tube and heated at 100° for six hours. After cooling to 20° and standing overnight the reaction mixture was evaporated to dryness under reduced pressure. The residual white solid was boiled for a few minutes with 20 cc. of benzene (to dissolve unchanged ester), and the mixture was allowed to cool. The colorless needles of the N-methylamide weighed 1.58 g. (73% yield) and melted at 197–197.5°. One recrystallization of this material from benzene gave long colorless needles, m. p. 198.5–199.5°. The N-methylamide is readily soluble in methanol, moderately soluble in hot benzene and very sparingly soluble in cold benzene.

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.21; H, 6.38. Found: C, 68.63, 68.74; H, 6.57, 6.46.

A similar reaction was carried out without the use of a bomb tube, by sealing the reaction mixture in a flask and allowing it to stand at room temperature for forty-eight hours. The isolation of the product was carried out as before but only 42% conversion to the amide was realized.

Reaction of the N-Methylamide of 3-Methylindole-2-carboxylic Acid with Ethoxalyl Chloride: 2,10-Dimethyl-1,2,3,4-tetrahydropyrazino[1.2-a]indole-1,3,4-trione (III).—A mixture of 0.84 g. (4.5 millimoles) of the N-methylamide, 40 cc. of dry benzene and 2.46 g. (18 millimoles) of ethoxalyl chloride was refluxed for 12 hours in a slow stream of nitrogen. The hot solution was filtered from a small amount of sediment, concentrated to a volume of 15 cc. and allowed to cool gradually to 20°. The crop of small, elongated yellow prisms which separated was collected and washed with 2 cc. of cold benzene. The product weighed 0.78 g. and melted at 208–209°. Concentration of the mother liquor to 4 cc. gave a further quantity of material, m. p. 207–208°. The total yield was 0.965 g. (90% of the theoretical). Recrystallization from benzene raised the melting point to 209–210°.

Anal. Calcd. for $C_{12}H_{10}O_3N_2$: C, 64.50; H, 4.13. Found: C, 64.66; H, 4.38.

Reaction of 3-Methylindole-2-carbonyl Chloride with N-Methylalanine Ester: 2,3,10-Trimethyl-1,2,3,4-tetrahydropyrazino[1.2-a]indole-1,4-dione (VII).—An ether solution of the acid chloride was prepared from 1 g. (5.7 millimoles) of 3-methylindole-2-carboxylic acid by means of phosphorus pentachloride, according to the procedure given above for 1-methylindole-2-carbonyl chloride. This solution was treated with an ether solution of the methyl ester of *dl*-α-N-methylalanine prepared by esterification of 2.08 g. (18 millimoles) of the amino acid. The mixture turned cloudy immediately, and on standing deposited a small amount of an oil (presumably N-methylalanine ester hydrochloride). The clear supernatant solution was decanted, washed with three 15-cc. portions of water, and dried over magnesium sulfate. After filtering and evaporating the solution to dryness on a steam-bath, there was obtained 0.82 g. (62% yield) of the yellow crystalline condensation product. Recrystallization from 50–50 benzene–petroleum ether (b. p. 60–70°) followed by crystallization from 50% aqueous methanol gave pale yellow crystals melting at 117.5–118.5°. This substance crystallizes quite slowly, and cooling at −10° for several hours is necessary to insure complete crystallization.

Anal. Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.43; H, 5.78. Found: C, 69.60, 69.50; H, 5.50, 5.36.

Summary

The synthesis of a series of model compounds of the α-pyrazindole and 2,9-pyridindole series has been described. Comparisons of absorption spectra and evidence from the synthetic investigations show that the selenium degradation product and the hydriodic acid reduction product from gliotoxin are α-pyrazindole derivatives. These observations suggest strongly that the carbon and nitrogen skeleton of gliotoxin itself is that of 2,3-dimethyl-1,2,3,4-tetrahydropyrazino-[1.2-a]indole.

ITHACA, N. Y. RECEIVED JANUARY 2, 1945

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Reactions Involving Ester-Exchange

BY WILLIAM S. JOHNSON AND ARTHUR GOLDMAN

In a previous communication[1] a report was given on the preparation, structures and configurations of all of the four possible isomeric half-esters (I, II, IV and V) of γ-methyl-γ-(2-naphthyl)-itaconic acid. It was demonstrated that ethyl 3-carboxy-4-(2-naphthyl)-*cis*-3-pentenoate (I) was cyclized by the action of acetic acid, acetic anhydride and sodium acetate to ethyl 3-methyl-6,7-benz-1-indone-2-acetate (III). Under the same conditions the isomeric 3-carbethoxy-4-(2-naphthyl)-*cis*-3-pentenoic acid (II) failed to cyclize into the aromatic nucleus. Parallel behavior was exhibited by the half-esters in the *trans* series. Thus 3-carbethoxy-4-(2-naphthyl)-*trans*-3-pentenoic acid (IV), but not the isomeric ethyl 3-carboxy-4-(2-naphthyl)-*trans*-3-pentenoate (V), cyclized to give ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VI).

