[Contribution from the Fermentation Division, Northern Regional Research Laboratory[1]]

THE ACTION OF HYDRAZINE HYDRATE ON OXAZOLONES

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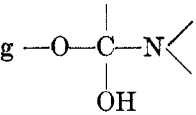
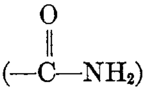
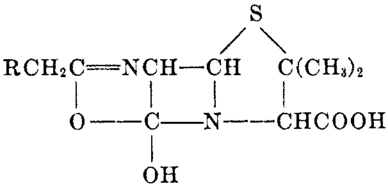
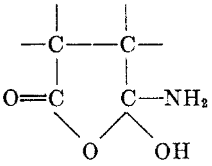
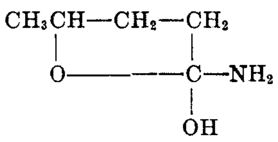
During the early work on the penicillins, structure I was considered as a possibility for this class of compounds. A search of the literature for reference to substances having the grouping  $-O-\underset{OH}{\overset{|}{C}}-N\langle$ disclosed that as early as 1890 Anschütz (1) had assigned structures II and III to the reaction products of ammonia with anhydrides and lactones. The easy loss of ammonia on heating was considered to be better explained by these structures than by the simple amide ( $-\overset{O}{\overset{\|}{C}}-NH_2$) formulations used up to that time.



I



II



III

In 1898, Cramer (2) considered the Anschütz type of formula for the product obtained by the action of ammonia on the lactone of *o*-hydroxyphenylacetic acid but rejected it in favor of the ordinary amide structure. Two years later, Wedel (3) came to the same conclusion after a study of the action of hydrazine hydrate on the same lactone. In 1903, however, Meyer and Maier (4) revived the Anschütz formulation as a means of explaining the properties of the addition product of *o*-phenylenediamine and succinic anhydride. Likewise Blaise and Luttringer (5) in 1905 assigned the Anschütz structure to the reaction products of hydrazine hydrate with aliphatic lactones. These compounds were given the name "hydrazinolactones." The lability of the hydrazine with sulfuric acid and the formation of benzalazine with benzaldehyde were offered as evidence for the structure proposed.

In 1905–6, Titherley and co-workers (6, 7) attempted to explain some anomalies in the behavior of the benzoyl derivatives of salicylamide by means of formulations IV and V.

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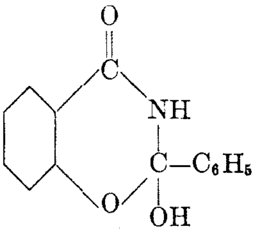
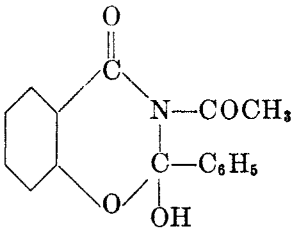
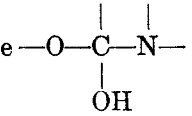


IV



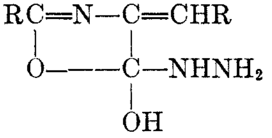
V

These structures, however, were considered by Auwers (8, 9) as unlikely for stable compounds although he conceded the possibility of their existence as intermediates in rearrangements (10).

In 1928, Anschütz (11), in a summary of his work on the addition products of ammonia and anhydrides, re-affirmed his belief in the  $-\mathrm{O}-\overset{|}{\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}}-\overset{|}{\mathrm{N}}-$ structure, particularly for compounds resulting from the addition of amines to substituted maleic anhydrides.

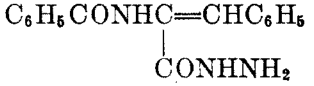
Darapsky, Berger, and Neuhaus (12) in 1936 re-opened the problem of the action of hydrazine hydrate on lactones and advanced good evidence in favor of the ordinary amide structure for the products.

The most recent advocates of the Anschütz formulation have been Vanghelovici and Stephanescu (13) who claim that hydrazine hydrate adds to oxazolones to give compounds of type VI. We were interested in these structures for, if they could have been shown at that time to be correct,



VI

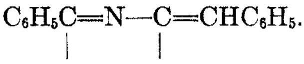
VII R = phenyl

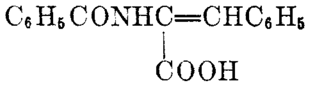


$$\mathrm{C_6H_5CONH\underset{\underset{CONHNH_2}{|}}{C}{=}CHC_6H_5}$$

VIII

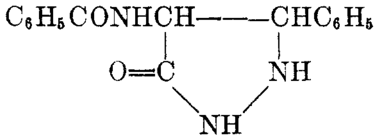
such hydrazine-oxazolone addition compounds would have been useful as models for penicillin structure studies.

