From these data we obtain 7.9×10^{-14} for the second acid dissociation constant of copper hydroxide

$$HCuO_2^- = H^+ + CuO_2^=$$

The relative proportions of bicuprate ($HCuO_2^-$) and cuprate ($CuO_2^=$) ions in the solutions are evaluated and it is shown that the second of these predominates even below 0.1 normal alkali.

The solubility of the oxide in pure water is found to be approximately 3×10^{-5} mole per liter, which is somewhat lower than values now in the literature.

An accurate potentiometric method of determining copper in low concentrations is described.

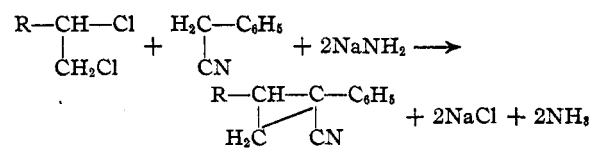
COLUMBUS, OHIO RECEIVED JULY 10, 1936

[CONTRIBUTION FROM THE WALKER CHEMICAL LABORATORY OF THE RENSSELAER POLYTECHNIC INSTITUTE]

Alkylene and Alkylidene Phenylacetonitriles and Derivatives. 1-Phenyl-2-ethylcyclopropanecarbonitrile, α-Phenyl-β-ethylacrylonitrile and α-Phenyl-β-isopropylacrylonitrile[1]

BY JAMES V. MURRAY AND JOHN B. CLOKE

It has been shown that 1-phenylcyclopropanecarbonitrile and its 2-methyl homolog can be prepared by the alkylenation of phenylacetonitrile with suitable dihalide derivatives, such as ethylene chloride and propylene chloride, in the presence of sodium amide, according to the reaction[2]



Directions have also appeared for the condensation of acetaldehyde[2] and *n*-butyraldehyde[3] with phenylacetonitrile by the action of sodium ethoxide as generalized below

$$RCHO + H_2C(CN)C_6H_5 = RCH{=}C(CN)C_6H_5 + H_2O$$

This work constitutes an extension of the work of Meyer and Frost[4] on the aromatic aldehydes to the aliphatic group.

The present paper describes the preparation of one alkylene phenylacetonitrile, 1-phenyl-2-ethylcyclopropanecarbonitrile, and two alkylidene phenylacetonitriles, *viz.*, α-phenyl-β-ethylacrylonitrile and α-phenyl-β-isopropylacrylonitrile, together with some of their derivatives.

The proof of the structures of the alkylidene phenylacetonitriles follows from (1) their method of preparation, if aldehydes are used, (2) their reaction with alkaline hydrogen peroxide to give glycidamides, R—CH(O)—C(C$_6$H$_5$)CONH$_2$,[3] although not all α,β-ethylenic nitriles react, and (3) their oxidation with potassium permanganate. On the other hand, the isomeric cyclopropanecarbonitriles may be recognized (1) by their reaction with hydrogen peroxide to give simple amides, if they react at all, and (2) by their stability in the presence of permanganate. In addition, molecular refractivities have been useful in the differentiation of the cyclopropane and ethylenic isomers, although they are less reliable than the chemical methods.

1-Phenyl-2-ethylcyclopropanecarbonitrile.—This nitrile was obtained in yields up to 40% by the interaction of phenylacetonitrile (I), 1,2-dichlorobutane and sodium amide, as indicated in the accompanying flow sheet. In this reaction it is advantageous to deviate from the original procedure of Knowles and Cloke by preparing the sodium amide in liquid ammonia, according to the method of Vaughn, Vogt and Nieuwland,[5] and using this solution in the initial stages of the reaction.

In passing, it may be pointed out that the glycidamide and Radziszewski reactions may be employed for the removal of phenylacetonitrile and α,β-ethylenic nitrile from the 1-phenyl-2-alkylcyclopropanecarbonitriles, since the latter are quite inert to the reagent.

Following the synthesis of 1-phenyl-2-ethylcyclopropanecarbonitrile (VI), it was essential to produce evidence for the presence of the cyclo-

(1) This paper is based upon a thesis presented by James Vincent Murray, Jr., to the Graduate School of the Rensselaer Polytechnic Institute in June, 1935, in partial fulfilment of the requirements for the degree of Master of Science.

(2) Knowles and Cloke, THIS JOURNAL, **54**, 2028 (1932).

(3) Murray and Cloke, *ibid.*, **56**, 2751 (1934).

