[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

The Synthesis of a Pseudoxazolone

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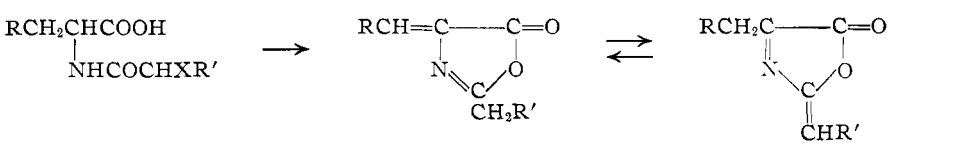
As an intermediate for use in connection with other work it was desirable to use 2-benzylidene-4-methylpseudoxazolone (XII). This substance has now been prepared by two totally different methods and some of its properties have been studied.

The first preparation of the material employed a little-used but not new reaction that was discovered by Bergmann[2a,b,c] and used[2d] in his syntheses of peptides. He found that certain α-N-(α-haloacyl)-amino acids, on treatment with acetic anhydride, preferably together with a base, yielded azlactones of α,β-unsaturated α-acylamino acids; this rather remarkable transformation was carried by him with N-(chloroacetyl)-phenylalanine (I), N-(chloroacetyl)-tyrosine (III), N-(α-bromopropionyl)-asparagine (V) and N-(α-bromopropionyl)-alanine (VII) to give, respectively, 2-methyl-4-benzylideneoxazolone (II), 2-methyl-4-(*p*-hydroxy)-benzylideneoxazolone (IV), 2-ethyl-4-carboxymethyleneoxazolone (VI) and 2-ethyl-4-methyleneoxazolone (VIII) or 2-ethylidene-4-methylpseudoxazolone (IX).

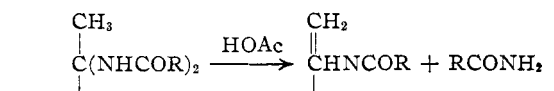


I, R = $-C_6H_5$, R′ = H, X = Cl
II, R = C_6H_5, R′ = H
III, R = C_6H_4OH-*p*, R′ = H, X = Cl
IV, R = C_6H_4OH-*p*, R′ = H
V, R = $CONH_2$, R′ = CH_3, X = Br
VI, R = COOH, R′ = CH_3
VII, R = H, R′ = CH_3, X = Br
VIII, R = H, R′ = CH_3
X, R = H, R′ = C_6H_5, X = Cl
XI, R = H, R′ = C_6H_5
XIII, R = H, R′ = C_6H_5, X = Br
IX, R = H, R′ = CH_3
XII, R = H, R′ = C_6H_5

The haloacylamino acid requisite for the preparation of XII was prepared from alanine. *dl*-Alanine on treatment with *dl*-α-chlorophenylacetyl chloride gave an 87% yield of the mixed stereoisomers of N-(α-chlorophenylacetyl)-alanine (X), and on treatment with *dl*-α-bromophenylacetyl bromide produced a 78% yield of the corresponding bromo derivative XIII. The chloro derivative X, when dissolved in a mixture of pyridine and acetic anhydride, formed the heterocyclic substance XI or XII in 91% yield; the same substance was similarly prepared in 96% yield from the bromo derivative XIII.

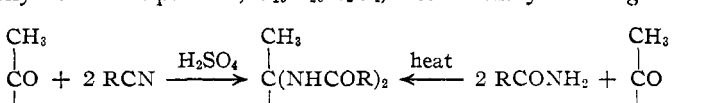
The second preparation of the substance XI or XII utilized several rather unusual reactions of which little mention is found in the chemical literature, the final step in the synthesis being the ring-closure by intramolecular dehydration of α-phenylacetylaminoacrylic acid (XIV).

In view of the fact that Bergmann and Grafe[3] had prepared α-acetaminoacrylic acid (XV) from α,α-diacetaminopropionic acid (XVI), it seemed reasonable to attempt the preparation of XIV from the corresponding diphenylacetylamino acid XVII.



