removed *in vacuo*. The resulting free base was dissolved in ethyl acetate and with stirring and cooling ethanolic hydrogen chloride was slowly added. The tan powder which precipitated was recrystallized from 3A alcohol to yield 24 g. (76%) of colorless crystals with the properties indicated in Table I.

The aminoketone hydrochloride was simultaneously debenzylated and converted to the aminoalcohol in aqueous solution using a Parr apparatus at 60° and palladium–charcoal as the catalyst. The filtrate from the catalyst was evaporated *in vacuo* to dryness and the product recrystallized from a mixture of ethanol and ether. It had the properties indicated in Table I.

**N-[β-Hydroxy-α,β-diphenylethyl]-pyrrolidine Hydrochloride (Method D, Compound 24).**—Twenty-one and two tenths grams (0.1 mole) of benzoin, 7.1 g. (0.1 mole) of pyrrolidine and 2 g. of phosphorus pentoxide were mixed and heated on a steam-bath for four hours. The cooled product was triturated with ether, the ether extracted with dilute hydrochloric acid and the acid solution was treated with decolorizing charcoal and filtered. The filtrate was basified with sodium hydroxide and extracted with ether. The ether layer was washed with water and dried, and to it was added a slight excess of ethanolic hydrogen chloride. The solid product was recrystallized from an ethanol–ether mixture to give 18 g. (60%) of colorless crystals with the properties indicated in Table I.

The above aminoketone hydrochloride was converted to the free base in ether and the ether solution dried. This solution (200 ml.) was added dropwise to a well-stirred and refluxing solution of 6 g. of lithium aluminum hydride in 200 ml. of dry ether. After the addition was complete, stirring and heating were continued for half an hour, after which time 25 ml. of water was added very carefully dropwise with cooling in an ice-bath. The mixture was poured into one liter of 10% sodium hydroxide solution, extracted with ether and the ether was washed and dried over sodium sulfate. The solvent was removed *in vacuo*, the product dissolved in ethyl acetate and a slight excess of ethanolic hydrogen chloride was added. The white crystalline solid was recrystallized from an ethanol–ether mixture to give 9 g. (50%) of colorless crystals having the properties indicated in Table I.

**N-[β-Hydroxy-α,β-diphenylethyl]-piperidine Hydrochloride (Method D).**—Following the procedure described above for the synthesis of α-pyrrolidyl-α-phenylacetophenone, piperidine was condensed with benzoin using a catalytic amount of phosphorus pentoxide. The solid free base of the resulting α-piperidyl-α-phenylacetophenone was isolated and recrystallized several times from 80% 3A alcohol, m.p. 82–84°, 57% yield. Lutz, Freek and Murphey[6] reported m.p. 82–83° (from desyl chloride and piperidine).

*Anal.* Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57; N, 5.01. Found: C, 81.85; H, 7.64; N, 5.02.

The hydrochloride was prepared by dissolving the free base in ethyl acetate and adding excess ethanolic hydrogen chloride. The gummy precipitate was recrystallized several times from ethanol–ether, m.p. 236–238° (dec.). Lutz, Freek and Murphey[6] reported m.p. 225–227° (dec.) while Goodson and Moffett[23] reported m.p. 239–242° (from desyl bromide and piperidine).

In an attempt to catalytically reduce α-piperidyl-α-phenylacetophenone hydrochloride to N-[β-hydroxy-α,β-diphenylethyl]-piperidine hydrochloride in water over 10% palladium charcoal, the hydrogen uptake started slowly but after four hours had rapidly advanced to 150% of theory. At this point the catalyst was removed and an oily layer was extracted out with benzene. Distillation of the benzene left a yellow oil with neutral odor, probably benzyl phenylcarbinol. Basification of the aqueous portion liberated a strong amine odor, probably piperidine. Extraction of the basic aqueous portion with ether, followed by addition of ethanolic hydrogen chloride yielded an oil and a solid. The oil was probably the very soluble piperidine hydrochloride while the solid had m.p. 236–237° (dec.) corresponding to the starting material.

In the same manner as the reduction of the α-pyrrolidyl-α-phenylacetophenone described above, the α-piperidyl-α-phenylacetophenone was reduced chemically with lithium aluminum hydride. The solid free base was isolated and recrystallized from 90% 3A-alcohol, m.p. 108–110°. Lutz, Freek and Murphey[6] reported m.p. 109–110° (aluminum isopropoxide reduction).

*Anal.* Calcd. for $C_{19}H_{23}NO$: C, 81.09; H, 8.23; N, 4.98. Found: C, 81.50; H, 8.22; N, 4.91.

The hydrochloride was prepared by dissolving the free base in ethyl acetate and adding excess ethanolic hydrogen chloride. It was recrystallized several times from an isopropyl alcohol–methanol mixture, m.p. 255–257°. Lutz, Freek and Murphey[6] reported m.p. 259–260°, while Goodson and Moffett[23] reported m.p. 240–243° (also aluminum isopropoxide reduction).