Accordingly we repeated and extended the work of Vanghelovici and Stephanescu; we found, however, no evidence for the Anschütz type of structure. Instead, we have been able to show that the compound of m.p. 153°, to which the formula VII was assigned by the Roumanian workers, is the normal hydrazide VIII. Our evidence is based on the ultraviolet absorption spectrum of the compound. The absorption curve (curve 1; figure 1) shows a peak at 2800 Å, as does the acid IX (curve 2; figure 1). This peak is at a considerably shorter wavelength than would be expected for the system  $\mathrm{C_6H_5\underset{|}{C}{=}N{-}\underset{|}{C}{=}CHC_6H_5}$.

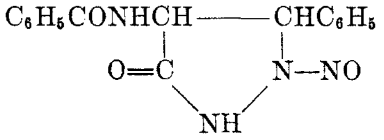


$C_6H_5CONH\underset{\displaystyle COOH}{C}{=}CHC_6H_5$

IX



X



XI

The azide formation and the reaction with aldehydes which were observed by Vanghelovici and Stephanescu are in agreement with hydrazide structure.

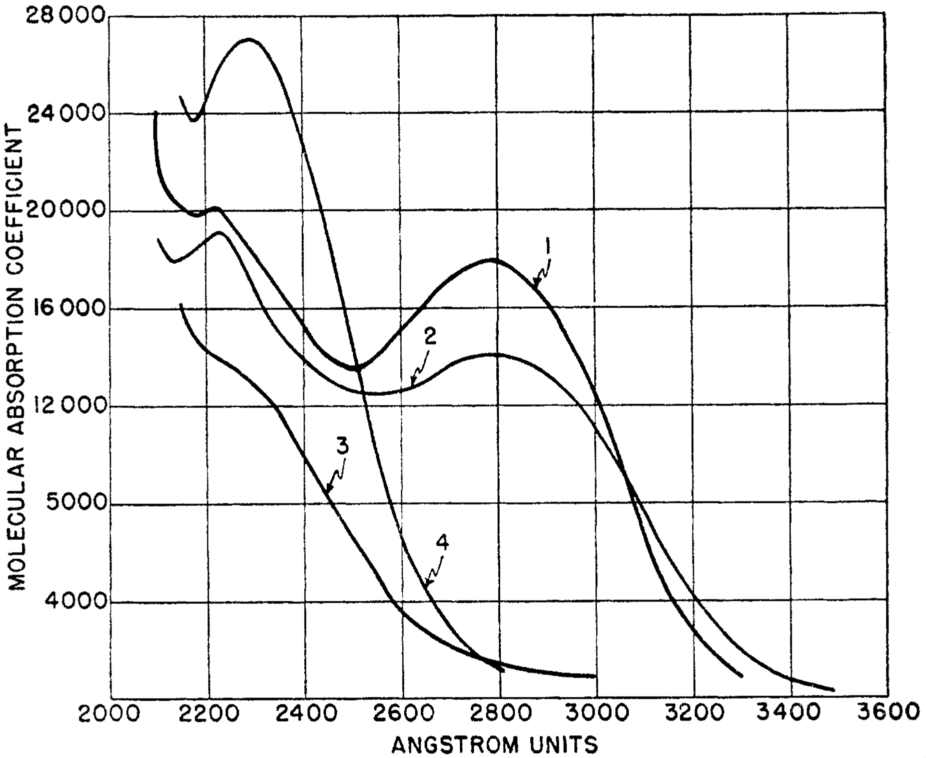


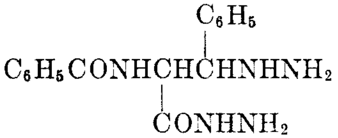
FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

Curve 1. α-Benzoylaminocinnamic acid hydrazide (VIII)
Durve 2. α-Benzoylaminocinnamic acid (IX) (8.736 mg. per liter)
Curve 3. 3-Phenyl-4-benzoylamino-5-pyrazolidone (X)
Curve 4. Diacetone derivative (XIII)

We have further been able to show that the compound of m.p. 229°, which Vanghelovici and Stephanescu assumed to be the normal hydrazide, is in reality the pyrazolidone X. It has already been observed by Knorr and Duden (14) that crotonic acid and phenylhydrazine react to form 1-phenyl-3-methyl-5-pyrazolidone. Rothenburg (15) has reported the preparation of pyrazolidone itself by the action of hydrazine hydrate on acrylic acid. The pyrazolidone formula here proposed is in accord with the absorption spectrum (curve 3; figure 1) which shows the disappearance of the peak at 2800 Å characteristic of the α,β-unsaturated acids. The inability of the compound to condense with aldehydes, and the formation of an acetyl derivative, are consistent with the the pyrazolidone structure. The claim of Vanghelovici and Stephanescu that they have formed an azide of this compound appears to be in error. We have succeeded in preparing the expected nitroso derivative XI which shows the properties to be anticipated on the basis of the work of Knorr and Duden (16), Muckermann (17), and Darapsky *et al.* (12).