During the course of this work it was found that if a catalytic amount of *zinc chloride*[2] was used in place of the sodium acetate in the cyclization reaction, the ring closure I → III proceeded more rapidly and quantitatively (*cf.* the 18% yield previously reported[1]). More striking, however, was the discovery that under these conditions the *half-ester II also was cyclized to the indoneacetic ester III.* This reaction obviously involved an ester-exchange; and, moreover, it likewise proceeded rapidly and in practically quantitative yield, which is all the more surprising considering the fact that acetic acid—a potential participant in the ester-exchange reaction—was used as a diluent. Since the results of the previously reported cyclization experiments held a prominent part in the argument of the proof of structures of the half-esters, it now appeared advisable, in view of the anomalous cyclization behavior with zinc chloride, to obtain further evidence for the structures. That the half-ester believed to be II, actually has the carbethoxyl group on the double bonded carbon was shown by ozonolysis. To avoid cleavage of the ester, the reaction was con-

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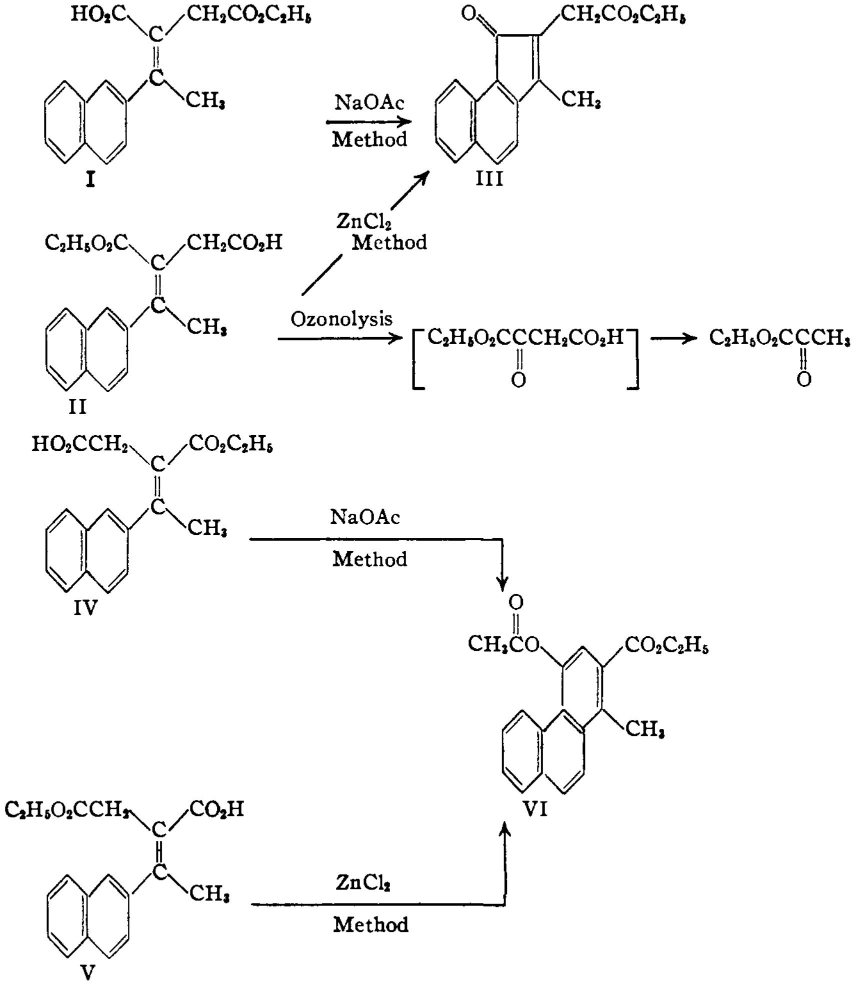
[1] Johnson and Goldman, THIS JOURNAL, **66**, 1030 (1944).

[2] *Cf.* Fieser and Hershberg, *ibid.*, **59**, 1028 (1937).

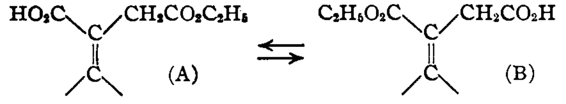


ducted in acetone solution and the ozonide was decomposed with Raney nickel.[3] The isolation of ethyl pyruvate by fractional distillation afforded proof beyond reasonable doubt that the structure II had been correctly assigned, since the half-ester (I) with the carbethoxyl further from the aryl group would not be expected to show such behavior. Indeed when I was ozonized in exactly the same way as II, no trace of ethyl pyruvate was detected. The remarkable ester-exchange reaction was exhibited also in the *trans* series. Thus the zinc chloride-catalyzed cyclization of the half-ester V gave the phenanthrene derivative VI in 67% yield.

In an effort to test the generality of this extraordinary type of ester-exchange the two half-esters VII and X of γ,γ-diphenylitaconic acid were examined. As previously reported[4] the sodium acetate method converted 3-carbethoxy-4,4-diphenyl-3-butenoic acid (VII) into the expected cyclization product, ethyl 1-acetoxy-4-phenylnaphthalene-3-carboxylate (VIII, R = COCH$_3$). Acid-catalyzed alcoholysis[1] gave the sparingly soluble phenolic ester VIII (R = H) in practically quantitative yield. The melting point (231–232°) of this ester is unusually high compared to the free carboxylic acid which melts at 212–214°.[5] In contrast to the above cyclization, the zinc chloride method converted VII into a mixture which consisted largely of ethyl 3-phenyl-1-indone-2-acetate (IX) which was separated in 79% yield. Only a small proportion of the normal cyclization product—isolated as the phenolic ester VIII (R = H) in 7% yield—was formed.

Ethyl 3-carboxy-4,4-diphenyl-3-butenoate (X) was obtained as a crystalline product in 89% yield by acid-catalyzed alcoholysis of the anhydride XI. On treatment with the sodium acetate cyclization mixture it was largely reconverted to the anhydride XI. A small amount of the indoneacetic ester IX also appeared to be formed, but was not isolated. The course of this cyclization is analogous to the similarly catalyzed ring closure of the half-ester I which also produced a large proportion of the corresponding anhydride. The zinc chloride-catalyzed cyclization of X, on the other hand, gave the indoneacetic ester IX in good (86%) yield, along with a small yield (1%) of the product (VIII) of abnormal ring closure.

