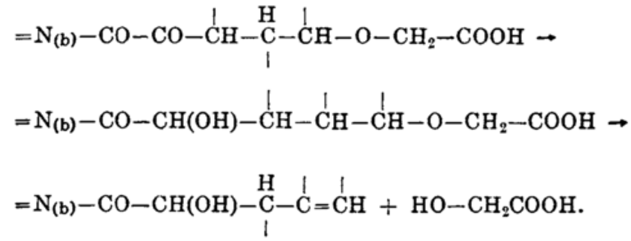
Leuchs and others discovered an important reaction : strychninolic acid is decomposed into strychninolone and glycolic acid when treated with alkali. Although strychninonic acid can hardly be broken up to produce glycolic acid by alkali, if it is reduced to strychninolic acid, the latter easily gives glycolic acid even by the action of dilute alkali. It is undoubtedly due to the fact that the carbonyl group of strychninonic acid is reduced to an alcoholic group. It must have therefore been assumed that, according to Leuchs's or Robinson's formula as shown below, the influence of the carbonyl or the alcohol group should extend so far as to the third carbon atom with the glycolic acid group.



$$=\mathrm{N_{(b)}-CO-CO-\overset{|}{C}H-\underset{|}{\overset{H}{C}}-\overset{|}{C}H-O-CH_2-COOH} \rightarrow$$

$$=\mathrm{N_{(b)}-CO-CH(OH)-\overset{|}{C}H-\overset{|}{C}H-\overset{|}{C}H-O-CH_2-COOH} \rightarrow$$

$$=\mathrm{N_{(b)}-CO-CH(OH)-\underset{|}{\overset{H}{C}}-\overset{|}{C}=\overset{|}{C}H + HO-CH_2COOH.}$$

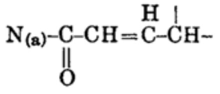
It seemed to be rather unreasonable. Further careful studies on strychninolone, produced by the above reaction, might very likely throw light upon the matters in question. For this reason the present investigation was started.

According to Leuchs's method, strychnine was oxidized with potassium permanganate in acetone solution and the formed precipitate was extracted with water. The aqueous solution was then extracted with chloroform. From the chloroform layer dihydroxystrychnine ($C_{21}H_{24}N_2O_4$, needles) was isolated as a by-product. Its hydrochloride crystallises in needles, and decomposes at 212°; its iodomethylate is also crystalline and melts at 322°. Thus it is shown that in Leuchs's oxidation the double bond is also first to be oxidized.

Leuchs informed that, besides strychninolone, the a-form (m.p. 228–231°, $[\alpha]$–112–4°), which was obtained from strychninolic acid treated with alkali, there were two more isomers: when the a-form was shaken with 0.5 N alkali, the b-form (m.p. 228–230°, $[\alpha]$–37°) was obtained; and when the a-form was heated with methyl alcoholic ammonia, the c-form (m.p. 252°, $[\alpha]$–176°). However, there is still some doubt about the identity of the reduction products of these compounds of Leuchs's. Therefore these isomers were first of all subjected to further investigation.

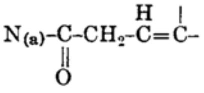
As Leuchs reported, strychninolone melting at 228–230° was obtained by the action of alkali upon strychninolic acid, but when it was subjected to fractional crystallization, it was found that the substance melting at 238–240°, which was designated strychninolone-β, was separated from the less soluble portion, and the substance melting at 224°, which was designated strychninolone-α, was separated from the more soluble portion. It is interesting that these two compounds have the same formula $C_{19}H_{18}N_2O_3$ and are reduced to a dihydro-compound by catalytic reduction.