*Anal.* Calcd. for $C_{19}H_{24}ClNO$: C, 71.79; H, 7.61; N, 4.41; Cl, 11.16. Found: C, 71.86; H, 7.66; N, 4.27; Cl, 11.14.

(23) L. H. Goodson and R. B. Moffett, THIS JOURNAL, **71**, 3219 (1949).

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

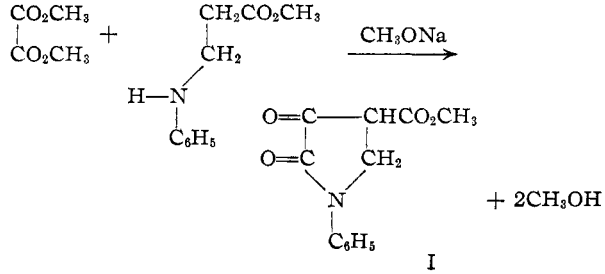
# The Condensation of Oxalic Esters with Esters of β-Alanine and N-Substituted β-Aminopropionic Acids. Synthesis of Some Derivatives of 2,3-Dioxopyrrolidine and 2-Oxo-3-methoxy-3-pyrroline

BY PHILIP L. SOUTHWICK AND ROBERT T. CROUCH[1]

RECEIVED MARCH 18, 1953

The condensation of methyl or ethyl oxalate with a series of N-substituted β-aminopropionic esters has yielded a series of 4-carbomethoxy and 4-carbethoxy-2,3-dioxopyrrolidines with phenyl, *p*-tolyl, *m*-chlorophenyl, *p*-methoxyphenyl, benzyl and cyclohexyl groups at position 1. A similar compound unsubstituted in position 1 is also described. The dioxopyrrolidines were converted into 4-carboalkoxy-2-oxo-3-methoxy-3-pyrrolines by treatment with diazomethane. The 4-carboalkoxy-1-benzyl-2,3-dioxopyrrolidines were hydrolyzed and decarboxylated to 1-benzyl-2,3-dioxopyrrolidine.

In a recent publication[2] from this Laboratory a synthesis was described for the compound 4-carbomethoxy-1-phenyl-2,3-dioxopyrrolidine (I)[3] by means of the condensation of methyl oxalate with methyl β-anilinopropionate in the presence of sodium methoxide




I

(1) Du Pont Fellow in Chemistry, 1951–1952.

(2) P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2532 (1949).

(3) Referred to as 1-phenyl-4-carbomethoxy-2,3-pyrrolidinedione in ref. 2.

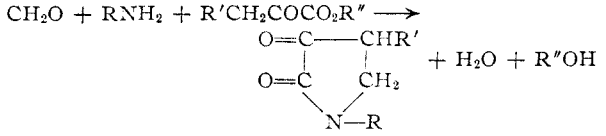
Since this reaction of an oxalic ester with an ester of a β-aminopropionic acid represented a new method for closure of the pyrrolidine ring, a study has been made of the value of similar reactions when applied to the preparation of 2,3-dioxopyrrolidines with other substituents (or hydrogen) on the nitrogen atom. Attention was directed primarily to the synthesis of 2,3-dioxopyrrolidine derivatives having no substituent at position 5, for no general method for obtaining such compounds has previously been available, and we have found reports in the literature of only two such compounds, 4-phenyl-2,3-dioxopyrrolidine[4,5] and 1,4-diphenyl-2,3-dioxopyrrolidine.[6,7]

The condensation reactions of the methyl and ethyl β-aminopropionates with the corresponding oxalates were conducted by use of the appropriate sodium alkoxides in suspension in the reaction mixtures. In the reactions of methyl oxalate with the methyl esters, ether was used to dissolve the solid methyl oxalate, but no solvent was needed in the condensations of ethyl esters with ethyl oxalate. However, better than average yields were obtained in the last of the preparations performed, in which sodium ethoxide was used in ethanol solution to give an initially homogeneous reaction mixture. This last procedure has been tested with only two of the compounds. In its application to the preparation of 4-carbethoxy-2,3-dioxopyrrolidine, the hydrochloride of ethyl β-aminopropionate was used and a second mole of sodium ethoxide was needed.

