

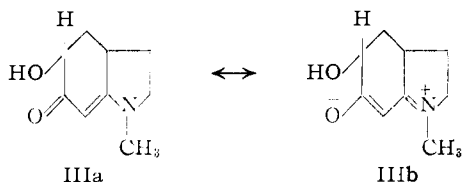
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE MOUNT SINAI HOSPITAL]

Hydrogenation of Epinochrome<sup>1</sup>

BY JOHN AUSTIN, J. D. CHANLEY AND HARRY SOBOTKA

The catalytic hydrogenation of epinochrome was investigated. Following a rearrangement to 5,6-dihydroxy-N-methylindole, two moles of hydrogen was absorbed. The hydrogenation product, on the basis of its absorption spectrum and chemical reactions, is formulated as 5-hydroxy-6-keto-1-methyl-2,3,4,5,6,9-hexahydroindole. Its analogy to the aminochromes is pointed out.

Because of the role ascribed to adrenochrome in certain enzymatic oxidation-reduction systems, we have studied the catalytic hydrogenation products of its desoxy-derivative epinochrome (I). We have recently reported<sup>2</sup> on the spontaneous rearrangement of solid crystalline epinochrome and on the catalysis of the same rearrangement by palladium-on-charcoal, leading in either case to 5,6-dihydroxy-N-methylindole (II). Whether one starts with epinochrome or with the isolated rearrangement product, shaking with palladium-charcoal in aqueous solution under hydrogen leads to the uptake of exactly two moles of hydrogen within one or two days. Since neither N-methylindole nor catechol may be hydrogenated under these conditions, the polyfunctional character of the starting material must account for the relative ease of this partial hydrogenation which leads in excellent yield to a white crystalline product  $C_9H_{13}O_2N$  (III). The properties of this compound may best be interpreted by its formulation as 5-hydroxy-6-keto-1-methyl-2,3,4,5,6,9-hexahydroindole IIIa  $\leftrightarrow$  b. Its ultraviolet absorption



spectrum shows a maximum at  $\lambda$  292  $m\mu$ . This value is consistent with a system of two conjugated double bonds with an adjacent N-atom carrying unshared electrons. Similar systems have been described by Bowden, *et al.*,<sup>3</sup> who point out that the nitrogen "in aliphatic systems possesses conjugating power similar to that of an ethylenic bond in many respects. This property is clearly to be ascribed to the presence of the unshared electron pair on the nitrogen atom and its capacity to provide a seat for a positive charge." The resonance system IIIa $\leftrightarrow$ b is not affected by alkali (see Table I); but acid, as is to be expected, changes it to the cationic form IIIc $\leftrightarrow$ d<sup>4,5</sup> with an absorption maximum which is lower by 15-17  $m\mu$ . The structure IIIa $\leftrightarrow$ b may be interpreted as the vinyllog of an amide, whereas most features expected of an  $\alpha$ -hydroxyketone remain masked.

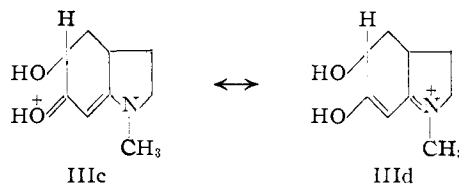
(1) This research was supported by a grant from the Life Insurance Medical Research Fund.

(2) J. Austin, J. D. Chanley and H. Sobotka, *THIS JOURNAL*, **73**, 2395 (1951).

(3) K. Bowden, E. A. Braude, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).

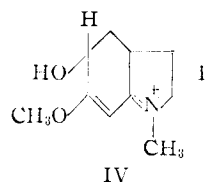
(4) N. V. Sedgwick, "Org. Chem. of Nitrogen," new edition by T. W. J. Taylor and W. Baker, Clarendon Press, Oxford, 1937, p. 144.

(5) M. J. S. Dewar, "Electronic Theory of Org. Chemistry," Clarendon Press, Oxford, 1949, p. 96.

