Anal. Calcd. for $C_{24}H_{23}NO_7$: C, 65.89; H, 5.30; N, 3.20; $COCH_3$, 9.84. Found: C, 66.78; H, 5.75; N, 3.42; $COCH_3$, 11.46.

2,7-Dihydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)-benzamido]-8-methylchromone (Novobiocic Acid, X).—A solution of 0.44 g. of monoacetylnovobiocic acid in 10 ml. of 2.5 *N* sodium hydroxide solution was allowed to stand at room temperature for 2 hours, cooled, and acidified with 10 ml. of 3 *N* hydrochloric acid. The yellow crystals were filtered, washed with water and dried, giving 0.4 g. of crude novobiocic acid. Four recrystallizations from dimethylformamide–water followed by drying at 150° (0.01 mm.) overnight yielded novobiocic acid, m.p. 218–234°; λ_{max}^{Nujol} 6.1, 6.10, 6.20, 6.30, 6.45 and 6.62 μ. The melting point was not depressed by novobiocic acid obtained by degradation of novobiocin.

Anal. Calcd. for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 66.86; H, 5.43; N, 3.76.

Novobiocin Acid by Degradation of Novobiocin.—A solution of 6.25 g. of novobiocin and 20 g. of concentrated sulfuric acid in 1 l. of purified dioxane was kept at room temperature for 22 hours. A solution of 17 g. of sodium hydroxide in 500 ml. of methanol and 100 ml. of water was added. The precipitated sodium sulfate was filtered and the filtrate was concentrated under reduced pressure to 200–300 ml. The product was precipitated by the addition of about 1 l. of water. The precipitate was filtered, washed with cold water and dried in a vacuum desiccator; 5.15 g. of crude novobiocic acid was obtained.

To purify this material, 4.69 g. of it was dissolved in 500 ml. of chloroform. After filtration to remove a small amount of insoluble material, the solution was placed on a column containing 350 g. of acid-washed alumina. Elution with chloroform removed practically nothing from the column. Elution with acetone gave 1.61 g. of residue after evaporation of the acetone. This residue was crystallized from ethanol–water, giving 1.0 g. of novobiocic acid, m.p. 217–232°; $\lambda_{max}^{0.1\ N\ NaOH}$ 247 mμ ($E_{1cm}^{1\%}$ 496), 264 mμ ($E_{1cm}^{1\%}$ 365), 325 mμ ($E_{1cm}^{1\%}$ 787); λ_{max}^{Nujol} 6.02, 6.12, 6.21, 6.31, 6.49 and 6.63 μ.

2,7-Dihydroxychromone[8] was prepared in the same manner as described above for 2,7-dihydroxy-8-methylchromone, using resorcinol in place of 2-methylresorcinol. The yield of 2,7-dihydroxychromone from 44 g. of resorcinol, 34 g. of ethyl cyanoacetate and 20 g. of zinc chloride was 14 g., m.p. 274–277° dec. after two recrystallizations from water; λ_{max}^{Nujol} 6.0, 6.1, 6.2 and 6.35 μ.

Anal. Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.40. Found: C, 60.88; H, 3.53.

2,7-Dihydroxy-3-nitrosochromone.—A solution of 202 mg. of 2,7-dihydroxychromone in 11.3 ml. of 0.1 *N* sodium hydroxide was cooled in an ice-bath and 82 mg. of sodium nitrite was added. The solution was kept at room temperature for 2 hours and then acidified with acetic acid. The yellow crystalline precipitate was filtered, washed with a little cold water and dried in a vacuum desiccator over phosphorus pentoxide; 183 mg. (78%) of 2,7-dihydroxy-3-nitrosochromone, m.p. 210–220° dec., was obtained. After sublimation at 150° (5 μ) a sample melted at 221–226° dec.

Anal. Calcd. for $C_9H_5NO_5$: C, 52.18; H, 2.43; N, 6.76. Found: C, 52.68; H, 2.12; N, 6.38.

3-Amino-2,7-dihydroxychromone Hydrochloride.—A solution of 97 mg. of 2,7-dihydroxy-3-nitrosochromone in 20 ml. of ethanol was added to a suspension of 0.5 g. of a prereduced palladium–Darco (10%) catalyst in 20 ml. of ethanol containing 0.6 ml. of 2.5 *N* hydrochloric acid. The mixture was shaken with hydrogen at room temperature and atmospheric pressure. Absorption of hydrogen stopped after 3 hours. The catalyst was filtered and the filtrate was evaporated to dryness under reduced pressure under nitrogen. Attempts to crystallize the residue did not succeed and it was acetylated without purification.

3-Acetamido-7-acetoxy-4-hydroxycoumarin.—The 3-amino-2,7-dihydroxychromone hydrochloride prepared above was dissolved in 4 ml. of pyridine. The solution was cooled in an ice-bath and 0.3 ml. of acetic anhydride was added. After standing overnight at room temperature the solution was poured into 20 ml. of ice-water. The mixture was acidified with hydrochloric acid and extracted with four 25-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from ethyl acetate, yielding 46 mg. of 3-acetamido-7-acetoxy-4-hydroxycoumarin, m.p. 249–255°. The compound was recrystallized from ethyl acetate and sublimed at 200° (0.01 mm.), m.p. 256–260°; λ_{max}^{Nujol} 5.70, 5.93, 6.10, 6.20, 6.30 and 6.45 μ.

