this is the case as shown by the sharp increase in racemization to 88% in the methanolysis of I as compared with the 46% observed with hydrogen 2,4-dimethyl-4-hexyl phthalate.

The racemizing effect of a phenyl group *vis-á-vis* an isobutyl group is considered to be in agreement with the mechanistic concept newly developed for solvolyses.[2] Increased internal stabilization of the forming reaction intermediate by phenyl group interaction would result in a decrease in the activation energy associated with frontside solvation, in an increase in the rearward solvating energy and in decreased asymmetry in the intermediate. While the stereochemical result obtained here does not distinguish uniquely between an interpretation of the solvolytic reaction in terms of activation energies and other concepts involving lifetimes of intermediate carbonium ions, the former hypothesis is preferred on the grounds of greater specificity.

Experimental[7]

Methanolysis of (+)-Hydrogen 2-Phenyl-2-butyl Phthalate (I).—A solution of 11 g. of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{24}\mathrm{D}$ +4.44°, in 150 ml. of absolute methanol was refluxed for 72 hours. The methanolic solution was poured into 1.5 l. of water, followed by extraction with ether. After washing the ether solution thoroughly with dilute sodium carbonate solution and acidification of the combined alkaline washes, no unreacted acid ester was separated, indicating that reaction had reached completion. The ether solution of 2-methoxy-2-phenylbutane (II) was washed with water and dried over potassium carbonate. After removal of the solvent there remained 5.5 g. (92%) of II which was evaporatively distilled at room temperature and 1 mm.: $[\alpha]^{23}\mathrm{D}$ +0.20° (α +0.19°), $n^{25}\mathrm{D}$ 1.4981, d^{25}_4 0.940.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.61; H, 9.85.

Racemization of (−)-2-Methoxy-2-phenylbutane (III).—Methyl ether (2.8 g.), $\alpha^{22}\mathrm{D}$ −5.84° (l = 1), in 60 ml. of absolute methanol containing 2.4 g. of phthalic acid, was refluxed for 72 hours, after which the methyl ether was recovered by the isolation procedure described above including final purification by evaporative distillation. A 46.5% loss in optical activity had occurred during the 72-hour period: $\alpha^{22}\mathrm{D}$ −3.12° (l = 1).

2-Methoxy-2-phenylbutane (II).—2-Phenylbutan-2-ol (1.8 g.), $[\alpha]^{25}\mathrm{D}$ +16.68°, was stirred vigorously with 0.5 g. of potassium sand in 100 ml. of hot benzene for four hours. To this solution was next added 2 g. of methyl iodide in 20 ml. of benzene. The slow precipitation of potassium iodide was allowed to proceed overnight. A blanket of nitrogen was maintained over the reaction mixture while water was added to destroy any unreacted potassium metal and to dissolve the inorganic salt. After separation of the aqueous layer the benzene solution was washed, dried and the solvent benzene removed by atmospheric distillation. The residual liquid was evaporatively distilled to give 1.1 g. (56%) of 2-methoxy-2-phenylbutane: $[\alpha]^{27}\mathrm{D}$ +29.58°; $n^{25}\mathrm{D}$ 1.4991; d^{25}_4 0.940; b.p. 201–202° (760 mm.). This methyl ether contained a trace of unreacted carbinol as reflected in a slightly higher refractive index than that of II obtained from the methanolysis and in the appearance of a weak O–H band in its infrared spectrum. Removal of carbinol by boiling the methyl ether over molten potassium resulted in some decomposition. However, the infrared spectra of II contaminated with carbinol or after treatment with potassium and of II resulting from methanolysis compared so closely as to warrant the conclusion that the extent of contamination was not large enough to be of appreciable significance in the calculation of configurational changes.

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[7] Optical rotations of methylethylphenylcarbinol and of its methyl ether II were measured without solvent. The rotation of its hydrogen phthalate I was determined in absolute ethanol.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

Base-catalyzed Condensation Reactions of *p*-Hydroxybenzaldehyde and Higher Keto Acids

BY GEORGE M. PICHA

RECEIVED JUNE 16, 1952

The condensation products resulting from the base-catalyzed reactions of *p*-hydroxybenzaldehyde with some higher aliphatic (ω-1)-keto acids have been shown to be the isomers which result from reaction of the terminal methyl group, in accordance with a generally applicable principle governing such condensations. These products have also served as intermediates in the preparation of a series of amino ester hydrochlorides differing both in the length of the aliphatic chain and the nature of the nitrogen-containing group.