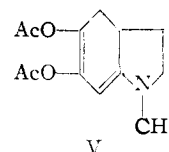


This interpretation of the compound under discussion is supported by numerous observations: (A) The substance may be extracted in unchanged form from aqueous alkaline solution with benzene. (B) Its ultraviolet absorption spectrum in aqueous alkali is the same as in water. (C) It does not react with reagents for the carbonyl group. (D) Having no acidic hydrogen, it is not methylated with diazomethane nor with dimethyl sulfate in alkaline solution. (E) It displays a stable red coloration with ferric chloride.

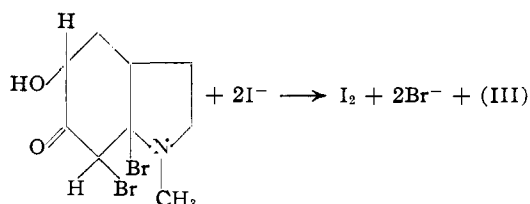
The compound adds methyl iodide and the resulting product shows the same absorption maximum as the parent compound exhibits in strongly acid solution; in addition a secondary maximum is seen at 226  $m\mu$ . It gives no coloration with ferric chloride and may on the basis of these observations be formulated as IV.



The  $\alpha$ -hydroxyketone character of III, although masked in most respects, is manifested by the formation of a diacetate of the presumable structure V.



Furthermore, compound III absorbs one mole of bromine; the solution of the resulting dibromide liberates one mole of iodine from potassium iodide.<sup>6</sup> These transformations are consistent with the structure



(6) E. Billman, *Rec. trav. chim.*, **36**, 313 (1917); **37**, 245 (1917).

The above formulation of the tetrahydro-derivative of epinochrome parallels the interpretation of adrenochrome (and epinochrome) as paraquinoid zwitterions,<sup>7</sup> which is based on the absorption spectra and the inability to form dicarbonyl derivatives.<sup>8</sup>

The structural formula III contains two centers of asymmetry, carbon atoms 5 and 9. Thus, the compound may exist in two diastereomeric racemates which might account for fluctuations of the melting point (see Experimental part). However, their steric relations in no way affect the preceding considerations.

In the Experimental part we also describe a dihydro derivative (VI) and a saturated compound (VII) which forms the end-product of vigorous catalytic hydrogenation.

### Experimental

**Absorption spectra** were measured in a Beckman spectrophotometer model DU. Unless otherwise indicated, the determinations were carried out in 95% ethanol.

**Epinochrome (I)** was prepared according to Sobotka and Austin.<sup>9</sup>

**Rearrangement<sup>2</sup> of Epinochrome to 5,6-Dihydroxy-N-methylindole (II) (a).**—A 100-mg. sample of epinochrome, upon standing in a sealed vial *in vacuo* for more than six months, had turned from red crystals to a grayish white powder. Recrystallization from petroleum ether (b.p. 85–100°) gave white needles (II) of m.p. 134°; reported 136°.<sup>9</sup>

**(b).**—One-hundred mg. of epinochrome dissolved in 50 ml. of water was shaken with 200 mg. of 5% palladium-on-charcoal in an atmosphere of nitrogen. After five minutes the solution turned colorless. After filtration of the catalyst and removal of the water *in vacuo*, the residue was recrystallized from petroleum ether yielding 5,6-dihydroxy-N-methylindole of m.p. 133°.

**(c).**—A solution of 330 mg. of epinochrome in 25 ml. of water was shaken with 100 mg. palladium-charcoal catalyst in the presence of hydrogen. The solution turned colorless at the end of 20 minutes, during which time the absorption of hydrogen was negligible. At this point the reaction was interrupted and the mixture was worked up as above. The yield of compound II, m.p. 133°, was almost quantitative. This rearrangement (method c) may also be carried out in methanol. Mixed melting points of all the above products with authentic 5,6-dihydroxy-N-methylindole prepared from adrenochrome<sup>9</sup> showed no depression. The substance gives a green coloration with alcoholic ferric chloride solution.

**5,6-Diacetoxy-N-methylindole.**—Acetylation of 100 mg. of 5,6-dihydroxy-N-methylindole was carried out by refluxing with 2 g. of sodium acetate in 10 ml. of acetic anhydride for one hour. After evaporation *in vacuo* under nitrogen to dryness, the residue was extracted with benzene; evaporation of the latter and trituration with petroleum ether (b.p. 40–60°) yielded the diacetate of m.p. 101°.