The experimental facts presented above may be rationalized *a priori* by a variety of mechanisms. An obvious hypothesis (*mechanism A*) is that under the conditions of the zinc chloride-catalyzed reaction a mobile equilibrium exists between the pairs of half-esters:



Thus the cyclization of the half-ester II would be pictured as proceeding via the half-ester I by the mechanism II $\leftrightarrows$ I $\rightarrow$ III. The fact that the yield of cyclized material III from II is nearly

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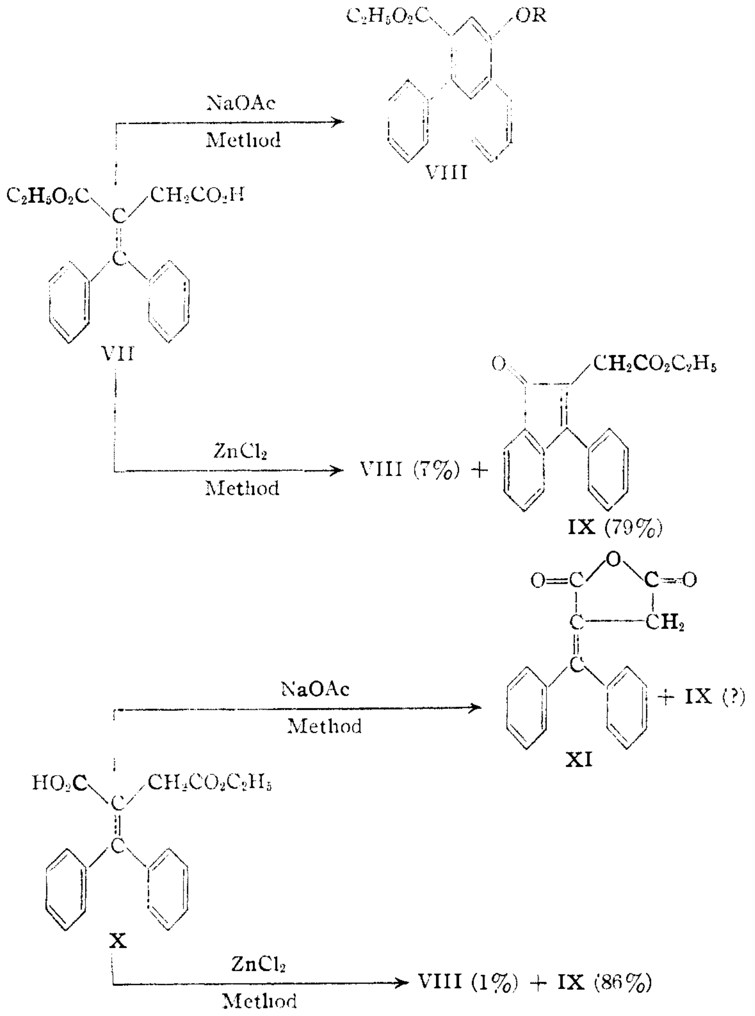
(3) Cook and Whitmore, THIS JOURNAL, **63**, 3540 (1941).

(4) Borsche, *Ann.*, **526**, 1 (1936).

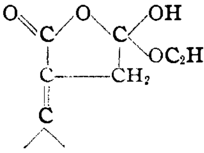
(5) No such abnormality is exhibited by the methyl ester which melts at 174–175° (ref. 4).



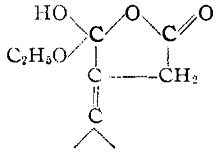
quantitative cannot be interpreted to mean that the hypothetical equilibrium II $\leftrightarrows$ I necessarily lies far in favor of I, since as the cyclization progresses this substance would be removed, thus displacing the equilibrium. According to this theory the cyclization of the half-ester V to VI would be interpreted similarly: V $\leftrightarrows$ IV $\rightarrow$ VI.

In the case of the diphenylitaconic acid derivatives the situation is more complex, since both of the half-esters VII and X are capable of cyclization. If these half-esters are considered as being in equilibrium, VII $\leftrightarrows$ X, it should be possible to obtain both cyclization products from either half-ester. This actually was observed. The over-all version may be expressed: VIII $\leftarrow$ VII $\leftrightarrows$ X $\rightarrow$ IX. It is interesting that the indoneacetic ester IX was invariably the predominant product and was formed in comparable yields regardless of which half-ester was cyclized. On the basis of the mechanism under consideration this would mean that (1) the ester-exchange equilibrium is very rapid compared to cyclization; and that (2) either the cyclization of X $\rightarrow$ IX is much more rapid than the cyclization of VII $\rightarrow$ VIII or the equilibrium lies far in favor of X. If the equilibrium step were extremely rapid in relation to the rates of cyclization, the proportion of products formed would be defined simply by a competition between the rates of the two irreversible cyclization steps. This situation apparently is not quite realized, since the observed proportions of VIII and IX were slightly in favor of the normal cyclization products. Thus the naphthalene derivative VIII was obtained in a *slightly* but *significantly* higher yield from VII than from X. The fact that the indoneacetic ester was invariably formed in preponderance is compatible with the previously reported observation of Borsche[4] that γ,γ-diphenylitaconic anhydride XI was cyclized to 3-phenyl-1-indone-2-acetic acid in 91% yield by the action of aluminum chloride in nitrobenzene. This greater susceptibility to formation of the indone ring system in the presence of metal halide (acid) catalysts, is not observed with the sodium acetate-catalyzed cyclization where the six-membered ring seems to be more readily closed.

