cyanopyrazine was 2.7 g. (29%); b.p. 116–117° (100 mm.), n^{20}_{D} 1.5343.

B. **Compounds XVII–XXVI.**—A mixture of 0.05 mole of the appropriate 2-bromopyrazine and 15 g. (0.168 mole) of cuprous cyanide in 40 ml. of anhydrous γ-picoline was refluxed for three hours (ten hours for cpd. XXVI) and poured while hot into a vigorously stirred mixture of 400 ml. of ice-cold 4 *N* hydrochloric acid and 100 ml. of chloroform. After one-half hour of stirring this was filtered and the solid was washed with 50 ml. of chloroform. The aqueous portion of the filtrate was further extracted with 100 ml. more chloroform and the combined, dried (magnesium sulfate) extracts were concentrated through a 15-inch packed column. Cyanopyrazines XVII–XXII were purified by distillation through a 10-inch Vigreux column. The phenylcyanopyrazines were dried under vacuum to remove chloroform and then XXIII was distilled (b.p. 117–118° at 0.2 mm.; m.p. 77–78°), XXVI was recrystallized from 500 ml. of toluene, and XXIV and XXV were recrystallized from 350 ml. of heptane.

IV. **2-Carboxamidopyrazines of Table III.**—A solution of 0.05 mole of the appropriate 2-cyanopyrazine in 25 ml. of concentrated sulfuric acid was heated at 120–125° for three hours and then poured onto 400 g. of ice. This solution was made alkaline with 50% aqueous sodium hydroxide and the amide was extracted with three 150-ml. portions of chloroform, filtering with Super-Cel when necessary to assist in separation of layers. After evaporation of the chloroform solutions, the crude amides were recrystallized from the solvents specified in Table III.

V. **2-Acetyl-5,6-diphenylpyrazine.**—A solution of 4.3 g. (0.0167 mole) of 2-cyano-5,6-diphenylpyrazine in 200 ml. of dry benzene was stirred at 25° while 7.0 ml. of 4.0 *molar* ethereal methylmagnesium bromide was added and then the mixture was refluxed for one hour and cooled to 10°. After addition of 50 ml. of 6 *N* hydrochloric acid, the hydrolysis mixture was refluxed with stirring for one hour and then diluted with 200 ml. of water. The solid residue from evaporation of the benzene solution was recrystallized from 20 ml. of acetone to give 3.5 g. (76%) of the ketone, small golden flakes, m.p. 152–153°.

Anal. Calcd. for $C_{18}H_{14}N_4O$: N, 10.22. Found: N, 10.16.

VI. **2-Acetyl-3,5,6-trimethylpyrazine.**—The reaction of 5.0 g. (0.034 mole) of 2-cyano-3,5,6-trimethylpyrazine with 13.0 ml. (0.052 mole) of 4.0 *molar* methylmagnesium bromide was performed as described in V for the diphenyl analog, except that the final reflux period (with 25 ml. of 6 *N* hydrochloric acid) was one-half hour. The benzene solution was then washed with water and with 2% aqueous sodium hydroxide, dried over magnesium sulfate and concentrated through a Vigreux column. Distillation of the residue gave 2.5 g. (45%) of the solid ketone, b.p. 113–114° (14 mm.). After recrystallization from pentane the analytical sample of soft white flakes melted at 61–62°.

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.07. Found: N, 17.28.

VII. **2-Amidino-3,5,6-trimethylpyrazine Hydrochloride.**—A cold (0°) solution of 2.0 g. (0.0136 mole) of 2-cyano-3,5,6-trimethylpyrazine in 5 ml. of anhydrous ethanol plus 15 ml. of pure dioxane was saturated with hydrogen chloride and stored at 25° for three days. The iminoether hydrochloride was filtered off, washed with dry ether and added with stirring to 100 ml. of cold (0°) saturated ammoniacal ethanol (anhydrous), and then this mixture was stored at 25° for three days. Ammonium chloride was filtered off and the filtrate was evaporated to dryness under vacuum. The solid was dissolved in 10 ml. of warm anhydrous ethanol and the solution was diluted with 20 ml. of acetone. After ten minutes, more ammonium chloride was filtered off and the filtrate was evaporated to a volume of 6 ml., diluted with 25 ml. of acetone and stored at 0° to give 2.0 g. (73%) of hard, cream-colored granules of the amidine hydrochloride, m.p. 170–171°.

Anal. Calcd. for $C_8H_{13}N_4Cl$: N, 27.92. Found: N, 27.98.

VIII. **2-Amidino-5,6-diphenylpyrazine Hydrochloride.**—A mixture of 2.0 g. (0.0078 mole) of 2-cyano-5,6-diphenylpyrazine and 2.4 g. (0.0316 mole) of dry ammonium thiocyanate was stirred at 180° for 45 minutes. After cooling the tarry mass was leached with 100 ml. of boiling water, decanting from the tar which was then leached with two 80-ml. portions of boiling 1% hydrochloric acid. The combined acid extracts were made alkaline with sodium hydroxide and chilled to precipitate the crude amidine which was filtered off. This was boiled with 70 ml. of 1% hydrochloric acid and the mixture was filtered. Buff granules of the amidine hydrochloride crystallized from the filtrate on cooling. The yield was 50 mg. (2%), m.p. 260–265° with decomposition.

Anal. Calcd. for $C_{17}H_{15}N_4Cl$: N, 18.02. Found: N, 17.90.

Acknowledgments.—We are grateful to the Ortho Research Foundation, which has permitted us to perform all experimental work in its laboratories, and to Mr. Joseph Grodsky for most of the microanalyses.