The investigation of the condensation reactions of unsymmetrical ketones has been one of the classical problems of organic chemistry. The nature of the reaction products resulting from the condensation of aromatic aldehydes with aliphatic keto acids has constituted one of the major aspects of this investigation.

Variant formulations given in the early literature[1] for the condensation products of benzaldehyde and levulinic acid, one of the first such reaction pairs to be studied, gave rise to confusion, dispute and occasionally polemics.

Of the various individuals studying this and similar reaction systems shortly before the turn of the century, Erdmann was the most successful in establishing the correct structures of these compounds. He demonstrated that condensation reactions effected by acidic and basic catalysts gave rise to different benzallevulinic acids, only one of which could be cyclodehydrated to 3-acetyl-1-naphthol. Several lines of evidence were adduced to prove that these were not *cis–trans* isomers, of which the most convincing was that the saturated keto acids produced by hydrogenation of the double bond were not identical.

Largely on the evidence of dehydration to a naph-

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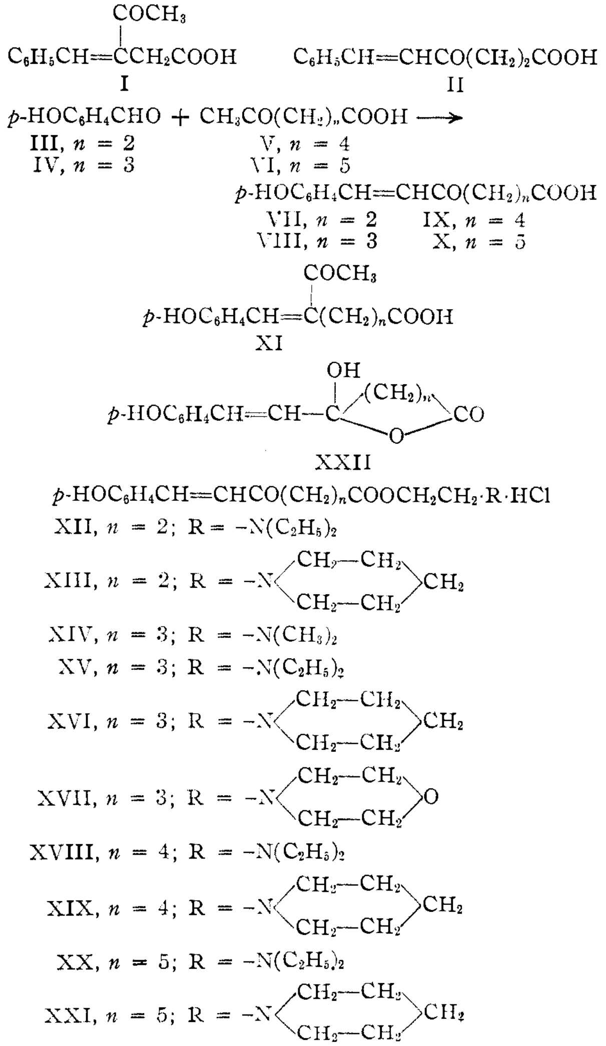
[1] (a) E. Erlenmeyer, Jr., *Ber.*, **23**, 74 (1890); (b) H. Erdmann, *ibid.*, **18**, 3441 (1885); (c) H. Erdmann, *ibid.*, **21**, 635 (1888); (d) H. Erdmann, *Ann.*, **254**, 182 (1889); (e) H. Erdmann, *ibid.*, **258**, 129 (1890); (f) H. Erdmann, *Ber.*, **24**, 3201 (1891); (g) A. Ludwig and E. A. Kehrer, *ibid.*, **24**, 2776 (1891); (h) E. A. Kehrer, *ibid.*, **24**, 4104 (1891); (i) E. A. Kehrer and W. Kleberg, *ibid.*, **26**, 345 (1893). The conclusions of Erdmann were apparently based in large part on the laboratory work contained in the Inaugural Dissertation (Halle, 1891) of F. Henke. This paper is not available to the author, and seems never to have been published elsewhere as an independent article.

thol derivative and oxidation to benzalsuccinic acid, the benzallevulinic acid (I) produced in an acid-catalyzed condensation was shown to result from condensation involving the methylene group adjacent to the ketone; the isomeric compound II which resulted from a base-catalyzed condensation was formed by reaction at the methyl group.