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.27; H, 3.90; N, 5.03.

Acknowledgment.—We wish to thank Mr. R. N. Boos and his associates for the microanalyses, and Dr. N. R. Trenner and Mr. R. W. Walker for the infrared spectra.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Cyclohepta[klm]benz[e]indene. Further Considerations on the Stability of Complex Polynuclear Systems

BY PETE D. GARDNER, CARL E. WULFMAN AND CLAIBORN L. OSBORN

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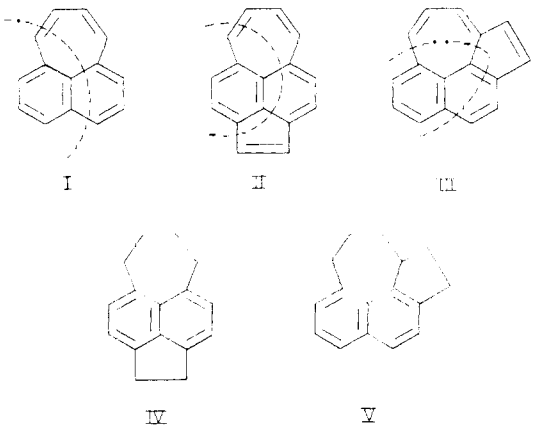
The synthesis of cyclohepta[klm]benz[e]indene (III) has been effected by application of the hydrogen-transfer reaction, using chloranil, to either the hexahydro derivative V or the tetrahydro derivative XV. This method similarly permitted the direct conversion of acepleiadane (IV) to acepleiadylene (II). The preparation of V, a necessary intermediate for this work, permitted the isolation of a second series of racemates, isomeric with that previously obtained. Calculations of resonance energy increments have been made, by an approximate L.C.M.O. method, for conversions leading to I, II and III, and these values correlated with the yields of conversion. The results are consistent with the yield–stability relation previously proposed, and this is shown to have some theoretical justification.

The observation that pleiadiene (I)[1,2] is less stable than acepleiadylene (II)[1] although a logical extension of the Hückel rule would suggest the converse for C_{14}- and C_{16}-cyclic polyenes, prompted the investigation of related systems. The present report is concerned with the synthesis and some of the properties of cyclohepta[klm]benz[e]indene (III). Substance III is a particularly useful choice for comparison with I and II since II and III are isomeric and contain the same total number of π-electrons as well as the same number of peripheral π-electrons. Moreover, a comparison of yields in the preparation of II and III from their hexahydro derivatives IV and V by an aromatization reaction would be interesting as it would bear

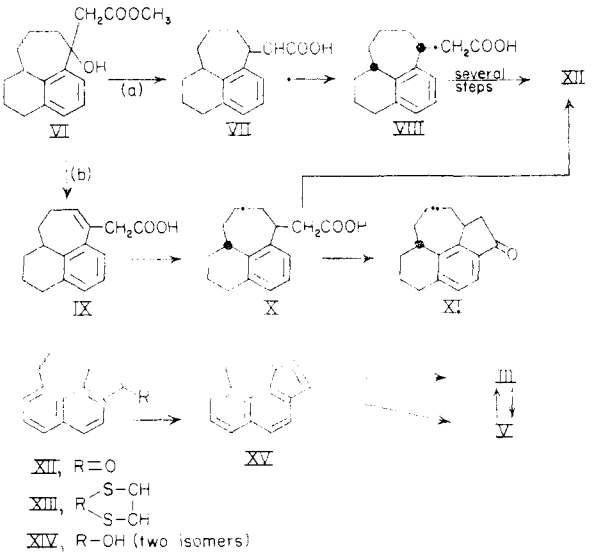
(1) V. Boekelheide and G. K. Vick, THIS JOURNAL, **78**, 653 (1956).
(2) P. D. Gardner and R. J. Thompson, *J. Org. Chem.*, **22**, 36 (1957).

upon the somewhat tenuous hypothesis[2] that a high yield in this reaction might reflect stability in the product. Compounds II and III would be expected to be of comparable, although not identical, stability, but they differ from each other with regard to formation from IV and V by aromatization in that one of the three double bonds to be introduced into IV is independent of the other two, whereas those double bonds to be introduced into V are adjacent to each other. This might be a mechanistically important consideration.