(4) Meyer and Frost, *Ann.*, **250**, 157 (1889).

(5) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

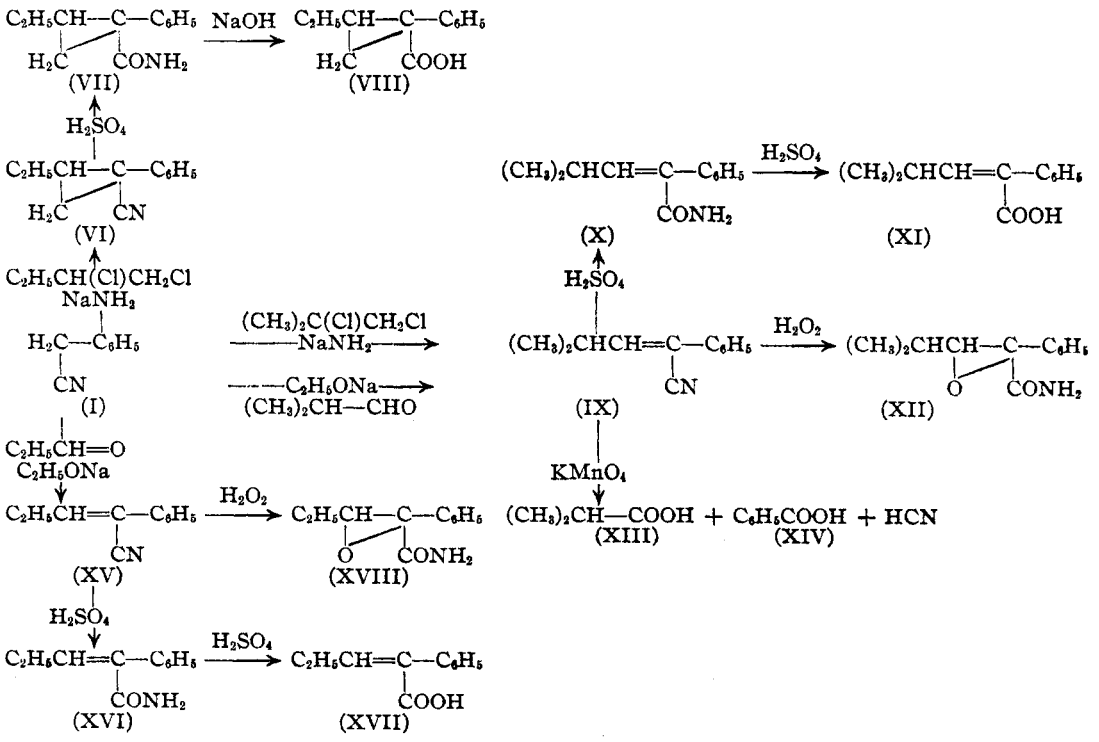
propane ring, since it appeared possible that the reaction might have given the isomeric 2-phenyl-3-hexenonitrile, which in the presence of alkali would be expected to rearrange to give an α-phenyl-β-*n*-propylacrylonitrile (V). The formation of a second series of nitriles is also possible if the secondary halogen atom of the 1,2-dichlorobutane were to react with the monosodium salt of (I).

Several lines of evidence point unquestionably to the cyclopropane structure for the nitrile (VI). In the first place, the nitrile (VI) differs widely from the isomeric ethylenic derivative (V).[3] Thus, the amide (VII) and the acid (VIII) derived from (VI) by hydrolysis are distinct from those obtained from (V). Furthermore, the molecular refractivities of the nitriles are different. In addition, the failure of (VI) to give a glycidamide with alkaline hydrogen peroxide, as well as its stability toward cleavage by alkaline potassium permanganate, definitely excludes the ethylenic structure. Moreover, its striking resistance toward hydrolysis and the ease with which it is altered by cold, concentrated sulfuric acid closely parallel the behavior of 1-phenyl-2-methylcyclopropanecarbonitrile (III), the next lower homolog. Finally, the good agreement between the observed molecular refractivity and that calculated on the basis of the cyclic structure indicates the presence of the cyclopropane nucleus in (VI).

α-Phenyl-β-isopropylacrylonitrile (IX).—With the expectation of obtaining 1-phenyl-2,2-dimethylcyclopropanecarbonitrile, phenylacetonitrile (I) was allowed to react with 1,2-dichloroisobutane and sodium amide. The resulting nitrile was obtained in yields up to 38%.

