[Contribution from the Department of Chemistry of the University of Michigan]

2,3-PYRROLIDINEDIONES. V. DOEBNER'S ANIL-ANILIDE

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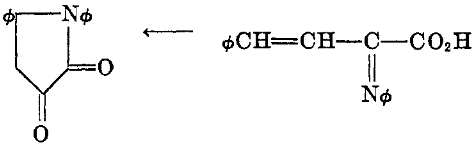
The 4-carbalkoxy-2,3-pyrrolidinedione structure originally proposed by Schiff and Bertini (1) for the products obtained from benzylideneaniline and esters of oxaloacetic acid is now strongly supported by an alternative synthesis *via* the Dieckmann cyclization of alkyl β-phenyl-β-N-methoxalyl-N-phenylaminopropionates which was reported by Southwick and Crouch (2) and performed independently in this laboratory (3). It is justifiable, therefore, to cite the apparent analogy between the benzylideneaniline-oxaloacetic ester condensation and the condensation of benzylideneaniline with pyruvic acid in support of the 2,3-pyrrolidinedione structure for the product of the latter reaction, as first proposed by Schiff and Gigli (4). Other evidence, presented in the preceding paper in this series (3), likewise strongly supports the 2,3-pyrrolidinedione structure, and there remains only an unequivocal degradation and synthesis to confirm the preponderant evidence already available.

The general tautomeric character of the 2,3-pyrrolidinediones has been investigated kinetically (5) and with the assistance of carbon-14 (3), and apart from specific degradation of 1,5-diphenyl-2,3-pyrrolidinedione-2-C^{14}, which remains to be carried out, the evidence all points to the unprecedented tautomerism:

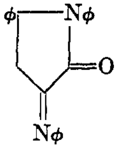


$\phi CH{=}CH{-}\underset{\underset{N\phi}{\|}}{C}{-}CO_2H$

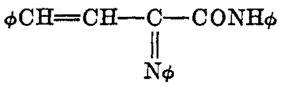
I II

in which the carboxyl carbon of II becomes the lactam carbonyl carbon of I.

The existence of such a tautomeric system at once raises a question concerning the structure of the products derived from I and primary amines. The parent member of this class has been "characterized" as 1,5-diphenyl-3-phenylimino-2-pyrrolidone (III) and is identical with the substance first produced by Doebner (6) while studying his well-known cinchoninic acid synthesis. Doebner, however, formulated his product as the anil-anilide of benzylidenepyruvic acid



III

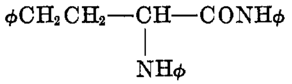


$\phi CH{=}CH{-}\underset{\underset{N\phi}{\|}}{C}{-}CONH\phi$

IV

(IV). At that time the 2,3-pyrrolidinedione srtucture had not been recognized, but subsequent to its discovery Garzarolli-Thurnlackh (7) undertook a "proof" of structure of Doebner's "anil-anilide" and formulated it as III. Still later Borsche (8) provided more data purporting to support the structure represented by III. Neither author is convincing, the less so since the interconvertibility of I and II has been recognized; but nonetheless the cyclic structure has become generally accepted. Bodforss (9), for example, states that Garzarolli-Thurnlackh (7) and Borsche (8) have proved the cyclic structure to be correct, and subsequent investigators have apparently accepted these statements.[1]

An unequivocal synthesis of IV seemed to be out of the question since methyl benzylidenepyruvate and aniline (heat) and benzylidenepyruvanilide with aniline and zinc chloride (heat) both had been shown to produce the substance which has been formulated as III (10). Consequently, it was decided to synthesize α-anilino-γ-phenylbutyranilide (V), to which IV, but not III, should be reducible. Accordingly, α-anilino-γ-phenylbutyric acid was prepared by hydrogenation of the sodium salt of α-phenylimino-β-benzylidenepropionic acid, with subsequent neutralization, and the product was treated with excess aniline near the reflux temperature according to the directions of Nastvogel (11) for the preparation of α-anilinoanilides to give:



$$\phi CH_2CH_2{-}\underset{\displaystyle NH\phi}{\underset{|}{C}H}{-}CONH\phi$$

V

The hydrogenation of the "anil-anilide" proved to be somewhat confusing inasmuch as it first appeared that two different products were obtained: one (A) after one equivalent of hydrogen (2H) had been absorbed and a second (B) after two equivalents of hydrogen (4H) had been absorbed. Since the infrared spectrum of the "anil-anilide" possesses a sharp band in the N—H stretching region of the infrared spectrum, these data suggested an equilibrium similar to that obtained in the 2,3-pyrolidinedione system, (A) being obtained from the cyclic form (III) and (B) from the acyclic form (IV). However, neither (A) nor (B) corresponded in physical properties with V. Therefore, the hydrogenation products were re-examined, and it was proved that (A) was a mixture containing unreduced "anil-anilide" while (B) was a mixture containing two reduction products. The difficulty arose from an insensitivity of the melting point of the reduction products to substantial quantities of the "anil-anilide." The reason for incomplete reduction lay in the rather marked insolubility of the "anil-anilide" in any satisfactory hydrogenation solvent.

In a separate run, the "anil-anilide" was reduced in glacial acetic acid over Adams' catalyst, and the hydrogenation was allowed to continue until a sharp break in the rate of uptake was observed. This occurred after approximately four equivalents of hydrogen (8H) had been absorbed, and the infrared spectrum of the crude reduction product was found to be essentially indistinguishable from that of the purified product, thus indicating that *only one* substance (VI) was obtained. Microanalysis confirmed the introduction of eight hydrogens and the acetyl derivative of this substance showed no absorption in the N—H stretch-

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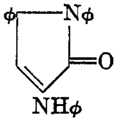
[1] *Cf.* for example Ref. (14–23).

ing region of its infrared spectrum. Thus, it would appear that *one* double bond and one benzenoid nucleus had been hydrogenated. This observation is incompatible with IV for the "anil-anilide" structure, since such reduction of IV would afford a product containing five equivalents of hydrogen (10H) and a non-acetylatable N—H grouping as well as an acetylatable one.

Consequently, the "anil-anilide" was once more hydrogenated—until about two equivalents (4H) had been absorbed—and the crude product was shown to be free from "anil-anilide" by infrared analysis. Careful fractional crystallization afforded a pure substance (VII), which analyzed for the "anil-anilide" + 2H and whose infrared spectrum was very similar to that of VI, but which melted some 18° higher. Acetylation was attempted on VII, but an uncrystallizable glass was obtained. However, formylation and benzoylation both afforded substances lacking the absorption in the N—H stretching region of their infrared spectra possessed by VII. Furthermore, the spectrum of VII was distinctly different from that of V as was its melting point and molecular formula. Thus, it was determined that (A) was a mixture, fortuitously composed of some VI, VII, and the original "anil-anilide," while (B) consisted principally of VI and VII.

It now becomes possible to argue that the "anil-anilide" consists entirely of one form, since but one reduction product is formed on "complete" hydrogenation. Furthermore, this form must be cyclic since on introduction of one equivalent of hydrogen (2H) a pure product is obtained which is not related to V, since it contains but *one* N—H group, that being in a secondary amine. The possibility that IV was hydrogenated at the azomethine link only is ruled out by the fact that VII may be reduced readily to VI, with the introduction of six atoms of hydrogen, no break being observed in the curve in which hydrogen uptake is plotted *vs.* time. Accordingly, the generally accepted structure for the anil-anilide (III) is very nearly correct.

That III does not exactly represent the structure is established by the strong absorption noted in the N—H stretching region of its infrared spectrum. Since this substance decomposes sharply at its melting point, the possibility of a mixture in the solid state seems rather unlikely. Furthermore, if an acyclic form having a formula such as IV were present, the hydrogenation data would demand a labile equilibrium in solution in which the cyclic form was reduced much more rapidly than the acyclic form.[2] Accordingly, the "anil-anilide" structure must be written:



VIII

as with the 2,3-pyrrolidinediones themselves, where the spectra require substantial enolization. The presence of a strong band at 6.10 μ which disappears on hydrogenation confirms the presence of the endocyclic carbon-carbon double

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[2] Such a situation is encountered with the p,p'-dimethoxy derivative of I (in the α-imino acid form), and there, both possible reduction products were isolated (5).

bond. The shift of the lactam carbonyl band from 5.98 μ in VIII to 5.92 μ in VI and VII indicates the loss of α,β-unsaturation. This same band, when arising from a conjugated lactam structure, is at the same wave length as in V, where it is due to a normal anilide structure.