The remarkable fact that acetic acid is employed asa diluent but is not involved in the acidolysis reaction implies that *the ester-exchange is intramolecular*[6] which is all the more plausible because of the juxtaposition of the carboxyl and carbethoxyl groups for ring formation.[7] Accordingly it is possible that pseudo esters of the type (C) and (D) are involved. Hypothetical intermediates of this type have been postulated before



(C)



(D)

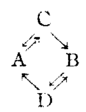


Fig. 1

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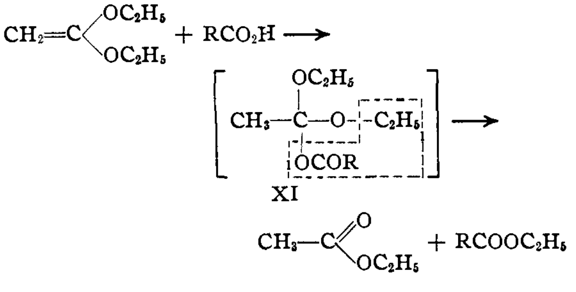
[6] Experimental tests have been conducted to eliminate the (unlikely) hypothesis that the ester-exchange is intermolecular, involving (1) elimination of ethyl alcohol from the half-ester to form the itaconic anhydride (the tendency toward this reaction already having been observed), followed by (2) the readdition of the alcohol either to the anhydride or to some subsequent intermediate in the cyclization reaction. When the anhydride corresponding to the half-esters I and II was treated with the zinc chloride cyclization mixture to which was added two equivalents of ethanol, not even a trace of the indoneacetic ester III was obtained.

[7] Note the exceptionally easy formation of the itaconic anhydrides, Stobbe, *Ann.*, **308**, 67 (1899).

for *inter*molecular ester-exchange reactions.[8] It is particularly noteworthy that the structures (C) and (D) are very much like the intermediate XI

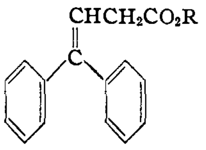


$$CH_2{=}C(OC_2H_5)_2 + RCO_2H \longrightarrow \left[CH_3-C(OC_2H_5)(OCOR)-O-C_2H_5\right] \longrightarrow CH_3-C(=O)OC_2H_5 + RCOOC_2H_5$$

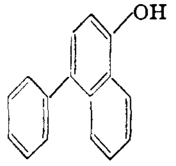
XI

which is most probably involved in the reaction between ketene acetal and a carboxylic acid.[9] The irreversible decomposition of XI serves as a model for the decomposition of (C) to (B) and of (D) to (A). According to such a mechanism an ester-exchange like (A) ⇆ (B) would involve two steps, one reversible and one irreversible. The complete process would be expressed by the sequence shown in Fig. 1. A similar mechanism affords an attractive rationalization also of *inter*molecular ester-exchange, at least where esters of primary and possibly secondary alcohols are involved.[10]

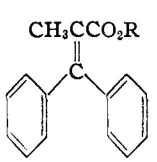
In an effort to demonstrate that the ester-exchange step took place before ring closure, the reaction time was reduced to a point where the cyclization of the half-ester II was just short of completion allowing for recovery of some acidic material. After heating for only four minutes cyclization proceeded to the extent of 96%. The acidic material (yield 1.5%), however, consisted largely of unchanged half-ester II as shown by mixed melting points. When submitted to the same treatment as above the half-ester I was cyclized quantitatively. Since zinc chloride in acetic acid is known to catalyze the ester-exchange reaction,[8] it seemed reasonable to omit the acetic anhydride from the reaction mixture. Under these conditions neither I nor II cyclized even after two hours of refluxing. In order to detect any ester-exchange after the half-ester II was so treated, the crude product was submitted to the sodium acetate treatment which has been shown to effect cyclization without ester-exchange. Blank runs showed that the half-ester I would have to be formed in at least 8% yield in order to be clearly detected by the red color imparted to the solution by the formation of the indone derivative III. Under the conditions investigated no conversion of II to I was detected. In order to eliminate the possibility that equilibrium actually was established, but that it was so far in favor of II that the color test failed to reveal the presence of I, the latter half-ester was treated in the manner described above. A deep red color developed during the cyclization step. These results do not necessarily invalidate the mechanism under consideration since the proper conditions for ester-exchange may not have been realized in the above experiments. On the other hand they do justify the consideration of mechanisms involving ester-exchange subsequent to the cyclization step.



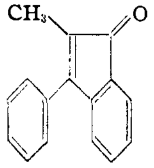
XII a (R = H)
XII b (R = C_2H_5)



XIII



XIV a (R = H)
XIV b (R = C_2H_5)



XV

The facts presented up to this point can be rationalized by a sequence of reactions (*mechanism B*) involving (1) direct cyclization of the ester group (of II for example) to form a hemiketal (E),[11] followed by (2) lactonization to give (F) and (3) rearrangement to (G) as in the ketene acetal sequence described above. The following experiments show that such a mechanism, if operating at all, is doing so probably only to a slight extent. When the diethyl ester corresponding to I or II was submitted to the zinc chloride-catalyzed treatment, cyclization proceeded very slowly. In sharp contrast to the case of the half-esters, it was estimated by color comparison that after two hours only about 2% of the full ester had cyclized. Comparisons were made also on the cyclization behavior of 4,4-diphenyl-3-butenoic acid (XIIa) and its ethyl ester (XIIb), and of 3,3-diphenyl-2-methylacrylic acid (XIVa) and its ethyl ester (XIVb). In each case the acids *but not the esters* were cyclized readily to give respectively the naphthol and indone derivatives XIII and XV. The esters were recovered largely unchanged. This clearly indicates that (under these reaction conditions) the carbethoxyl group *per se* is much less susceptible to cyclization than the free carboxyl group.

A significant difference between the half-esters and the full-esters studied in connection with mechanism B lies in the fact that the former are structurally capable of pseudo ester formation.

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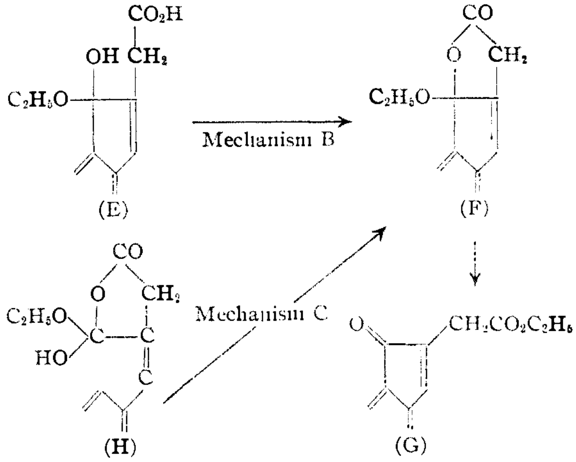
[8] *Cf.* for example Sowa, THIS JOURNAL, **60**, 654 (1938).