RARITAN, NEW JERSEY

[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

The Japp–Klingemann Reaction with γ,δ-Unsaturated β-Ketoesters. Synthesis of Pyridazinones[1]

BY D. SHAPIRO, R. A. ABRAMOVITCH AND S. PINCHAS

RECEIVED NOVEMBER 14, 1955

Ethyl 2,3-dioxo-octadec-4-enoate-2-phenylhydrazone (Ia) is found to isomerize in alcohol to ethyl 1,2,3,4-tetrahydro-1-phenyl-6-tridecylpyridazin-4-one-3-carboxylate (IIIa) which, on reduction with zinc and acetic acid, suffers ring-opening with loss of ammonia to give ethyl 3-hydroxy-5-anilino-octadec-2,4-dienoate (IVa). These structures are confirmed by infrared measurements. The isomerization to pyridazinones is of potentially general applicability with products of the Japp–Klingemann reaction of γ,δ-unsaturated β-ketoesters and constitutes an original route to this heterocyclic system.

The key intermediate in the total synthesis of sphingosine[2a] is ethyl 2,3-dioxo-octadec-4-enoate-2-phenylhydrazone (Ia), which is prepared by the Japp–Klingemann reaction[3] of benzenediazonium chloride with ethyl α-hexadec-2-enoylacetoacetate. Occasionally, instead of the required product Ia there was obtained an isomeric product A, tentatively formulated as IIa,[2b] which differed from Ia in melting point and was lighter in color. Molecular weight determinations eliminated the possibility that A was a polymeric form of Ia. Zinc and

---

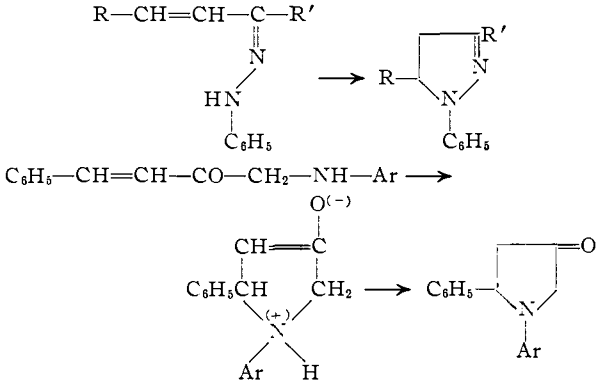
(1) Part of this work was embodied in a lecture by D. Shapiro at the International Congress on Pure and Applied Chemistry, Zürich, 1955.

(2) (a) D. Shapiro and K. Segal, THIS JOURNAL, **76**, 5849 (1954); (b) D. Shapiro and R. A. Abramovitch, Congress Handbook, XIVth International Congress of Pure and Applied Chemistry, Zürich, 1955, p. 340.

(3) R. Japp and F. Klingemann, *Ber.*, **20**, 2942, 3284, 3398 (1887).

acetic acid reduction of Ia in the presence of acetic anhydride gave the acetamido compound V, $C_{22}H_{39}O_4N$, m.p. 62–65°, with elimination of acetanilide, whereas under the same conditions A only lost ammonia giving a compound IVa, $C_{26}H_{41}O_3N$, m.p. 37–38°, the analysis showing that the anilino group was retained. It was subsequently found that in alcoholic solution, the phenylhydrazone Ia is gradually transformed into A. V, on the other hand, was not transformed into IVa. It was therefore necessary to determine the nature of the isomerization and hence the structures of A and IV.

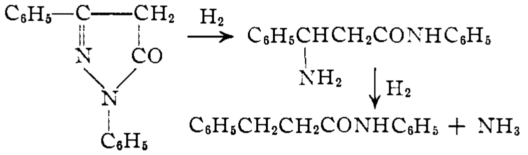
It was clear from the outset that the isomerization must involve the double bond, for the corresponding saturated phenylhydrazone[2a] could not be isomerized, whereas ethyl 5-phenyl-2,3-dioxopent-4-enoate-2-phenylhydrazone (Ib), obtained[4] by the reaction of benzenediazonium chloride with ethyl α-cinnamoylacetoacetate, isomerized to a product (A′) on recrystallization from alcohol. The simplest possibility was that ring-closure had taken place by an internal Michael-type addition of the phenyl–nitrogen to the double bond, thus leading to a substituted pyridazinone (II). This assumption was subsequently confirmed, though a slight modification as to the position of the double bond in the ring had to be introduced. Cyclizations of this type leading to five-membered heterocyclic nitrogen rings are common. Thus the phenylhydrazones of unsaturated aldehydes and ketones change easily and sometimes uncontrollably into pyrazolones, the change usually being accompanied by a lightening in color.[5–8] Southwick and Dimond[9a,b] showed that arylaminomethyl styryl ketones could be isomerized to N-arylpyrrolidones simply by boiling with 50% ethanol.

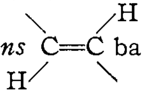


Various attempts to degrade compounds A, IVa, A′ or its zinc and acetic acid reduction product IVb under strong or mild acid or alkaline conditions failed to give any identifiable products.

A and IV both contain carbethoxyl groups. A keto-group is present in A (but not in IV) since it reacts with 2,4-dinitrophenylhydrazine to give a derivative. IV, on the other hand, gives a positive ferric chloride test for an enol grouping, whereas A does not. The ultraviolet absorption curve of A is not very characteristic, showing a rather flat band at λ_{max} 380 mμ (ε 13,500).