In the early stages of this work the cyclic structure for the nitrile was inferred on the basis of the method of preparation. However, consistently high values observed for the molecular refractivity cast considerable doubt on the cyclic structure, but were in harmony with the value computed for the ethylenic structure (IX). The cyclopropane structure was definitely excluded when it was found that the nitrile (IX) gave the glycidamide (XII), when it was subjected to the action of alkaline hydrogen peroxide. Still further confirmation of the ethylenic structure was obtained when it was observed that the nitrile (IX), upon oxidation with potassium permanganate in alkaline solution, absorbed three atoms of oxygen with the formation of isobutyric acid (XIII), benzoic acid (XIV), and hydrogen cyanide. This oxidation will be discussed more fully in a future communication.

Synthetic proof for the ethylenic structure (IX)



was also secured by the preparation of the nitrile in an 85% yield by the alkylidenation of phenylacetonitrile with isobutyraldehyde in the presence of dilute sodium ethoxide. The complete identity of the two nitriles was established by the fact that both yield the same amide (X), acid (XI), and glycidamide (XII) as shown by mixed melting point determinations.

It will be noted that the formation of the α-phenyl-β-isopropylacrylonitrile (IX) by the condensation of the 1,2-dichloroisobutane with phenylacetonitrile by the action of sodium amide involves a rearrangement. It is clear that the primary halogen atom of the dichloride must react with the phenylacetonitrile. This reaction is probably accompanied by the elimination of the remaining halogen atom with an adjacent hydrogen atom to give the β,γ-nitrile, $(CH_3)_2C{=}CH{-}CH(C_6H_5)CN$, which then rearranges to give the α,β-nitrile (IX), although other paths are possible.

α-Phenyl-β-ethylacrylonitrile (XV).—This nitrile, which may also be called propylidenephenylacetonitrile, was obtained in a 60% yield by the condensation of propionaldehyde with phenylacetonitrile by the use of sodium ethoxide. The structure is established by its method of preparation; the formation of the glycidamide, when it is treated with alkaline hydrogen peroxide; its instability toward alkaline potassium permanganate; and its refractivity. On hydrolysis, it yields the corresponding amide (XVI) and acid (XVII).

Experimental Part

Preparation of 1-Phenyl-2-ethylcyclopropanecarbonitrile (VI).—A two-liter, three-necked, round-bottomed flask was fitted with a dropping funnel, a reflux condenser provided with a lime tower, and an efficient mechanical stirrer which operated through a mercury seal.

One and one-half liters of liquid ammonia was placed in the reaction flask followed by 2 g. of bright sodium. The stirrer was set in motion and 1.5 g. of $Fe(NO_3)_3{\cdot}6H_2O$[5] (in later runs the hydrated chloride was used) was introduced and then 46 g. (2 atoms) of sodium in the form of small chips was added over the course of twenty minutes. The reaction mixture was then allowed to stand until the initial deep blue color had faded, denoting the completion of the reaction.

At this point, 117 g. (1 mole) of freshly distilled phenylacetonitrile[6] was cautiously added to the sodium amide solution during a period of one hour. The mixture in the flask was then stirred while 700 cc. of anhydrous ether was added at about the same rate at which the liquid ammonia evaporated. When the reaction mixture attained room temperature, it was refluxed gently for one hour.

At the end of this first stage, the sodium phenylacetonitrile mixture was cooled to −5° in an ice–salt bath and 127 g. (1 mole) of 1,2-dichloro-*n*-butane was added slowly over the course of one hour. Stirring was continued overnight while the bath came to room temperature. Following this, the reaction mixture was refluxed gently for two hours. Finally water was added to dissolve the solid precipitate and the mixture was acidified with acetic acid. The ether layer was removed and dried over anhydrous sodium sulfate. The fractionation of the dried ether extract gave 35 g. of a fraction boiling at 77–80° at less than 1 mm., which was mainly unchanged phenylacetonitrile, and a 68 g. fraction boiling at 93–94° at the same pressure. This corresponds to a 40% yield on the basis of the starting quantity of phenylacetonitrile. The nitrile possessed the following properties: d^{20}_4 0.9921; $n^{20}D$ 1.52457; MR_D (obsd.), 52.70; MR_D (calcd.), 52.29.[7] *Anal.* (micro.) Calcd. for $C_{12}H_{13}N$: N, 8.18. Found: N, 8.17, 8.25.

