[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Ring Closure of N-Alkoxalyl-β-anilinopropionic Acids

BY PHILIP L. SOUTHWICK AND LOUIS L. SEIVARD[1,2]

In the course of some studies concerned with the reactions of β-amino and β-anilino acids and their derivatives, an attempt was made to prepare N-methoxalyl-β-anilino-β-phenylpropionic acid (I) by the action of an excess of methoxalyl chloride on β-anilino-β-phenylpropionic acid in the presence of pyridine. It was found, however, that the reaction which occurred was not simple acylation of the nitrogen atom, but a more complex process leading to the formation of an acid of the formula $C_{18}H_{15}O_4N$, which corresponds to a dehydration product of the expected derivative. The unknown compound could be obtained in yields of 25–30% and was the only water-insoluble acid isolated from the reaction mixtures. The remainder of the product consisted of a dark-brown, glassy material which was apparently a complex mixture of neutral substances. Efforts to separate pure compounds from this neutral fraction were unavailing.

Consideration of the possible products which might result from the dehydration of the expected N-methoxalyl derivative (I), appeared to lead to only one reasonable choice for the structure of the unknown acid, namely, that of 1,5-diphenyl-2-keto-3-methoxy-Δ^3-pyrroline-4-carboxylic acid (V), formed from I by ring closure. It has been possible to demonstrate that the acid does have the pyrroline structure (V), and that it can be formed in similar yield by ring closure of the methoxalyl derivative (I), which is obtained by treatment of β-anilino-β-phenylpropionic acid with methoxalyl chloride in the absence of pyridine. The ring closure of I was readily accomplished by treatment with an additional quantity of methoxalyl chloride in the presence of pyridine. It was later found that reactions of this type could be effected by the use of mixtures of acetic anhydride and pyridine.

Judged from the over-all result, the ring closure was a condensation of the aldol type in which the α-methylene group of a carboxylic acid had reacted with the carbonyl group of an ester. It was brought about under mild conditions of temperature by the relatively weak base, pyridine. It seemed, therefore, to be abnormal in the following respects:

1. A single carboxyl group had apparently provided a sufficient activating effect to allow the attached methylene group to participate in an aldol condensation.

2. A strong base was not required to promote the reaction of an ester carbonyl group with this α-methylene group.

3. Although when the carbonyl group of an ester reacts with an enolate anion the normal result is the loss of an alkoxide ion as in the Claisen or Dieckmann condensations, the reaction observed was an alternative one whereby water was eliminated and the alkoxyl group was retained.[3]

In the accompanying chart is outlined a suggested mechanism for the reaction. It seems likely that the apparently unusual reactivity of the α-methylene group of the carboxylic acid (I) may be attributed to conversion of the acid to a mixed anhydride (A) by reaction with methoxalyl chloride in the presence of pyridine. The reaction of acids with acid chlorides in the presence of pyridine is a well-known method of preparation for acid anhydrides.[4] Although attempts to isolate a substance corresponding to structure A were unsuccessful, the assumption that anhydride formation is the first step in the ring closure reaction is supported by several observations. Pyridine does not promote the reaction in the absence of an acylating agent. It was found, for example, that N-ethoxalyl-β-anilino-β-phenylpropionic acid (II, Table I) was recovered unchanged after heating at 100° in pyridine solution. However, the addition of acetic anhydride to such a solution caused the ring closure to proceed. Acetic anhydride is, of course, capable of converting acids into acid anhydrides.[5] The role of acetic anhydride in the reaction may not be confined to the anhydride formation postulated as the first step (see discussion below), but that this is one of its functions seems indicated by the fact that methyl N-methoxalyl-β-anilino-β-phenylpropionate, the methyl ester of the acid (I), was recovered unchanged after heating with pyridine and acetic anhydride; if anhydride formation is prevented by prior esterification of the carboxyl group, no ring closure occurs. That anhydride formation occurs when alkoxalyl chlorides are used to cause the ring closure is indicated by the interesting result of an experiment in which triethylamine was substituted for pyridine in conducting the reaction of ethoxalyl chloride with β-anilino-β-phenylpropionic acid. In that instance, a very small amount of the pyrrolinecarboxylic acid (VIII, Table II) was isolated, and a larger portion of the product consisted of cinnamanilide. The carboxyl group of the acid must

(1) Institute Graduate Fellow in Organic Chemistry, 1948.