XVI, R = CH_3
XVII, R = $CH_6C_2H_5$
XV, R = CH_3
XIV, R = $CH_2C_6H_5$

The synthesis of XVII was claimed by Bottinger[4] who discovered a very ingenious synthesis of α,α-diacylaminopropionic acids. He slowly added benzonitrile to a cold concentrated sulfuric acid solution of pyruvic acid and, after allowing the mixture to thicken and pouring it on ice, obtained α,α-dibenzoylaminopropionic acid (XVIII). He claimed that benzyl cyanide similarly gave XVII, m. p. 145°, $C_{19}H_{20}N_2O_4$, but no analysis was given.



XVI, R = CH_3
XVII, R = $CH_2C_6H_5$
XVIII, R = C_6H_5
XIX, R = CH_2Cl

Apparently the reaction was forgotten until Bergmann and Grafe used it to prepare XVI, in confirmation of the structure of this substance prepared in a different manner. They heated pyruvic acid and acetamide together under vacuum and obtained XVI; when chloroacetamide was used the product was XIX.

We have prepared XVII by both methods and

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(2) (a) Bergmann and Stern, *Ann.*, **448**, 20 (1926); (b) Bergmann, Kann and Miekely, *ibid.*, **449**, 135 (1926); (c) Bergmann, Zervas and Lebrecht, *Ber.*, **64**, 2315 (1931); (d) Bergmann, Stern and Witte, *Ann.*, **449**, 277 (1926).

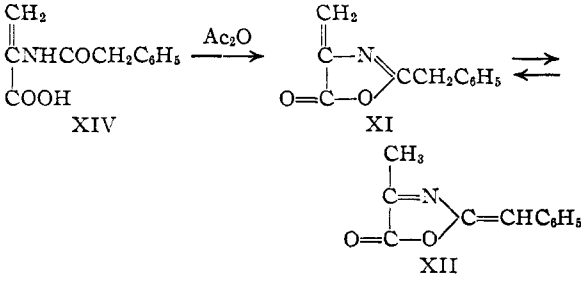
(3) Bergmann and Grafe, *Z. physiol. Chem.*, **187**, 187 (1930).

(4) Bottinger, *Ber.*, **14**, 1599 (1881).

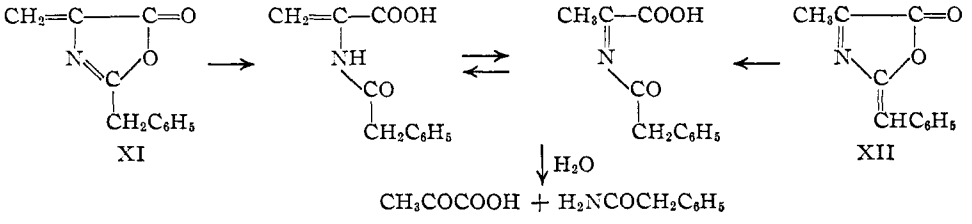
found the same product in each case, thereby proving its structure; the benzyl cyanide procedure gave an 87% yield while the phenylacetamide method gave only a 16% yield. Although we found the analytically pure material to melt at 152–152.5°,[5] there is little doubt that Bottinger very probably made XVII, even though he gave the m. p. as 145° and reported no analytical data.

Bergmann and Grafe heated XVI with glacial acetic acid under very closely regulated conditions and obtained XV; by the same method, after the proper conditions were experimentally determined for this particular substance, we were able to convert XVII into XIV in 58% yield.

Cyclodehydration of XIV with acetic anhydride gave about 2% yield of XI or XII, identical with the same material prepared by the first method.



Chemical degradation of the substance XI or XII merely indicated that it contained the expected 1,3-oxazole ring but did not permit a choice to be made in the location of the double bonds. One and one-half equivalents of sodium hydroxide solution at room temperature hydrolyzed the material to α-phenylacetylaminoacrylic acid, some of which was further hydrolytically cleaved to phenylacetamide. The same hydrolysis could be effected by 5% sodium carbonate solution or even by 5% aqueous ammonia. Bromination of the substance in methylene chloride, carbon tetrachloride, carbon disulfide or acetic acid led to no homogeneous product.