The presence of an anilino group in IVa was indicated both by the analytical figures and by its ultraviolet absorption spectrum which showed a strong band at 274 mμ, the high intensity (ε 24,000) of which indicates the likely presence of a conjugated C_6H_5N– grouping. Further, hydrogenation of A in ethanol in the presence of Adams catalyst gave a 32% yield of free ammonia together with an unidentified oil, four moles of hydrogen having been taken up. These results are only compatible with an intramolecular cyclization linking the phenyl–nitrogen to the long chain, and find a parallel in the hydrogenolysis of certain pyrazolones, *e.g.*, 1,3-diphenylpyrazol-5-ones, to give ammonia and amides.[10]



Evidence for the pyridazine ring formation was obtained from a study of the corresponding infrared spectra. Thus, ethyl 2,3-diketo-octadec-4-enoate-2-phenylhydrazone (Ia) showed the characteristic *trans*  $\overset{\diagdown\quad\diagup H}{\underset{H\diagup\quad\diagdown}{C{=}C}}$ band at 983 cm.$^{-1}$,[11] phenyl bands at 1511 and 1580 cm.$^{-1}$, and a band at 1645 cm.$^{-1}$ attributed to a conjugated $>C{=}N—$ linkage. A strong absorption at 1708 cm.$^{-1}$, thought to be due to a strongly chelated ester carbonyl group overlapping a ketonic carbonyl group, is discussed in detail later. The effects of the carbon–carbon α,β-unsaturation and the conjugated carbon–nitrogen double bond (which is partially polarized to $\overset{+}{C} - \overset{-}{N}$) on the ketonic carbonyl absorption probably cancel each other. The spectrum of Ib is very similar.

The spectrum of A no longer shows bands for a *trans* H–C=C–H but, surprisingly, it does not have bands for a C=N though it contains an α,β-unsaturated keto-group as indicated by the absorption at 1685 cm.$^{-1}$. Another interesting feature is the return of the ester band in A to its normal position[12] at 1726 cm.$^{-1}$ (*i.e.*, no longer chelated) which once more points to a cyclization. Again A′ shows the same characteristics, and in addition also a marked band at 1353 cm.$^{-1}$ which is attributed to the C_6H_5N-g rouping. A weak band at 1590–1596 cm.$^{-1}$ in both compounds can be due either to a phenyl group or to a conjugated carbon–carbon double bond.

---

[4] C. Bülow and E. Hailer, *Ber.*, **35**, 933 (1902), were unable to couple diazotized sulfanilic acid with ethyl α-cinnamoylacetoacetate under different conditions, and claimed to have obtained the starting material unchanged.

[5] (a) Kohler, *Am. Chem. J.*, **42**, 375 (1904); (b) K. Auwers and K. Müller, *Ber.*, **41**, 4232 (1908).

[6] H. Nisbet and C. Gray, *J. Chem. Soc.*, 839 (1933).

[7] R. L. Shriner and A. G. Sharp, THIS JOURNAL, **62**, 2245 (1940).

[8] Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. IV, p. 779.

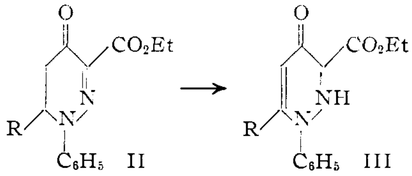
[9] (a) P. L. Southwick and H. L. Dimond, THIS JOURNAL, **76**, 5667 (1954); (b) P. L. Southwick, L. A. Pursglove and D. I. Sapper, *ibid.*, **72**, 4940 (1950).

[10] C. F. Winans and H. Adkins, *ibid.*, **55**, 4167 (1933).

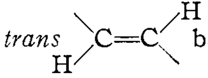
[11] K. Mislow, *ibid.*, **74**, 5155 (1952).

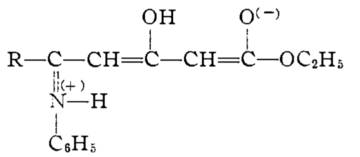
[12] J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

The absence of a C=N- linkage and the presence of an α,β-unsaturated keto-group in A can only be interpreted if a migration of the double bond occurs following the cyclization

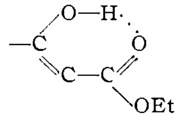


II → III

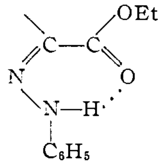
Such a migration probably begins by a 1 → 3 migration of the hydrogen atom bound to carbon atom 6 to the 2 nitrogen atom. An analogous migration can be found in the tautomeric migration of a methyl hydrogen atom to the nitrogen atom in acetophenone cyclohexylimide and similar substances.[13] Thus, the isomerization product of I should be formulated as III. This view is strongly supported by the fact that A gives 0.65 atom of active hydrogen which is only compatible with formula III. Also, the spectrum and properties of IVa can only be interpreted satisfactorily if the double bond is as in III. For example compound IVa also did not show the *trans*  band. In chloroform solution strong bands were present at 1564 and 1636 cm.$^{-1}$ and weak bands at 1713 and 3480 cm.$^{-1}$. In a Nujol mull, however, the bands at 1713 and 3480 cm.$^{-1}$ were not observed. Similar results were obtained with IVb. On the basis of the known presence of ester, enol and anilino groups in IV the following interpretation of the above bands seems the most plausible: (a) The band at 1564 cm.$^{-1}$ is due to the N-H bending of the strongly conjugated =C--NH— grouping. This band, which in secondary amines is usually weak (*cf.* ref. 14a) is strong here because of polar resonating structures such as being similar to the monosubstituted amide group which absorbs strongly in this region[14b] (the presence of an ethoxyl function precludes the presence of such an amide grouping in IV). (b) The strong band at 1636 cm.$^{-1}$ is attributed to the stretching of the ester carbonyl group chelated to the enolic hydroxyl,[15-17] which is present in equilibrium with the *unchelated enol*—and not the keto form—, solvent (chloroform) interaction probably being strong enough to prevent chelation partially. This small amount of strongly conjugated unchelated ester gives rise to the weak band at 1713 cm.$^{-1}$. The absence of two distinct bands for unsaturated ketone (1680) and saturated ester (1740) groups[12] shows the non-occurrence of keto-enol tautomerism. The great stability of the enol form is attributed to the extended conjugation of that form. In Nujol, the only bands observed are those due to the chelated enol-ester. The OH band is probably masked by the C-H absorptions.