1,2,8,9,10,10a-Hexahydrocyclohepta[klm]benz-[e]indene (V) was prepared as previously reported[3] from the Reformatsky product, methyl 7-hydroxy-1,2,3,7,8,9,10,10a-octahydro-7-cyclohepta[de]-naphthylacetate (VI), through route a (Table I) below. The product of dehydration and hydrolysis was formulated correctly as the side-chain unsaturated acid (VII).[3] A subsequent large-scale preparation of VII afforded a second acid at that stage of the sequence (denoted as route b below) which is formulated as the ring-unsaturated acid on the basis of spectral evidence. The chain-unsaturated acid VII led to a series of intermediates previously described, while IX afforded the other of the two possible series of racemates X and XI. Examination of molecular models of VII and IX indicates rather clearly that each has a more "open" side such that, upon reduction, two racemates should be formed having relative configurations as indicated in VIII and X. The difference in approach of the double bond in VII and IX to the catalyst surface results from the well defined puckering of the seven-membered ring and this difference is manifest in a virtually quantitative yield of the indicated reduction product in each case, none of the other racemate being obtained. Cyclization of X gave ketone racemate, XI. Dehydrogenation of the ester of X over palladium–charcoal, followed by hydrolysis and cyclization, afforded a ketone identical with that[3] (XII) obtained from the other racemate.

The reduction of the naphthalenic ketone XII by the Clemmensen method[3] proved to be unreliable and other methods for converting it to V were sought. Hydrogenolysis of the ethylene thioketal derivative was unsuccessful. Direct catalytic hydrogenation of XII afforded a small yield of the desired product but the method was too inefficient to be practical. The most satisfactory conversion was the three-step sequence involving reduction to the two isomeric carbinols (XIV) followed by dehydration to 8,9,10,10a-tetrahydrocyclohepta-[klm]benz[e]indene (XV) and subsequent reduction to V.



The synthesis of III was effected in one step from V by dehydrogenation using chloranil. Under conditions which gave 7% of I,[2] there was obtained 32% of III. The latter substance absorbed 2.5 mole-equivalents of hydrogen upon reduction to yield the starting material, thus establishing that more fundamental changes did not occur in the hydrogen-transfer reaction. The ultraviolet spectrum of III is indicated in Fig. 1. Treatment of XV with chloranil under the same conditions afforded 18% of III.

The direct conversion of acepleiadane (IV) to acepleiadylene (II) has not been reported, although II has been obtained through the disproportionation of acepleiadiene. Treatment of IV with chloranil under conditions used in the preparation of III gave a 15% yield of II. These results are summarized in Table I.

TABLE I

	Conversion	Yield, %	ΔE_{796}
a	Tetrahydrocyclohepta-[de]naphthalene → I	7	0.4
b	IV → II	15	1.2
c	V → III	32	1.6
d	XV → III	18	

If the following (almost minimal) hypotheses are made, an interpretation of these data results which brings out some rather interesting points, and which at the same time is consistent with the yield–stability relation previously proposed.[2] The hypotheses are: 1. In the absence of steric complications, the rate at which the chloranil dehydrogenations proceed depends in a monotonically increasing manner upon the increment in resonance energy resulting from the reaction. This hy-

(3) P. D. Gardner and W. J. Horton, THIS JOURNAL, **74**, 657 (1952).

pothesis is due to Braude and co-workers and is well supported by their kinetic work.[4,5] 2. The rates of side reactions and of secondary reactions of the final product do not increase with increasing resonance stabilization of the desired final product. The latter is not merely a restatement of the conclusion drawn; it means simply that the rate of polymerization, Diels–Alder addition, etc., of the product is related to the degree of resonance stabilization in that substance.

Coulson and Longuet-Higgins have shown that increasing the extent of a conjugated system always leads to an increase in resonance energy ("Conjugation energies are always positive."[6]), though conjugation energies do not necessarily increase when atoms in the same conjugated system are joined by an additional bond.[6] Dewar has shown that upon increasing the length of a conjugated system, atom by atom, the conjugation energy increments are always of the same order of magnitude,[7] and it also follows directly from his work that upon closing a ring of conjugation by (theoretically) combining two odd AH radicals there is never, to the same degree of accuracy, any resonance energy decrement.[8] The small deviations from these results that do exist will have little effect on the rate of a chloranil dehydrogenation because only about 10% of the resonance energy increment appears in the activation energy.[4] It may be expected then that in a several stage chloranil dehydrogenation, only those stages which involve closing a ring of conjugation are likely to prove critical. Consideration of steric or entropy effects leads to the same conclusion, for these effects also become most critical at just such stages. If these last effects are fairly constant, the rate of the ring completion step will therefore depend primarily upon the resonance energy increment involved in this step. From hypothesis 2 and the previously mentioned work of Dewar it then follows that the over-all *yield* in chloranil dehydrogenations involving similar numbers of stages should roughly parallel the over-all increment in resonance energy from starting material to final product.

To check this conclusion, calculations of the appropriate resonance energy increments were made by an approximate L.C.M.O. method of Dewar,[8] partitioning the molecules as shown by the dotted lines in I, II and III and using a comparable resonance energy for naphthalene, calculated by partitioning it as a benzyl and an allyl radical. The results are presented in Table I and in cases a, b, c are seen to bear out the hypothesis that yields parallel resonance energy increments.