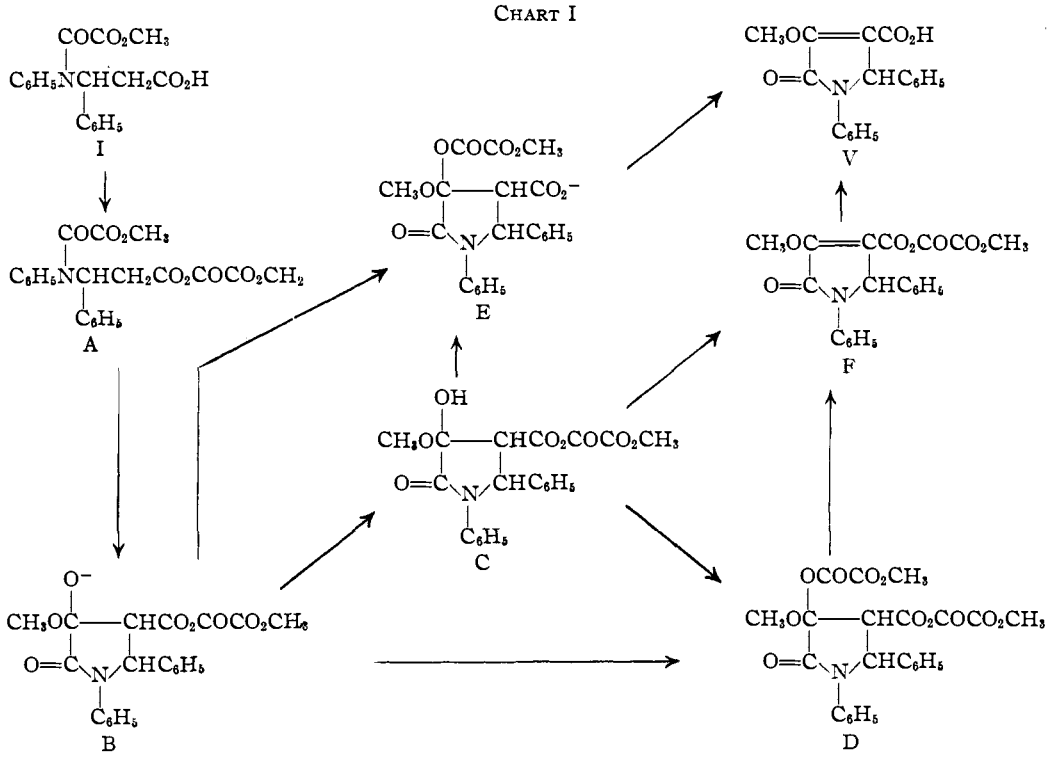
(2) Present address: Shell Development Company, Emeryville, California.

(3) Certain reactions which yield oxygen heterocycles, such as the flavone synthesis of Allan and Robinson, *J. Chem. Soc.*, 2192 (1924); 2334 (1926), may, however, proceed by mechanisms similar to that of the reaction described here.

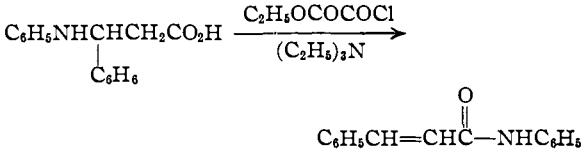
(4) See, for example, (a) Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **33**, 406 (1901); *Chem. Centr.*, **72**, II, 543 (1901); (b) Wedekind, *Ber.*, **34**, 2070 (1901); (c) Heap and Robinson, *J. Chem. Soc.*, 69 (1929).

(5) (a) Autenrieth, *Ber.*, **34**, 168 (1901); (b) Autenrieth and Thomae, *Ber.*, **57**, 423 (1924).

CHART I



have been converted into a functional group capable of accomplishing acylation under mild conditions, and the formation of an anhydride or mixed anhydride therefore seems indicated. The exact



process by which the cinnamanilide was formed is obscure, however, and merits further investigation. That the yields of the pyrrolinecarboxylic acids from the ring closure are not higher may be due to competing processes which are related to this reaction. The decomposition of β-anilinopropionic acids in the course of acylation reactions conducted under alkaline conditions has been observed previously.[6]

If anhydride formation is the first step in the conversion of N-methoxalyl-β-anilino-β-phenylpropionic acid (I) to the pyrrolinecarboxylic acid (V), then the reaction may be regarded as a variation of the Perkin reaction, since it is an aldol condensation involving the α-methylene group of an acid anhydride and results in the formation of an α,β-unsaturated acid. It is significant that pyridine, the base which promotes this reaction, has been found to serve as a catalyst for the usual Perkin reaction.[7] The fact that in this instance the ester group participates in a condensation promoted by a weak base, whereas sodium alkoxides are normally required, may perhaps be ascribed to the high reactivity of esters of oxalic acid, and to the favorable spacial disposition of the reacting groups.

There remains, however, the problem of explaining the fact that in this ester condensation the usual displacement of the alkoxide ion has not occurred, at least in the formation of the product isolated. This result can probably be explained on the basis of two significant differences between the conditions prevailing here and those of the usual Claisen condensation. These are the presence, in this case, of the relatively acidic pyridine salts and also of strong acylating agents. The second and third steps of the reaction process would presumably be reversible transformations in which the base pyridine removes a proton from the α-methylene group of the mixed anhydride (A) and the resulting enolate anion reacts intramolecularly to yield a cyclic anion (B). Anions such as B have been assumed to be intermediates in the Claisen and Dieckmann condensations,[8] although their salts are not isolated because of the rapid loss of the alkoxide ion which usually occurs. If it be assumed that the loss of the methoxide ion does not take place instantly, it would be reasonable to expect the cyclic anion (B) to react rapidly with the pyridinium ion to acquire a proton and yield

(6) Elderfield, Gensler, Bembry, Kremer, Brody, Hageman and Head, THIS JOURNAL, **68**, 1259 (1946).

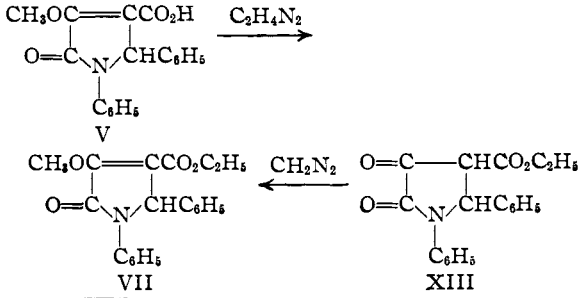
(7) Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 236-240.