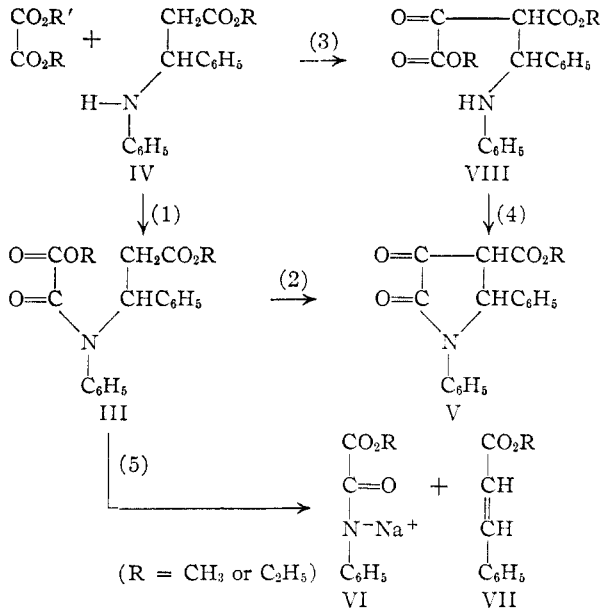
The formation of the pyrrolidine ring by the method reported here involves a Claisen ester condensation and the formation of an amide (or lactam) linkage. The results of experiments with the N-alkoxalyl derivatives (III) suggest that such compounds are not important as intermediates in the formation of the 2,3-dioxopyrrolidines (V) by the oxalate condensation, for treatment of the compounds III with sodium alkoxides gave very low yields of the dioxopyrrolidines V and resulted chiefly in an elimination reaction (reaction (5)) yielding the cinnamates VII and the sodium salts of oxanilides (VI).

It is possible that N-alkoxalyl derivatives similar to III are important as intermediates in the conversion of some of the other amino propionates into dioxopyrrolidines *via* reactions such as (1) and (2), but it seems likely that in most cases the initial Claisen condensation (reaction (3)) to compounds similar to VIII, followed by lactam ring-closure (reaction (4)) represents the principal path of reaction.

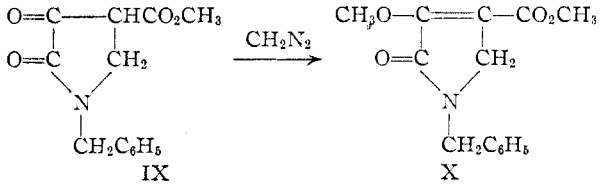
(4) H. Rupe and B. Pieper, *Helv. Chim. Acta*, **12**, 637 (1929).
(5) C. F. Winans and H. Adkins, THIS JOURNAL, **55**, 4167 (1933).
(6) W. Borsche, *Ber.*, **42**, 4072 (1909).
(7) To prepare 2,3-dioxopyrrolidines with no substituent in position 5 by means of one of the variations of the previously employed general method (reaction of an aldehyde, a primary amine and a pyruvic acid derivative) would require the use of formaldehyde



There appears to be only one report of the successful use of formaldehyde in such a synthesis (see ref. 6), and the method failed in an attempted preparation of compound I (P. L. Southwick and L. L. Seivard, unpublished work).



Data on the 2,3-dioxopyrrolidines obtained are provided in Table I. These compounds displayed the properties expected of readily enolized substances. They gave red colors with ferric chloride and showed a sufficient acidity to be converted into sodium or potassium enolates upon contact with aqueous sodium or potassium bicarbonate solutions. The salts have only a limited solubility in water and give rise to soapy solutions or suspensions. The acidity of the compounds is also manifest in their rapid reactions with diazomethane to give high yields of 2-oxo-3-methoxy-3-pyrrolines,[2] as illustrated by the equation



Data on the compounds prepared in this way are presented in Table II. The assumption that the reaction with diazomethane resulted in methylation of the oxygen at position 3, and hence to the formation of 3-methoxy-3-pyrroline derivatives is supported by the results of previous work[2] and by the preparation of the compound X (although only in low yield) through use of another method of ring closure[2] which can lead only to a methoxyl derivative of this type

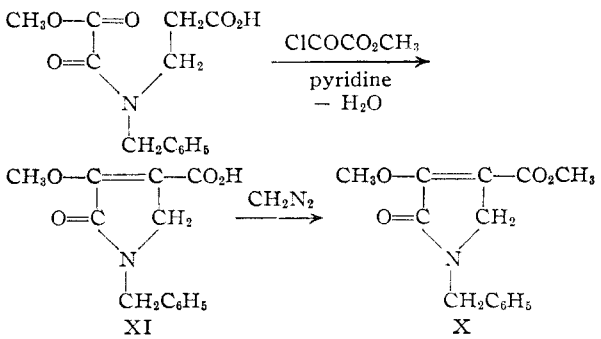
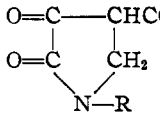