The yield in conversion d apparently contradicts hypothesis 2 or the M.O. arguments which imply that all paths to product are approximately equivalent. Moreover, it has been found previously that no. I could be isolated from the chloranil dehydrogenation of dihydrocyclohepta[de]naphthalene under conditions which gave 7% of I from the tetrahydro derivative. Another, perhaps better, interpretation is that these results are a reflection of the known catalytic activity of the hydroquinone in a quinone dehydrogenation.[4] Thus, for conversions a, b and c, hydroquinone, resulting from quinone reacted in previous stages of the reaction, would be available to catalyze the difficult last stage. In these two reactions hydroquinone would be unavailable, or available only at a lower concentration than in cases a, b and c. This and several other aspects of the chloranil reaction are presently under investigation.

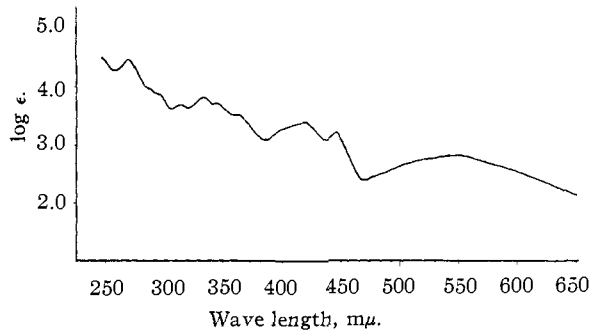
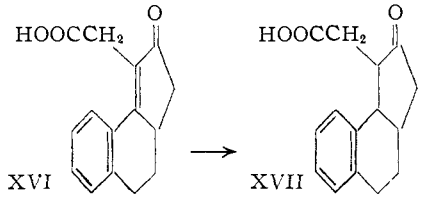


Fig. 1.—Ultraviolet spectrum of cyclohepta[klm]benz[e]-indene (III).

Early in this work other, more convenient syntheses of the ring system of III were sought. One such approach is that utilizing the tricyclic acid XVI, readily available through a two-step procedure from α-tetralone.[9] Lithium–ammonia reduction gave XVII which could not readily be utilized in the problem as it behaved abnormally in an attempted Wolff–Kishner reduction. Catalytic hydrogenation of XVI under a variety of conditions was unsuccessful.



The homologous tricyclic acid XIX was an even more lucrative intermediate as it appeared to be available by a sequence of reactions analogous to that affording XVI, and its further transformation products could be obtained without the use of chain-lengthening reactions. However, the only product obtained upon hydrolysis of the appropriate furan derivative XVIII, obtained from benzosuber-5-one and furfural, was the isomeric furan compound XX. The course taken by this reaction has been observed previously in a few other systems[9] but was surprising in the present case because of the very successful preparation of XVI. To determine whether this course is favored by the seven-membered ring, the simpler derivative XXI was prepared, along with the bis derivative

(4) E. A. Braude, L. M. Jackman and R. P. Linstead, *J. Chem. Soc.*, 3548, 3564 (1954).

(5) E. A. Braude, A. G. Brook and R. P. Linstead, *ibid.*, 3569 (1954).

(6) C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A195**, 188 (1948).

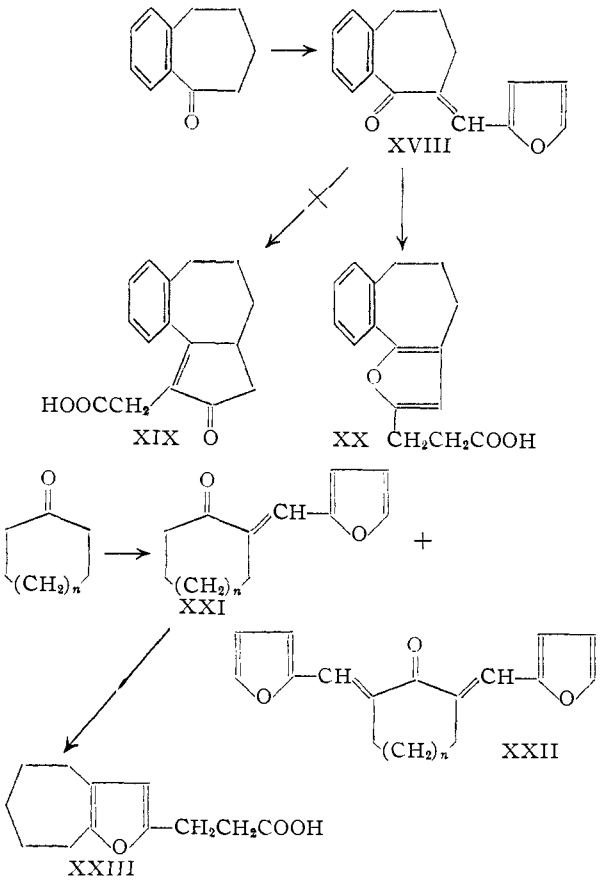
(7) M. J. S. Dewar, THIS JOURNAL, **74**, 3346 (1952), theorems 18 and 19.