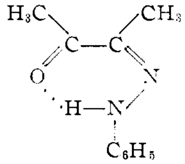
$$R-\underset{\substack{\|(+)\\ N-H\\ |\\ C_6H_5}}{C}-CH=\overset{\substack{OH\\ |}}{C}-CH=\overset{\substack{O^{(-)}\\ |}}{C}-OC_2H_5$$



The strong band at 1708 cm.$^{-1}$ in the spectrum of the phenylhydrazone I mentioned above is assigned to the stretching of the ester carbonyl group chelated with the phenylhydrazone group as



To verify this assignment the infrared spectra of ethyl pyruvate phenylhydrazone and ethyl 2-phenylazoacetoacetate were examined. In chloroform solution, the former had a strong band at 1698 cm.$^{-1}$, the latter at 1712 cm.$^{-1}$, but neither had the normal ester band at 1740 cm.$^{-1}$ (in carbon tetrachloride). Isherwood and Lumley Jones[18] found a similar shift of about 30 cm.$^{-1}$ in the characteristic absorption frequency of the carboxyl carbonyl group in pyruvic acid phenylhydrazones. Diacetyl monophenylhydrazone[19] also shows a decrease in the carbonyl frequency to 1666 cm.$^{-1}$, probably because of a structure such as



In III, chelation with the formation of a six-membered ring containing two conjugated double bonds is no longer possible and the ester absorption returns to 1728–1729 cm.$^{-1}$.

The reactions can therefore be represented by the Chart; IVa gives 1.4 atoms of active hydrogen; it is insoluble in dilute mineral acids, but is slowly hydrogenated in the presence of 5% palladium-charcoal giving a compound VI which is soluble in dilute acids and reprecipitated by alkalies. VI has a carbethoxyl group and contains two active hydrogens (NH and OH). Its formulation as ethyl 5-anilino-3-hydroxyoctadecanoate is supported by its infrared absorption spectrum (bands at 3530 cm.$^{-1}$ (in dilute chloroform solution) (OH), 3450 cm.$^{-1}$ (—OH and —NH—), 1723 cm.$^{-1}$

---

(13) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 186 (1952).

(14) (a) Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen & Co., Ltd., London, 1954, p. 213; (b) p. 176.

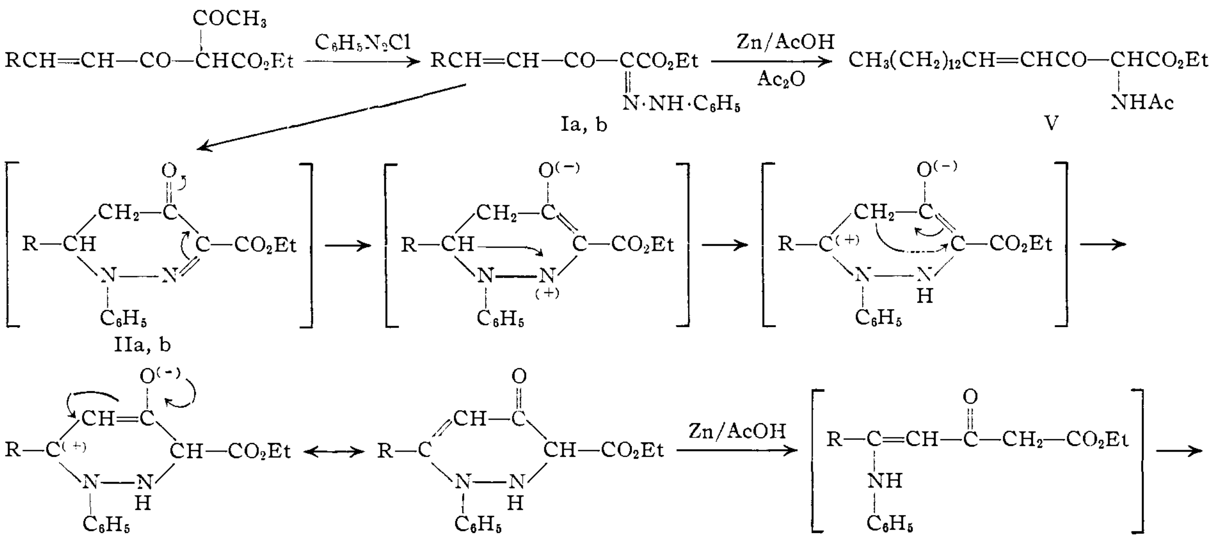
(15) L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954).

(16) R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949); R. S. Rasmussen and R. R. Brattain, *ibid.*, p. 1073.

(17) J. Lecomte, *Bull. soc. chim.*, 728 (1955).

(18) F. A. Isherwood and R. Lumley Jones, *Nature*, **175**, 419 (1955).

(19) E. Benary, *Ber.*, **59**, 2198 (1926).