In the interests of obtaining spectrographic data on bands characteristic of the VII structure a number of related substances, previously known, were prepared in which the same substituent in the same location appears in the phenyl groups attached to the two nitrogens: VIIIa, *p*-methyl (12); VIIIb, *p*-chloro (8); VIIIc *m*-chloro (8); VIIId, *m*-nitro (8). All of these substances showed absorption between 3.06 and 3.10 μ, attributable to the N—H stretching vibration, thus the 3-anilino-Δ^3-2-pyrrolinone structure appears to be the preferred one.

The "anil-anilide" structure is most readily synthesized by adding an ethereal (or alcoholic) solution of an aromatic primary amine to a similar solution of an aromatic aldehyde (benzaldehyde in all cases in the present study) and pyruvic acid at room temperature (8, 9). The use of equimolar quantities of each reagent appears to provide the most satisfactory yields (9). However, the compounds can be prepared from I, or its aryl substituted derivatives, by warming with excess primary aromatic amine. The question of consequent structure (9) when using an amine different from that involved in the original synthesis of I will be deferred until further study is possible.

The mildness of the reaction conditions is perhaps the most significant feature to be considered in attempting to explain the reaction. Borsche's suggestion (8) that the aniline adds to benzylidenepyruvic acid with subsequent ring closure to the 2,3-pyrrolidinedione with further reaction at the 3-position to give the anil must be discarded since the anil formation from I requires more energy than direct formation of the "anil-anilide" (9). Likewise, it seems most improbable that the open-chain α-phenyliminobenzylidenepropionic acid reacts directly with the amine to give the anilide which then rearranges to the cyclic form. Thus, one is forced to the conclusion that the "anil-anilide" is most probably formed either directly from two moles of amine, one of aldehyde and one of pyruvic acid (*cf.* ref. 7) or from a presently unidentified intermediate either in the tautomeric equilibrium between the 2,3-pyrrolidinedione and α-iminoacid, or more likely in the formation of one or the other members of the tautomeric pair.

EXPERIMENTAL[3]

Preparation of the "anil-anilides" [III (VIII)], VIIIa, VIIIb, VIIIc, VIIId. These substances were prepared essentially by Bodforss' procedure (9) in which solutions of 3.5 g. of pyruvic acid and 4.2 g. of benzaldehyde in 25 ml. of ether were treated with 3.7 g. of the appropriate aromatic amine in 5 ml. of ether. The products were recrystallized from glacial acetic acid to give somewhat higher m.p.'s than previously reported: III (VIII) (from aniline) 224–225°d. [224–225°d. (9)]; VIIIa (from *p*-toluidine) 216–217°d. [204–205°d. (12)]; VIIIb (from *p*-chloroaniline) 207–208°d. [203–204°d. (8)]; VIIIc (from *m*-chloroaniline) 202–203°d. [199–200°d. (8)]; VIIId (from *m*-nitroaniline) 216–217°d. [211–212°d. (8)]. It was subsequently found that III (VIII) could be better purified by recrystallization from absolute ethanol in which it is more stable but much less soluble: m.p. 227–228°d. Each

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[3] Melting points are uncorrected.

"anil-anilide" possessed a strong band in its infrared spectrum between 3.06 and 3.10 μ, and the spectra of all five were very similar.

Hydrogenation of III (VIII). Optimum conditions for hydrogenation required reaction with hydrogen at atmospheric pressure of the "anil-anilide" suspended in 100 times its weight of acetic acid containing 0.10 the weight of the "anil-anilide" of Adams' catalyst.

Run A. Interrupted after 1 mole of hydrogen had been absorbed. The crude product, obtained after filtration from the catalyst and evaporation to dryness, showed appreciable contamination with starting material. Recrystallization from ethanol afforded a product, m.p. 194–195°. On subsequent mixing with III (VIII) no depression was observed, nor was an appreciable alteration detected with the product of run *B*.

Anal. Calc'd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53.
Found:[4] C, 80.56; H, 5.87; N, 8.59.