(8) M. J. S. Dewar, *ibid.*, theorem 20. Note that the HC. RS, need not be an "even AH" as stated. This is evident both from the proof and from later use of the theorem, *e.g.*, in theorem 23.

(9) D. L. Turner, *ibid.*, **71**, 612 (1949).

XXII (n = 2) and hydrolyzed in the same manner. As in the case of XVIII only one product could be isolated and it was found to be a furan derivative (XXIII).

Hydrolysis of the six-membered homolog XXI (n = 1) gave a resin from which no pure substance could be isolated.



Experimental[10]

1,2,3,9,10,10a-Hexahydro-7-cyclohepta[de]naphthylacetic Acid (IX).—The preparation of the Reformatsky product VI was effected as previously described[3] except that reaction time was decreased to 3.5 hr. and efficient mechanical stirring was employed. In this manner, 148.0 g. of VI resulted from the reaction between 141.5 g. of 7-keto-1,2,3,7,8,9,-10,10a-octahydrocyclohepta[de]naphthalene and 269.0 g. of methyl γ-bromocrotonate. Large scale preparations of VI proved to be hazardous due to erratic heat evolution. The reaction was conducted at gentle reflux, but with a large container of ice and water at hand.

Dehydration and base hydrolysis of VI (148 g.) gave a mixture of the isomeric unsaturated acids. Concentration of an ethereal solution of these to a small volume induced partial crystallization. Collection of the solid by suction filtration and recrystallization from aqueous acetic acid gave 20.4 g. (16%) of IX as colorless plates, m.p. 176–177°. The sample for analysis, purified by further crystallization, had m.p. 177–178°. The ultraviolet spectrum exhibited λ_{max} 259 mμ, log ε 4.03. The spectrum of 1-methyl-3,4-dihydronaphthalene shows λ_{max} 259 mμ, log ε 3.8.[11]

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.91; H, 7.45.

(10) Melting points are corrected. Infrared spectra were determined in potasium bromide wafers. Ultraviolet spectral data were obtained in 95% ethanol solution.

(11) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, curve 30.

The previously prepared chain-unsaturated acid VII was the major product of the reaction and was obtained from the crystallization liquors.

1,2,3,7,8,9,10,10a-Octahydro-7-cyclohepta[de]naphthylacetic acid (β-isomer) (X) was obtained quantitatively by the reduction of IX over palladium–charcoal in acetic acid. Surprisingly, reaction could not be effected using platinum as a catalyst. Purification from acetic acid or from ethanol gave pure X as colorless prisms, m.p. 152.0–153.5°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.55; H, 8.13.

2-Keto-1,2,5,6,7,7a,8,9,10,10a-decahydrocyclohepta-[klm]benz[e]indene (β-Isomer) (XI).—Treatment of 1.43 g. of X with 30 g. of polyphosphoric acid at 135° until the mixture became homogeneous and then for an additional 10 min. at 100° gave, after hydrolysis with ice and water, 0.92 g. (65%) of XI, m.p. 81.0–82.5° after recrystallization from methanol–water. The sample for analysis was prepared by further crystallization and final sublimation at 0.02 mm., m.p. 81.5–82.5°. When mixed with a sample of the racemate previously reported[3] (m.p. 86.5–87.5°) the m.p. was depressed to 55°.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.78; H, 7.88.

7,8,9,10-Tetrahydro-7-cyclohepta[de]naphthylacetic Acid from X.—The methyl ester of X was prepared by refluxing 4.50 g. in 50 ml. of methanol containing 1.5 ml. of concd. sulfuric acid for a period of 12 hr. Isolation in the usual manner by dilution with water and extraction with ether gave the methyl ester as a viscous colorless liquid. This was heated with 3.0 g. of 40% palladium–charcoal (nitrogen) at 300°. A volume of 650 ml. of hydrogen was collected during 1.5 hr. and the product, after isolation by filtration of an ethereal solution, was hydrolyzed to give the naphthalenic acid. Crystalization from ethyl acetate–petroleum ether (60–66°) gave 1.71 g. (38% over-all) of colorless solid, m.p. and mixed m.p. 128–129°. The conversion of this substance to V was made as previously described.

Ethylenethioketal Derivative of 2-Keto-1,2,8,9,10,10a-hexahydrocyclohepta[klm]benz[e]indene (XIII).—This preparation followed the general procedure of Fieser.[12] To 1.00 g. of XII was added 2 ml. of ethanedithiol and 2 ml. of boron trifluoride etherate. The brown complex which formed quickly was stirred for 5 min. and treated with 15 ml. of methanol. An oil separated and crystallized. Collection by suction filtration and washing with methanol afforded 1.27 g. (95%) of the thioketal XIII, m.p. 130–133°. The sample for analysis, prepared by recrystallization from heptane or from isopropyl alcohol–water as lustrous plates, had m.p. 133.0–135.5°, unchanged by further purification attempts.

Anal. Calcd. for $C_{18}H_{18}S_2$: C, 72.43; H, 6.08; S, 21.5. Found: C, 72.50; H, 5.99; S, 21.5.