The finding that methylene and methyl condensations are favored by acidic and basic catalysts has been successfully extended to many other reactions of unsymmetrical ketones of the type CH_3COCH_2R and is of great value, but the principle is by no means without important exceptions. For example no such rule can be uniformly applied even to the simplest such compound, methyl ethyl ketone.[2] Benzaldehyde with phenoxyacetone[3] seems always to give methylene condensation, with methyl isobutyl ketone[4] always methyl condensation, irrespective of the acidic or basic nature of the catalyst. The former result appears due to the presence of a strongly electronegative group adjacent to the methylene carbon, the latter possibly to steric factors.



$C_6H_5CH{=}\overset{COCH_3}{\overset{|}{C}}CH_2COOH$ I $\qquad C_6H_5CH{=}CHCO(CH_2)_2COOH$ II

$p\text{-}HOC_6H_4CHO + CH_3CO(CH_2)_nCOOH \longrightarrow$

III, $n = 2$ V, $n = 4$
IV, $n = 3$ VI, $n = 5$

$p\text{-}HOC_6H_4CH{=}CHCO(CH_2)_nCOOH$

VII, $n = 2$ IX, $n = 4$
VIII, $n = 3$ X, $n = 5$

$p\text{-}HOC_6H_4CH{=}\overset{COCH_3}{\overset{|}{C}}(CH_2)_nCOOH$ XI

XXII

$p\text{-}HOC_6H_4CH{=}CHCO(CH_2)_nCOOCH_2CH_2\cdot R\cdot HCl$

XII, $n = 2$; R = $-N(C_2H_5)_2$
XIII, $n = 2$; R = $-N\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH_2$
XIV, $n = 3$; R = $-N(CH_3)_2$
XV, $n = 3$; R = $-N(C_2H_5)_2$
XVI, $n = 3$; R = $-N\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH_2$
XVII, $n = 3$; R = $-N\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle O$
XVIII, $n = 4$; R = $-N(C_2H_5)_2$
XIX, $n = 4$; R = $-N\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH_2$
XX, $n = 5$; R = $-N(C_2H_5)_2$
XXI, $n = 5$; R = $-N\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle CH_2$

The present investigation has been undertaken with the joint objectives of preparing and identifying the base-catalyzed condensation products of p-hydroxybenzaldehyde with some higher aliphatic keto acids (III–VI),[5] and of examining the properties of a number of their amino ester hydrochlorides. According to evidence to be presented the products (VII–X) of the aldol-type[6] condensation result from the (normal) reaction at the methyl group.

As with the typical aldol-type condensation, VII–X are produced in relatively small yield, along with much tarry by-product. The preparation of each presents somewhat individual problems, but in general it was found advisable to use more drastic reaction conditions than have been found suitable for the synthesis of other compounds of their type. For example only a very small amount of VIII could be isolated by following the general procedure of Erlenmeyer[1a] for the preparation of II.

All of the esters described in this paper are new, as are all of the parent acids, with a probable exception. A compound prepared in a similar manner by Sen and Roy[7] has been assigned the structure of VII, although the preparations seem to differ greatly. The earlier workers reported a melting point of 109°, whereas the value found in this study was 146–147°.

Proof of structure of VII, as a representative member of the series of condensed acids, was carried out by identifying the fragments resulting from its ozonolysis. When VII was ozonized in the usual manner, and the ozonide decomposed with water and dilute alkaline hydrogen peroxide, two crystalline materials were obtained by chromatography of the crude reaction product. The aromatic fragment, which plays only a minor role in structure proof, was shown to be chiefly hydroquinone. This is regarded as being formed from p-hydroxybenzaldehyde by a Dakin reaction.

The aliphatic fragment, which is vital to structure proof, was identified as succinic acid. Its formation is readily ascribed to peroxide degradation of α-ketoglutaric acid[8] or the corresponding half aldehyde, the latter of which is regarded as the primitive aliphatic fragment. It will be apparent that whereas succinic acid is an easily-visualized oxidative degradation product of VII, there is no sequence of oxidation steps (and certainly not the combination of ozone and alkaline hydrogen peroxide employed here) that could lead to the formation of succinic acid from XI, $n = 1$.

Additional support for the assignment of structures VII–X was obtained by application of the iodoform test. As reference compounds, the keto

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[2] H. Haeussler and C. Brugger, *Ber.*, **77**, 152 (1944).

[3] R. Stoermer and R. Wehlen, *ibid.*, **35**, 3549 (1902).