The foregoing procedure was varied in several runs by using commercial sodium amide or the specially prepared salt with ether exclusively as the reaction medium. These variations, however, markedly decreased the yield. Low yields were likewise obtained when liquid ammonia was used throughout as the reaction solvent, no provision being made for reflux periods.

1-Phenyl-2-ethylcyclopropanecarbonamide (VII).—In a 125-cc. acetylation flask were placed 10 cc. of water, 10 cc. of concentrated sulfuric acid, 10 cc. of glacial acetic acid, and 2 g. of 1-phenyl-2-ethylcyclopropanecarbonitrile. The mixture was refluxed for five hours and then poured into ice water. The aqueous solution was extracted with ether and this extract was then washed with 10% sodium carbonate solution. Evaporation of the ether solution gave the crude amide, which after decolorization and recrystallization from hot water yielded the pure amide as needles which melted at 84°.

The same amide was also obtained by hydrolysis of the nitrile with alcoholic potassium hydroxide. This method however, requires a reflux period of about sixty hours. Attempts to hydrolyze the nitrile by means of 100% phosphoric acid or by alkaline hydrogen peroxide were unsuccessful. *Anal.* Calcd. for $C_{12}H_{15}ON$: N, 7.41. Found: N, 7.35, 7.43.

1-Phenyl-2-ethylcyclopropanecarboxylic Acid (VIII).—A weight of 2 g. of the 1-phenyl-2-ethylcyclopropanecarbonamide was refluxed for fifty hours with *N* alcoholic potassium hydroxide. The crude acid was isolated in the usual manner and after recrystallization from hot water the pure acid melted at 105–105.5° (corr.).

Preparation of α-Phenyl-β-isopropylacrylonitrile (IX).—This nitrile was prepared by two different methods.

Method 1.—When phenylacetonitrile (1 mole) was allowed to react with 1,2-dichloroisobutane (1 mole) and sodium amide (2 moles) according to the procedure described for the preparation of (VI), the nitrile (IX) was obtained in yields up to 38%. After repeated fractiona-

(6) Adams and Thal, "Organic Syntheses," Coll. Vol. I, p. 101.

(7) The molecular refractivities were calculated on the basis of Eisenlohr's data. Ostling's value of 0.7 unit is added for the cyclopropane ring. Corrections for conjugation, distribution of groups, etc., have not been included.

tion of the reaction product, the nitrile boiled at 94.5–95° at less than 1 mm.

Method 2.—A solution of 58.5 g. (0.5 mole) of phenylacetonitrile and 54 g. (0.75 mole) of isobutyraldehyde in 120 cc. of absolute alcohol was cooled to −10° and a volume of 10 cc. of 20% sodium ethylate was added at such a rate that the temperature did not rise above −5°. The resulting solution, contained in a tightly stoppered flask, was allowed to stand in the refrigerator for one week. The reaction mixture was then poured into 700 cc. of ice water and was neutralized with acetic acid. The oily layer was taken up in an equal volume of ether and the resulting solution washed with water and dried over sodium sulfate. Fractionation of the dried product gave 73 g. of the nitrile boiling at 95–95.2° at less than 1 mm. which corresponds to a yield of 85%. The nitrile possessed the following properties: d^{20}_4 0.9613; $n^{20}D$ 1.53530; MR_D (obsd.) 55.41; MR_D (calcd.) 53.32.[8] *Anal.* Calcd. for $C_{12}H_{13}N$: N, 8.18. Found: N, 8.25, 8.19, 8.22, 8.20.

α-Phenyl-β-isopropylacrylamide (X).—A weight of 2 g. of the nitrile (IX) was hydrolyzed by the acetic acid–sulfuric acid method utilized in the case of the nitrile (VI). The ether solution, after extraction with 10% sodium carbonate, deposited the impure amide upon evaporation. Recrystallization of the crude product from boiling water gave the pure amide melting at 123–124° (corr.).

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.41. Found: N, 7.45, 7.52.

α-Phenyl-β-isopropylacrylic Acid (XI).—The sodium carbonate extract from the foregoing hydrolysis was acidified with dilute sulfuric acid and the impure α-phenyl-β-isopropylacrylic acid precipitated. Recrystallization of the crude product from hot water gave the pure acid as fine, white needles melting at 133–134° (corr.).

Hydrolysis of the α-phenyl-β-isopropylacrylonitrile prepared by either of the two methods resulted in the same products. The identity of the derivatives from the two nitriles was established by mixed melting point determinations.