The hydrogenolysis of this substance, using massive quantities of Raney nickel in the conventional manner,[13] did not give V. The product of the reaction has not yet been characterized.

2-Hydroxy-1,2,8,9,10,10a-Hexahydrocyclohepta[klm]-benz[e]indene (XIV).—A solution of 4.00 g. of XII in 100 ml. of methanol was treated with 0.80 g. of sodium borohydride in one portion. The mixture was swirled for 15 min. and another 0.80-g. portion of the hydride was added. After 15 minutes longer the process was repeated. Dilution of the solution with 200 ml. of water, followed by acidification with concd. hydrochloric acid, induced precipitation of the α-isomer of XIV. Recrystallization from methanol gave 3.95 g. (98%) of colorless plates melting 157–160°. Further purification in the same manner gave the sample for analysis, m.p. 157–159°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.80; H, 7.18.

Another preparation of XIV (3.0 g. of XII), duplicating as nearly as possible the procedure described above, gave a liquid product which crystallized on standing. It could not be recrystallized from methanol but the use of acetic acid gave solid material. Recrystallization of the latter from ethanol–water afforded 1.30 g. (43%) of the β-isomer, m.p.

(12) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

(13) See, for example, H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, *ibid.*, **76**, 3693 (1954).

87–89°. Further purification from methanol gave a sample as long colorless needles, m.p. 85.5–87.0°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.63; H, 7.54.

8,9,10,10a-Tetrahydrocyclohepta[klm]benz[e]indene (XV).—A mixture of 2.00 g. of the α-isomer of XIV and 0.21 g. of sodium hydrogen sulfate was heated (oil-bath) in a distillation flask equipped for vacuum distillation. Upon melting, the mixture rapidly evolved water and solid material began to sublime into the receiver (0.25 mm.). The temperature was raised gradually until all volatile material had been sublimed into the delivery tube and receiver. Collection of this solid, by washing out the delivery tube and receiver with hot ethanol and cooling the solution, gave 0.92 g. (50%) of XV, m.p. 99.0–101.5°. The sample for analysis had m.p. 100–102°.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.16; H, 6.91.

Reduction of this substance with hydrogen (1 atm.) over 5% palladium–charcoal suspended in ethanol gave a quantitative yield of the hexahydro compound (V), m.p. 66–67° (lit.[3] 65–67°).

Cyclohepta[klm]benz[e]indene (III). (a) **From V.**—A solution of 0.183 g. of V and 0.650 g. of purified chloranil in 10 ml. of xylene was heated in an oil-bath at 135° and stirred magnetically in an atmosphere of nitrogen for 20 hr. The solution was transferred to a separatory funnel using ether and washed five times with 15-ml. portions of 10% aqueous sodium hydroxide or until the washings were colorless. The entire washing operation with base and water was repeated and the combined aqueous solutions were then re-extracted with ether and this ethereal solution processed as was the original. The combined organic solutions were dried and freed of solvent *in vacuo*. The residue, dissolved in a small volume of petroleum ether (60–66°), was charged to a column of 350 g. of acid-washed alumina and the column developed first with petroleum ether and then with 10% ether in petroleum ether. The former eluted a yellow mobile band (chloranil) and the latter a well-defined gray band (III). Removal of solvent from the latter fraction gave 0.057 g. (32%) of black plates, m.p. 178–186°. Pure III was obtained by recrystallization from petroleum ether followed by sublimation at 0.1 mm., m.p. 197–200°. Further purification attempts did not change this value. This substance appears black in the solid state but gives solutions having a gray-purple coloration. The ultraviolet spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{16}H_{10}$: C, 95.05; H, 4.95. Found: C, 95.03; H, 4.81.

Hydrogenation of 15.6 mg. of III in ethanol over platinum showed 2.5 double bonds and gave V, identified by m.p. and mixed m.p.

(b) **Preparation of III from XV.**—The reaction of 0.110 g. of XV with 0.280 g. of chloranil and isolation of the product, all as described above for the reaction of V, gave 0.01 g. (18%) of III, m.p. 187–193°.

The chromatographically isolated products described here and above, although having melting points somewhat lower than that of a highly purified sample, are believed to be quite pure. This substance has poor melting characteristics and suffers a considerable depression of m.p. by even slight contamination by other materials. Considerable effort was devoted to the development of this isolation and it is believed to be one giving a reliable measure of the quantity of product formed in the reaction.

Preparation of Acepleiadylene (II) from Acepleiadane (IV).—A 1.00-g. sample of IV[14] was allowed to react with 3.80 g. of chloranil exactly as described above for III. Chromatography of the product, after preliminary extraction and washing as described above, gave 0.152 g. (15%) of II, m.p. 153–156°. Recrystallization from heptane raised the m.p. to 156–161° (lit.[1] 156–162°).