(8) The sequence of reactions up to this point is assumed to be essentially the same as in the Claisen condensation. See (a) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); (b) Hauser, *ibid.*, **60**, 1957 (1938); (c) Arndt and Eistert, *Ber.*, **69**, 2381 (1936).

the hemiketal (C), or to react with methoxalyl chloride to give the methoxalyl derivative (D). Compound D might also be formed by the acylation of the hemiketal (C). It is possible that acylation might take place in an intramolecular manner to yield an anion of structure E, since the anion (B) or the hemiketal (C) could assume configurations in which the anhydride group is in the proper position for the occurrence of such a reaction *via* a transitory six-membered ring. If, then, from structures D or E the elimination of the carboxylic acid rather than of the alcohol is favored, as might reasonably be expected in a base-catalyzed process, the formation of the observed product (V) is explained. The role of methoxalyl chloride in these reactions could be taken by acetic anhydride when the latter reagent is used for effecting the ring closure. The product could also be accounted for by the direct loss of water from the hemiketal (C) to yield an unsaturated anhydride (F), but the loss of methanol from an intermediate such as C to yield a β-keto acid or its enol might be expected to be at least a competitive process. The suggestion has been made that acylation may be a step in the elimination of the elements of water which takes place in the usual Perkin reaction.[9]

The formation of a product by an ester condensation in which the alkoxyl group is retained is evidence that at least in some instances anions of the type B, postulated as intermediates in the Claisen condensation, may persist long enough to undergo reactions other than loss of the alkoxide ion. The loss of the alkoxide ion which is observed under the conditions of the Claisen condensation may be the consequence of the fact that no other forward path of reaction is immediately available.

The proof of the structure of the pyrrolinecarboxylic acid (V) was achieved by esterifying it with diazoethane; the product was compared with a sample of ethyl 1,5-diphenyl-2-keto-3-methoxy-Δ^3-pyrroline-4-carboxylate (VII) prepared by treating the previously known compound, ethyl 1,5-diphenyl-2,3-pyrrolidinedione-4-carboxylate (XIII), with diazomethane. The pyrrolidinedione (XIII) was prepared from benzal aniline and ethyl oxalacetate by the method of Schiff and Bertini.[10] Samples of VII prepared by the two different routes were identical in all respects and the melting point of a mixture of the two was not depressed. Treatment of the pyrrolinecarboxylic acid (V) with diazomethane produced methyl 1,5-diphenyl-2-keto-3-methoxy-Δ^3-pyrroline-4-carboxylate (VI, Table II), which was also obtained by an alternative synthesis. Benzalaniline reacted with methyl oxalacetate to give methyl 1,5-diphenyl-2,3-pyrrolidinedione-4-carboxylate (XII, Table II); treatment of this substance with diazomethane gave a product (VI) identical with that produced by the diazomethane esterification of the carboxylic acid (V). It is of interest that the action of diazomethane upon the pyrrolidinediones produced the 3-methoxy-Δ^3-pyrrolines in high yield, and there was no indication of the simultaneous formation of appreciable quantities of ethylene oxide derivatives such as occurs with ethyl acetoacetate, for example.[11]



Additional experiments were performed to test the possibility of extending the ring closure reaction to the preparation of other pyrroline derivatives of similar structure. Properties of compounds prepared in the course of this work are listed in Tables I and II. Treatment of β-anilino-β-phenylpropionic acid with an excess of ethoxalyl chloride gave results entirely similar to those obtained with methoxalyl chloride. In the presence of pyridine the product was 1,5-diphenyl-2-keto-3-ethoxy-Δ^3-pyrroline-4-carboxylic acid (VIII). In the absence of pyridine the normal acylation product, N-ethoxalyl-β-anilino-β-phenylpropionic acid (II), was obtained. Treatment of the latter substance in the presence of pyridine with ethoxalyl chloride, methoxalyl chloride, or acetic anhydride gave the pyrrolinecarboxylic acid (VIII). Esterification of the acid (VIII) with diazomethane yielded the corresponding methyl ester (IX). The identity of the ester (IX) was verified by comparison with the product obtained by the action of diazoethane on methyl 1,5-diphenyl-2,3-pyrrolidinedione-4-carboxylate (XII).

β-Anilinopropionic acid reacted with ethoxalyl chloride in the same manner as did β-anilino-β-phenylpropionic acid. In the presence of pyridine the product was 1-phenyl-2-keto-3-ethoxy-Δ^3-pyrroline-4-carboxylic acid (X); in the absence of pyridine, the acyl derivative, N-ethoxalyl-β-anilinopropionic acid (III), was obtained. The latter compound underwent ring closure to the pyrrolinecarboxylic acid (X) when treated with ethoxalyl chloride in the presence of pyridine. Esterification of the acid (X) with diazomethane yielded methyl 1-phenyl-2-keto-3-ethoxy-Δ^3-pyrroline-4-carboxylate (XI), a product which was identical with that obtained by the action of diazoethane on methyl 1-phenyl-2,3-pyrrolidinedione-4-carboxylate (XIV). This pyrrolidinedione was prepared by means of the condensation of methyl β-anilinopropionate with methyl oxalate in the presence of sodium methoxide

(9) Reference 7, p. 216.

(10) Schiff and Bertini, *Ber.*, **30**, 602 (1897).

(11) *Cf.* Arndt, Loewe, Severge and Türegün, *Ber.*, **71**, 1640 (1938).