α-Phenyl-β-isopropylglycidamide (XII).—Following the procedure of Murray and Cloke,[3] 2 g. of α-phenyl-β-isopropylacrylonitrile and 25 cc. of 10% hydrogen peroxide were dissolved in acetone and enough 10% sodium carbonate added to make the solution definitely alkaline. After standing for one day, the acetone was evaporated and the residue was recrystallized from boiling water. The resulting α-phenyl-β-isopropylglycidamide melted at 148–149° (corr.). *Anal.* Calcd. for $C_{12}H_{15}O_2N$: N, 6.82. Found: N, 6.72, 6.86.

The Oxidation of α-Phenyl-β-isopropylacrylonitrile.—A weight of 30 g. of α-phenyl-β-isopropylacrylonitrile was placed in a glass-stoppered Pyrex bottle containing 5 cc. of 10% sodium carbonate solution and 100 cc. of water. Solid potassium permanganate was added in small portions with shaking until the purple color persisted. This required 54.2 g. of permanganate and corresponds to the absorption of three gram atoms of oxygen per mole of nitrile.

Extraction of the alkaline solution with petroleum ether showed no unreacted nitrile. Acidification of the filtered aqueous solution gave a precipitate of benzoic acid (XIV), which was identified by a mixed melting point determination with a known sample of the acid. After the removal of the benzoic acid, the filtrate was made alkaline and evaporated to dryness. From the residue isobutyric acid was isolated and identified as the anilide. The presence of cyanide ion was demonstrated by the Prussian blue test.

Preparation of α-Phenyl-β-ethylacrylonitrile (XV).—A solution of phenylacetonitrile (0.4 mole) and propionaldehyde (0.5 mole) in 100 cc. of absolute alcohol was treated with 9 cc. of 20% sodium ethylate according to the procedure used for the preparation of the nitrile (IX) by method 2. Purification of the nitrile gave a 55% yield of the desired product boiling at 112–112.5° at 3 mm. The nitrile possessed the following properties: d^{20}_4 0.9897; $n^{20}D$ 1.54300; MR_D (obsd.), 50.00; MR_D (calcd.), 48.69.[8] *Anal.* Calcd. for $C_{11}H_{11}N$: N, 8.92. Found: N, 8.97, 9.00.

An earlier run of the nitrile, originally started by Rogers[9] and allowed to stand for one year, was found on purification to give a somewhat lower yield. A considerable amount of a brown, tarry material appeared during the distillation. Rogers' first run, which was allowed to stand for three days only at a temperature not far from 0°, gave a low yield, which was difficult to separate.

α-Phenyl-β-ethylacrylamide (XVI).—Hydrolysis of the α-phenyl-β-ethylacrylonitrile by the acetic acid–sulfuric acid method gave the amide, which after recrystallization from water melted at 130° (corr.). *Anal.* Calcd. for $C_{11}H_{13}ON$: N, 8.00. Found: N, 7.93, 8.06.

α-Phenyl-β-ethylacrylic Acid (XVII).—Following the usual procedure, the α-phenyl-β-ethylacrylic acid was isolated from the foregoing hydrolysis mixture. The pure acid after recrystallization from hot water melted at 67.5–68.5°.

α-Phenyl-β-ethylglycidamide (XVIII).—The glycidamide,[9] obtained in the usual manner by the action of alkaline hydrogen peroxide on the nitrile (XV), was recrystallized from boiling water and found to melt at 155° (corr.). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: N, 7.33. Found: N, 7.26, 7.30.

Summary

1. 1-Phenyl-2-ethylcyclopropanecarbonitrile has been prepared in yields up to 40%. Several derivatives and reactions of this nitrile have been discussed in connection with the proof of its cyclic structure.

2. α-Phenyl-β-isopropylacrylonitrile was prepared by two different methods in yields of 38 and 95%. Proof for the ethylenic structure is given and several derivatives of the nitrile are described.

3. The preparation of α-phenyl-β-ethylacrylonitrile is described together with a number of its derivatives.

(8) These abnormally high exaltations (not included in the calculations) have been observed in all of the alkylidene-phenylacetonitriles so far prepared. The exaltation apparently arises from a combination of conjugation of multiple linkages and distribution of groups about the ethylenic bond. Further, the anomaly appears to depend also upon the nature of the hydrocarbon residue in the β-position.

(9) D. T. Rogers, Master's Thesis, Rensselaer Polytechnic Institute, 1934.