[9] McElvain and Kundiger, *ibid.*, **64**, 256 (1942).

[10] Cohen, *ibid.*, **66**, 1395 (1944), has advanced evidence that supports a carbonium ion mechanism for the acid-catalyzed acetolysis of *t*-butyl benzoate. In this connection we hope to investigate the cyclization behavior of the half *t*-butyl esters of itaconic acids.

[11] Sulfuric acid is known to promote the cyclization of an ester (as well as the free acid) to form cyclic ketones. See for example (a) Ramage and Robinson, *J. Chem. Soc.*, 607 (1933); (b) de Fazi, *Gazz. chim. ital.*, **49**, II, 253 (1919).



This suggests another *mechanism C* in which the hydroxyl group of the pseudo ester (H) is involved in the cyclodehydration giving rise directly to the lactone (F) which rearranges to (G). This sequence of steps is quite compatible with the available facts and is at present at least as satisfactory an explanation as mechanism A.

Experimental Part[12]

Zinc Chloride-Catalyzed Cyclizations. (*a*) *Of Ethyl 3-Carboxy-4-(2-naphthyl)-cis-3-pentenoate* (*I*).—A solution of 0.442 g. of the half-ester I and 0.05 g. of fused zinc chloride in 5 cc. each of acetic anhydride and acetic acid was boiled under reflux for two hours. Water was added, cautiously at first to decompose the anhydride, to the hot, deep-red solution to the point of incipient cloudiness. On cooling 0.371 g. (89% yield) of orange needles was obtained, m. p. 96–97°. This material was identical (mixed m. p.) with ethyl 3-methyl-6,7-benz-1-indone-2-acetate (III) obtained in 18% yield by the previously described sodium acetate-catalyzed cyclization of I.[1]

In another experiment 0.25 g. of half-ester was used with one-half of the above quantities of cyclizing reagents. The heating period was shortened to four minutes, and the product was worked up by removing the solvents in a stream of air and dissolving the residue in ether. The solution was washed with water, followed in turn by 5% sodium bicarbonate solution and saturated sodium chloride solution. After drying over anhydrous potassium carbonate the ether was evaporated. The crystalline residue amounted to 0.235 g. (quantitative yield) of red indone ester III, m. p. 92.5–95.5°.

(*b*) *Of 3-Carbethoxy-4-(2-naphthyl)-cis-3-pentenoic Acid* (*II*).—A solution of 0.508 g. of this half-ester and 0.05 g. of zinc chloride in 5 cc. each of acetic anhydride and acetic acid was treated for two hours exactly as described in the first part of (a) above. The yield of pure indoneacetic ester (III) was 0.448 g. (94%), m. p. 95–96°.

When 0.50 g. of the half-ester was given the four-minute treatment and worked up as in the second part of (a) the yield of crude indone ester III was 0.45 g. (96%), m. p. 86–93°. Acidification of the bicarbonate washings liberated 7.6 mg. of half-ester, m. p. 111–114.5° with previous softening. The mixed m. p. with pure II was 113–118°, and with pure I was over a wide range below 100°.

(*c*) *Of Ethyl 3-Carboxy-4-(2-naphthyl)-trans-3-pentenoate* (*V*).—The half-ester (0.40 g.) was treated for two hours with 0.05 g. of zinc chloride in 5 cc. each of acetic anhydride and acetic acid as described in (a) above. After treatment with water the violet colored solution deposited 0.290 g. (67% yield) of crystalline ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VI), m. p. 124.5–126°. The m. p. was not depressed on mixing with a specimen of VI prepared by the previously described cyclization of the half-ester IV.[1]

Ozonolysis. (*a*) *Of 3-Carbethoxy-4-(2-naphthyl)-cis-3-pentenoic Acid* (*II*).—A solution of 5.5 g. of pure half-ester II in 200 cc. of anhydrous acetone was chilled in an ice-bath and treated with a slight excess (detected by starch-iodide test) of ozone. The solution was then stirred for fifteen hours at room temperature with 4–5 g. of Raney nickel.[3] After filtering, the acetone was removed carefully through a modified Widmer column. The residue was roughly fractionated to separate the lower boiling fraction from 2-acetylnaphthalene which was known to be present from previous experiments.[1] The fraction which distilled when the bath temperature was 100–290° was redistilled at atmospheric pressure from a small modified Claisen flask. Two fractions were collected: (1) 0.576 g., b. p. 90–145°; (2) 0.187 g., b. p. 145–155°. The reported b. p. for ethyl pyruvate is 155°.[13] Like ethyl pyruvate, both fractions formed semicarbazones very rapidly with an aqueous solution of semicarbazide hydrochloride and sodium acetate. Thus a portion (0.115 g.) of fraction (1) gave 0.047 g. of colorless needles, m. p. 207–208° (dec.). A sample (0.058 g.) of fraction (2) yielded 0.056 g. of the same material, m. p. 206–207° (dec.). Both of these specimens when mixed with an authentic sample of the semicarbazone of ethyl pyruvate (m. p. 208–209° (dec.)) showed no depression of the m. p. (mixed m. p. 207–208° (dec.)). The yield of semicarbazone obtained from pure ethyl pyruvate (0.054 g.) by the technique described above was 0.065 g. or 81%. Using this factor, the total amount of ethyl pyruvate in the ozonolysis fractions was estimated to be 0.345 g., a 16% yield.