It is considered, therefore, that the substance melting at 228–230° or Leuchs's strychninolone-a is a mixture of strychninolone-α (m.p. 224°) and strychninolone-β (m.p. 240°). Since these two substances give the same reduction product, they are believed to be isomeric with each other, simply showing the difference in the position of a double bond. This consideration well agrees with the following fact. Leuchs already reported that when acetylbrucinolone is oxidized with potassium permanganate, there are obtained barium salts of two isomeric carboxylic acids, each of which produces oxalic acid and malonic acid. Taking the above-mentioned fact into account, the two following formulas for the two isomeric strychninolones may be considered :



$$N_{(a)}\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH{=}\overset{H}{C}\text{-}\overset{|}{C}H\text{-}$$

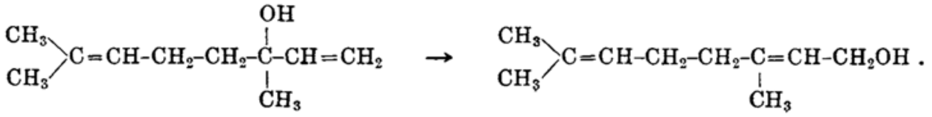
I



$$N_{(a)}\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2\text{-}\overset{H}{C}{=}\overset{|}{C}\text{-}$$

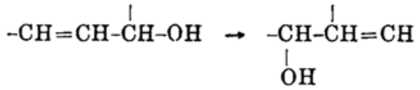
II

If formula II represents strychninolone-α, formula I belongs to strychninolone-β. (Such a representation is convenient to the following explanation.) The mixture of the two compounds which were found to melt at 228–230° was shaken with 0.5 N NaOH solution for five days, no visible reaction occurred. But when it was warmed with 10% KOH solution in the presence of a small amount of alcohol, γ-isomer $C_{19}H_{18}N_2O_3$ melting at 254° was obtained. It forms not only dihydro-derivative $C_{19}H_{20}N_2O_3$ but also mono-acetyl-derivative $C_{21}H_{20}N_2O_4$, and it is therefore no doubt an isomer. Since its reduction product is not identical with that of other isomers, it cannot but be considered an isomer caused by the shift of the hydroxyl group. For such an explanation the linalool-geraniol isomerism is often taken as an example :



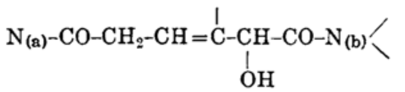
$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}CH\text{-}CH_2\text{-}CH_2\text{-}\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}\text{-}CH{=}CH_2 \;\rightarrow\; \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C{=}CH\text{-}CH_2\text{-}CH_2\text{-}\underset{\underset{CH_3}{|}}{C}{=}CH\text{-}CH_2OH\,.$$

If it is assumed that such an isomeric change occurs between strychninolone-α and strychninolone-γ, the isomerism will be quite readily understood :



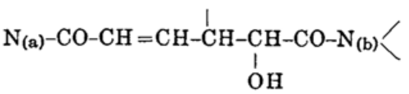
$$\text{-}CH{=}CH\text{-}\overset{|}{C}H\text{-}OH \;\rightarrow\; \text{-}\underset{\underset{OH}{|}}{C}H\text{-}\overset{|}{C}H{=}CH$$

If the assumption be correct, strychninolone-α, strychninolone-β, and strychninolone-γ will be represented by formulas III, IV, and V, respectively, and the number of carbon atoms between $N_{(a)}$ and $N_{(b)}$ of the strychninolone molecule will be six :



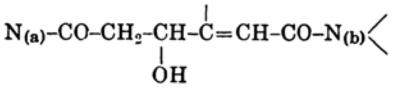
$$N_{(a)}\text{-}CO\text{-}CH_2\text{-}CH{=}\overset{|}{C}\text{-}\underset{\underset{OH}{|}}{C}H\text{-}CO\text{-}N_{(b)}\!<$$

III



$$N_{(a)}\text{-}CO\text{-}CH{=}CH\text{-}\overset{|}{C}H\text{-}\underset{\underset{OH}{|}}{C}H\text{-}CO\text{-}N_{(b)}\!<$$

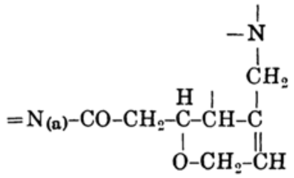
IV



$$\mathrm{N_{(a)}{-}CO{-}CH_2{-}\underset{\underset{\displaystyle OH}{|}}{C}H{-}\overset{|}{C}{=}CH{-}CO{-}N_{(b)}\!<}$$

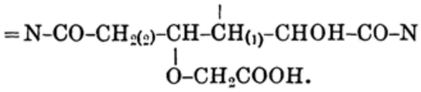
V

Consequently there must be an atomic group represented by VI in the strychnine molecule.