Run B. Interrupted after 2 moles of hydrogen had been absorbed. The product was isolated and purified as before: m.p. 187–188°. This melting point was raised somewhat by admixture with III (VIII).

Anal. Calc'd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48.
Found:[4] C, 80.30; H, 6.27; N, 8.40.

Run C. Run B was repeated and the product was fractionally crystallized from absolute ethanol to give a product (VII) with a slightly higher melting point (188–189°) but possessing an identical infrared spectrum, with a strong band at 3.10 μ.

Anal. Calc'd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53.
Found:[4] C, 80.55; H, 6.05; N, 8.40.

Acetylation of VII afforded an uncrystallizable glass. However, on refluxing for 10 min. with excess 98% formic acid there was produced a formyl derivative: m.p. 148–149° from ether, if filtered at once. If the crystals were allowed to stand in contact with the mother liquor a second form, m.p. 168–169°, was obtained. The lower-melting form was analyzed.

Anal. Calc'd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86.
Found:[5] C, 77.38; H, 5.56; N, 7.76.

A benzoyl derivative of VII was prepared by the customary Schotten-Baumann procedure: m.p. 170–171°, from aqueous methanol.

Anal. Calc'd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48.
Found:[5] C, 80.30; H, 5.76; N, 6.68.

Neither acyl derivative showed any absorption in the N—H stretching region of their infrared spectra.

Run D. A sharp break in the curve for the uptake of hydrogen *vs.* time was noted after 4 moles had been absorbed. The reaction was interrupted at this point and the product was isolated as in the preceding runs. The crude product from evaporation of the solvent and the purified product (from ethanol), m.p. 170.5–171.0° (VI), possessed identical infrared spectra with a strong band at 3.10 μ.

Anal. Calc'd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38.
Found:[4] C, 78.93; H, 7.70; N, 8.51.

Acetylation of VI was effected by refluxing in excess acetic anhydride for 1 hr. The acetyl derivative was recrystallized from 50% aqueous ethanol, m.p. 177.5–178.0°. Its infrared spectrum showed no absorption attributable to N—H.

Anal. Calc'd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44.
Found:[4] C, 76.71; H, 7.36; N, 7.60.

Hydrogenation of VII. Under identical conditions to those used for the preceding runs 0.66 g. of VII was reduced. The product was identified as VI by melting point, mixture melting point, and identity of infrared spectra.

Preparation of α-anilino-γ-phenylbutyric acid. α-Phenyliminobenzylidenepropionic acid

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[4] Microanalysis by Anna B. Griffin, University of Michigan.

[5] Spang Microanalytical Laboratory, Plymouth, Michigan.

(13) (8.0 g.) was dissolved in 330 ml. of absolute ethanol in which 0.77 g. of sodium had been dissolved. To the resulting solution was added 0.55 g. of Adams' catalyst, and the mixture was shaken with hydrogen at 3-4 atm. until no further uptake was observable (about 12 hr.). After filtration from the catalyst and through a layer of Norit, the solution was evaporated to dryness, the residue being taken up in water and treated dropwise with conc'd hydrochloric acid to *p*H 7. The aminoacid precipitated at once (7.2 g.) and was recrystallized from glacial acetic acid, m.p. 192–194°d.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49.
Found:[4] C, 74.94; H, 6.52; N, 5.65.

The anilide (V) was prepared by heating the acid (5 g.)[6] with aniline (7 ml.) according to the procedure of Nastvogel (11). The anilide tended to supersaturate excessively on recrystallization from 95% ethanol, but some 2.4 g. were obtained as crude product which was recrystallized to constant m.p. 147.5–148.5° (V).

Anal. Calc'd for $C_{22}H_{22}N_2O$: C, 79.97; H. 6.71; N, 8.48.
Found:[4] C, 79.87; H, 6.64; N, 8.26.

SUMMARY

The structure of Doebner's "anil-anilide" has been studied, and the generally accepted but previously unconfirmed cyclic structure has been found to be essentially correct. The compound appears to be 1,5-diphenyl-3-phenylamino-Δ^3-2-pyrrolinone rather than the accepted 1,5-diphenyl-3-phenylimino-2-pyrrolidone.

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[6] When unrecrystallized acid was used a very small first crop was obtained which infrared analysis indicated to be VII.