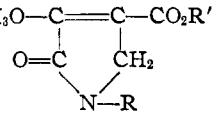
TABLE I

4-CARBOALKOXY-2,3-DIOXOPYRROLIDINES, 

| R | R′ | Yield,[a] % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| *p*-$CH_3C_6H_4$ | $CH_3$ | 45(A) | 193–194[b] | $C_{13}H_{13}O_4N$ | 63.15 | 63.09 | 5.30 | 5.33 | 5.66 | 5.50 |
| *p*-$CH_3C_6H_4$ | $C_2H_5$ | 52(B) | 156[c] | $C_{14}H_{15}O_4N$ | 64.35 | 64.02 | 5.79 | 5.70 | 5.36 | 5.50 |
| *m*-$ClC_6H_4$ | $CH_3$ | 29(A) | 185–186[b] | $C_{12}H_{10}O_4NCl$ | 53.84 | 53.47 | 3.73 | 3.76 | 5.23 | 5.45 |
| *m*-$ClC_6H_4$ | $C_2H_5$ | 37(B) | 142–143[c] | $C_{13}H_{12}O_4NCl$ | 55.42 | 55.36 | 4.30 | 4.51 | 4.97 | 4.90 |
| *p*-$CH_3OC_6H_4$ | $CH_3$ | 30(A) | 209–210[d] | $C_{13}H_{13}O_5N$ | 59.31 | 59.50 | 4.98 | 4.97 | 5.32 | 5.22 |
| *p*-$CH_3OC_6H_4$ | $C_2H_5$ | 55(B) | 160–161[e] | $C_{14}H_{15}O_5N$ | 60.64 | 60.50 | 5.45 | 5.50 | | |
| $C_6H_5$ | $C_2H_5$ | 48(A) | 153[c] | $C_{13}H_{13}O_4N$ | 63.15 | 62.96 | 5.30 | 5.15 | 5.66 | 5.61 |
| Cyclo-$C_6H_{11}$ | $CH_3$ | 29(A) | 178–179[b] | $C_{12}H_{17}O_4N$ | 60.23 | 60.05 | 7.16 | 7.15 | 5.85 | 6.16 |
| Cyclo-$C_6H_{11}$ | $C_2H_5$ | 65(B) | 188[c] | $C_{13}H_{19}O_4N$ | 61.64 | 61.51 | 7.56 | 7.59 | 5.53 | 5.88 |
| $C_6H_5CH_2$ | $CH_3$ | 75(A) | 183–184[b] | $C_{13}H_{13}O_4N$ | 63.15 | 63.34 | 5.30 | 5.36 | 5.66 | 5.72 |
| $C_6H_5CH_2$ | $C_2H_5$ | 75(B) | 135–136[c] | $C_{14}H_{15}O_4N$ | 64.35 | 64.56 | 5.79 | 5.88 | 5.36 | 5.41 |
| | | | | | | 64.18 | | 5.79 | | |
| H | $C_2H_5$ | 72(C) | 185–186[f] | $C_7H_9O_4N$ | 49.12 | 49.43 | 5.30 | 5.32 | 8.13 | 8.00 |

[a] The letters A, B and C following yield figures indicate the procedure used in the preparation (see Experimental section). Figures represent conversions uncorrected for amounts of recovered amino ester, which were appreciable in cases of low conversions. [b] Colorless needles from methanol. [c] Colorless needles from ethanol. [d] Yellow needles from methanol. [e] Yellow needles from ethanol. [f] White plates from ethanol. M.p. obtained with bath preheated to 175°.

TABLE II

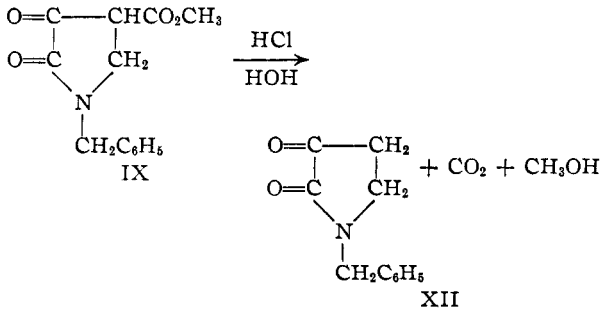
4-CARBOALKOXY-2-OXO-3-METHOXY-3-PYRROLINES, 

| R | R′ | Yield, % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| *p*-$CH_3C_6H_4$ | $CH_3$ | 95 | 141–142[a] | $C_{14}H_{15}O_4N$ | 64.35 | 64.58 | 5.79 | 5.87 | | |
| *p*-$CH_3C_6H_4$ | $C_2H_5$ | 95 | 82–83[b] | $C_{15}H_{17}O_4N$ | 65.44 | 65.23 | 6.23 | 6.05 | 5.09 | 5.24 |
| *m*-$ClC_6H_4$ | $CH_3$ | 86 | 115–116[a] | $C_{13}H_{12}O_4NCl$ | 55.42 | 55.43 | 4.30 | 4.27 | | |
| *m*-$ClC_6H_4$ | $C_2H_5$ | 91 | 140–141[b] | $C_{14}H_{14}O_4NCl$ | 56.86 | 56.56 | 4.77 | 4.78 | 4.74 | 4.70 |
| *p*-$CH_3OC_6H_4$ | $CH_3$ | 94 | 133–134[c] | $C_{14}H_{15}O_5N$ | 60.64 | 60.85 | 5.45 | 5.45 | | |
| *p*-$CH_3OC_6H_4$ | $C_2H_5$ | 95 | 109–110[b] | $C_{15}H_{17}O_5N$ | 61.84 | 61.55 | 5.88 | 5.80 | 4.81 | 5.06 |
| Cyclo-$C_6H_{11}$ | $CH_3$ | 95 | 103–104[a] | $C_{13}H_{19}O_4N$ | 61.64 | 61.91 | 7.56 | 7.55 | | |
| Cyclo-$C_6H_{11}$ | $C_2H_5$ | 91 | 86–87[b] | $C_{14}H_{21}O_4N$ | 62.90 | 62.99 | 7.92 | 7.77 | 5.24 | 5.50 |
| $C_6H_5CH_2$ | $CH_3$ | 95 | 77–78[a] | $C_{14}H_{15}O_4N$ | 61.64 | 61.91 | 7.56 | 7.55 | | |
| $C_6H_5$ | $C_2H_5$ | 95 | 76–77[b] | $C_{14}H_{15}O_4N$ | 64.35 | 64.38 | 5.79 | 5.82 | 5.36 | 5.50 |
| H | $C_2H_5$ | 74 | 105–106[a] | $C_6H_{11}O_4N$ | 51.81 | 51.90 | 5.99 | 5.85 | 7.57 | 7.25 |
| | | | | | | 51.84 | | 5.58 | | |