TABLE I

N-ALKOXALYL DERIVATIVES OF β-ANILINO AND β-AMINOPROPIONIC ACIDS, ROCOCO—N(R₂)(R₃)—CHCH₂CO₂H

Number	R	R₂	R₃	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	CH_3	C_6H_5	C_6H_5	85	127–128[a]	$C_{18}H_{17}O_5N$	66.04	5.24	66.01	5.37
II	C_2H_5	C_6H_5	C_6H_5	78	111–113[a]	$C_{19}H_{19}O_5N$	66.85	5.61	66.84	5.74
III	C_2H_5	C_6H_5	H	58	91–92[a]	$C_{13}H_{15}O_5N$	58.86	5.70	58.89	5.74
IV	C_2H_5	H	C_6H_5	43	116–118[b]	$C_{13}H_{15}O_5N$	58.86	5.70	58.65	5.66

[a] White needles. [b] White plates.

TABLE II

PYRROLINE AND PYRROLIDINEDIONE DERIVATIVES, ROC=CCO₂R₂[a] / O=C–N(C₆H₅)–CHR₃

Number	R	R₂	R₃	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
V	CH_3	H	C_6H_5	196–198[b]	$C_{18}H_{15}O_4N$	69.89	4.89	69.86	4.89
								69.73	4.68
VI	CH_3	CH_3	C_6H_5	128.5–130	$C_{19}H_{17}O_4N$[c]	70.57	5.30	70.38	5.36
VII	CH_3	C_2H_5	C_6H_5	83–85	$C_{20}H_{19}O_4N$	71.20	5.68	71.17	5.50
VIII	C_2H_5	H	C_6H_5	214–215[b]	$C_{19}H_{17}O_4N$	70.57	5.30	70.39	5.33
IX	C_2H_5	CH_3	C_6H_5	91–92	$C_{20}H_{19}O_4N$[d]	71.20	5.68	71.42	5.37
								71.25	5.41
X	C_2H_5	H	H	189–191[b]	$C_{13}H_{13}O_4N$	63.15	5.30	63.13	5.24
XI	C_2H_5	CH_3	H	75.5–77	$C_{14}H_{15}O_4N$	64.36	5.79	64.51	5.66
XII	H	CH_3	C_6H_5	201–203	$C_{18}H_{15}O_4N$	69.89	4.89	70.06	5.18
XIII	H	C_2H_5	C_6H_5	173–175[e]	$C_{19}H_{17}O_4N$	...	..	...	..
XIV	H	CH_3	H	185–187	$C_{12}H_{11}O_4N$	61.80	4.76	61.63	4.69

[a] The formula represents 2,3-pyrrolidinedione derivatives in the enol form, *i.e.*, as 3-hydroxy-Δ^3-pyrroline derivatives. [b] Melt with decomposition and preliminary darkening. [c] *Anal.* Calcd.: N, 4.33; methoxyl, 19.20. Found: N, 4.50; methoxyl, 19.01. [d] *Anal.* Calcd.: N, 4.15. Found: N, 4.28. [e] Schiff and Bertini[10] gave the m. p. 171°; Simon and Conduche, *Ann. chim.*, [8] 12, 50 (1907), the m. p. 173°.

$$C_6H_5NHCH_2CH_2CO_2CH_3 \xrightarrow[NaOCH_3]{CH_3OCOCO_2CH_3} O{=}C(-CHCO_2CH_3)-C(=O)-N(C_6H_5)-CH_2$$

XIV

An attempt to bring about the ring closure of N-ethoxalyl-β-amino-β-phenylpropionic acid (IV) using conditions which were successful with the corresponding anilino derivative (II) apparently caused decomposition of the starting material, and no pure products were isolated from the reaction mixture.

Experimental[12,13]

Methoxalyl and Ethoxalyl Chlorides.—These acid chlorides were prepared by treatment of the crystalline potassium methyl and potassium ethyl oxalates with thionyl chloride. It was found that pure products were more easily obtained by this method than by those based upon the reaction of phosphorus pentachloride with methyl or ethyl oxalate.[14] The potassium salts were easily prepared by the action of potassium acetate on solutions of methyl and ethyl oxalate in methanol and ethanol, respectively.[15]

(A) **Methoxalyl Chloride.**—The reaction was conducted in a flask equipped with a dropping funnel and a reflux condenser protected from moisture by a calcium chloride tube. To 142 g. (1 mole) of potassium methyl oxalate, m.p. 192–195°, 119 g. (1 mole) of thionyl chloride was added over a period of thirty minutes. The mixture was then heated for three hours on a steam-bath. The product was distilled from the cake of potassium chloride and the distillate collected at 114–118° (90 g.) was redistilled to give 80 g. (65%) of a colorless, fuming liquid boiling at 118–120°. This is the boiling point reported by Anschütz.[14a]

(B) **Ethoxalyl Chloride.**—This compound was prepared from potassium ethyl oxalate, m. p. 222–225°, by the procedure described above for methoxalyl chloride. The crude product (b.p. 132–136°) from 156 g. (1 mole) of potassium salt weighed 98 g., and was redistilled to yield 81 g. (59%) of a colorless product boiling at 133–135°. Anchütz reported the b. p. 135–136°.[14a]

Methyl β-Anilinopropionate and β-Anilinopropionic Acid.—Methyl β-anilinopropionate was prepared by the addition of aniline to methyl acrylate using a procedure based upon the excellent method recently described by Elderfield, *et al.*,[6] for the preparation of ethyl β-(*p*-anisidino)-propionate. A mixture of 279 g. (3 moles) of redistilled aniline and 75 ml. of glacial acetic acid was placed in a flask equipped with a reflux condenser, stirrer and dropping funnel. Freshly distilled methyl acrylate (258 g., 3 moles)

(12) Melting points are corrected.