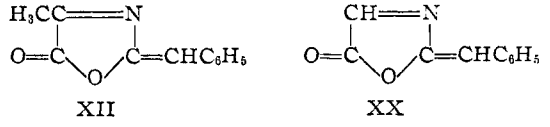


The possibility of the prototropic rearrangement of XI ⇄ XII during the formation from either X, XIII or XIV invalidates any deductions based upon the method of synthesis which might be made regarding the structure of the oxazole.[6]

Since the chemical methods used did not permit a choice to be made between XI and XII, recourse was had to theoretical considerations and to the ultraviolet absorption spectrum of the substance.

One would normally expect the oxazole to assume the double-bond arrangement with the most extensive conjugation; in II, IV and VI this is the oxazolone structure in which the semicyclic double bond at the 4-position is conjugated with the double bond(s) of R. In VIII and IX neither R nor R′ contains an unsaturation; the former structure has three unsaturations in crossed conjugation and the latter has three unsaturations in linear conjugation; Bergmann and Stern did not essay a preference for either structure. However, in the case of the pair XI and XII the oxazolone structure has only three unsaturations in crossed conjugation, forcing RCH to become an exocyclic methylene group; the pseudoxazolone structure, in contrast, contains not only three linear conjugations but these are also conjugated with the double bonds of the phenyl group R′, giving a much longer conjugated system and permitting the 4-substituent to be a methyl rather than a methylene group. For this reason it seemed desirable to assign to the substance structure XII, the pseudoxazolone.

The ultraviolet absorption spectrum of the substance seems to us to confirm our ultimate choice of structure XII. Two peaks were present (Fig. 1): $\lambda_{max.}$ 240, ϵ 8100 and $\lambda_{max.}$ 354, ϵ 20150. These agree closely with the location of the maxima on the curve for the 4-unsubstituted substance, 2-benzylidenepseudoxazolone[7] (XX) which cannot have an oxazolone structure and which exhibits $\lambda_{max.}$ 242, ϵ 2100 and $\lambda_{max.}$ 356, ϵ 7500.

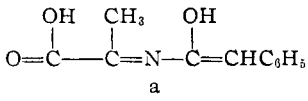


Although the ultraviolet absorption spectra of the acylaminoacrylic acids XIV and XV were determined, little can be said regarding their actual structure. The spectra did show (Fig. 1) that in XIV the grouping $-\overset{|}{C}(OH)=CHC_6H_5$ is not present; both XIV and XV had $\lambda_{max.}$ 243 and hence must be considered as having the same double-bond arrangement. If XIV were a

(5) On one occasion, by repeated recrystallization, we obtained a sample of the acid melting at 158°.

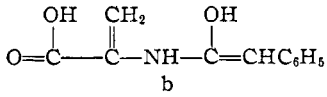
(6) For a discussion of the somewhat analogous case of azophenol ⇄ quinone hydrazone tautomerism see Lauer and Miller, THIS JOURNAL, 57, 520 (1935). The tautomerism of diazoamino compounds and of *p*-nitrosophenol ⇄ quinone monoxime is likewise similar, in that one cannot assume the structure of the product merely by knowing its method of synthesis. For an extensive discussion see Baker, "Tautomerism," Routledge and Sons, London, 1934.

(7) This substance was prepared by Cavallito and Haskell of these laboratories in connection with other work.