VI

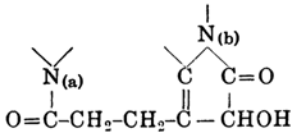
By the same explanation, the fact that glycolic acid does not split from strychninonic acid but does from strychninolic acid, may be well understood. If strychninonic acid forms an enol structure in an alkaline medium, the hydrogen atom of $C_{(1)}$ migrates to the oxygen atom of the adjacent carbonyl group and there will be no opportunity for glycolic acid to be split off. Hence it is regarded that strychninolic acid does not form an enol structure, the hydrogen atom remaining in $C_{(1)}$, and it splits readily glycolic acid.

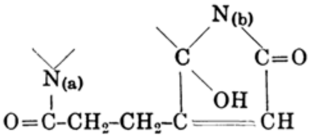


$$\mathrm{{=}N{-}CO{-}CH_{2(2)}{-}\underset{\underset{\displaystyle O{-}CH_2COOH.}{|}}{C}H{-}\overset{|}{C}H_{(1)}{-}CHOH{-}CO{-}N}$$

Now a question arises whether such a compound as strychninonic acid forms an enol structure or not. Strychninone $C_{19}H_{16}N_2O_3$ (m.p. 273°), obtained from strychninolone by oxidation with chromic acid, readily dissolves in alkali in slightly yellowish colour and precipitates on passing carbon dioxide in the solution. When dihydrostrychninolone is oxidized with chromic acid, dihydrostrychninone is also obtained; the compound dissolves slowly in alkali to a colourless solution, and, moreover, does not precipitate with carbon dioxide. It may be assumed that the hydrogen atom of $C_{(2)}$ may be removed in order to split glycolic acid from strychninolic acid molecule, the keto form, $\mathrm{{=}N_{(a)}{-}CO{-}CH_2{-}\overset{|}{C}H{-}O{-}CH_2{-}COOH}$. If the assumption mentioned above is correct, glycolic acid also has to split off from strychninonic acid, but actually the reaction does not occur.

Two following isomeric formulas for strychninolones may also be considered:


VII


VIII

Really strychninolone-δ, an isomer melting at 286°, is obtained from strychninolone-a by heating it with sodium ethylate. Strychninolone-δ can not be reduced in the presence of Pd at room temperature, but gives an acetyl derivative. Considering the fact that neostrychnine and Tafel base are not easily reduced at room temperature, the position of the double bond of these compounds may be the same with that of strychninolone-δ.

Leuchs's method, action of methyl alcoholic ammonia upon strychninolone-a, was repeated and the neutral substances in the reaction product were treated with hot water. From the more soluble portion was obtained strychninolone-γ, and from the less soluble portion a new isomer, which was recrystallized from water and melted at 241–243°. The isomer, expressed by the name strychninolone-ε, was readily reduced by catalytic reduction and gave a mono-acetyl-derivative. Since strychninolone-γ is obtained by the same method, strychninolone-ε is regarded to be produced also by the shift of OH-group. Therefore strychninolone-ε is represented by formula VIII and consequently strychninolone-δ by formula VII.

Supposing the ring of the molecule opens in one position and closes in another, one more isomer can be obtained. The confirmation of this idea is left for future investigation.

Melting points of strychninolone isomers and their derivatives

Strychninolone		Dihydro-derivative	Acetyl derivative
α $C_{19}H_{18}N_2O_3$	224°	274°	240–243°
β $C_{19}H_{18}N_2O_3$	238–240°	274°	253°
γ $C_{19}H_{18}N_2O_3$	254°	215–217°	260°
δ $C_{19}H_{18}N_2O_3 \cdot 3H_2O$	286°	—	340–350°
ε $C_{19}H_{18}N_2O_3 \cdot H_2O$	240–243°	257°	214–215°

Experimental Part.