[4] C. V. Gheorghiu and B. Arwentiew, *J. prakt. Chem.*, **118**, 295 (1928). See also R. P. Mariella, THIS JOURNAL, **69**, 2670 (1947).

[5] For the chemistry of some compounds similarly related to the special cases of pyruvic acid and acetoacetic acid (or derivatives) see: (a) M. Reimer, *ibid.*, **48**, 2454 (1926); (b) W. Borsche and C. Walter, *Ber.*, **60**, 2113 (1927); (c) I. M. Heilbron and F. Irving, *J. Chem. Soc.*, 936 (1929); (d) R. N. Sen and B. K. Sen, *J. Indian Chem. Soc.*, **11**, 411 (1934).

[6] The term is used here and elsewhere in this paper to denote not only the initial condensation but the spontaneous dehydration as well. The process involved is essentially that of the Claisen–Schmidt condensation.

[7] R. N. Sen and B. C. Roy, *J. Indian Chem. Soc.*, **7**, 401 (1930).

[8] Numerous parallel degradations of other α-keto acids are known and are stated to proceed with ease.

acids III–VI were each found to give an immediate and copious precipitate of iodoform when they were treated with aqueous, alkaline hypoiodite. Compounds of type XI should behave similarly,[9] whereas those resulting from methyl condensation would be expected to give no iodoform unless base-catalyzed reversal of the condensation reaction regenerated some of the original keto acid.

When the four condensed acids were treated with alkaline hypoiodite, the behavior of all of them was essentially identical. In each case no iodoform could be produced at the beginning of the test; after an induction period of several minutes, small amounts could be precipitated. The significance of this result was determined by a pair of companion experiments. In experiment A about 30 mg. of X was dissolved in 2 ml. of 5% sodium hydroxide, warmed at 60° for 20 minutes, and cooled. Then another 30-mg. sample of X (experiment B) was quickly dissolved in 2 ml. of 5% sodium hydroxide, and the two solutions were treated simultaneously with equal amounts of iodine–potassium iodide solution. An immediate precipitate of iodoform resulted in A; from B no immediate reaction occurred, and only after a period of five to ten minutes was a trace of iodoform detectable. When no additional iodoform could be produced from either mixture, they were both allowed to stand for 24 hours, at the end of which time each of them again gave a positive test.

These results demonstrate that the source of the iodoform is only the aliphatic keto acid produced by a reversal, to a point of equilibrium, of the condensation steps; and they support the conclusion that the acids VII–X are those resulting from condensation of the terminal methyl group. Many other α,β-unsaturated ketones are known to be split similarly in basic solution, and Erlenmeyer[1a] seems to have recognized that such a process could take place with a benzallevulinic acid.

The amino ester hydrochlorides are white, crystalline, relatively non-hygroscopic compounds. Their structure follows from analogy with the parent acids and is confirmed by their solubility properties. They are all readily soluble in water, although those derivatives in which $n = 5$ (XX and XXI) begin to show decreased water solubility and exhibit a sharp solubility gradient between 25 and 40°. The free bases are precipitated and are ether-extractable by the addition of potassium bicarbonate solution, but immediately redissolve in cold sodium hydroxide.

In the very early stages of this work a striking property of the amino ester hydrochlorides was noted, in the fact that they gave colorless solutions in alcohols or distilled water, but yellow solutions in tap water. While initially puzzling, this color change was eventually shown to result solely from a slight change in *p*H, to which these compounds are extremely sensitive. In our experiments they have proved capable of detecting the change in *p*H caused by the addition of 1% of tap water to their solutions in ordinary distilled water. Thus, a solution of 5 mg. of XV in 5 ml. of distilled water, colorless within the limits of visual acuity, gave a detectable yellow color by the addition of one drop of tap water, or 5 micrograms of potassium bicarbonate. Color changes approaching completeness were produced by four times these amounts. This property is shared to a certain degree by the parent acids, but it is much less apparent.

Ultraviolet Absorption Spectra (See Table I).—All four of the condensed acids show primary absorption maxima at about 324 mμ, secondary maxima at about 235 mμ, and minima at about 256 mμ. These values are characteristic for the conjugated system $(p\text{-HOC}_6\text{H}_4\text{CH}{=}\text{CHC}{=}\text{O})$–, and are not significantly altered in the esterified compounds XX and XXI.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

Compound	Maxima, mμ	log ε[a]	Compound	Maxima, mμ	log ε[a]
VII	323	4.37	X	323	4.37
	234	3.99		235	3.97
VIII	325	4.38	XX	325	4.39
	235	3.97		235	3.91
IX	324	4.37	XXI	325	4.39
	235	3.97		234	3.97

[a] Determined at 0.02 mg. per ml. in methanol.