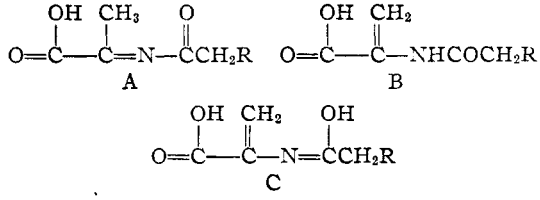
a

(which it would assume in preference to b



b

because the former tautomer would have greater conjugation) the $\lambda_{max.}$ should be shifted noticeably toward the longer wave lengths. One has left as possibilities A, B and C. Both XIV and XV behave as A in their hydrolytic behavior to produce



pyruvic acid and an amide.[3] However, Bergmann and Grafe[3] found that XV formed a pyrazoline with diazomethane, thus reacting as B or C. These α-acylaminoacrylic acids, then, appear to belong to the large class of substances which exhibits triad prototropy and hence cannot be assigned any one structure on the basis of chemical behavior. It is quite possible that measurements of the infrared absorption spectra would clearly delineate the discrete vibrational frequencies and permit a choice to be made between the alternatives A, B and C.

Acknowledgment.—We wish to thank Dr. Galen W. Ewing of these laboratories for his kindness in making the spectral measurements on compounds XII, XIV, XV and XX. We also wish to acknowledge the original suggestion of Sir Robert Robinson and co-workers that the oxazole derivative is the pseudoxazolone XII rather than the oxazolone XI because of its spectral similarity to 2-benzylidenepseudoxazolone (XX).[8]

Experimental Part[9,10]

***dl*-α-Chlorophenylacetyl Chloride.**—This was prepared from *dl*-mandelic acid (100 g., 0.67 mole) and phosphorus pentachloride (250 g., 1.2 moles) by the method of Walden[11] in 48% yield, or from *dl*-mandelic acid (76 g., 0.50 mole) and purified thionyl chloride (130 g., 1.10 moles) in 37% yield; the product b. p. 118° (24 mm.); 124–126° (40 mm.).

N-(α-Chlorophenylacetyl)-alanine (X).—*dl*-Alanine (26.8 g., 0.30 mole) was dissolved in water (200 cc.) containing sodium hydroxide (25.0 g., 0.62 mole) and maintained at 5 ± 2°. To this stirred solution there was added dropwise *dl*-α-chlorophenylacetyl chloride (57.0 g., 0.30 mole). About 1 cc. of insoluble oil was extracted with ether and the clear aqueous solution was acidified (hydrochloric acid) to give a heavy oil which was rapidly extracted with chloroform. On chilling, the chloroform solution deposited 51.0 g. of white crystalline solid, m. p. 134–150°. Removal of the solvent from the filtrate, followed by trituration of the residue with Skellysolve A, gave 12.0 g. more solid; total wt. 63.0 g. (87% yield). No attempt was made to separate the four stereoisomers.

Anal. Calcd. for $C_{11}H_{12}ClNO_3$: N, 5.78. Found: N, 5.95.

***dl*-α-Bromophenylacetyl Bromide.**—This was prepared by the method of Hell and Weinzweig[12] except that phenylacetic acid was substituted for mandelic acid. The product, b. p. 146–148° (30 mm.), was obtained in 44% yield.

N-(α-Bromophenylacetyl)-alanine (XIII).—*dl*-Alanine (45.0 g., 0.50 mole) was dissolved in water (1000 cc.) containing sodium hydroxide (42 g., 1.05 moles) and maintained at less than 5°. To this stirred solution there was added dropwise *dl*-α-bromophenylacetyl bromide (139 g., 0.50 mole). About 1–2 cc. of unchanged bromide was extracted with carbon tetrachloride and the clear aqueous solution was acidified with hydrochloric acid. The precipitated oil crystallized almost immediately and weighed 112 g. (78% yield), m. p. 144–148°. No attempt was made to separate the four stereoisomers.

Anal. Calcd. for $C_{11}H_{12}BrNO_3$: N, 4.89. Found: N, 4.84.

Fischer and Schmidlin,[13] who prepared α-bromophenylacetylalanine from optically active bromophenylacetyl chloride and *dl*-alanine, separated their product into two isomers.