(13) Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(14) (a) Anschütz, *Ann.*, **254**, 1 (1889); (b) Barre, *Bull. soc. chim.*, **41**, 47 (1927); (c) Kindler, Metzendorf and Dschi-yin-Kwok, *Ber.*, **76**, 308 (1943).

(15) The procedures for the salts were those of Crum Brown and Walker, *Ann.*, **274**, 41 (1893), except that 4-5% of water was added to the solvent alcohols.

was added during a period of one hour, while the mixture was stirred and heated on a steam-bath. Heating and stirring were continued for eight hours after completion of the addition. The resulting deep red mixture was washed twice with 600 ml. portions of water, then 600 ml. of ether was added and the solution was washed with 500 ml. of 5% sodium bicarbonate solution, and with 600 ml. of water. The solution was dried over Drierite, the ether was removed by distillation, and the residual oil was distilled at reduced pressure. The fraction collected at 141–145° (1 mm.) consisted of methyl β-anilinopropionate and weighed 302 g. (57% yield). The slightly yellow product solidified upon standing, and was recrystallized from a methanol–water solution to yield colorless plates, m. p. 37–38°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31. Found: C, 66.95; H, 6.95.

Howton,[16] who prepared the substance in 14% yield by conducting the same reaction in methanol solution, reported the m. p. 37.6–38.3°.

The β-anilinopropionic acid used in the experiments described below was prepared by the method of Bischoff and Mintz[17] from β-iodopropionic acid and aniline. It now appears that this substance can be obtained much more conveniently by the saponification of methyl β-anilinopropionate. To a solution of 21 g. of the ester in 25 ml. of methanol, a solution of 7.8 g. of potassium hydroxide in 25 ml. of methanol was added. The mixture was heated for one hour on a steam-bath and the methanol was allowed to distill until the volume of solution was about 35 ml. After the mixture had cooled, it was diluted with ether added in small portions with shaking until the final volume was about 200 ml. The precipitated potassium salt formed well-defined white crystals when the mixture was allowed to stand overnight. The salt (20.3 g.) was removed by filtration and dissolved in 50 ml. of water. Addition of 17 ml. of 6*N* sulfuric acid to the solution precipitated β-anilinopropionic acid as a nearly colorless oil which was extracted into 50 ml. of chloroform. Evaporation of the chloroform solution (dried over sodium sulfate) at reduced pressure left an oil which solidified completely to nearly colorless crystals, m. p. 53–57°. The yield was 12.5 g. (65%). A single crystallization from carbon tetrachloride raised the m. p. to 59–60°, the value given by Bischoff and Mintz[17]; the product was shown by the mixed melting point test to be the same as that obtained by the older method.

β-Anilino-β-phenylpropionic Acid.—This compound was obtained by the alkaline hydrolysis of its lactam, which was conveniently prepared by the method of Gilman and Speeter.[18] It had previously been made by the reaction of β-bromo-β-phenylpropionic acid with aniline.[19]

A solution of 50 g. of the lactam, m. p. 151–152°, and 20 g. of potassium hydroxide in 500 ml. of alcohol was heated for three hours at the reflux temperature. The mixture was poured into 2.5 liters of water, treated with Darco at the boiling point for fifteen minutes, and filtered. After the solution had cooled, the acid was precipitated by the addition of 15% hydrochloric acid until a *p*H of approximately 4 was reached. The product was removed by filtration, washed with water, and dried. The yield was 49 g. (97%) of a product melting at 135–137°. Fourneau and Billeter[19] reported a melting point of 134°.

N-Methoxalyl and N-Ethoxalyl Derivatives of β-Anilino and β-Amino-propionic Acids (Table I).—An excess of methoxalyl or ethoxalyl chloride was used as the solvent in the preparation of these derivatives. The β-anilino acids, β-anilinopropionic acid and β-anilino-β-phenylpropionic acid, were heated for one-half hour on a steam-bath with twice their weight or slightly more of the acid chloride. In the case of β-amino-β-phenylpropionic acid[20] it was necessary to use a larger quantity of the ethoxalyl chloride (five times the weight of acid) and a longer heating period (two hours) because of the insolubility of the acid. After the heating period, the resulting clear solutions were diluted with approximately five volumes of ether, washed twice with water, and extracted with an excess of 5% sodium bicarbonate solution. The bicarbonate extracts were then acidified with 5% hydrochloric acid and the products were extracted into ether. The final ether solutions were then washed twice with water, dried over Drierite, and concentrated at reduced pressure. The residues, which crystallized upon standing, were recrystallized from chloroform–petroleum ether mixtures. It is noteworthy that when the alkoxalyl chlorides were used in excess, as described, the β-anilino acids were converted into their alkoxalyl derivatives in yields (Table I) well above 50%, although there was no base present to remove the hydrogen chloride formed.