The same product was obtained from 500 mg. of epinochrome by shaking overnight with 40 ml. of acetic anhydride and 40 ml. of pyridine. The color changed from red to reddish-brown and the clear solution was poured on 200 g. of ice. The residue of the ether extract was extracted, in turn, with hot petroleum ether (b.p. 85–100°). On cooling there was obtained a small yield of white needles, m.p. 101–102°; no m.p. depression with the preceding preparation. The m.p. of 5,6-diacetoxy-N-methylindole prepared by reductive acetylation of iodoadrenochrome is 101°.<sup>10</sup>

**C<sub>9</sub>H<sub>13</sub>O<sub>2</sub>N (III) from Epinochrome.**—A freshly prepared solution of 1.02 g. of epinochrome in 50 ml. of water was hydrogenated at 25° and 778 mm. pressure in the presence of 200 mg. of 5% palladium-on-charcoal. After 20 minutes (hydrogen absorption, 6 ml.) the solution turned colorless and after two days the absorption of hydrogen ceased (total,

312 ml.); calcd. for two moles hydrogen, 303 ml. The rate of hydrogenation in a series of runs depends on the amount of catalyst. The mixture was filtered with the aid of Hy-Flo and evaporated to dryness *in vacuo* under nitrogen. The residue was extracted with several small portions of boiling benzene. The combined extracts, after treatment with Norite, were evaporated to 15 ml. and petroleum ether was added to turbidity. On standing 0.83 g. (80% yield) of compound III was obtained; recrystallization from benzene-petroleum ether afforded pure material of m.p. 101–102°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>O<sub>2</sub>N: C, 64.55; H, 7.84; N, 8.38; mol. wt., 167.20. Found: C, 64.10; H, 7.64; N, 8.50; mol. wt. (Rast in camphor), 179.

It was observed that the substance, originally transparent crystals, turned opaque on drying. Furthermore, the compound after melting or sometimes after repeated recrystallizations, showed m.p. ranges from 101–111°. However, the spectral data, the diacetyl derivative and the analytical values were always identical with those obtained from the sharp melting original product. This behavior is ascribed to variations in the ratio of the two diastereomeric racemates.

Compound III may also be obtained in small yield by prolonged hydrogenation of adrenochrome in methanol over palladium-charcoal. This is plausible in view of Harley-Mason's observation<sup>9</sup> that adrenochrome on partial hydrogenation yields 5,6-dihydroxy-N-methylindole.

**C<sub>9</sub>H<sub>13</sub>O<sub>2</sub>N (III) from 5,6-Dihydroxy-N-methylindole.**—A solution of 200 mg. of compound II in 50 ml. of water was hydrogenated at 22° and 757 mm. over 100 mg. of palladium-charcoal. The hydrogen absorption terminated after 28 hr. and totalled 55 ml. (calcd. for two moles hydrogen, 58 ml.). The solution was worked up as above yielding 170 mg. of compound III, m.p. 103–105° (no melting point depression with the previous preparation).

Compound III shows a stable red coloration with ferric chloride. The substance was recovered unchanged after treatment with diazomethane in ether. It cannot be methylated in dimethyl sulfate in alkaline solution. It is extracted unchanged by benzene from 10% aqueous sodium hydroxide. No derivatives were obtained with semicarbazide, hydroxylamine, 2,4-dinitrophenylhydrazine or *o*-phenylenediamine. It fails to give a color reaction with vanillin in methanolic hydrochloric acid in contrast to N-methylindole, 5,6-dihydroxy-N-methylindole (II), the diacetate of the latter and its dihydro compound (VI) (see below).

The hydrochloride of III was obtained by passing dry hydrogen chloride through the solution of the base in benzene. It was recrystallized from ethanol-ether under nitrogen and gives the same red color test with ferric chloride as the base; m.p. 160–161°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>O<sub>2</sub>NCl: N, 7.23. Found: N, 7.19.

The picrate of III was prepared according to Shriner and Fuson<sup>11</sup>; yellow rods, m.p. 168° (dec.).

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>O<sub>9</sub>N<sub>4</sub>: C, 45.46; H, 4.07. Found: C, 45.92; H, 4.14.