Dihydroxy-strychnine. Strychnine was oxidized with potassium permanganate in acetone solution. In order to separate(1) the oxidized substance, the precipitate was extracted with cold water and the aqueous extract was shaken with chloroform. When the solvent

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(1) *Ber.*, **41** (1908), 1711; *ibid.*, **46** (1913), 3693.

was distilled off, needle crystals were obtained. This substance was recrystallized from methanol. It bubbles at 100°, solidifies again on further heating, contracts at about 155°, and melts finally at 240°. The crystals obtained from methanol solution gave the following results by analysis: Found: C, 66.15, 66.27; H, 6.84, 6.60. Calc. for $C_{21}H_{24}N_2O_4 \cdot CH_3OH$: C, 66.00; H, 7.00%. The crystals from aqueous solution showed the following results by analysis: Found: C, 61.39, 61.23; H, 7.21, 7.12. Calc. for $C_{21}H_{24}N_2O_4 \cdot 2^1/_2 H_2O$: C, 61.02; H, 7.02%. The above substance was dehydrated by heating in the xylene bath under reduced pressure and subjected to analysis: 3.618 mg. gave 9.070 mg. CO_2 and 2.264 mg. H_2O. Found: C, 68.37, 68.12; H, 7.00, 6.76. Calc. for $C_{21}H_{24}N_2O_4$: C, 68.5; H, 6.50%.

Dihydroxystrychnine Hydrochloride. When dihydroxystrychnine was dissolved in hydrochloric acid and the solution evaporated, needle crystals were obtained. They were recrystallized from water. Needles, decomposing at 212° with bubbling: (Found: C, 58.93, 59.16; H, 6.64, 6.68. Calc. for $C_{21}H_{24}O_4 \cdot HCl \cdot H_2O$: C, 59.64; H, 6.39%).

Dihydroxystrychnine-iodomethylate. Dihydroxystrychnine in methanol was treated with methyliodide, and dihydroxystrychnine iodomethylate was obtained. It was recrystallized from water, m.p. 322°. (Found: C, 52.30, 52.18; H, 5.59, 5.21. Calc. for $C_{21}H_{24}N_2O_4 \cdot CH_3I$ C, 51.75; H, 5.29%.)

Purification of Strychninolones (Separation of α- and β-Isomers). Strychninolone obtained from strychninolic acid by the action of cold alkali was found to melt at 215–225°. It was subjected to fractional crystallization from methanol. The first crop of crystals melted at 238–240°, and further four crops, melting at 235–237°, 232–234°, 228–230°, and 222–224°, respectively, were obtained from the mother liquor. The first crop melting at 238–240° was recrystallized from ethyl alcohol, methanol, and other solvents, but its melting point was not raised. The portion melting at 222–224° was recrystallized from alcohol and its melting point was found to be 223–224°. The crops obtained between these two crops were finally separated into the above two substances by repeated crystallization. The substances melting at 223-224° or α-isomer was analyzed: Found: C, 70.38, 70.47; H, 6.03, 6.07. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59%. The substance melting at 238–240° or β-isomer was analyzed as follows: Found: C, 70.77, 70.70; H, 5.82, 5.81. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59%.

Catalytic Reduction of Strychninolone-α and Strychninolone-β. Strychninolone-α (m. p. 224°), strychninolone-β (m.p. 240°) and strychninolone-a (m.p. 228-230°) were respectively dissolved in alcohol or glacial acetic acid and shaken in the current of hydrogen gas for three hours in the presence of Pd-catalyst. When the absorption of hydrogen ceased, the reaction mixture was filtered in order to separate Pd, and the solvent was distilled, when the reduction product was obtained in crystalline form. It was recrystallized from methanol. The above-mentioned three substances gave the identical reduction product; needles melting at 274°. (Found: C, 70.77, 70.78; H, 6.15, 6.16. Calc. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17%.)