Methyl N-Methoxalyl-β-anilino-β-phenylpropionate.—To a suspension of 4 g. of N-methoxalyl-β-anilino-β-phenylpropionic acid in ether, an ethereal solution of diazomethane[21] was added in portions until a faint yellow color showed the presence of a slight excess of diazomethane. The ether was then removed by evaporation, and the product was recrystallized from a methanol–water mixture. There was obtained 3.5 g. (83%) of white needles, m. p. 75–77°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61. Found: C, 66.64, 66.54; H, 5.89, 5.60.

An effort to bring about the ring closure of this compound to methyl 1,5-diphenyl-2-keto-3-methoxy-Δ^3-pyrroline-4-carboxylate (VI) by heating with acetic anhydride and pyridine was unsuccessful; the solution remained nearly colorless and the starting material was recovered unchanged.

Ring Closure of N-Alkoxalyl-β-anilinopropionic Acids (I, II, III) to 1-Phenyl-2-keto-3-alkoxy-Δ^3-pyrroline-4-carboxylic Acids (V, VIII, X).—Procedure A. Pyridine-Alkoxalyl Chloride Method.—N-Methoxalyl-β-anilino-β-phenylpropionic acid (I), N-ethoxalyl-β-anilino-β-phenylpropionic acid (II), or N-ethoxalyl-β-anilinopropionic acid (III) and an equal weight of ethoxalyl or methoxalyl chloride were dissolved in dry chloroform, using approximately 2 ml. of chloroform per gram of acid. (Dioxane was also used as the solvent with similar results.) Anhydrous pyridine was then added slowly to the solution until a weight of pyridine equal to the weight of acid had been introduced. If the mixture was not cooled during the addition, the temperature was observed to rise to about 50°, and a deep-red color developed immediately; with cooling, the color developed more slowly. The mixtures were allowed to stand for a period of about one-half hour at room temperature, then were diluted with about five volumes of chloroform and the resulting solutions were shaken with an equal volume of water in a mechanical shaker for two hours to remove the pyridine and complete the decomposition of excess acid chloride. After the solutions had been washed with water, the products were extracted by shaking for several hours with an excess of 5% sodium bicarbonate solution. The extracts were heated with Darco, filtered and acidified with 5% hydrochloric acid to precipitate the products, which separated completely only after the solutions had been cooled and allowed to stand for several hours. The crude pyrroline-carboxylic acids as obtained by this procedure usually melted within five or six degrees of the melting points of the purified compounds. Representative yields were as follows: Compound V, 26%; Compound VIII, 32%; Compound X, 15%. Final purification was by recrystallization from ethanol–water or methanol solutions, from which each of the compounds separated in the form of white needles. The pyrroline-carboxylic acids reduced solutions of potassium permanganate in acetone–water quite rapidly at room temperature; the N-alkoxalyl-β-anilinopropionic acids did not.

No tendency for the exchange of the alkoxyl group of

(16) Howton, *J. Org. Chem.*, **10**, 277 (1945).

(17) Bischoff and Mintz, *Ber.*, **25**, 2351 (1892).

(18) Gilman and Speeter, THIS JOURNAL, **65**, 2255 (1943).

(19) Fourneau and Billeter, *Bull. soc. chim.*, **7**, 593 (1940).

(20) Prepared by the method of Posner, *Ber.*, **38**, 2320 (1905).

(21) Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

the pyrroline with that of the solvent alcohol was noticed when these were different as, for example, when methanol was used for the recrystallization of the 3-ethoxy derivative (VIII). There was no difference in the result when the alkoxalyl group of the acid chloride used for the ring closure was not the same as that of the N-alkoxalyl-β-anilinopropionic acid; when methoxalyl chloride was used for the ring closure of N-ethoxalyl-β-anilino-β-phenylpropionic acid, the product was the 3-ethoxypyrroline derivative (VIII).

By suitable modification of the original experiment which led to the discovery of this reaction, the pyrroline-carboxylic acids could be prepared from β-anilinopropionic acids in approximately the same yields without isolation of the intermediate N-alkoxalyl derivatives. In the one-step process, the best results were obtained when the quantities of alkoxalyl chloride and pyridine mentioned above were doubled. Otherwise the procedure was the same, except that in some successful experiments, no solvent other than pyridine was used.

Concentration of the chloroform solutions from which the pyrroline-carboxylic acids had been extracted left red-brown glassy materials. Efforts to separate pure products from these neutral fractions were usually unsuccessful. However, in an experiment in which 2.7 g. of ethoxalyl chloride was added to a solution of 2.5 g. of β-anilino-β-phenylpropionic acid and 3.3 g. of triethylamine in 15 ml. of chloroform, treatment of the neutral fraction with 15 ml. of saturated alcoholic potassium hydroxide solution dissolved a portion of the material and left an insoluble residue which melted at 148° after several recrystallizations from alcohol. The melting point of this substance was not depressed when it was mixed with an authentic sample of cinnamanilide. Only a trace of the pyrroline-carboxylic acid (VIII) was isolated from this run.

Procedure B. Pyridine–Acetic Anhydride Method.—The ring closure by means of acetic anhydride and pyridine was investigated only in the case of N-ethoxalyl-β-anilino-β-phenylpropionic acid (II). To a solution of 3 g. of that substance in 7 g. of acetic anhydride, 7 g. of anhydrous pyridine was added. The mixture was heated for three hours on a steam-bath while it gradually assumed a deep red color. Most of the pyridine, acetic acid and excess acetic anhydride were then removed by distillation at reduced pressure, and the remaining dark red oil was dissolved in 50 ml. of chloroform. The product was isolated from this solution as in procedure A. The yield was 0.29 g. (10%) of a white powder melting at 195–200° with decomposition. Recrystallization from 95% ethanol raised the melting point to 214–215°. A mixture of this product with one obtained by procedure A showed no depression in melting point.