**Methyl Iodide Addition Compound of III (IV).**—A solution of 0.63 g. of III in 10 ml. of freshly distilled methyl iodide was kept overnight in the dark. A first crop of 0.15 g. of crystalline material separated and, on addition of ether, the bulk of the material is precipitated; combined yield 90%. Recrystallized from ethanol-ether, the product melted at 162° (dec.).

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>NI: N, 4.53; I, 41.05. Found: N, 4.57; I, 43.06.

On addition of one drop of aqueous ferric chloride solution to a few mg. of this product in ethanol a yellow coloration extractable with carbon tetrachloride was observed, due to liberation of iodine. This color did not mask the deep red ferric chloride test, observed upon addition of a trace of the original compound III to the yellow solution. This experiment demonstrated that the methyl iodide addition compound itself does not give the typical red reaction with ferric chloride.

**Diacetyl Derivative of III (V).**—One-half gram of III was refluxed with 20 ml. of acetic anhydride and 2 g. of sodium

(7) J. Harley-Mason, *Experientia*, **4**, 307 (1948).

(8) H. Sobotka and J. Austin, *This Journal*, **73**, 3077 (1951); the title of this paper should read "Betaine Hydrazones of Aminochromes."

(9) J. Harley-Mason, *J. Chem. Soc.*, 1276 (1950).

(10) F. Bergel and A. L. Morrison, *ibid.*, 48 (1943).

(11) R. L. Shriner and R. C. Fuson, "Identification of Org. Cpds.," Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

acetate for three hours. After evaporation *in vacuo* under nitrogen to dryness, the residue was extracted with hot benzene from which the diacetate was obtained as colorless short needles; m.p. 174° (recrystallized from benzene), absorption spectrum see Table I; no coloration with ferric chloride. Upon hydrolysis with 0.5 *N* aqueous hydrochloric acid, compound III was recovered in small yield.

*Anal.* Calcd. for C<sub>15</sub>H<sub>17</sub>O<sub>4</sub>N: C, 62.13; H, 6.82; N, 5.57. Found: C, 62.17; H, 6.78; N, 5.79.

TABLE I

Compound	Solvent and pH	ABSORPTION SPECTRA	
		$\lambda_{\max}$ , m $\mu$	$\epsilon_{\max}$
III	aq. 6.8	293	35,000
III	aq. 12.3	293	35,000
III	aq. 1.2	278	24,000
III	0.2 <i>N</i> HCl	276	25,500
III	95% EtOH	290	33,000
III	Ether	282	6,000
IV	aq. neutral	226	15,500
		276	24,200
		221	10,100
IV	MeOH	277	24,800
		290	24,500
V	aq. neutral	290	24,000
V	0.1 <i>N</i> HCl	290	24,000
V	95% EtOH	290	22,000
V	Ether	289	20,900

**Titration of III with Bromine.**—A solution of 200 mg. of III in 40 ml. of abs. ethanol was carefully titrated with 0.34 *N* solution of bromine in ethanol until the yellow color persisted. Calcd.: 8.2 ml. for 2 atoms of bromine. Found: 7.6 ml. After acidification with hydrochloric acid and addition of 2 g. of potassium iodide, the solution was warmed. The released iodine was titrated with sodium thiosulfate; since the release of iodine was slow, the solution had to be kept warm during the titration. Calcd.: 25.8 ml. 0.1 *N* Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> for 7.6 ml. solution. Found: 24.0 ml.

**Aromatization of III.**—One-half gram of III was intimately mixed with 250 mg. of 5% palladium-on-charcoal and subjected to dry distillation. The temperature of the air-bath was raised during one hour to 250°. The presence of methylamine or ethylamine was indicated in the first fraction by smell. Later on, indole (or *N*-methylindole) was identified by its smell as well as by a positive indole test with vanillin, while ferric chloride gave no coloration. At about 200–250° a small quantity of an oil was collected which on repeated crystallization from petroleum ether (b.p. 85–100°) gave colorless needles of m.p. 135–136°. This compound gave both a green reaction with ferric chloride and a positive indole test. A mixture of this product with 5,6-dihydroxy-*N*-methylindole (II) showed a melting point depression; however, a mixture of this distillation product with an authentic sample of 5,6-dihydroxyindole<sup>12</sup> (m.p. 140°) melted at 135–136°. Because of lack of material no more definite identification was attempted.