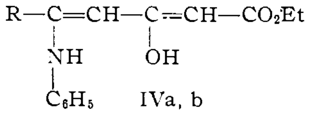


Ia, b

V

IIa, b

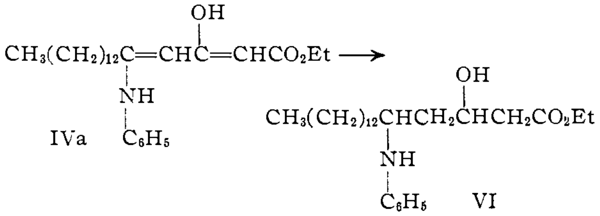
IIIa, b



IVa, b

a, R = $CH_3—(CH_2)_{12}—$
b, R = $C_6H_5—$

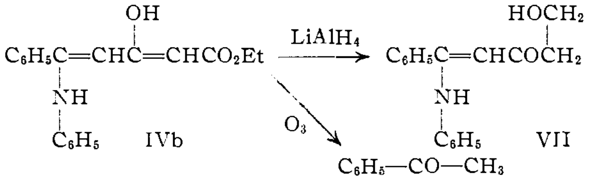
(ester) and 1599 cm.$^{-1}$ (phenyl); absence of a band for $\begin{matrix}R_1\\R_2\end{matrix}\!\!>C=C<\!\!\begin{matrix}R_3\\H\end{matrix}$ (in CS_2) and for —NH—C= (1530 cm.$^{-1}$)).



$$CH_3(CH_2)_{12}\underset{\substack{|\\NH\\|\\C_6H_5}}{C}=CH\overset{\substack{OH\\|}}{C}=CHCO_2Et \longrightarrow CH_3(CH_2)_{12}\underset{\substack{|\\NH\\|\\C_6H_5}}{C}HCH_2\overset{\substack{OH\\|}}{C}HCH_2CO_2Et$$

IVa VI

Lithium aluminum hydride reduction of IVb gave a mixture from which a yellow solid was isolated. This was the α,β-unsaturated keto-alcohol VII (strong infrared bands at 3300 (OH), 1662 (α,β-unsaturated ketone), 1597 (phenyl and conjugated C=C) and 1532 cm.$^{-1}$ (—NH—C=)), reduction of the enol grouping probably being prevented by the formation of a salt which can, therefore, not ketonize until decomposition of the complex.



$$C_6H_5\underset{\substack{|\\NH\\|\\C_6H_5}}{C}=CH\overset{\substack{OH\\|}}{C}=CHCO_2Et \xrightarrow{LiAlH_4} C_6H_5\underset{\substack{|\\NH\\|\\C_6H_5}}{C}=CHCO\overset{\substack{HOCH_2\\|}}{CH_2}$$
$$\xrightarrow{O_3} C_6H_5—CO—CH_3$$

IVb VII

Acetophenone was isolated from the ozonization products of IVb and identified as the 2,4-dinitrophenylhydrazone the infrared spectrum of which was identical with that of an authentic sample.

In the hope of determining the cause of the occasional formation of the pyridazinone during the Japp–Klingemann reaction itself, the influence of the pH was examined. Changes in pH were found not to affect the nature of the product, but only its quality and yield, the optimum pH being about 6.2. Further details are given in the Experimental part.

The above Japp–Klingemann reaction followed by isomerization provides, therefore, a route to substituted pyridazin-4-ones not available by other means, and which promises to be quite general.

Experimental

Infrared measurements were carried out using a Perkin-Elmer model 12C spectrophotometer equipped with a rock salt prism. pH measurements were carried out using a Beckman model H-2 continuous reading pH meter.

Ethyl 2,3-Dioxo-octadec-4-enoate-2-phenylhydrazone (Ia).—A partially neutralized solution of benzenediazonium chloride was prepared as follows: aniline (28 g.) in 100 ml. of concentrated hydrochloric acid and 335 cc. water was diazotized with a solution of sodium nitrite (21 g.) in water (40 ml.); a portion (250 cc.) was treated at −6 to −4° with a solution of sodium carbonate (18 g.) in water (180 cc.).

A solution of 3.6 g. of ethyl α-hexadec-2-enoylacetoacetate[2a] in 250 cc. of ethanol was treated successively with 50% aqueous sodium acetate solution (8 cc.) and solid sodium acetate or ammonium acetate (5 g.). To the stirred suspension at 10–12° was added 30 cc. of the above diazonium solution during 1–2 min. Stirring was continued for 0.5 hr., the solution was cooled to 0°, and ether (25 cc.) was added. After a further 0.5 hr. of stirring at 0° the flocculent precipitate which had separated was collected; yield 3.5 g., m.p. 38–40°. Recrystallization from light petroleum (b.p. 60–80°) gave deep yellow needles, m.p. 37–39°.

Anal. Calcd. for $C_{26}H_{40}O_3N_2$: C, 72.9; H, 9.4; N, 6.5. Found: C, 72.9; H, 9.8; N, 6.1.

The pH of the diazonium solution was varied from 0.2 to 2.3 without altering the nature of the product but only the yield and purity, the optimum pH being at about 0.95, when the pH of the reaction mixture varied regularly from *ca.* 7.8 to *ca.* 5.95, whether the addition of the diazonium solution was carried out in 2 min. or over a period of 1 hr. The pH changed mainly during this addition but remained very nearly constant after the addition of the diazonium solution and during and after the addition of the ether. In a blank run not using the ester the pH varied just as regularly during the addition of the diazonium solution from 8.65–6.35. Small variations in the pH of the suspension before addition of the diazonium solution were also without result in that the by-product was in no case obtained. The added solid sodium acetate could very advantageously be replaced by solid ammonium acetate (which is soluble in the medium) which gave a very pure product. Solid sodium chloride, on the other hand, gave rise to an oil (after dilution with water) which is probably a mixture of the product and its isomer. No product was obtained if neither solid ammonium acetate nor sodium acetate was added, though dilution with water gave an oil which could not be crystallized. It could not be determined whether the effect of the added solid was one of salting out or otherwise. Addition of the ether after two-thirds of the diazonium solution had been added (during a 1-hr. run) gave the correct product on vigorous stirring and cooling in ice.