[a] Colorless needles from methanol. [b] Colorless needles from ethanol. [c] Light-yellow needles from methanol.

Except for ethyl β-aminopropionate itself (made by esterification of β-alanine), the β-aminopropionic esters required for the synthesis of the dioxopyrrolidines were prepared by the addition of primary amines to methyl or ethyl acrylate. The addition of the aromatic amines was conducted in the presence of acetic acid[8] or stannic chloride[9] to serve as catalysts; the addition of the other amines did not require such catalysis. Table III records the pertinent data concerning the amino esters prepared in the course of this work which were new or prepared by methods other than those described for them in the literature.

The hydrolysis and decarboxylation of 4-carbomethoxy-1-benzyl-2,3-dioxopyrrolidine (IX) was investigated. By boiling this compound (or the corresponding ethyl ester) with 20% hydrochloric acid it was converted into 1-benzyl-2,3-dioxopyrrolidine



IX XII

It is likely that other simple 2,3-dioxopyrrolidines of the type illustrated by XII can be made by acid hydrolysis of the corresponding 4-carboalkoxy derivatives.

An investigation of the reactions of the dioxopyrrolidines and 3-pyrrolines described here is in progress.

(8) R. C. Elderfield, W. J. Gensler, T. H. Bembry, C. B. Kremer, F. Brody, H. A. Hageman and J. D. Head, THIS JOURNAL, **68**, 1259 (1946).

(9) W. S. Johnson, E. L. Woroch and B. G. Buell, *ibid.*, **71**, 1901 (1949).

TABLE III

β-AMINOPROPIONATES, R—NH—$CH_2CH_2CO_2R'$

| R | R' | Yield,[a] % | B.p., °C. | Mm. | M.p. of hydrochloride, °C. | Formula[c] | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *p*-$CH_3C_6H_4$ | $CH_3$ | 67(C) | 145–150[b] | 5–6 | | $C_{11}H_{15}O_2N$ | 68.37 | 68.58 | 7.82 | 7.81 | 7.25 | 7.30 |
| *p*-$CH_3C_6H_4$ | $C_2H_5$ | 50(B) | 142–144 | 2–3 | 92–93[d] | $C_{12}H_{18}O_2NCl$ | 59.13 | 59.35 | 7.44 | 7.52 | 5.74 | 5.92 |
| Cyclo-$C_6H_{11}$ | $CH_3$ | 90(A) | 125–128 | 4–5 | 163–164[e] | $C_{10}H_{20}O_2NCl$ | 54.17 | 54.41 | 9.09 | 9.06 | 6.32 | 6.64 |
| Cyclo-$C_6H_{11}$ | $C_2H_5$ | 85(A) | 133–135 | 3–5 | 145–146[f] | $C_{11}H_{22}O_2NCl$ | 56.04 | 56.38 | 9.41 | 9.36 | 5.94 | 5.92 |
| $C_6H_5CH_2$ | $CH_3$ | 92(A) | 145–147 | 7 | 164–165[g] | $C_{11}H_{16}O_2NCl$ | 57.51 | 57.98 | 7.02 | 7.23 | 6.10 | 6.15 |
| $C_6H_5$ | $C_2H_5$ | 63(B) | 139–146 | 1–2 | 98–99[h] | | | | | | | |

[a] The letters A, B and C following the yield figures indicate the procedure used in the preparation (see Experimental section). [b] Methyl *p*-toluidinopropionate solidified; gives light yellow plates, m.p. 60–61°, from benzene–petroleum ether. [c] Formulas are for solid form analyzed, either amino ester or its hydrochloride. [d] White needles from absolute ethanol. [e] White needles from methanol. [f] Colorless needles from absolute ethanol. [g] White plates from methanol. [h] Agrees with m.p. reported by J. R. Thayer and S. M. McElvain, THIS JOURNAL, **49**, 2862 (1927).