**Leuco-epinochrome (VI).**—In some of the hydrogenation experiments with epinochrome ether extraction of the aqueous filtrate from the catalyst yielded small amounts of a compound which formed, on recrystallization from petroleum ether (b.p. 85–100°), colorless needles melting at 140–141°. It gave a green ferric chloride test and a positive indole reaction with vanillin (see above); ultraviolet absorption:  $\lambda_{\max}$  290 m $\mu$ ;  $\epsilon_{\max}$  25,000. This compound is believed to be 5,6-dihydroxy-*N*-methyl-2,3-dihydroindole, the true leuco form of epinochrome.

*Anal.* Calcd. for C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>N: C, 65.43; H, 6.71. Found: C, 65.79; H, 6.87.

**Perhydrogenation Product (VII).**—A solution of III in glacial acetic acid over platinum oxide absorbs two to three moles of hydrogen. The hydrochloride of the resulting perhydrogenated product melts at 231–233° (recrystallized from ethanol).

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>O<sub>2</sub>NCl: C, 52.04; H, 8.73; N, 6.74; Cl, 17.07. Found: C, 52.29; H, 8.43; N, 6.59; Cl, 17.19.

(12) R. J. S. Beer, K. Clarke, H. G. Khorana and A. Robertson, *J. Chem. Soc.*, 2223 (1948). We are indebted to Prof. Robertson for a sample of this compound.

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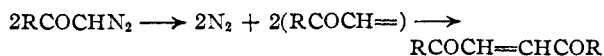
[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY OF LOUISIANA STATE UNIVERSITY]

## Diazoketones as Reagents for the Identification of Organic Acids

By J. L. E. ERICKSON, J. M. DECHARY AND M. R. KESLING

The cupric chloride-catalyzed decomposition of several  $\alpha$ -diazacetophenones in dioxane solution in the presence of an organic acid yielded phenacyl esters. The *p*-bromo- and *p*-phenylphenacyl esters of eleven representative organic acids have been prepared by the use of two new reagents, *p*-bromo- and *p*-phenyl- $\alpha$ -diazacetophenone, and their melting points have been compared with values obtained from the literature. In the absence of protonic reagents the cupric chloride-catalyzed decomposition of diazoacetophenone yielded dibenzoyl ethylene.

Diazoketones lose nitrogen when catalytically decomposed, and if no opportunities are present for reaction with protonic reagents, the unstable radical which is formed may couple with itself to form ethylenic compounds.<sup>1</sup> If an inorganic acid such as hydrochloric acid is present during the



decomposition of diazoketones,  $\alpha$ -chloroketones<sup>2</sup> are formed, and recently Newman and Beale<sup>3</sup> have shown that  $\beta$ -phenethyl diazomethyl ketone yields di-(4-phenyl-2-ketobutyl) sulfate when treated with concentrated sulfuric acid. With the

aid of boron trifluoride as a catalyst they were able to obtain  $\alpha$ -alkoxyacetophenones<sup>3</sup> when diazoacetophenones were decomposed in the presence of alcohols. Bradley, *et al.*,<sup>4</sup> observed the formation of phenacyl acetate when diazoacetophenone was warmed in glacial acetic acid.

These results suggested that the decomposition of *p*-bromo- and *p*-phenyl- $\alpha$ -diazacetophenones in the presence of an aliphatic or an aromatic acid might afford a convenient method for the preparation of *p*-bromo- and *p*-phenylphenacyl esters. These esters are ordinarily prepared from the corresponding *p*-bromo- and *p*-phenylphenacyl bromides, compounds which are disagreeable to use because of their lachrymatory properties. Even

(1) C. Grundmann, *Ann.*, **536**, 29 (1938).

(2) D. A. Clibbens and M. Nierenstein, *J. Chem. Soc.*, **107**, 1491 (1915); F. Arndt, B. Elstert and W. Partale, *Ber.*, **60B**, 1364 (1927).

(3) M. S. Newman and P. F. Beale, *THIS JOURNAL*, **72**, 5161 (1950).

(4) W. Bradley and R. Robinson, *J. Chem. Soc.*, 1310 (1928); W. Bradley and G. Schwartzbach, *ibid.*, 2904 (1928).