2-Benzylidene-4-methylpseudoxazolone (XII). A.—To N-(α-bromophenylacetyl)-alanine (112 g., 0.39 mole) there was added a mixture of pyridine (200 cc., dried over potassium hydroxide) and acetic anhydride (1000 cc.). The solution was allowed to stand one hour at room temperature, during which it warmed to about 40° and deposited a white precipitate. The entire mixture was poured onto ice (4 kg.) and the resultant light tan solid

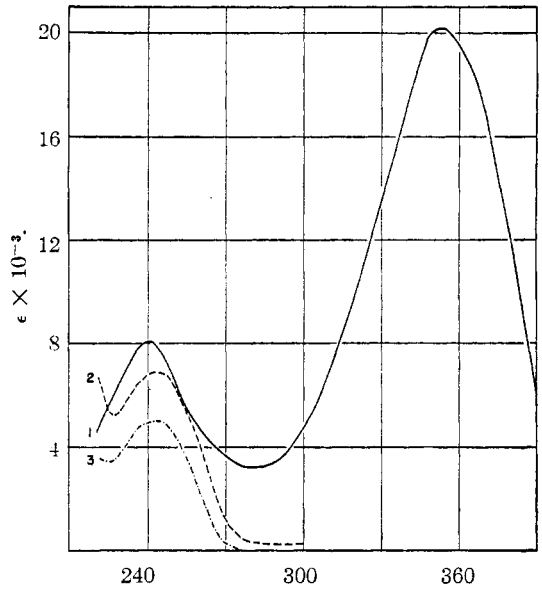


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of: (1), 2-benzylidene-4-methylpseudoxazolone (XII); (2), α-phenacetylaminoacrylic acid (XIV); (3), α-acetaminoacrylic acid, (XV).

(8) The oxazole derivative was synthesized independently and practically simultaneously in these laboratories and at Oxford University; see CPS., p. **68, 212, 272.**

(9) Melting points and boiling points are uncorrected.

(10) Microanalyses are by Misses Alice Rainey and Patricia Curran of these laboratories.

(11) Walden, *Ber.*, **28**, 1287 (1895).

(12) **Hell and Weinzweig, *ibid.*, 28, 2445 (1895).**

(13) **Fischer and Schmidlin, *Ann.*, 340, 194 (1905).**

removed by filtration and dried in a vacuum desiccator; wt. 70.9 g. (96% yield); m. p. 106–109°.

B. To N-(α-chlorophenylacetyl)-alanine (30.0 g., 0.125 mole) there was added a mixture of pyridine (60 cc., dried over potassium hydroxide) and acetic anhydride (300 cc.). The solution warmed up slightly and after thirty minutes turned red and deposited some solid. The entire mixture was poured onto ice (1.5 kg.) and the light yellow solid was removed by filtration and dried in a vacuum desiccator; wt. 21.3 g. (91% yield); m. p. 105–115°. When mixed with the same material (m. p. 106–109°) prepared from the analogous chloro derivative, it melted at 105–112°.

This pseudoxazolone can be recrystallized only with difficulty and accompanied by considerable loss; it polymerizes easily, either in solution or when heated in the dry state; it is an extremely potent irritant to both the skin and the nasal passages. The material can be recrystallized from carbon disulfide at −20°, but the best recrystallization solvent appears to be Skellysolve B, in which there is less loss than in most solvents. Careful and repeated recrystallization of the material will produce pale yellow needles that melt at 122–123°.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.82; N, 7.48. Found: C, 70.79; H, 5.18; N, 7.49.

α,α-Diphenylacetylaminopropionic Acid (XVII). A. From Benzyl Cyanide.—Concentrated sulfuric acid (250 cc.) was cooled to −20° and pyruvic acid (22 g., 0.25 mole) was added. Benzyl cyanide (59 g., 0.50 mole) was then added dropwise to the stirred mixture, after which the mixture was stirred at −10° for six and one-half hours, during which the reaction mixture became progressively more viscous. The mixture was then poured onto ice (2 kg.) and stirred until the somewhat tacky white solid turned to a powder. The white powder was removed by filtration and dissolved in sodium carbonate (one liter of 12% solution); acidification of the filtered solution gave a tacky solid which again became powdery. This powdery solid was recrystallized from 850 cc. of 10:7 aqueous ethanol to give the crystalline diamide. The dry product weighed 74 g. (87% yield) and melted at 152–152.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.06; H, 5.88; N, 8.23. Found: C, 66.68; H, 5.78; N, 7.93.