The ozonolysis product was characterized further as follows. A sample of the semicarbazone was saponified by gently warming with 5% sodium hydroxide solution. Acidification gave an acid semicarbazone which melted at 201° (dec.). A mixture with an authentic sample of pyruvic acid semicarbazone (m. p. 202° (dec.)) showed no depression of the decomposition point. The phenylhydrazone prepared in dilute acetic acid from a portion of fraction (2), melted after recrystallization from petroleum ether (boiling range 60–68°) at 116.5–117.5°. The mixed melting point with an authentic specimen (m. p. 116.5–117.5°) was not depressed.

(*b*) *Of Ethyl 3-Carboxy-4-(2-naphthyl)-cis-3-pentenoate* (*I*).—A sample (5.0 g.) of the half-ester I was ozonized and further treated just as described above for the half-ester II. The final distillation yielded two fractions (1) 0.428 g., b. p. 72–80° (possibly ethyl acetate) and (2) 0.220 g., b. p. 100–140°. Neither of these fractions yielded semicarbazones when treated as described in (*a*).

Treatment of the anhydride of 3-carboxy-4-(2-naphthyl)-*cis*-3-pentenoic acid with the zinc chloride cyclizing reagent and ethanol (see reference 6) was carried out using 1.0 g. (0.004 mole) of the anhydride (m. p. 153–154°),[1] 0.1 g. of fused zinc chloride, 10 cc. each of acetic acid and acetic anhydride, and 0.47 cc. (0.008 mole) of ethanol. After boiling for two hours, the solution was evaporated and the residue triturated with ether. The insoluble portion amounted to 0.832 g. of unchanged anhydride, m. p. 153–154.5°. The ether layer was extracted with 5% sodium bicarbonate solution which on acidification yielded 0.037 g. of red solid, m. p. 212–216°. This apparently was 3-methyl-6,7-benz-1-indone-2-acetic acid,[1] since the mixed m. p. with a pure sample of the latter (m. p. 215.5–219.5°) was not depressed. On evaporation of the neutral ether solution 0.104 g. of yellow oil was obtained. Trituration of this with a small amount of ether yielded an additional 0.079 g. of the itaconic anhydride, m. p. 152.5–153.5°.

Experiments on the Equilibration of the Half-esters I and II.—A solution of 0.502 g. of the half-ester II and 0.05 g. of fused zinc chloride in 6 cc. of acetic acid was boiled under reflux for fifteen minutes. The light-yellow solution was evaporated in a stream of air, taken up in ether, washed well with water, and dried over anhydrous sodium

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[12] All melting points are corrected.

[13] v. Braun, Leistner and Münch, *Ber.*, **59**, 1950 (1926).

sulfate. The residue obtained on evaporation of the ether was treated with 0.13 g. of sodium acetate and 3 cc. each of acetic acid and acetic anhydride. After three hours of refluxing—conditions which have been shown previously[1] not to effect ring closure of II—the solution was only a pale yellow. The same results were obtained when the initial "equilibration" heating time was increased to two hours, and when the amount of zinc chloride was increased up to five times. When still larger amounts of zinc chloride were used cyclization was promoted during the first stage as evidenced by the development of the characteristic red color. When the above reaction mixtures were worked up, considerable amounts of the itaconic anhydride were isolated.

When the half-ester I (0.1 g.) was treated with 0.02 g. of zinc chloride in 2 cc. of acetic acid for two hours, the residue after subjection to the sodium acetate cyclization developed a deep-red color.

The sensitivity of the color test for the half-ester I was determined by heating various amounts of I for two hours in a solution of 3 cc. each of acetic acid and anhydride containing 0.13 g. of fused sodium acetate. When 40 mg. of I was used a definitely orange colored solution resulted. Smaller amounts of I produced lighter colors, which although darker than any of the solutions obtained in the above experiments, contained no orange color.

Cyclization of 3-Carbethoxy-4,4-diphenyl-3-butenoic Acid (VII).—The half-ester VII was prepared by the method of Stobbe.[7] The material which was purified by two recrystallizations from ether-petroleum ether, melted at 121-122.5° (reported[7] 124.5-125.5°).

(*a*) *By the Sodium Acetate Method.*—A solution of 1.00 g. of the half-ester VII and 0.27 g. of fused sodium acetate in 6 cc. each of acetic acid and acetic anhydride was boiled under reflux for three hours. The light-yellow solution was evaporated, and the residue was boiled for fifteen minutes with 10 cc. of 5% sodium bicarbonate solution to hydrolyze any itaconic anhydride. The insoluble material was extracted with ether, washed with saturated salt solution, and dried over anhydrous potassium carbonate. The solution was then concentrated, and petroleum ether added to the point of incipient cloudiness. On cooling 0.846 g. (78%) of ethyl 1-acetoxy-4-phenylnaphthalene-3-carboxylate (VIII, R = $COCH_3$) crystallized, m. p. 81-83°. After two recrystallizations from dilute methanol it formed colorless needles, m. p. 86-87° (reported[4] 87-88°). A sample (0.757 g.) of this substance (m. p. 84-86°) was treated with 10 cc. of ethanol saturated with hydrogen chloride. The solution, at first homogeneous, rapidly deposited colorless needles while boiling under reflux for fifteen minutes These crystals of ethyl 1-hydroxy-4-phenylnaphthalene-3-carboxylate (VIII, R = H) amounted to 0.408 g., m. p. 228-230°. Concentration of the mother liquors yielded an additional 0.242 g. of material, m. p. 222-225°, making the total yield 98%. A sample purified for analysis by repeated recrystallization from alcohol formed fine colorless needles, m. p. 231.5-232.5°.

Anal.[14] Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.05; H, 5.60.

Acetylation of the above product with acetic anhydride and pyridine effected a quantitative reconversion to the acetate, m. p. 85-86°.