Since levulinic acid is sometimes thought to exist largely in a lactonic form, it was originally felt that some of the condensed acids, and particularly VII and VIII, might have the structure of XXII. The close conformance of the absorption spectra of each of the acids to the others, to their ester derivatives, and to *p*-hydroxybenzalacetone[10] does not support the postulate that this lactone structure is present in methanol solution.

Acknowledgments.—The author is greatly indebted to Edward A. Brown, Robert W. Hamilton, and John Saylor for the preparation of the aliphatic keto acids, and to Anne M. Jaeger and Marjorie M. Ziebell for technical assistance with chromatography.

Experimental

All melting points were taken with totally-immersed thermometers; boiling points are uncorrected. Analytical samples were dried for two hours at 78° in a vacuum. Analyses were carried out by Dr. Robert T. Dillon and staff.

Aliphatic Keto Acids.—**Levulinic acid** (III) (Eastman Kodak) was used without further purification.

5-Ketocaproic acid (IV), b.p. 101–104° (0.3 mm.) was prepared by hydrolyzing and decarboxylating the condensation product of ethyl β-bromopropionate and the sodium derivative of ethyl acetoacetate.[11]

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(9) A referee has pointed out that competing iodination of the phenolic ring may cause such compounds to give equivocal results in the iodoform reaction. To determine the degree to which this factor may be operative in the experiments here described, the author has established that *p*-hydroxybenzalacetone, a compound which is very similar with respect to electronic influences on aromatic substitution, gives a normal test and an immediate precipitate of iodoform. While simultaneous iodination of the ring may indeed occur, it would appear that in this type of compound cleavage of the acetyl group proceeds at an adequate rate.

(10) A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, Jr., T. L. Johnson and C. H. Shunk, THIS JOURNAL, **69**, 1985 (1947).

(11) W. H. Bentley and W. H. Perkin, Jr., *J. Chem. Soc.*, **69**, 1510 (1896); reported b.p. 195–200° (65 mm.). See also N. F. Albertson, THIS JOURNAL, **70**, 670 (1948), for a probably superior method; reported b.p. 107.5–109° (5 mm.).

6-Ketoenanthic acid (V), b.p. 126–132° (1.2 mm.) was prepared by hydrolyzing and decarboxylating the condensation product of γ-bromobutyronitrile and the sodium derivative of ethyl acetoacetate,[12] and alternatively by oxidizing 2-methylcyclohexanol with chromium trioxide.[13]

7-Ketocaprylic acid (VI), b.p. 144–146° (1.0 mm.) was prepared by hydrolyzing the boron trifluoride-catalyzed acylation product of cyclohexanone and acetic anhydride.[14]

(*p*-Hydroxyphenyl)-ketoalkenoic acids were synthesized by procedures described individually. Their **amino ester hydrochlorides** were prepared by one of the following two methods.

Procedure A.—A solution or suspension of 1.00 equivalents of the acid in hot isopropyl alcohol (5 to 10 ml. of alcohol for each gram of acid) was treated by the addition of 1.05 equivalents of dialkylaminoethyl chloride (or piperidinoethyl chloride or morpholinoethyl chloride), and the reaction mixture was heated under reflux for a period of from five to eight hours. Best results were obtained by using an amine which was freshly released from the hydrochloride and redistilled; even under these circumstances the insoluble product presumably formed by bimolecular quaternization precipitated from the solution in variable amounts and caused trouble with bumping. The hot reaction mixture was filtered, and when the filtrate was cooled and allowed to stand it deposited the crystalline hydrochloride. In order to get a satisfactory yield of the more alcohol-soluble derivatives it was occasionally necessary to isolate additional product by concentrating the filtrate or by diluting it with ether. The hydrochlorides were purified directly by recrystallization from isopropyl alcohol or from mixtures of this solvent with methanol. The average yield of good quality product was 60–65%, of almost constant melting material, 50–60%. While this method is quick and produces a relatively high yield, it is not well-adapted to removing traces of the by-product resulting from dimerization of the chloro amine.