B. From Phenylacetamide.—A mixture of pyruvic acid (33.5 g., 0.38 mole) and phenylacetamide (92.0 g., 0.68 mole) was heated in an oil-bath for twelve hours at 160° (20 mm.). The cooled reaction mass was taken up in hot ethyl acetate and chilled to precipitate phenylacetamide. The ethyl acetate filtrate was extracted with 5% caustic solution, acidification of which yielded a heavy oil that crystallized on standing overnight. The crude solid weighed 19 g. (16% yield). After several recrystallizations from aqueous alcohol it melted at 150–151° alone or when mixed with the same material prepared by method A.

α-Phenylacetylaminoacrylic Acid (XIV).—A solution of α,α-diphenylacetylaminopropionic acid (119 g., 0.35 mole) in glacial acetic acid (500 cc.) was refluxed ninety minutes then poured into 2.5 liters of cold water. The aqueous acid solution was extracted with three 800-cc. portions of ethyl acetate and the combined ethyl acetate extract was extracted with three 800-cc. portions of aqueous potassium carbonate (containing a total of 400 g. of potassium carbonate). The carbonate solution was acidified and chilled and the product was removed by filtration. After being dried in a vacuum desiccator it weighed 41.5 g. (58%) and melted at 168–170°. The material readily decolorized a solution of bromine in carbon tetrachloride.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.86; N, 6.83. Found: C, 64.16; H, 5.52; N, 7.07.

2-Benzylidene-4-methylpseudoxazolone (XII).—α-Phenylacetylaminoacrylic acid (4.10 g., 0.02 mole) and acetic anhydride (25 cc.) were heated thirty minutes on a steam-cone. Acetic anhydride and acetic acid were removed under vacuum and the residue was extracted with 50 cc. of hot Skellysolve B. The extract was concentrated to 25 cc. and a small amount of dark material was removed by filtration; the clear filtrate was evaporated to dryness to leave about 50 mg. of yellow crystalline material which was a very pure sample of 2-benzylidene-4-methylpseudoxazolone, m. p. 125–126°, undepressed when mixed with the same material, m. p. 123°, prepared by the first method.

Hydrolysis of 2-Benzylidene-4-methylpseudoxazolone to α-Phenylacetylaminoacrylic Acid.—A. 2-Benzylidene-4-methylpseudoxazolone (0.93 g., 0.005 mole) was suspended in cold water (20 cc.) containing sodium hydroxide (0.30 g., 0.0075 mole). The mixture was allowed to stand one hour at room temperature, during which time the yellow pseudoxazolone dissolved and a white crystalline precipitate formed. The precipitate was phenylacetamide, m. p. 153–156°. The clear filtrate, on acidification, gave a white crystalline precipitate, m. p. 163°; when mixed with an authentic sample of the acrylic acid derivative it melted at 161–164°.

B. An aqueous suspension of the pseudoxazolone, on being shaken with 5% sodium carbonate solution, gradually went into solution. Acidification yielded α-N-(phenylacetylamino)-acrylic acid, m. p. 166–168°, undepressed when mixed with an authentic sample.

C. The use of 5% aqueous ammonium hydroxide gave similar results.

Spectral Measurements.—The spectra were determined on a Beckman Quartz Spectrophotometer. The molecular extinction coefficient ϵ is calculated from the definition $\epsilon = 1/cd \log_{10} I_0/I$, where c is the concentration in moles per liter, d the cell thickness (1 cm.), I_0 and I the incident and transmitted light, respectively; solvent, 95% ethanol.

Summary

Bergmann's oxazolone synthesis has been used for the preparation of 2-benzylidene-4-methylpseudoxazolone. The same material has been prepared by azlactonization of α-phenylacetylaminoacrylic acid. Some of the properties of this material have been studied and its structure has been deduced from spectral data.

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