Saponification of the phenolic ester gave 1-hydroxy-4-phenylnaphthalene-3-carboxylic acid, m. p. 212-214° (reported,[4] 212-214°).

(*b*) *By the Zinc Chloride Method.*—A solution of 1.00 g. of the half-ester VII and 0.10 g. of fused zinc chloride in 5 cc each of acetic acid and anhydride was boiled under reflux for two hours. The orange-red solution was evaporated, and the residue was dissolved in ether and extracted with 5% sodium bicarbonate solution which on acidification yielded only a trace of acidic oil. Had the indoneacetic *acid* been formed it would have appeared at this point. The neutral red oily mixture of VIII (R = $COCH_3$) and IX obtained on evaporation of the ether was not amenable to efficient separation by fractional crystallization; therefore the oil was treated for fifteen minutes with 5 cc. of refluxing ethanol saturated with hydrogen chloride, to convert the acetate into the phenol VIII (R = H). Because of the sparing solubility of the latter the separation was easily accomplished by removing the solvent and triturating the residue with petroleum ether. Thus was obtained 0.067 g. (7% yield) of slightly yellow phenolic ester VIII (R = H), m. p. 226-228°. The mixed m. p. with a sample of the pure substance described under (a) above was 227-229°. The petroleum ether solution was concentrated, and on cooling 0.625 g. of orange crystals of ethyl 3-phenyl-1-indone-2-acetate (IX) separated, m. p. 74-76°. From the filtrate an additional 0.120 g. of material having the same m. p. was obtained, making the total yield 79%. The oily residue undoubtedly contained more of IX which did not crystallize readily. Twice recrystallized from petroleum ether the indoneacetic ester took the form of orange plates, m. p. 78-79° (reported[15] plates 77° and prisms 81.5°).

In order further to characterize the indoneacetic ester, 0.200 g. was hydrolyzed in a mixture of 2 cc. of acetic acid and 4 cc. of concentrated hydrochloric acid. After refluxing for twenty-four hours, the solvent was evaporated in a current of air, and the residue was dissolved in ether, washed with water and extracted thoroughly with 5% sodium carbonate solution. Acidification of the aqueous layers gave 0.144 g. of orange 3-phenyl-1-indone-2-acetic acid, m. p. 167-169°. From benzene the product crystallized in orange prisms, m. p. 169-170° (reported[15] 167.5°).

Ethyl 3-Carboxy-4,4-diphenyl-3-butenoate (X).—γ,γ-Diphenylitaconic anhydride (XI) was prepared from the half-ester VII by saponification followed by dehydration of the dibasic acid with acetyl chloride.[7] After recrystallization from chloroform-petroleum ether the anhydride had the m. p. 153-154° (reported[7] 151-152°).

A suspension of 0.610 g. of the above anhydride in 10 cc. of ethanol containing one drop of concentrated sulfuric acid was boiled until solution was complete. After standing at room temperature for a few hours the solvent was evaporated in a current of air, and the residue was dissolved in ether, washed with water and then extracted with 5% sodium bicarbonate solution. Acidification of the latter gave 0.640 g. (89.5% yield) of colorless half-ester, m. p. 129-131°. After two recrystallizations from ether-petroleum ether this product was obtained as colorless plates, m. p. 131-132° (reported[15a] 130-131°).

Anal.[14] Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.61; H, 5.77.

Cyclization of Ethyl 3-Carboxy-4,4-diphenyl-3-butenoate (X). (*a*) *By the Sodium Acetate Method.*—A solution of 0.514 g. of the half-ester X and 0.15 g. of fused sodium acetate in 3 cc. each of acetic acid and acetic anhydride was boiled under reflux for three hours. The orange solution was evaporated in a current of air, and the residue was dissolved in ether, washed with water, 5% sodium bicarbonate solution and finally dried over anhydrous sodium sulfate. Acidification of the bicarbonate extracts yielded only a trace of acidic oil. Evaporation of the ether left a red oil which on crystallization from chloroform-petroleum ether gave 0.176 g. of brown material, m. p. 146-149°. Recrystallization raised the m. p. to 150-151° which was not depressed by pure γ,γ-diphenylitaconic anhydride (XI).

The residual oil was boiled for thirty minutes with 5 cc. of 5% sodium bicarbonate solution to hydrolyze any remaining anhydride. Acidification of the aqueous solution gave 0.164 g. of yellow oil which probably contained some dibasic acid. The fraction which was unaffected by the bicarbonate hydrolysis amounted to 0.111 g. of intractable red oil which undoubtedly contained some of the indoneacetic ester IX. Attempts to purify this material by the acid-catalyzed alcoholysis described above failed.

(*b*) *By the Zinc Chloride Method.*—One gram of pure half-ester X (m. p. 131-132°) was treated with 0.10 g. of fused zinc chloride and 5 cc. each of acetic anhydride and

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[14] Microanalysis kindly performed by Jack W. Petersen.

[15] Stobbe and Vieweg, *Ber.*, **35**, 1727 (1902).

[15a] Stobbe, *ibid.*, **44**, 1297 (1911).

acetic acid just as described above in the procedure (b) for the isomeric half-ester VII. The neutral portion, 0.94 g. of red oil, was submitted to the acid-catalyzed alcoholysis. Thus was obtained 0.011 g. (1% yield) of the petroleum ether-insoluble phenolic ester VIII (R = H), m. p. 228-230°. The mixed m. p. with an authentic specimen of VIII (R = H) was 229-230.5°. From the petroleum ether solution there was obtained 0.736 g. of crystalline indoneacetic ester (IX), m. p. 75-77° (soft at 73°). The second crop amounted to 0.078 g., m. p. 76-77°, making the total yield of crystalline material 86%. The m. p. of this product was not depressed by the sample of the indoneacetic ester prepared from the half-ester VII.