4. Some preliminary work on the oxidation of α,β-ethylenic nitriles is described.

5. Whereas the condensation of ethylene, propylene and α-butylene dichlorides with phenylacetonitrile gives cyclopropanecarbonitriles, the use of isobutylene dichloride under the same conditions leads to the formation of an ethylenic nitrile.

TROY, NEW YORK RECEIVED JULY 28, 1936

[CONTRIBUTION FROM THE DEPARTMENT OF MINERALOGY, OXFORD UNIVERSITY, AND THE LABORATORY FOR ENDOCRINE RESEARCH, THE JOHNS HOPKINS UNIVERSITY]

The Molecular Weight of Cinobufagin

BY DOROTHY CROWFOOT AND H. JENSEN

It has been suggested[1] that cinobufagin ($C_{25}H_{32}O_6$) can be considered as the acetyl derivative of an unsaturated hydroxylactone, $C_{23}H_{30}O_5$, and apparently is closely related chemically to certain plant aglucones which are also C_{23} derivatives.[1] The x-ray crystallographic examination of this principle by Crowfoot[2] has given values, however, which do not agree with the proposed formula $C_{25}H_{32}O_6$ and which indicate that the compound probably contains twenty-six carbon atoms.

In order to check these results, x-ray measurements have now been made on two derivatives of cinobufagin, namely, acetylcinobufagin and cinobufagone. The measurements obtained on these compounds provide two independent determinations of the molecular weight of cinobufagin and both more nearly agree with the formulas derived from C_{26}. Thus the molecular weight of acetylcinobufagin was found to be 487 ± 10, the calculated values for the acetyl derivatives of $C_{26}H_{34}O_6$ and $C_{25}H_{32}O_6$ being, respectively, 484 and 470. Cinobufagone has a molecular weight of 443 ± 10 which is in agreement with the formula $C_{26}H_{32}O_6$, 440, and not $C_{25}H_{30}O_6$, 426. Details of the crystallographic measurements are given below.

The analytical values previously reported for cinobufagin and certain of its derivatives[3] agree with the formula $C_{26}H_{34}O_6$. This new formula would bring cinobufagin into very close relationship to bufotalin (present in the secretion of *Bufo vulgaris*) to which Wieland and co-workers[4] assigned the formula $C_{26}H_{36}O_6$ and which they showed can be considered as an acetyl derivative of an unsaturated hydroxylactone ($C_{24}H_{34}O_5$). It might be mentioned, in connection with this, that the results of the pharmacological studies by Chen and Chen[5] on the action of the various animal cardiac principles indicate that their physiological properties show more resemblance to the physiological action of scillaridin than of other plant aglucones. Chemical researches by Stoll and co-workers[6] have shown that scillaridin is a C_{24} derivative, while most other plant aglucones have been found to be C_{23} derivatives. The investigation of Wieland and co-workers[4] on bufotalin indicates that the lactone ring in the animal cardiac principles is a six-membered ring probably similar to that found by Stoll and co-workers[6] for scillaridin. In view of our findings on the molecular weight of cinobufagin, it appears that arenobufagin and regularobufagin are also probably C_{24} rather than C_{23} derivatives as originally suggested by Jensen.[7] Further research on the exact chemical composition of these two principles has been undertaken in order to answer this question.

It should be added that the crystallographic examination of cinobufagone and acetylcinobufagin alone would not exclude molecular weights of twice the magnitude deduced since the asymmetric unit in each case contains two C_{26} molecules. This possibility, however, is excluded by the original measurements on cinobufagin itself in which the single molecule is the asymmetric unit.

The actual crystal structures indicated by the measurements for cinobufagin, acetylcinobufagin and cinobufagone do not seem to bear very simple relation to one another or to those of any of the compounds in the cardiac aglucone series so far examined. This is not surprising since the introduction of many hydroxyl groups is known to produce considerable variation in the crystallo-

(1) Jensen, *Science*, **75**, 53 (1932).
(2) Crowfoot, *Chemistry & Industry*, **54**, 568 (1935).
(3) Jensen and Evans, Jr., *J. Biol. Chem.*, **104**, 307 (1934).
(4) Wieland and Hesse, *Ann.*, **517**, 22 (1935).
(5) Chen and Chen, *J. Pharmacol.*, **49**, 561 (1933).
(6) Stoll, Hofmann and Peyer, *Helv. Chim. Acta*, **18**, 1247 (1935).
(7) Jensen, THIS JOURNAL, **57**, 1765 (1935).