Acetylation of Strychninolone-α. Strychninolone-α (0.5 g.) in 10 c.c. of acetic anhydride with a small amount of anhydrous sodium acetate was heated at 100° for four hours provided with an air condenser. After removal of acetic anhydride under reduced pressure, the reaction mixture was dissolved in water and shaken with chloroform. The chloroform layer was separated from aqueous solution and the solvent was distilled. When a few drops of alcohol was added to the residue, a crystalline substance appeared. It was recrystallized from ethyl alcohol or methanol. Needles, melting at 240-243°. (Found: C, 68.89; H, 6.05. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.23; H, 5.52%.)

Acetylation of Strychninolone-β. The procedure of the acetylation of strychninolone-α was followed in every particular. Needles, m.p. 253°. (Found: C, 69.40, 69.23; H, 5.94, 5.93. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.23; H, 5.52%.)

Formation of Strychninolone-γ. To strychninolone-a was mixed with 10% potassium hydroxide solution and a few drops of alcohol, and the mixture was warmed on the water bath, when the solid was dissolved in a short time. After cooling the mixture, it was treated with hydrochloric acid, when there appeared a white precipitate. Allowing the precipitate to settle down for one day, it was separated by filtration and recrystallized from alcohol. Needles, m.p. 254°; yield 70%. (Found: C, 71.15, 70.81; H, 6.05, 6.10. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59%.)

Catalytic Reduction of Strychninolone-γ. Strychninolone-γ, dissolved in glacial acetic acid, was shaken in the current of hydrogen in the presence of catalytic Pd. When it ceased to absorb hydrogen, the reaction mixture was filtered to remove the catalyst and the solvent was distilled under reduced pressure, when crystalline residue was obtained. It was recrystallized from ethyl alcohol and methanol successively, prisms melting at 215°. (Found: C, 70.13, 69.90; H, 6.31, 6.46. Calc. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17%.)

Acetylation of Strychninolone-γ. To strychninolone-γ, (0.4 g.), was added 10 c.c. of acetic anhydride and a small amount of anhydrous sodium acetate. The mixture was warmed at 100° for four hours, using an air condenser. Then acetic anhydride was distilled under reduced pressure, the residue dissolved in water, and the solution shaken with chloroform. When the chloroform layer was separated from the aqueous solution, the solvent distilled, and a few drops of alcohol were added to the residue, crystals separated out. They were recrystallized from ethyl alcohol or methanol. Needles, m.p. 260°. (Found: C, 69.07, 69.24; H, 6.00, 5.98. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.23; H, 5.52%.)

Formation of Strychninolone-δ: Reaction of Sodium Ethylate upon Strychninolone-a. To 1 g. strychninolone-a was added a solution of sodium ethylate (prepared from 1 g. of sodium) in absolute alcohol, and the mixture was heated on the water bath under a reflux condenser for two hours. Then the alcohol was distilled. When a small amount of water, a few drops at a time, was added to the residue, needle crystals appeared. It was recrystallized from dilute alcohol. It was found to melt at 285–286° with bubbling: (Found: C, 60.54, 60.36; H, 6.46, 6.66. Calc. for $C_{19}H_{18}N_2O_3 \cdot 3H_2O$: C, 60.63; H, 6.38%). When it was dehydrated under reduced pressure on a xylene bath, 4.253 mg. of the substance lost 0.554 mg. or 13.1% of the original weight, whereas the theory requires 14%: (Found: C, 70.36, 70.68; H, 6.01, 5.92. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80, H, 5.59%).

It was subjected to reduction in the current of hydrogen gas in the presence of Pd but no reaction was observed.

Acetyl-strychninolone-δ. For the preparation of this compound the directions given in the case of acetyl-strychninolone-γ were followed· It was obtaind in needles and recrystallized from methanol; its melting point was above 340°: (Found: C, 65.54, 65.49; H, 6.07, 5.54; H_2O, 4.0. Calc. for $C_{21}H_{20}N_2O_4 \cdot H_2O$: C, 65.96; H, 5.54; H_2O, 4.8. Calc. for $C_{23}H_{22}N_2O_5 \cdot H_2O$: C, 65.10; H, 5.66; H_2O, 4.2%.)