Heating of the N-ethoxalyl derivative (II) at 100° with either pyridine or acetic anhydride in the absence of the other failed to bring about the ring closure; the starting material was recovered unchanged.

Methyl and Ethyl 1,5-Diphenyl-2,3-pyrrolidinedione-4-carboxylates (XII, XIII).—These compounds were made by procedures based on the work of Schiff and Bertini.[10] Both gave characteristic deep red-brown colors with ferric chloride solution.

Methyl Ester.—To a solution of 1.72 g. of benzalaniline in 25 ml. of ether was added 1.52 g. of methyl oxalacetate.[22] The solution was refluxed for fifteen minutes and allowed to stand overnight. At the end of this period the product had precipitated in the form of fine, white needles, and was removed by filtration. The yield was 2.15 g. (66%) of a product melting at 198–200°. Recrystallization from 95% ethanol raised the m. p. to 201–203° (Table II).

Ethyl Ester.[10]—An ethereal solution of ethyl oxalacetate was prepared by suspending 100 g. of the sodium enolate (U. S. Industrial Chemicals) in water, acidifying the mixture with 20% sulfuric acid, and extracting the free ester into 600 ml. of ether. After the resulting solution had been washed with water and dried, 70 g. of benzalaniline was added and the mixture was heated for fifteen minutes at the reflux temperature, then allowed to stand overnight. At the end of this period, 55 g. of the pyrrolidinedione, m. p. 170–174°, had precipitated. Some additional product was obtained by concentration of the solution. Following recrystallization from ethanol, 49 g. (40% based on benzalaniline) of the compound was obtained in the form of faintly yellow needles, m. p. 173–175° (Table II).

Methyl 1-Phenyl-2,3-pyrrolidinedione-4-carboxylate (XIV).—A solution of 7.2 g. of methyl β-anilinopropionate and 4.8 g. of methyl oxalate in 50 ml. of anhydrous ether was added over a period of fifteen minutes to a suspension of 2.5 g. of sodium methoxide in 50 ml. of anhydrous ether. A pale-yellow precipitate formed immediately. The mixture was heated at the reflux temperature for two hours, then the precipitate was removed by filtration and washed with 25 ml. of anhydrous ether. This material, which consisted in part of the sodium enolate of the pyrrolidinedione, weighed 8.5 g. It was dissolved in 250 cc. of hot water, and the solution was acidified by the addition of 5% hydrochloric acid. The product precipitated in the form of a white powder, m. p. 145–170°; the yield of this crude material was 3.4 g. (38%). After crystallization from methanol, white needles, m. p. 185–187°, were obtained (Table II). The substance gives a deep red color with ferric chloride solution.

Preparation of 3-Alkoxy-Δ³-pyrroline Derivatives (VI, VII, IX, XI) by Esterification of the Pyrrolinecarboxylic Acids (V, VIII, X).—The pyrrolinecarboxylic acids V, VIII and X were esterified by the use of ethereal solutions of diazomethane and diazoethane prepared from nitrosomethylurea and nitrosoethylurea, respectively.[21,23] The diazoethane solutions were distilled before use, but the diazomethane solutions were not. The acids were suspended in ether and the solutions of the diazo compounds were added in small portions until the acids dissolved and a slight excess of the diazo compound was indicated by the faint yellow color of the solution. The ether was removed by distillation and the esters were crystallized from methanol–water solutions. Compounds VI, VII, IX and XI were obtained in this way as colorless needles. Yields of once-recrystallized products, which in every case melted within 2° of the melting point of the fully-purified samples, ranged from 81% (XI) to 93% (VI).

Preparation of 3-Alkoxy-Δ³-pyrroline Derivatives (VI, VII, IX, XI) from 2,3-Pyrrolidinediones (XII, XIII, XIV).—The pyrrolidinediones were suspended in ether and treated with etheral solutions of diazomethane or diazoethane in the same manner as were the pyrroline-carboxylic acids. The reactions were rapid. After removal of the ether, the products were recrystallized from methanol–water mixtures. The yields of once-recrystallized products, which in each case melted within 2° of the melting point of pure samples, ranged from 83% (VII) to 95% (VI).

Each of these substances was compared with the corresponding compound obtained by the esterification of the appropriate pyrrolinecarboxylic acid, as described in the section above. In each case the products secured by the two routes were identical in melting point and in no case was the melting point of a mixture of the two depressed.

Summary

1. The N-methoxalyl and N-ethoxalyl derivatives of β-anilino-β-phenylpropionic acid and the N-ethoxalyl derivatives of β-anilinopropionic acid and β-amino-β-phenylpropionic acid have been described.

2. The N-alkoxalyl derivatives of β-anilinopropionic acid and β-anilino-β-phenylpropionic acid have been found to undergo ring closure to 1-phenyl and 1,5-diphenyl-2-keto-3-alkoxy-Δ³-pyrroline-4-carboxylic acids respectively, in the pres-

(22) Wislicenus and Grossman, *Ann.*, **277**, 375 (1893).

(23) Werner, *J. Chem. Soc.*, **115**, 1093 (1919).

ence of pyridine and methoxalyl or ethoxalyl chloride, or in the presence of pyridine and acetic anhydride. A pyrroline-carboxylic acid was not obtained under the same conditions from N-ethoxalyl-β-amino-β-phenylpropionic acid.