Procedure B.—The reaction was carried out in the same manner. After the period of reflux the mixture was evaporated to dryness, extracted with water, and filtered from an insoluble residue. The filtrate (usually still cloudy) was made basic with 5% potassium bicarbonate solution, chilled, and extracted with ether. The aqueous layer and any material which failed to dissolve in ether were discarded, but occasionally the free base crystallized from the ether, necessitating the use of additional solvent. The organic layer was washed with a few portions of water, dried over anhydrous calcium sulfate, and filtered. (In most cases the free base could be obtained crystalline at this point by evaporation of the ether solution, but none of the free bases was purified or characterized.) When the ether solution was treated with only a very slight excess of dry hydrogen chloride, the white, almost pure hydrochloride precipitated and was collected on a filter (average yield 40–45%). One or two recrystallizations from methanol or methanol–isopropyl alcohol invariably gave a pure product (average yield 30–40%). This method gives a lower yield, obviously reflecting loss of material to the aqueous liquors, and is much more time-consuming, but gives a demonstrably purer product.

6-(*p*-Hydroxyphenyl)-4-keto-5-hexenoic Acid (VII).—A solution of 70 g. of levulinic acid, 60 g. of *p*-hydroxybenzaldehyde, 72 g. of sodium hydroxide and 1200 ml. of water was heated at 85° for 3.5 hours and then allowed to stand for 20 hours at room temperature. The reaction mixture was filtered from a slight residue, and the filtrate was added dropwise or in a very slow stream, with constant stirring, to an excess of dilute hydrochloric acid. A dark-colored, oily product separated; traces of crystallization were apparent after it was refrigerated overnight. The crude product was covered with 40% ethanol, chilled to about −10°, and allowed to stand at this temperature for two hours, during which time complete crystallization occurred. The product, m.p. 138–146°, was collected on a filter and washed rapidly with cold, dilute ethanol. Two recrystallizations from dilute ethanol gave 17 g. (16%, based on aldehyde) of product melting largely at 145–147°. However, close inspection of the melt showed that it was not entirely clear at that temperature or at a point several degrees higher. A carefully-observed third crystallization showed that initially plates, m.p. about 145°, came out of solution, but that after a few hours a second crystallizate, m.p. over 190° (not sharp) began to separate. A fourth crystallization, with the obvious precautions, gave large, thin, almost colorless plates, m.p. 146–147° (clear melt).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49; mol. wt., 220.22. Found: C, 65.51, 65.41; H, 5.35, 5.31; mol. wt., 215.

The higher melting by-product was not investigated.

The **diethylaminoethyl ester hydrochloride (XII)** (procedure A) melted at 142–143°.

Anal. Calcd. for $C_{18}H_{26}O_4NCl$: C, 60.75; H, 7.37; N, 3.94; Cl, 9.96. Found: C, 60.79, 60.44; H, 7.67, 7.57; N, 3.80, 3.65; Cl, 10.07, 10.35.

The **piperidinoethyl ester hydrochloride (XIII)** (procedure B) melted at 170–171°.

Anal. Calcd. for $C_{19}H_{26}O_4NCl$: C, 62.03; H, 7.12; N, 3.81. Found: C, 62.57, 62.44; H, 7.04, 6.99; N, 4.02, 4.04.

7-(*p*-Hydroxyphenyl)-5-keto-6-heptenoic Acid (VIII).—A solution of 39 g. of 5-ketocaproic acid (IV), 33 g. of *p*-hydroxybenzaldehyde, 36 g. of sodium hydroxide and 600 ml. of water was heated on a steam-bath for five hours and allowed to stand overnight at room temperature. When the reaction mixture was acidified exactly in the manner described previously, the crude product (25 g., 40%) was always obtained as a tan, granular product, m.p. about 180°. (Of the four condensed acids this one has the greatest crystallizing tendencies and the highest melting point, as well as unexpectedly low solubility in water and alcohols.) Several crystallizations from 95% ethanol gave yellow crystals, m.p. 193–194.5°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.87, 66.46, 66.69; H, 6.18, 6.07, 5.93.

When the **dimethylaminoethyl ester hydrochloride (XIV)** was prepared by a modification of procedure A, after many crystallizations the product still had an unsatisfactory melting point, and its analysis indicated the presence of over 10% of the dimer of dimethylaminoethyl chloride as an impurity. When a sample was purified through the free base (procedure B) it melted fairly sharply at 166–168°.