Reduction of 3,3a,4,5-Tetrahydro-2H-benz[e]indene-2-one-1-acetic Acid (XVI).—To a solution prepared by dissolving 3.5 g. of lithium in 600 ml. of liquid ammonia was added a slurry of 22.0 g. of XVI[9] in 100 ml. of purified dioxane. The solution was stirred at reflux temperature for 0.75 hr. and then treated with solid ammonium chloride, in portions, until the blue color faded. Ammonia was allowed to evaporate over 12 hr. and the residue was dissolved in water. This solution was first extracted with ether and then acidified whereupon a solid separated. Filtration and recrystallization from ethanol gave 18.1 g. (83%) of the dihydro derivative XVII, m.p. 179–181°. Further crystallization gave colorless needles melting over the same range. This substance was soluble in aqueous sodium hydrogen carbonate and readily formed carbonyl derivatives. The ultraviolet spectrum exhibited only very weak absorption indicating a chromophore no more extensive than an isolated benzene ring. The infrared spectrum exhibited a closely-spaced doublet at 5.8 μ (carbonyl).

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 74.05; H, 6.22. Found: C, 74.18; H, 6.38.

2-Furfurylidenecycloheptanone (XXI, $n = 2$).—A solution was prepared by dissolving 96.0 g. of cycloheptanone[15] and 80.0 g. of freshly distilled furfural in 100 ml. of ethanol. While stirring, 1 ml. of 45% aqueous potassium hydroxide was added to the cooled solution (5°). The addition of 1-ml. quantities of the base with the same temperature control was continued until a total of 5 ml. had been added. After stirring for 1 hr. at 12° the temperature was allowed to rise to 25° where it was maintained for an additional 2 hr. Following the addition of 300 ml. of benzene, the solution was washed twice with saturated sodium chloride solution and twice with water and freed of solvent by distillation at the aspirator using a steam-bath and a 12-in. Vigreux column. Continued distillation gave a mixture of starting materials and then 44.4 g. (28%) of XXI, b.p. 185–188° (29 mm.).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.59; H, 7.42. Found: C, 75.68; H, 7.27.

This substance darkened very quickly on standing and the above values were obtained only by distilling the sample immediately prior to the combustion.

The dinitrophenylhydrazone, formed in ethanol and purified by recrystallization from chloroform–methanol, appeared as dark red needles, m.p. 157.0–158.5°.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: C, 58.37; H, 4.90. Found: C, 58.24; H, 4.97.

The pot residue from the above distillation was diluted with a small volume of ethyl acetate and cooled. The resulting solid was recrystallized from ethyl acetate–petroleum ether (60–68°) to give 6.7 g. (6%) of 2,7-bisfurfurylidenecycloheptanone (XXII, $n = 2$), m.p. 110–112°. Further purification from the same solvents did not change the m.p.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.22; H, 6.01.

The dinitrophenylhydrazone was prepared in ethanol and recrystallized from chloroform–methanol as purple needles, m.p. 222–223°.

Anal. Calcd. for $C_{23}H_{20}O_6N_4$: C, 61.60; H, 4.50. Found: C, 61.60; H, 4.52.

Acid Hydrolysis of 2-Furfurylidenecycloheptanone (XXI, $n = 2$).—To 95.0 g. of XXI dissolved in 200 ml. of 95% ethanol was added 100 ml. of concd. hydrochloric acid. The solution was heated at 55° for 1 hr. and then under reflux for 1.5 hr. The liquid portion was decanted into a separatory funnel and the black residue stirred repeatedly with 100-ml. portions of hot petroleum ether (60–66°). The aqueous layer was then extracted with the combined petroleum ether solution. Following removal of solvent under reduced pressure, the residue was further distilled through a short-path system to give 21.0 g. of yellow liquid boiling over the range 125–170° (26 mm.). This liquid was refluxed for 1.5 hr. with 7.0 g. of potassium hydroxide in 150 ml. of water. After an extraction with ether, the aqueous solution was acidified to give 7.5 g. of dark solid which melted over a wide range. Recrystallization from ethyl acetate–petroleum ether gave 3.8 g. (4%) of 5,6,7,8-tetrahydrocyclohepta[b]furan-2-propionic acid (XXIII) as light tan needles, m.p. 103–105°. The sample for analysis, prepared by several recrystallizations from cyclohexane followed by sublimation at 0.1 mm., melted at 103.0–104.5°. It did not form carbonyl derivatives.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.24; H, 7.80.

2-Furfurylidenecyclohexanone (XXI, $n = 1$).—The re-

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action of 100 g. of furfural with 98.2 g. of cyclohexanone, when conducted exactly as described above, gave 31.3 g. (18%) of XXI, n = 1, m.p. 46–47° (lit.[16] 47°). The purple dinitrophenylhydrazone, prepared and purified as were those above, melted at 190–192°.

Anal. Calcd. for $C_{17}H_{16}O_5N_4$: C, 57.30; H, 4.53. Found: C, 57.21; H, 4.66.

In addition, there was obtained 81.5 g. (32%) of 2,6-bisfurfurylidenecyclohexanone (XXII, n = 1), m.p. 143–145° (lit.[16] 145°).

Acid hydrolysis of the mono derivative gave resinous material, from which nothing could be extracted.