The infrared spectrum was measured on a 0.057 g.-1 cc. CCl_4 solution in a 0.1-mm. cell. Bands were observed at 2945, 2880, 1708, 1645, 1580, 1511, 1459, 1396, 1377, 1267, 1200, 1138, 1118, 1088 and 983 cm.$^{-1}$.

Ethyl 3-Oxo-2-acetamido-octadec-4-enoate (V).—The above phenylhydrazone (11.25 g.) in glacial acetic acid (100 cc.) (solution prepared in the cold) was added dropwise and with vigorous stirring to a suspension of zinc powder (15 g.) in a mixture of glacial acetic acid (60 cc.) and acetic anhydride (24 cc.), the temperature being kept at 19–22° throughout the addition. After an additional 0.5 hr. of stirring the colorless suspension was filtered at the pump and the filtrate poured into an equal volume of ice-water. The solid which separated (9 g.) was collected and recrystallized from methanol giving colorless needles, m.p. 63–65°.

Anal. Calcd. for $C_{22}H_{39}NO_4$: C, 69.3; H, 10.2; N, 3.6. Found: C, 69.8; H, 10.6; N, 4.0.

Ethyl 1,2,3,4-Tetrahydro-1-phenyl-6-tridecylpyridazin-4-one-3-carboxylate (IIIa).—The phenylhydrazone was dissolved in hot alcohol and the cold solution treated dropwise with water until a turbidity appeared. After standing for 2 days yellow prisms had separated. Recrystallization from a small volume of alcohol gave yellow prisms, m.p. 47–48°.

Anal. Calcd. for $C_{26}H_{40}O_3N_2$: C, 72.9; H, 9.4; N, 6.5; OEt, 10.5; mol. wt., 428. Found: C, 72.8; H, 9.4; N, 6.5; OEt, 10.4; mol. wt. 364; active H, 0.15 (0.65 atom); λ_{max} 380 mμ, ϵ, 13400 (in ethanol).

With 2,4-dinitrophenylhydrazine it gives a compound, m.p. 178–180°. *Anal.* Found: C, 53.3; H, 5.9; N, 20.5.

The infrared spectrum was measured on a 0.052 g.-1 cc. $CHCl_3$ solution in a 0.1-mm. cell. Bands were observed at 1726, 1685, 1596, 1480, 1377, 1336, 1141, 1081 and 1036 cm.$^{-1}$.

Ethyl 3-Hydroxy-5-anilino-octadec-2,4-dienoate (IVa).—A solution of the pyridazinone IIIa (0.75 g.) in glacial acetic acid (6 cc.) was added dropwise to a stirred suspension of zinc dust (0.9 g.) in a mixture of glacial acetic acid (3.5 cc.) and acetic anhydride (1.4 cc.). After 0.5 hr. the colorless suspension was filtered, the residue washed with a little acetic acid and the filtrate diluted with an equal volume of ice-water. The oil which separated (0.4 g.) crystallized after remaining in the refrigerator overnight. It was recrystallized from a small volume of methanol giving colorless rods, m.p. 37–38°; λ_{max} 275 mμ; ϵ, 24000 (95% ethanol). In dilute alcohol solution it gives a blue–green color with 1% $FeCl_3$ solution. The infrared spectrum of a 0.052 g.-1 cc. $CHCl_3$ solution in a 0.1-mm. cell showed bands at 3480, 2940, 2860, 1713, 1636, 1564, 1433, 1338, 1156 and 1092 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{41}O_3N$: C, 75.1; H, 9.9; N, 3.4; OEt, 10.8. Found: C, 75.7; H, 9.7; N, 3.25; OEt, 12.0; active H, 0.33% (1.4 atoms).

Ethyl 5-Phenyl-2,3-dioxopent-4-enoate-2-phenylhydrazone (Ib).—Ethyl α-cinnamoylacetoacetate[20] (2.6 g.) in ethanol (50 cc.) was treated successively with a 50% solution (8 cc.) of sodium acetate in water and ammonium acetate (5 g.). The stirred solution was treated at 10–12° with the partially neutralized diazonium solution (30 cc.) (see preparation of Ia above) during 1–2 min. Stirring at 0° was continued for 0.5 hr., ether (25 cc.) was added and, after a further 0.5 hr. stirring at 0°, the orange precipitate was filtered off and dried (2.3 g.). It sinters at *ca.* 84° and melts at 84–88°. Recrystallization from light petroleum (b.p. 60–80°) gave bright orange needles, m.p. 86–87°.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.8; H, 5.6. Found: C, 71.1; H, 5.8.

The infrared spectrum was measured on a 0.036 g.-1 cc. CCl_4 solution in a 0.2-mm. cell. Bands were present at 3075, 2990, 2940, 1708, 1634, 1503, 1462, 1373, 1340, 1297, 1270, 1204, 1193, 1166, 1123, 1081, 988, 902 and 872 cm.$^{-1}$.

Ethyl 1,2,3,4-Tetrahydro-1,6-diphenylpyridazin-4-one-3-carboxylate (IIIb).—The phenylhydrazone Ib was dissolved in boiling ethanol and the cold solution scratched with a glass rod. After 7 hr. a few crystals had appeared; on allowing to stand overnight all the isomerization product had separated. Several recrystallizations from alcohol gave pale yellow crystals, m.p. 104–105°.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.8; H, 5.6; N, 8.7. Found: C, 70.5; H, 5.5; N, 8.6.

The infrared spectrum of a 0.01-1 cc. CCl_4 solution in a 2-mm. cell shows bands at 3380, 3040, 2980, 2890, 1729, 1695, 1590, 1484, 1454, 1387, 1353, 1318, 1304, 1207, 1169, 1126, 1068, 1031, 952, 895 and 863 cm.$^{-1}$.