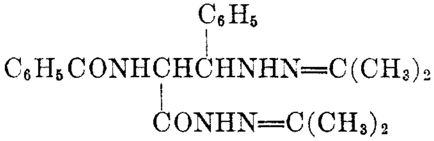
An attempt was made to prepare the normal hydrazide by the action of hydrazine on the methyl ester of IX in methanol at room temperature. The crystalline product which separated, however, appeared to be XII since on treatment with acetone it yielded a compound analyzing as XIII, the absorption spectrum (curve 4; figure 1) of which shows the disappearance of the cinnamic acid double bond. The addition of hydrazine to the double bond was observed by Darapsky *et al.* (12) in the case of coumarin.

When hydrazine hydrate acted on the methyl ester of IX in more dilute solution and for a longer time, the product was found to have the structure XIV. Such a reducing action on double bonds by hydrazine hydrate has already been observed by Hanuš and Voříšek (18) in the oleic acid series.



$$C_6H_5CONH\underset{\substack{|\\ CONHNH_2}}{CH}\overset{\substack{C_6H_5\\ |}}{C}HNHNH_2$$

XII



$$C_6H_5CONH\underset{\substack{|\\ CONHN{=}C(CH_3)_2}}{CH}\overset{\substack{C_6H_5\\ |}}{C}HNHN{=}C(CH_3)_2$$

XIII

$$C_6H_5CONH\underset{\substack{|\\ CONHNH_2}}{CH}CH_2C_6H_5$$

XIV

ACKNOWLEDGMENT

We are indebted to E. H. Melvin and C. H. Van Etten of the Analytical and Physical Chemical Division of this Laboratory for the ultraviolet absorption spectra and the elementary analyses, respectively.

EXPERIMENTAL

All melting points are uncorrected.

α-Benzoylaminocinnamic acid hydrazide (VIII). Two grams of 2-phenyl-4-benzal-5-

oxazolone was triturated with 5 cc. of water, 15 cc. of methanol, and 4 cc. of 85% hydrazine hydrate until a clear solution resulted. A few minutes later white crystalline blades formed. After one hour at room temperature, 25 cc. of water was added and the reaction mixture kept at 0° overnight. Filtration gave 2.23 g. of fine white crystals which melted at 140–145° (evolution of gas) after air-drying. Recrystallization of this material from methanol-ethylene dichloride yielded 1.41 g. of air-dried product, m.p. 151–153° (gas evolution). Vanghelovici and Stephanescu report m.p. 153–154°. The compound analyzes as a monohydrate.

Anal. Calc'd for $C_{16}H_{17}N_3O_3 \cdot H_2O$: C, 64.20; H, 5.73; N, 14.04.
Found: C, 63.8; H, 6.00; N, 14.0 (Dumas).

Drying over phosphorus pentoxide to constant weight (three and one-half hours at 1 mm.) gave a very hygroscopic anhydrous product.

Anal. Calc'd for $C_{15}H_{17}N_3O_3$: C, 68.31; H, 5.38.
Found: C, 68.1; H, 5.50.

3-Phenyl-4-benzoylamino-5-pyrazolidone (X). Five grams of 2-phenyl-4-benzal-5-oxazolone was refluxed with 5 cc. of 85% hydrazine hydrate for thirty minutes. The crystals which deposited during the heating were triturated with water; yield, 3.83 g. Recrystallization from ethyl alcohol gave white needles of 3-phenyl-4-benzoylamine-5-pyrazolidone, m.p. 225–227° (Vanghelovici and Stephanescu, 229°).

Anal. Calc'd for $C_{16}H_{17}N_3O_3$: C, 68.31; H, 5.38; N, 14.94.
Found: C, 68.4; H, 5.66; N, 14.9 (Dumas).