## Experimental[10,11]

**Preparation of the β-Aminopropionates.**—The three methods used in preparing these compounds are illustrated by the following examples:

**Procedure A.**[12]—A solution of 49.5 g. (0.5 mole) of cyclohexylamine and 43 g. (0.5 mole) of freshly-distilled methyl acrylate in 400 ml. of absolute methanol was allowed to stand for 24 hours. The solvent was removed by distillation and the residual oil was fractionated at reduced pressure. The colorless fraction boiling at 125–128° (4–5 mm.), methyl β-cyclohexylaminopropionate, weighed 83 g. (90% yield). A hydrochloride was precipitated by passing dry hydrogen chloride through a solution of the amino ester in dry benzene and was recrystallized from methanol.

**Procedure B.**[13]—A solution of 53.5 g. (0.5 mole) of *p*-toluidine, 50 g. (0.5 mole) of freshly-distilled ethyl acrylate[14] and 20 g. of glacial acetic acid was refluxed for 24 hours. The deep red solution was distilled at reduced pressure to give 52 g. (50% yield) of ethyl β-*p*-toluidinopropionate as a colorless liquid boiling at 142–144° (2–3 mm.). The hydrochloride was prepared as described under procedure A, above.

**Procedure C.**[15]—A solution of 35.3 g. (0.33 mole) of *p*-toluidine, 28.4 g. (0.33 mole) of methyl acrylate, 40 ml. of dry benzene and 10 drops of anhydrous stannic chloride was heated under reflux for 24 hours. The deep-red solution was distilled at reduced pressure to give 42.5 g. (67% yield) of methyl β-*p*-toluidinopropionate, boiling at 145–150° (5–6 mm.). The liquid crystallized in the receiver and was recrystallized from benzene–petroleum ether to give light-yellow plates, m.p. 60–61°.

The amino esters, methyl β-*m*-chloroanilinopropionate,[9] ethyl β-*m*-chloroanilinopropionate,[8] methyl β-*p*-anisidinopropionate,[9] ethyl β-*p*-anisidinopropionate[8] and ethyl β-benzylaminopropionate[12] were prepared according to directions from the literature.

**Preparation of 4-Carboalkoxy-2,3-dioxopyrrolidines.**—The three different procedures used for the preparation of the dioxopyrrolidines are illustrated by the following examples.

**Procedure A.** (Used only for condensations of methyl esters with methyl oxalate).—To a well-stirred suspension of 5.4 g. (0.1 mole) of sodium methoxide in 50 ml. of anhydrous ether was added 11.8 g. (0.1 mole) of methyl oxalate, followed by a solution of 19.3 g. (0.1 mole) of methyl β-benzylaminopropionate in 50 ml. of anhydrous ether. The solution was stirred and heated at the reflux temperature for 0.5 hour, and the ether was then removed by distillation. The residual salt was added to 500 ml. of warm water and the mixture was acidified with dilute hydrochloric acid. After a period of several hours during which the mixture was allowed to stand to complete the precipitation, the product was filtered out and recrystallized from methanol to give 18 g. (75%) of 4-carbomethoxy-1-benzyl-2,3-dioxopyrrolidine in the form of white needles, m.p. 180–182°. Further recrystallization raised the melting point to 183–184°.

**Procedure B.**—To a solution prepared from 19.9 g. (0.1 mole) of ethyl β-cyclohexylaminopropionate and 14.6 g. (0.1 mole) of ethyl oxalate was added 6.8 g. (0.1 mole) of sodium ethoxide. A vigorous reaction began at once and the contents of the flask solidified. The mixture was heated under reflux on a steam-bath for 1 hour, and the solid was removed by filtration and washed with ether after the mixture had cooled, then was suspended in 500 ml. of warm water. Following acidification of the mixture and several hours standing to complete the precipitation, the resultant 4-carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine was collected by filtration and recrystallized from 95% ethanol to yield 16.5 g. (65% yield) of white needles, m.p. 185–186°. Further recrystallization raised the m.p. to 188°.

**Procedure C.**—A solution of 10.3 g. (0.038 mole) of ethyl β-anilino-β-phenylpropionate, and 6.1 g. (0.041 mole) of ethyl oxalate in 25 ml. of absolute ethanol was added to a solution of 2.8 g. (0.041 mole) of sodium ethoxide in 50 ml. of absolute ethanol. The ethanol was removed by distillation on a steam-bath, leaving a light tan liquid residue, which was dissolved in 300 ml. of warm water. Acidification with 20% hydrochloric acid precipitated a light tan solid, which was recrystallized from ethanol to give 9 g. (73% yield) of 4-carbethoxy-1,5-diphenyl-2,3-dioxopyrrolidine as white needles, m.p. 172–174°.[2]

**Preparation of 3-Pyrroline Derivatives.**—Reactions of the 2,3-dioxopyrrolidine derivatives with diazomethane were all performed in the manner illustrated by the following example: To a suspension of 2 g. of 4-carbethoxy-1-*p*-tolyl-2,3-dioxopyrrolidine in 10 ml. of ether was added an excess of an ethereal solution of diazomethane. The dioxopyrrolidine dissolved as it reacted. After the reaction was complete, excess diazomethane was consumed by addition of acetic acid, and the solvent was removed by evaporation. The residual light-yellow oil was crystallized from ethanol, giving 2 g. (95% yield) of 4-carbethoxy-1-*p*-tolyl-3-methoxy-2-oxo-3-pyrroline, m.p. 82–83°.