3. The pyrroline-carboxylic acids were esterified with diazomethane and diazoethane. The products so obtained were identical with pyrroline derivatives prepared by the reaction of diazomethane and diazoethane upon the methyl and ethyl esters of 1,5-diphenyl-2,3-pyrrolidinedione-4-carboxylic acid, and the methyl ester of 1-phenyl-2,3-pyrrolidinedione-4-carboxylic acid.

4. A mechanism has been proposed for the ring closure reaction which relates it to the Perkin reaction and to the Claisen condensation.

PITTSBURGH 13, PENNSYLVANIA
RECEIVED JANUARY 22, 1949

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Pteridines. V. Deamination Studies on Certain Aminopteridines

BY E. C. TAYLOR, JR.,[1] AND C. K. CAIN

A previous paper[2] has described the different behavior toward acid hydrolysis of amino groups in the 2- and 4- positions of certain pyrimidine derivatives. There is also a difference in the reactivity of amino groups in the 2- and 6-positions of the purine nucleus, most strikingly demonstrated by the selective action of nitrous acid. Fischer[3] observed that the amino group of 2-amino-6-hydroxypurine (guanine) can be replaced by a hydroxyl group upon treatment with hot dilute (6 *N*) sulfuric acid and sodium nitrite but that 6-amino-2-hydroxypurine (isoguanine) is unaffected under the same conditions.[4] The latter has also been noted by other workers.[5,6] Hydrolysis of the amino group of isoguanine was effected, however, by boiling with 6 *N* hydrochloric acid for forty-five hours,[6,7] conditions which are also effective in hydrolyzing the amino group of guanine.[8]

A corresponding difference in the reactivity toward nitrous acid of the amino groups in the 2- and 4-positions of certain substituted pteridines was also observed. The amino group of 2-amino-4,6,7-trihydroxypteridine (leucopterin) may be replaced by a hydroxyl group upon treatment with strong (29 *N*) sulfuric acid and sodium nitrite,[9,10] whereas 4-amino-2,6,7-trihydroxypteridine (isoleucopterin) is not affected under the same conditions.[11] Likewise, a 2-amino-4-hydroxypteridine derivative (rhizopterin) is deaminated by the action of nitrous acid on a solution of the compound in a mixture of hydrochloric and acetic acids.[12] The substituents on the pyrazine portion of the pteridine nucleus seem to have a profound influence on the reactivity of the entire molecule, for 2-amino-4,6-dihydroxypteridine (xanthopterin) is deaminated normally under the conditions used above for rhizopterin,[12] although the molecule is completely disrupted by the action of nitrosylsulfuric acid.[13]

The purpose of the present investigation was to ascertain whether this behavior is confined to pterins of the xanthopterin–leucopterin series or is a general phenomenon and to find if possible some correlation between chemical reactivity and structure.

Studies on several variously substituted pteridines have shown that this difference in reactivity of amino groups in the 2- and 4-positions is not restricted to the above examples. An amino group in the 2-position of certain pterins may be replaced by a hydroxyl group by the action of nitrous acid. For example, 2-amino-4-hydroxypteridine and 2-amino-4-hydroxy-6,7-dimethylpteridine are smoothly converted to the corresponding 2,4-dihydroxypteridines by the addition of sodium nitrite solution to a solution of the pterin in boiling 7 *N* sulfuric acid. However, 2-amino-4-hydroxy-6,7-diphenylpteridine is unaltered not only under these conditions but even when a sulfuric acid solution is heated with nitrosylsulfuric acid. An amino group in the 4-position has been shown to be resistant to the action of nitrous acid; for example, 4-amino-2-hydroxypteridine and 4-amino-2-hydroxy-6,7-diphenylpteridine are unaffected under any of the above conditions. Contrary to expectation, it has been found that several 2,4-diaminopteridines are unaltered by nitrous acid regardless of the substitution on the pyrazine portion of the nucleus.

We have found that although an amino group in the 4-position of the pteridine nucleus is resistant to the action of nitrous acid, it may be removed readily by hydrolysis with dilute mineral acid under even milder conditions than required for the analogous hydrolysis in the purine series mentioned above. 2,4-Diaminopteridine, 2,4-diamino-6,7-dimethylpteridine and 2,4-diamino-

(1) U. S. Rubber Company Fellow in Chemistry, 1948–1949.
(2) Taylor and Cain, THIS JOURNAL, **71**, 2282 (1949).
(3) Fischer, *Ann.*, **215**, 253 (1882).
(4) Fischer, *Ber.*, **30**, 2226 (1897).
(5) Cherbuliez and Bernhard, *Helv. Chim. Acta*, **15**, 464 (1932).
(6) Purrmann, *Ann.*, **544**, 182 (1940).
(7) Spies, THIS JOURNAL, **61**, 350 (1939).
(8) Fischer, *Ber.*, **43**, 805 (1910).
(9) Wieland, Metzger, Schöpf and Bulow, *Ann.*, **507**, 226 (1933).
(10) Wieland and Purrmann, *ibid.*, **544**, 163 (1940).
(11) Wieland and Liebig, *ibid.*, **555**, 146 (1944).
(12) Wolf, Anderson, Kaczka, Harris, Arth, Southwick, Mozingo and Folkers, THIS JOURNAL, **69**, 2753 (1947).
(13) Schöpf and Kottler, *Ann.*, **539**, 128 (1939).