Action of Methyl Alcoholic Ammonia upon Strychninolone-a (Formation of Strychninolone-ε). To strychninolone-a was added methyl alcoholic ammonia (saturated at 20°) and the mixture was heated in a sealed tube for three hours. The sealed tube was allowed to cool overnight and opened. When methanol was evaporated, crystals were obtained. They were treated with hydrochloric acid and shaken with chloroform; when the chloroform layer was separated and evaporated, crystals melting at 240° separated out. They were treated with hot water and subjected to fractional crystallization. From the more soluble part, fine needles were obtained by cooling the hot solution. They were recrystallized from water and found to melt at 240–243°C: (Found: C, 67.50; H, 6.21; H_2O, 5.4. Calc. for $C_{19}H_{18}N_2O_3 \cdot H_2O$: C, 67.05; H, 5.99; H_2O, 5.3%). The dehydrated substance obtained by warming in a xylene bath under reduced pressure was found to melt at 208°. (Found: C, 70.51, 70.37; H, 6.09, 5.76. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59%.)

The part less soluble in water was recrystallized from methanol. Its melting point was found to be 252–253° and was not lowered by admixture with strychninolone-γ. Thus the identity of the compound with γ-derivative was established.

Catalytic Reduction of Strychninolone-ε. Strychninolone-ε (m.p. 240–243°) was dissolved in alcohol and subjected to reduction in the current of hydrogen gas in the presence of Pd-black. After shaking the mixture for three to four hours, the current of hydrogen gas was stopped and the solution was filtered in order to remove Pd-black. When the filtrate was evaporated, crystals melting at 208–210° were obtained. When they were recrystallized from a large amount of methanol, unchanged strychninolone-ε separated first and dihydro-strychninolone-ε crystallized out next upon further evaporation of the solvent; its melting point was 257°. It was again recrystallized from alcohol and obtained in prisms; the melting point was still 257°. (Found: C, 68.09, 68.29; H, 6.67, 6.77. Calc. for $C_{19}H_{20}N_2O_3 \cdot {}^1/_2H_2O$: C, 68.46; H, 6.30%. Found for dehydrated substance: C, 70.42, 70.44; H, 6.13, 5.99. Calc. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17%.)

Acetyl-strychninolone-ε. For the preparation of acetyl-strychninolone-ε, the directions given for the preparation of the acetyl derivative of strychninolone-α were followed. It was purified by recrystallization from methanol and ethanol. Needles, m.p. 214–215°. (Found: C, 69.17, 69.27; H, 5.99, 5.82. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.23; H, 5.52%.)

Oxidation of Strychninolone-a with Chromic Acid: Formation of Strychninone. To 3g. of strychninolone, dissolved in 200c.c. of glacial acetic acid, 1.2g. of chromic anhydride, dissolved in 100c.c. of glacical acetic acid, were added little by little with constant stirring. The mixture was allowed to stand overnight and the glacial acetic acid was distilled under reduced pressure. The residue was dissolved in water and shaken with acetic ester. The acetic ester was separated and washed with water. After the removal of the solvent, the residue was treated with a small amount of methanol, and the methanol was evaporated until the odour of acetic acid almost vanished, when a crystalline substance separated out. It was dissolved in a small amount of methanol, filtered, and acetic ester was added to the solution, when crystals melting at 273° were obtained. They dissolve in dilute alkali in slight yellow colour and are reprecipitated with carbon dioxide. (Found: C, 71.39, 71.41; H, 5.37, 5.37. Calc. for $C_{19}H_{16}N_2O_3$: C, 71.25; H, 5.00%.)

Oxidation of Dihydrostrychninolone-a with Chromic Acid. To 2g. of dihydrostrychninolone-a (m.p. 275°), dissolved in glacial acetic acid, 1.0g. of chromic anhydride, dissolved in glacial acetic acid, was added drop by drop. The mixture was allowed to stand overnight and the solvent was distilled under reduced pressure. The residue was treated with water and shaken with acetic ester. The layer of acetic ester was separated, dried with anhydrous sodium sulphate, and when the solvent was distilled, crystals came out. They were recrystallized from acetic ester, m.p. 314°. They dissolve slowly in alkali. (Found: C, 71.25, 71.07; H, 5.61, 6.11. Calc. for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.59%.)