**Treatment of Methyl N-Methoxalyl-β-anilino-β-phenylpropionate (III) with Sodium Methoxide.**—To a solution of 5 g. of methyl N-methoxalyl-β-anilino-β-phenylpropionate[2] in 50 ml. of dry methanol was added a solution of 0.81 g. of sodium methoxide in 25 ml. of methanol. A gelatinous white precipitate (2.1 g.) of the sodium salt of methyl oxanilide (VI) separated immediately. It was filtered from the solution and triturated with acetic acid to give 1 g. of methyl oxanilide, m.p. 111–112°.

After the removal of the sodium salt of methyl oxanilide, the reaction mixture was evaporated to dryness and the residual solid was extracted with water. Acidification of the aqueous extracts and recrystallization of the resulting precipitate from methanol gave 0.4 g. (9% yield) of 4-carbomethoxy-1,4-diphenyl-2,3-dioxopyrrolidine,[2] m.p. 199–200°. The residue from the water extraction (0.3 g.) was methyl cinnamate, m.p. 32–33°. The identity of each of the three products was confirmed by a mixed melting point test.

**Hydrolysis and Decarboxylation of 4-Carbethoxy-1-benzyl-2,3-dioxopyrrolidine to 1-Benzyl-2,3-dioxopyrrolidine (XII).**—A mixture of 2.0 g. of 4-carbethoxy-1-benzyl-2,3-dioxopyrrolidine and 150 ml. of 20% hydrochloric acid was

(10) Melting points are corrected.

(11) Microanalyses by Micro-Tech Laboratories, Skokie, Illinois, and by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(12) Based on a procedure for ethyl β-benzylaminopropionate by G. Stork and S. M. McElvain, THIS JOURNAL, **69**, 971 (1947).

(13) Based on a procedure for ethyl β-*p*-anisidinopropionate by R. C. Elderfield, *et al.*, ref. 8.

(14) The authors are indebted to the Rohm and Haas Company for a supply of ethyl acrylate.

(15) Based on a procedure for methyl β-*p*-anisidinopropionate by W. S. Johnson, *et al.*, ref. 9.

refluxed for 3 hours. During this period the starting material dissolved. The reaction mixture was cooled, filtered to remove a small amount of suspended solid and extracted several times with chloroform. Removal of the chloroform by evaporation left a light-tan oil which crystallized on standing. The compound was recrystallized (with some difficulty) from benzene, giving 1.2 g. (83% yield) of white needles, m.p. 99–100°. Crystallization from commercial heptanes is less difficult.

*Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.10; H, 5.95; N, 7.63.

The compound was obtained in 69% yield by a similar hydrolysis of the corresponding methyl ester, 4-carbomethoxy-1-benzyl-2,3-dioxopyrrolidine (IX).

**Preparation of β-Benzylaminopropionic Acid.**—A mixture of 30 g. of ethyl β-benzylaminopropionate[12] and 150 ml. of 10% sodium hydroxide solution was refluxed until the ester layer disappeared. The solution was neutralized with dilute hydrochloric acid and evaporated to dryness. The resulting white solid was extracted with boiling absolute ethanol, and the alcohol extract was cooled to give 22.5 g. (87%) of white needles of β-benzylaminopropionic acid, m.p. 182–183°. The reported[16] m.p. is 181°.

**Preparation of N-Methoxalyl-β-benzylaminopropionic Acid.**—A mixture of 5 g. of β-benzylaminopropionic acid and 10 g. of methoxalyl chloride was heated on the steam-bath for 30 minutes. The solution was diluted with 100 ml. of ether and washed with water, then extracted with an excess of 5% sodium bicarbonate solution. Acidification of the sodium bicarbonate solution precipitated a light yellow oil, which crystallized on standing. This solid was recrystallized from chloroform–petroleum ether (or ether–petroleum ether) and gave 5 g. (68%) of white plates of N-methoxalyl-β-benzylaminopropionic acid, m.p. 99–100°.

*Anal.* Calcd. for $C_{13}H_{15}O_5N$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.86; H, 5.52; N, 5.37.

**Preparation of 1-Benzyl-2-oxo-3-methoxy-3-pyrroline-4-carboxylic Acid (XI).**—To a solution of 8 g. of N-methoxalyl-β-benzylaminopropionic acid and 8 g. of methoxalyl chloride in 25 ml. of anhydrous chloroform was added 8 g. of anhydrous pyridine. The solution was allowed to stand for 2 hours and it assumed a deep red color. The chloroform solution was washed with water, then heated on the steam-bath with 400 ml. of 5% sodium bicarbonate solution. The bicarbonate extract was decolorized with charcoal and filtered. Acidification of the solution precipitated 2.2 g. of an unidentified acid, which was removed by filtration. Chloroform extraction of the filtrate yielded 0.5 g. of 1-benzyl-2-oxo-3-methoxy-3-pyrroline-4-carboxylic acid (XI), obtained as very small white needles, m.p. 139–140°, after crystallization from chloroform–petroleum ether.