Anal. Calcd. for $C_{17}H_{24}O_4NCl$: C, 59.73; H, 7.08; N, 4.10. Found: C, 59.27, 59.54; H, 6.93, 7.10; N, 4.25.

The **diethylaminoethyl ester hydrochloride (XV)** (procedure A) melted at 152–154°.

Anal. Calcd. for $C_{19}H_{28}O_4NCl$: C, 61.69; H, 7.63; N, 3.79; Cl, 9.59. Found: C, 61.60, 61.75; H, 7.86, 7.70; N, 3.86, 3.89; Cl, 10.00.

The **piperidinoethyl ester hydrochloride (XVI)** (procedure B) melted at 169–170.5°, and did not significantly depress the melting point of its homolog XIII. A mixture of the two began to shrink very slightly at 164° and melted at 169–174°; *i.e.*, the principal melting range lay in part above the melting point of either component. This behavior was again observed after solidification and remelting, and was checked by simultaneous determinations. The probable phase relationships of this mixture are equivocal, and the fragmentary data at hand are completely inadequate to predict whether it constitutes one of the rare systems in which the liquidus and solidus curves coincide at a sharp maximum at some point.

Anal. Calcd. for $C_{20}H_{28}O_4NCl$: C, 62.90; H, 7.39; N, 3.67. Found: C, 62.94, 62.71; H, 7.36, 7.25; N, 3.62, 3.69.

The **morpholinoethyl ester hydrochloride (XVII)** (procedure A) melted at 203–205°, and markedly depressed the melting point of morpholinoethyl chloride hydrochloride. Compound XVII was the only amino ester hydrochloride of this series which failed to give a yellow color in tap water.

Anal. Calcd. for $C_{19}H_{26}O_5NCl$: C, 59.45; H, 6.83; N, 3.65. Found: C, 60.12, 60.14; H, 6.88, 6.79; N, 3.61, 3.62.

8-(*p*-Hydroxyphenyl)-6-keto-7-octenoic Acid (IX).—A solution of 27.7 g. of 6-ketoenanthic acid (V), 20.7 g. of *p*-hydroxybenzaldehyde, 23.7 g. of sodium hydroxide and 390 ml. of water was heated at 85–90° for four hours, allowed to

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[12] C. G. Derick and R. W. Hess, THIS JOURNAL, **40**, 548 (1918); reported b.p. 135° (1 mm.), 181–182° (25 mm.), 160° (13 mm.).

[13] J. R. Schaeffer and A. O. Snoddy, *Org. Syntheses*, **31**, 3 (1951), reported b.p. 122–123° (1 mm.).

[14] (a) C. R. Hauser and J. T. Adams, THIS JOURNAL, **66**, 345 (1944); (b) J. T. Adams and C. R. Hauser, *ibid.*, **67**, 284 (1945); (c) C. R. Hauser, F. W. Swamer and B. I. Ringler, *ibid.*, **70**, 4023 (1948); reported b.p. 160–162° (4 mm.).

stand overnight at room temperature, and acidified with hydrochloric acid in the manner previously described. The crude, gummy product was washed by decantation with water, suspended in about 30 ml. of 95% ethanol, and chilled at about −20° for one hour. The resulting 10 g. of solid product (24%, m.p. about 140°) was recrystallized from ethanol. The pure compound formed dense, virtually white crystals, m.p. 151–152°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.80, 67.68; H, 6.37, 6.38.

The **diethylaminoethyl ester hydrochloride** (XVIII) (procedure A) melted at 137–139°.

Anal. Calcd. for $C_{20}H_{30}O_4NCl$: C, 62.57; H, 7.88; N, 3.65. Found: C, 62.51, 62.49; H, 7.75, 7.74; N, 3.91, 3.92.

The **piperidinoethyl ester hydrochloride** (XIX) (procedure B) melted at 187–188°.

Anal. Calcd. for $C_{21}H_{30}O_4NCl$: C, 63.70; H, 7.64; N, 3.54. Found: C, 63.46; H, 7.49; N, 3.51, 3.47.

9-(*p*-Hydroxyphenyl)-7-keto-8-nonenoic Acid (X).—A solution of 51 g. of 7-ketocaprylic acid (VI), 35 g. of *p*-hydroxybenzaldehyde, 40 g. of sodium hydroxide and 650 ml. of water was heated on a steam-bath for four hours, allowed to stand overnight at room temperature, and acidified with hydrochloric acid in the manner previously described. The crude product consisted of 32 g. (42%) of a gummy solid, principal melting range 110–130°, plus a few grams of oil which was discarded. Successive crystallizations from dilute ethanol gave a good recovery of dense, white crystals of the pure compound, m.p. 133–135°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.76, 68.26, 68.50; H, 6.95, 6.67, 6.73.