Ethyl 5-Phenyl-5-anilino-3-hydroxypent-2,4-dienoate (IVb).—The above 1,6-diphenylpyridazinone (IIIb) (1 g.) in glacial acetic acid (6 cc.) was added slowly to a stirred suspension of zinc dust (1.9 g.) in glacial acetic acid (5 cc.) containing acetic anhydride (2.8 cc.), and worked up as above. The oil which separated was recrystallized from methanol giving colorless prisms (0.6 g.), m.p. 112–113° (depressed on admixture with acetanilide). One further recrystallization from methanol raised the m.p. to 114.5–115.5°. The compound gives a positive ferric chloride test for an enolic group.

Anal. Calcd. for $C_{19}H_{19}O_3N$: C, 73.8; H, 6.2; N, 4.5. Found: C, 73.55; H, 5.7; N, 4.7.

The same product was obtained, but in smaller yield, from the attempted reduction of the phenylhydrazone Ib, presumably due to isomerization in acetic acid solution prior to reduction.

The infrared spectrum was measured both on a 0.098 g.-1 cc. $CHCl_3$ solution in a 0.1-mm. cell and on a mull in Nujol. The first showed bands at 3480, 3310 as well as at 2690, 1822, 1706, 1624, 1596, 1550, 1520, 1430, 1383, 1352, 1324, 1099, 1072, 1017 and 966 cm.$^{-1}$. The second showed a weak band at 2550 cm.$^{-1}$ but no bands in the OH region. Neither did it show a band at about 1700 cm.$^{-1}$.

Catalytic Reduction of IVa.—The pyridazinone (1 g.) in ethanol (40 cc.) was hydrogenated at room temperature and pressure in the presence of platinum oxide (0.2 g.), 4 moles of hydrogen being absorbed after 6.5 hr. The filtrate was analyzed for free ammonia by distillation and micro-titration. A 32% yield of free ammonia was obtained. Evaporation of the solvent gave an oil which could not be purified (dec. on distillation) and hence identified.

Ethyl 5-Anilino-3-hydroxyoctadecanoate (VI).—Ethyl 3-hydroxy-5-anilino-octadec-2,4-dienoate (1 g.) in absolute ethanol (25 cc.) was reduced with hydrogen at room temperature and pressure in the presence of 5% palladium–charcoal (1 g.). Reduction was very slow and was allowed to proceed overnight. Filtration, evaporation of the solvent, dissolution of the residue in light petroleum (b.p. 60–80°), filtration and cooling to 0° gave a mass of colorless needles (0.8 g.), m.p. 75–76°. It does not give a ferric chloride test or a positive test for a keto-group. Recrystallization from light petroleum (b.p. 60–80°) gave soft needles, m.p. 77–78°. The compound dissolves in dilute mineral acid in the cold, an oil separating out on heating and redissolving on cooling and is reprecipitated by the addition of alkali.

Anal. Calcd. for $C_{26}H_{45}O_3N$: C, 74.4; H, 10.8. Found: C, 74.5; H, 11.4; active H, 0.50% (2.1 atoms).

The infrared spectrum of a 0.15 g.-1 cc. $CHCl_3$ sample in a 0.2-mm. cell showed an OH band at 3450 cm.$^{-1}$ (which on high dilution moved to 3530 cm.$^{-1}$ being probably due to an internally hydrogen bonded OH group) an ester band at 1723 cm.$^{-1}$ and a phenyl band at 1599 cm.$^{-1}$.

5-Phenyl-5-anilino-3-oxopent-4-ene-1-ol (VII).—A solution of ethyl 1,2,3,4-tetrahydro-1,6-diphenylpyridazin-4-one-3-carboxylate (1 g.) in ether (50 cc.) was added dropwise to a stirred suspension of lithium aluminum hydride (1 g.) in ether (10 cc.). After heating and stirring for 1 hr., ethyl acetate (5 cc.) was added followed, after 0.5 hr., by ice-water. The ether layer was separated and the aqueous layer extracted with ether, the combined extracts dried ($MgSO_4$) and evaporated. The orange oily solid residue (0.3 g.) was recrystallized from benzene giving the keto-alcohol as orange prisms, m.p. 183–184°.

Anal. Calcd. for $C_{17}H_{17}O_2N \cdot {}^1/_3C_6H_6$: C, 77.8; H, 6.5. Found: C, 77.5; H, 6.1.

The infrared spectrum of a 0.055 g.-1 cc. $CHCl_3$ solution

---

[20] J. English and L. J. Lapides, THIS JOURNAL, **65**, 2466 (1943).

in a 0.1-mm. cell showed bands at 3300, 1662, 1597, 1576, 1532, 1486 and 1454 cm.$^{-1}$.

Ozonolysis of Ethyl 1,2,3,4-Tetrahydro-1,6-diphenylpyridazin-4-one-3-carboxylate.—A solution of the pyridazinone (1 g.) in ethyl acetate (50 cc., AnalaR) was cooled in a Dry Ice–alcohol-bath and treated with ozonized oxygen (9 l./hr., 6–7%). After absorption was complete the suspension was allowed to reach room temperature, the solvent removed under reduced pressure and water added to the residue. The mixture was heated on the water-bath (effervescence) for 0.5 hr. and then distilled in steam. The distillate was extracted with ether and the solvent evaporated. The oily residue gave acetophenone 2,4-dinitrophenylhydrazone, m.p. 237–238°, on treatment with 2,4-dinitrophenylhydrazine. The melting point was undepressed on admixture with an authentic specimen but was depressed to 208–212° on admixture with benzaldehyde 2,4-dinitrophenylhydrazone (which also melts at 238°). Recrystallization of the 2,4-dinitrophenylhydrazone from glacial acetic acid gave needles, m.p. 244–245°, whose infrared absorption spectrum (Nujol mull) was identical with that of the authentic specimen.