*Anal.* Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.77, 63.03; H, 5.02, 4.97; N, 5.64.

Esterification of this compound with diazomethane yielded 4-carbomethoxy-1-benzyl-2-oxo-3-methoxy-3-pyrroline (X), m.p. 77–78°, identical with the product obtained by the treatment of 4-carbomethoxy-1-benzyl-2,3-dioxopyrrolidine (IX) with diazomethane.

The unidentified acid mentioned above was purified by solution in aqueous potassium hydroxide and reprecipitation with hydrochloric acid, followed by recrystallization from aqueous ethanol. Very small pale yellow plates, m.p. 245–246°, were obtained.

*Anal.* Found: C, 55.32, 55.17; H, 3.53, 3.27; N, 5.85.

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(16) J. A. King and F. H. McMillan, THIS JOURNAL, **68**, 1468 (1946).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Stereochemistry of the β-Phenylserines: Characterization of Allophenylserine[1]

BY KENNETH N. F. SHAW[2] AND SIDNEY W. FOX

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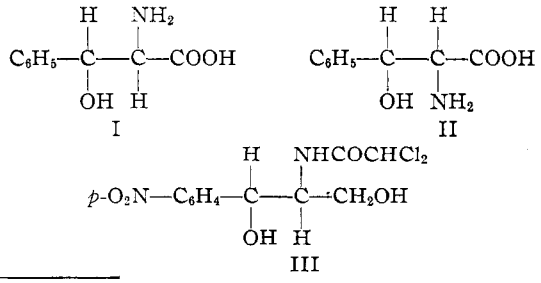
Phenylserine was converted *via* lithium aluminum hydride reduction of its esters to racemic chloramphenicol. *Threo* configuration of the hydroxyamino acid was thus indicated. In addition to phenylserine, the disputed allophenylserine was obtained from condensation of benzaldehyde with glycine. This diastereomer was separated from the crude reaction product as the ethyl ester hydrochloride. Its structure and configuration were established by conversion of the ethyl ester to *erythro* intermediates in the chloramphenicol series.

Although phenylserine (I) has been well known for six decades, its diastereomer, allophenylserine (II), has been a subject of contention, partly due to its confusion with one of the two α-hydroxy-β-amino acids, the β-phenylisoserines. Interest in clarifying the stereochemistry of the phenylserines and their analogs arises from their structural similarity and possible biochemical relation to natural products, such as epinephrine, chloramphenicol (III) and the α-amino acids.



I II

III

Synthesis of III from I, which was the initial aim of the present study, had been achieved[3] when reports of similar but earlier investigations[4,5] became available. Subsequent publications[6–11] have reflected the parallel interest of other workers in this problem. In view of such activity, attention in this Laboratory was turned to phenylserine synthesis, with emphasis on the disputed II. It may be noted that discrepancies between different reports have been attributed to possible contamination of I by II.[7]

I was first prepared by Erlenmeyer[12,13] by con-

(1) Work supported by the Industrial Science Research Institute of Iowa State College. Presented before the Division of Organic Chemistry at the 118th Meeting of the American Chemical Society, Chicago, September, 1950.

(2) From the Ph.D. dissertation of Kenneth N. F. Shaw, 1951.

(3) K. N. F. Shaw and S. W. Fox, Abstracts of Papers, 118th Am. Chem. Soc. Meeting, p. 28N (1950).

(4) C. G. Alberti, B. Asero, B. Camerino, R. Sannicolò and A. Vercellone, *Chimica e industria* (Milan), **31**, 357 (1949).

(5) G. Carrara and G. Weitnauer, *Gazz. chim. ital.*, **79**, 856 (1949).

(6) K. Vogler, *Helv. Chim. Acta*, **33**, 2111 (1950).

(7) C. F. Huebner and C. R. Scholz, THIS JOURNAL, **73**, 2089 (1951).

(8) K. Hayes and G. Gever, *J. Org. Chem.*, **16**, 269 (1951).

(9) G. W. Moersch (to Parke, Davis and Co.), U. S. Patent 2,538,792 (Jan. 23, 1951).

(10) E. D. Bergmann, H. Bendas and W. Taub, *J. Chem. Soc.*, 2673 (1951).

(11) H. E. Carter and E. H. Flynn (to Eli Lilly and Co.), U. S. Patent 2,556,868 (June 12, 1951).

(12) E. Erlenmeyer, Jr., *Ber.*, **25**, 3445 (1892).

(13) E. Erlenmeyer, Jr., and E. Früstück, *Ann.*, **284**, 36 (1894).