The **diethylaminoethyl ester hydrochloride** (XX) (procedure B) melted at 124–125° and showed somewhat reduced solubility in water at room temperature.

Anal. Calcd. for $C_{21}H_{32}O_4NCl$: C, 63.38; H, 8.11. Found: C, 63.81, 63.56; H, 8.20, 8.20.

The **piperidinoethyl ester hydrochloride** (XXI) (procedure B) melted at 142–144° and showed somewhat reduced solubility in water at room temperature.

Anal. Calcd. for $C_{22}H_{32}O_4NCl$: C, 64.45; H, 7.87; N, 3.42. Found: C, 64.25, 64.06; H, 7.79, 7.71; N, 3.30, 3.30.

Ozonolysis of 6-(*p*-Hydroxyphenyl)-4-keto-5-hexenoic Acid (VII).—A solution of 110 mg. of VII in 30 ml. of ethyl acetate, maintained at −10 to −15°, was treated with 98% of the calculated amount of ozone. After removal of the solvent, the waxy ozonide was decomposed by heating it with water on the steam-bath for 30 minutes. The resulting solution was cooled, treated with potassium carbonate solution and hydrogen peroxide, allowed to stand at room temperature for 30 minutes, acidified with hydrochloric acid, and evaporated to dryness. The organic portion of the residue was removed by digestion with acetone, and the material thus obtained was subjected to chromatography on a column prepared with five grams of silica. Elution with 10:1 benzene–acetone resulted in the isolation of 21 mg. (38%) of slightly impure hydroquinone, identified by its characteristic conversion to quinhydrone.

Elution with 6:1 benzene–acetone resulted in the isolation of 28 mg. (47%) of almost pure succinic acid. After one recrystallization it melted at 187–188° and did not depress the melting point of an authentic sample. For further confirmation of its identity it was converted to the diphenacyl ester, m.p. 147–149°.

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[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH AND FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

The Dienone–Phenol Rearrangement with Mineral Acids[1,2]

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RECEIVED NOVEMBER 7, 1952

The aromatization of 1,4-androstadiene-3,17-dione with aqueous mineral acids yielded mostly 1-methylestrone and also some 1-hydroxy-4-methyl-3-desoxyestrone. Under the same conditions, 10-methyl-2-keto-$\Delta^{1:9,3:4}$-hexahydronaphthalene rearranged to 4-methyl-ar-2-tetralol and a small amount of 4-methyl-ar-1-tetralol. The differences between aqueous acid and anhydrous media for the dienone–phenol rearrangement are discussed.

The media which have been used for the acid-catalyzed aromatization of cyclohexadienones can be divided into two types: (a) aqueous mineral acids, and (b) anhydrous media such as acetic anhydride with an acid catalyst. In the one case where both media were applied to the same compound, santonin,[3,4] the result was the same and the dienone–phenol rearrangement was formulated as a general acid-catalyzed reaction.[5,6] The present experiments show that the course of this reaction may depend on the nature of the medium.

Only anhydrous acid conditions have been extensively applied to steroids. While it was originally thought that this method transformed steroidal 1,4-diene-3-ones (such as I) into 1-methyl-3-hydroxysteroids (such as III),[7,8] it is now known that the products actually are 1-hydroxy-4-methylsteroids (such as II).[6,9] The 1-methyl-3-hydroxysteroids could be prepared by this method only when an additional double bond was present at the 6,7-position.[10]

The direct conversion of I into III can be accomplished in 55% yield by the use of concentrated aqueous hydrochloric or hydrobromic acid, in which I is readily soluble. A small amount (10%) of II is also formed. The two phenolic steroids were separated by taking advantage of the greater alkali solubility of III or by chromatographic ad-

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[1] Taken in part from a thesis submitted by Walter J. Pummer to the Graduate School of Wayne University in partial fulfillment of the requirements for the Master of Science degree.

[2] This work was supported in part by a Research and Development Contract between the Detroit Institute of Cancer Research and the United States Atomic Energy Commission. Support was also provided by institutional grants from the Michigan Cancer Foundation, The American Cancer Society, Inc., and the S. S. Kresge Foundation.

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