Anal. Calcd. for $C_{14}H_{12}O_4N_4$: C, 56.0; H, 4.0. Found: C, 56.1; H, 4.2.

The residue from the steam distillation had a nitrobenzene-like smell though no product could be isolated from it.

Diacetyl monophenylhydrazone was prepared by the method of Benary[19] from ethyl methyl ketone and ethyl formate followed by reaction of the product with benzenediazonium chloride.

REHOVOTH, ISRAEL

[CONTRIBUTION NO. 2044 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY[1]]

On the Ultrasonic Cleavage of the Pyridine Ring

BY L. ZECHMEISTER AND EUGENE F. MAGOON

RECEIVED OCTOBER 27, 1955

On ultrasonic treatment of a solution of pyridine in aqueous silver nitrate roughly 5% of the ring atoms are precipitated as a mixture of silver acetylide, silver diacetylide and silver cyanide. The resolution of such mixtures and the estimation of the three components is described. Nicotine shows a similar behavior.

The exposure of bromobenzene in aqueous silver nitrate suspension to ultrasonic waves has been shown recently[2] to bring about partial cleavage of the aromatic ring. The resulting silver bromide precipitate was found to contain both silver acetylide and diacetylide, the quantities of which corresponded to about 10% of the original carbon atoms. This process may be considered as a reversal, at near room temperature, of Berthelot's pyrogenic synthesis of benzene from acetylene.[3]

We find that the analogous synthesis of pyridine from acetylene and hydrogen cyanide, as predicted by Dewar[4] and first realized by Ramsay,[5] can also be reversed ultrasonically. In this particular instance the presence of halogen is not required. Indeed, it has been observed that unsubstituted pyridine can be converted, to an extent of 5%, into a mixture of the silver salts of acetylene, diacetylene and hydrogen cyanide.

After the silver cyanide had been eliminated from the precipitate by extraction with ammonia, the remaining two explosive silver salts were determined either titrimetrically[2,6] or (after bromination in chloroform solution) gravimetrically.[2,7] The analysis was completed by a colorimetric estimation of the cyano group after its conversion into prussian blue.[8]

That the cleavage of the six-membered heterocyclic ring is not restricted to unsubstituted pyridine was demonstrated by the behavior of nicotine in aqueous silver nitrate solution which, upon ultrasonic treatment, deposited a slightly explosive mixture of silver salts. Some cyanide was also formed from nicotine, although in smaller yields than from pyridine. In these experiments about 2% of the ring atoms initially present in the pyridyl group of the nicotine molecule has been recovered.

Some of our results appear in Table I.

TABLE I

YIELDS OF ACETYLENE, DIACETYLENE AND CYANO GROUP OBTAINED BY ULTRASONIC TREATMENT FOR 20 HR. OF 1 ML. (980 MG.) OF PYRIDINE OR 1 ML. (1010 MG.) OF NICOTINE DISSOLVED IN 50 ML. OF AQUEOUS SILVER NITRATE

AgNO$_3$, mmoles	Wt. of ppt., mg.	Anal. meth. used for acetylene and diacetylene	C-Atoms of the pyridine ring recovered,[a] %, as			N-atoms of pyridine ring recvd. as CN,[a] %	Pyridine ring atoms recovd.,[a] %
			Acetylene[b]	Diacetylene	Cyano group		
			Pyridine				
5.0	412	Titr.[2,6]	2.7	..	0.9	4.7	3.8
1.25	620	Titr.	2.9	..	0.9	4.3	3.9
2.5	657	Titr.	4.0	..	1.7	8.2	5.6
2.5	638	Titr.	2.6	..	1.6	7.7	4.8
2.5	555	Grav.[2,7]	1.6	0.8	1.2	5.9	4.0
2.5	658	Grav.	1.5	.7	1.8	9.1	4.9
2.5	685	Grav.	1.0	.6	1.0	5.1	3.0
			Nicotine				
2.5	510	Titr.[2,6]	1.9	..	0.5	2.7	2.5
2.5	476	Grav.[2,7]	0.6	0.3	.4	2.1	1.5
2.5	366	Grav.	0.6	.2	.4	2.1	1.4

[a] "100% yield" would mean that the total carbon and nitrogen content of the pyridine ring had appeared in the form of acetylene + diacetylene + cyano group. [b] The titrimetric values are expressed as "acetylene" but represent the sum of acetylene and diacetylene (ratio, for example, 2:1).

---

[1] This research was supported by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command.

[2] L. Zechmeister and L. Wallcave, THIS JOURNAL, **77**, 2853 (1955).

[3] M. Berthelot, *Compt. rend.*, **63**, 479 (1866).

[4] J. Dewar, *Z. Chem.*, **14**, 116 (1871); *Trans. Soc. Edinburgh*, **26**, 289 (1870).

[5] W. Ramsay, *Phil. Mag.*, [5] **2**, 269 (1876).

[6] R. Willstätter and E. Maschmann, *Ber.*, **53**, 939 (1920).

[7] *Cf.* A. A. Noyes and C. W. Tucker, *Am. Chem. J.*, **19**, 123 (1897); F. G. Müller, *Helv. Chim. Acta*, **8**, 826 (1925); F. Straus and L. Kollek, *Ber.*, **59**, 1664 (1926).

[8] J. H. Yoe, "Photometric Chemical Analysis," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1928, p. 152; *cf.* A. Viehoever and C. O. Johns, THIS JOURNAL, **37**, 601 (1915).