2-Nitroso-3-phenyl-4-benzoylamino-5-pyrazolidone (XI). Two grams of 3-phenyl-4-benzoylamino-5-pyrazolidone (X) was dissolved in 100 cc. of concentrated hydrochloric acid. After addition of 100 cc. of water the solution was cooled to +5° and an equimolar amount (490 mg.) of sodium nitrite in 5 cc. of water was added gradually to the stirred liquid below the surface. A creamy precipitate appeared during the addition and was removed by filtration after ten minutes standing. The precipitate was immediately treated with 10 cc. of cold water containing 600 mg. sodium bicarbonate. A small amount of undissolved material was filtered off and the filtrate acidified with concentrated hydrochloric acid. The amorphous white precipitate which formed was separated and dried over phosphorus pentoxide at 0° *in vacuo*. It then melted at 107–110° with evolution of gas. The compound gave a deep red color with ferric chloride in alcohol; it also produced a deep blue color with a solution of diphenylamine in concentrated sulfuric acid (Angeli and Castellana modification of the Liebermann reaction). The nitroso compound was quite unstable at room temperature, some preparations giving nitrous fumes after only a few hours. Stored at 0° it appeared to be stable for some months. Because of the instability of the product and the difficulty of removing the solvent completely, the compound was analyzed as the barium salt, which retained two molecules of water of crystallization, even after long drying *in vacuo* over phosphorus pentoxide at 0°.

Anal. Calc'd for $C_{32}H_{26}BaN_8O_6 \cdot 2H_2O$: C, 48.52; H, 3.82; N, 14.15; Ba, 17.34.
Found: C, 48.9; H, 3.94; N, 13.8; Ba, 16.9.

α-Benzoylamino-β-hydrazinodihydrocinnamic acid hydrazide (XII). Five hundred mg. of methyl α-benzoylaminocinnamate was dissolved in the minimum amount (3 cc.) of methanol at room temperature and 0.5 cc. of 85% hydrazine hydrate added. In thirty minutes the clear solution deposited crystals which were filtered off at the end of two hours. Dried in air, the product (445 mg.) melted at 129–131° with vigorous evolution of gas, solidified and melted at 210–215°. This behavior suggested the elimination of hydrazine at the melting point with the formation of 3-phenyl-4-benzoylamino-5-pyrazolidone (X). To confirm this a sample of the addition compound was heated at 135° and 1 mm. pressure until evolution of gas ceased. The melting point of the resulting solid (220–224°) was not depressed by admixture with 3-phenyl-4-benzoylamino-5-pyrazolidone (X). The X-ray patterns of the two products were also identical.

The hydrazino compound slowly decomposes at room temperature. The melting point was lowered to 112–114° in four days. For analysis it was converted to the stable acetone derivative XIII. One hundred mg. was dissolved in 8 cc. of acetone at room temperature. The crystals (84 mg.) which appeared were filtered off after several days, m.p. 194–196° (evolution of gas). Recrystallization from methanol gave 40 mg. of the product having the same melting point.

Anal. Calc'd for $C_{22}H_{27}N_5O_2$: C, 67.2; H, 6.92; N, 17.80.
Found: C, 67.3; H, 6.96; N, 17.6 (Dumas).

α-Benzoylaminodihydrocinnamic acid hydrazide (XIV). One hundred mg. of methyl α-benzoylaminocinnamate was dissolved in about 10% more ethanol than that required for solution at room temperature and 0.20 cc. of 85% hydrazine hydrate added. Crystals appeared after six days and one day later were filtered off; yield, 39 mg.; m.p. 186–187°. Recrystallization from methanol-ethanol gave 20 mg. of α-benzoylaminodihydrocinnamic acid hydrazide as needles melting at 189–190°.

Anal. Calc'd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83.
Found: C, 68.1; H, 6.00; N, 14.5.

This hydrazide was shown by mixed melting point test and X-ray diffraction patterns to be identical with the hydrazide obtained from methyl α-benzoylaminodihydrocinnamic acid. The product could also be prepared in small yield (15 mg.) by heating 100 mg. of α-benzoylamino-β-hydrazinodihydrocinnamic acid hydrazide (XII) and 1 cc. of 85% hydrazine hydrate for three hours on the steam-bath.

SUMMARY

Under mild conditions hydrazine hydrate gives the expected hydrazide with 2-phenyl-4-benzal-5-oxazolone; at elevated temperature the product is 3-phenyl-4-benzoylamino-5-pyrazolidone. These structures differ from those assigned to the same products by Vanghelovici and Stephanescu. It has been found that the double bond in methyl-α-benzoylaminocinnamate adds hydrazine under some conditions and under other conditions the double bond is reduced.

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