6-Furfurylidenebenzosuber-5-one (XVIII).—A solution of 80.0 g. of benzosuberone[17] and 50.0 g. of furfural in 200 ml. of ethanol was treated with 3 ml. of 45% potassium hydroxide solution and cooled under running water as required to keep the temperature below 50°. After the exothermic reaction had subsided, the mixture was allowed to stand for 2 hr. at 25°, diluted with 250 ml. of water, cooled and filtered with suction. Recrystallization of the damp cake from ethyl acetate gave, in two crops, 116 g. (98%) of XVIII, m.p. 126–127°. The m.p. was not changed by further purification.

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(17) W. J. Horton and F. E. Walker, THIS JOURNAL, **74**, 758 (1952).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.28; H, 5.95.

Acid Hydrolysis of XVIII.—A mixture of 112 g. of XVIII, 600 ml. of 95% ethanol and 275 ml. of concd. hydrochloric acid was heated under reflux on a steam-bath for 18 hr. Nearly all solvent was removed by slow distillation through a 24-in. Vigreux column (20 mm.). The black residue was refluxed with 700 ml. of acetic acid for 4 hr. and diluted with 2 l. of water. The mixture was extracted with ether (2 × 1 l.) and the ethereal layer was washed with water (2 × 500 ml.) and then with 500 ml. of 10% sodium hydroxide solution. Acidification of the basic wash afforded 13 g. of black semi-solid which, after three recrystallizations from benzene, afforded 3.3 g. (3%) of 5,6-dihydrobenzocyclohepta[3.4-b]furan-2-propionic acid (XX), m.p. 133–134°. A colorless sample, having the same m.p., was obtained by sublimation at 0.1 mm. This substance did not form carbonyl derivatives.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.98; H, 6.28.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

Imidazole Catalysis. II. The Reaction of Substituted Imidazoles with Phenyl Acetates in Aqueous Solution

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The reaction of imidazole with p-nitrophenyl acetate in aqueous solution, previously shown to be pseudo first order in the liberation of p-nitrophenol, has now been shown to be first order in acetate liberation by the same rate law. The study of the dependence of rate on basicity has been extended through the determination of the second-order rate constants for the reaction with p-nitrophenyl acetate of 21 imidazoles of various pK_a'. The second-order rate constants do not obey a simple Brönsted catalysis law since both the neutral and anionic species exhibit catalytic properties. By means of a linear relationship of pK_2' to pK_1' for the imidazoles (*i.e.*, $pK_2' = 0.94pK_1' + 7.43$) equation 15 was derived and found to adequately correlate the apparent second-order rate constant, k_2', to the value of pK_1' for 4(5)-substituted imidazoles. The application of this equation, as well as the factors influencing the fit of the experimental data to the equation are discussed. Some attempts to realize a Lowry type catalysis of p-nitrophenyl acetate and phenyl acetate hydrolysis are described and discussed in the light of catalyzed reactions which have been proposed to be of this type. The hydrolysis of p-nitrophenyl acetate was found to be catalyzed by pyrimidoimidazoles (purines) at 2×10^{-4} M but not by pyrimidines at this concentration. For the purines there is no apparent direct relationship of pK_a' to k_2'.

Introduction.—The implication of an imidazolyl group of histidine as essential to the activity of numerous hydrolytic enzymes[2] has led to studies of the ability of imidazoles to catalyze the hydrolysis of substrates of several hydrolytic enzymes. Thus, it has been found that imidazole compounds catalyze the hydrolysis of thiol esters,[3,4] phenyl acetates,[4,5] N-acetylamides,[6] fluorophosphates[7] and, at high catalyst concentrations, phosphoamides.[8] In this paper we report on the continuation of our studies of the reaction of imidazoles with phenyl acetates.

(1) Public Health Predoctoral Fellow of the National Institutes of Health, 1956–1957.

(2) For pertinent references on this topic see ref. 4 and 5.

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Experimental

Imidazoles.—Benzimidazole, imidazole, 4-hydroxymethylimidazole hydrochloride, 4-methylimidazole hydrochloride and 4-bromoimidazole were samples used in a previous study.[5] 6-Nitrobenzimidazole was an Eastman Kodak Co. white label product while 2-(2'-hydroxyphenyl)-benzimidazole,[9] 4-nitroimidazole,[10] 2-methylbenzimidazole,[11] L-histidine methyl ester dihydrochloride,[12] 6-aminobenzimidazole·H_2O·$^1/_2HCl$[13] and 2-methylimidazole[14] were prepared by recorded procedures. Dr. C. E. Carter provided us with a sample of histamine acid phosphate while the various purines and pyrimidines were obtained from Dr. H. G. Mautner, and N-acetyl-DL-histidine hydrate was obtained from Dr. J. S. Fruton. Dr. Morris Engelman and Dr. H. B. Gillespie of the Department of Biochemistry, Columbia University, College of Physicians and Surgeons, provided us with the following compounds[15]: 6-amino-4-hydroxy-2-methylbenzimidazole sulfate·$^1/_2H_2O$, 6-amino-4-hydroxy-

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