The treatment of ethyl 3-carbethoxy-4-(2-naphthyl)-*cis*-3-pentenoate[1] with the zinc chloride cyclizing reagent was carried out with 0.50 g. of the ester, 0.05 g. of zinc chloride, and 5.0 cc. each of acetic acid and anhydride. After refluxing for two hours the solution had turned to a shade of orange which matched the color of a solution of 10 mg. of the indone ester III in 10 cc. of acetic acid.

Cyclization of 4,4-Diphenyl-3-butenoic Acid (XIIa). (*a*) *By the Sodium Acetate Method.*—A solution of 0.314 g. of the acid XIIa,[4] m. p. 117-118°—prepared by the decarboxylation of γ,γ-diphenylitaconic acid—and 0.1 g. of fused sodium acetate in 3 cc. each of acetic acid and acetic anhydride was boiled under reflux for three hours. After evaporation, ether was added, and the solution was washed with water and with 2% potassium hydroxide which removed only a trace of acidic material. The ether layer after drying over anhydrous potassium carbonate was evaporated, and the residue was treated with 3 cc. of ethanol saturated with hydrogen chloride. After refluxing for one hour the solution was evaporated and the solid residue recrystallized from benzene–petroleum ether. The yield of 4-phenyl-1-naphthol (XIII) thus obtained was 0.253 g. (87%), m. p. 138-139°. Recrystallization raised the m. p. to 139-140° (reported[1] 139-140°). A dilute alcoholic solution of the phenol gave an intense blue color with ferric chloride.[4]

(*b*) *By the Zinc Chloride Method.*—A solution of 1.0 g. of the acid and 0.1 g. of fused zinc chloride in 7 cc. each of acetic acid and acetic anhydride was boiled under reflux for two hours. The mixture was worked up as in (a) above. The alkaline extraction yielded 0.220 g. of uncyclized acid m. p. 112-116°. The neutral portion after alcoholysis with 8 cc. of ethanol saturated with hydrogen chloride yielded 0.420 g. (45% yield) of recrystallized naphthol, m. p. 139-140°. A mixed m. p. with the sample obtained in the previous experiment gave no depression.

Treatment of ethyl 4,4-diphenyl-3-butenoate (XIIb)[16] with the zinc chloride cyclizing reagent was carried out in exactly the same manner as described for the acid XIIa above (procedure b). The amounts of materials were the same except that 1.02 g. of the ester was used. The potassium hydroxide extracts gave only a trace of acidic material. The neutral fraction after treatment with alcoholic hydrogen chloride failed to give a color with ferric chloride, and consisted largely of starting material as shown by saponification to the acid, m. p. 114-116°, not depressed by authentic XIIa. The yield in this step was 72%, and the remaining neutral material gave no color with ferric chloride, indicating the absence of the phenol VIII (R = H).

Cyclization of 3,3-Diphenyl-2-methylacrylic Acid (XIVa).—A solution of 0.25 g. of the acid XIVa, m. p. 163.5-164.5°, (prepared by saponification of the ethyl ester XIVb described below) in 2.5 cc. each of acetic acid and anhydride containing 0.025 g. of fused zinc chloride was allowed to reflux for four minutes. The solvent was removed in a current of air, and the residue treated with dilute potassium hydroxide solution. The orange crystalline 2-methyl-3-phenylindone-1 (XV) was filtered and washed with water, m. p. 82-83.3°. The yield was 0.22 g. (95%). Recrystallization from alcohol gave flat, orange rods, m. p. 83-84° (reported 83-84°[17] and 87-87.5°[18]).

Ethyl 3,3-Diphenyl-2-methylacrylate (XIVb).—Ethyl 3,3-diphenyl-3-hydroxy-2-methylpropionate was prepared by the Reformatsky reaction of ethyl α-bromopropionate and benzophenone according to the directions of Rupe, Steiger and Fiedler.[19] The hydroxy ester, m. p. 102-103° (reported 101-102°[19]) after recrystallization from petroleum ether, was dehydrated with anhydrous hydrogen chloride according to the procedure of Natelson and Gottfried.[20] Dehydration was complete after four hours and the product distilled at 202-203° (19-20 mm.). The yellow distillate solidified on standing, m. p. about 82-87°, yield practically quantitative. It crystallized from ether in large colorless prisms m. p. 87-88°. This substance has been reported before as melting at 84°, but no analysis was given.[21]

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.75; H, 6.80.

The attempted cyclization of XIVb (0.25 g.) was carried out as described above for the acid XIVa except that the heating period was extended to two hours. At the end of this time the orange product was worked up by saponification, which yielded 0.22 g. of 3,3-diphenyl-2-methylacrylic acid, m. p. 163.5-164.5°. The small unsaponified fraction (red oil) probably contained some of the indone XV.

Summary

In a study of the acid-catalyzed cyclization of the half-esters of arylitaconic acids, four examples of intramolecular ester-exchange have been encountered. The rearrangement appears to be general for this type of compound and proceeds in excellent yields, which is striking in view of the fact that acetic acid—a potential participant in the ester-exchange—is used as a diluent without effecting acetolysis.

Experiments have been performed in an effort to elucidate the mechanism of the ester-exchange. The most satisfactory schemes which have been evolved, necessitate the postulation of a cyclic pseudo-ester type of intermediate.

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[16] This ester was prepared from the acid XIIa by the conventional method with ethanol and hydrogen chloride. It was a colorless liquid boiling at 140-145° (0.05 mm.). The product has been previously reported (ref. 4) to boil at 165-170° (0.1 mm.).

(17) Smith and Hanson, THIS JOURNAL, **57**, 1326 (1935).

(18) de Fazi, *Gazz. chim. ital.*, **54**, 996 (1924).

(19) Rupe, Steiger and Fiedler, *Ber.*, **47**, 63 (1914).

(20) Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

(21) Bergmann and Weiss, *Ann.*, **480**, 64 (1930).