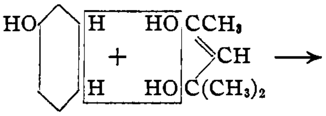
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Alkylated Phenolic Hydroxy Indenes and Indanes.[1] Their Synthesis Involving the Condensation of Diacetone Alcohol or of Pinacol with Phenols

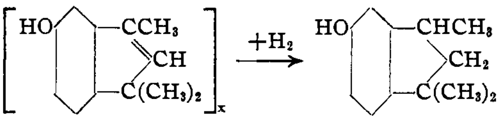
BY JOSEPH B. NIEDERL, VICTOR NIEDERL AND S. REZNEK[2]

With the elucidation of the structural formulas of physiologically active compounds related to the sterols and containing a cyclopentene or pentane ring, several syntheses of non-phenolic compounds containing the indene or hydrindene (indane) ring were recently reported.[3] The method of preparation of alkylated phenolic indenes and hydrindenes (indanes), set forth in this communication and appearing to be within the above-mentioned scope of interest, involves the condensation of diacetone alcohol with phenols, by refluxing molar mixtures of these compounds in presence of zinc chloride, following essentially the method of Liebmann, Fischer and Gruetzner.[4] The polymeric 1,3,3-trimethyl-6-hydroxyindene (II) appears to be the main initial reaction product. Pyrolysis of this polymer then yielded the 1,3,3-trimethyl-6-hydroxyindane (I) in small quantities (10–15%) in a manner similar to the formation of indane from indene.[5]

Schematically the course of this reaction may be presented as follows



Diacetone alcohol (enol)



1,3,3-Trimethyl-6-hydroxyindene polymer (b. p. 250–255° (3 mm.))

1,3,3-Trimethyl-6-hydroxyindane (m. p. 119°)

Of the above 1,3,3-trimethyl-6-hydroxyindane (I) the dinitro (Ia), the dibromo (Ib) derivative and the monobromo derivative of its methyl ether (Ic) were prepared. Oxidation of this compound with concd. nitric acid yielded a mixture of oxidation products out of which: 4-hydroxyphthalic acid (m. p. 190–192°), its anhydride (m. p. 150–155°) and *m*-hydroxyacetophenone (m p. 90°) could be isolated, thus substantiating the above given structural formula.

Extension of these condensations to the three cresols yielded non-crystalline tetramethyl-6-hydroxyindanes (b. p. 250–270°) which were not further investigated. Oxidation of these products with concd. nitric acid yielded in the case of the *o*-cresol condensation product, oxalic acid, while in the other two cases, acids, which gave a positive fluorescein reaction, were obtained. Guaiacol formed the 1,3,3-trimethyl-6-hydroxy-x-methoxyindane (III).

Attempted resynthesis of the 1,3,3-trimethyl-6-hydroxyindane from mesityl oxide hydrohalides (chloride, bromide and iodide) and sodium phenolate followed by rearrangement and ring closure, failed, as the necessary tertiary alkyl phenyl ether, the 2-methyl-2-phenoxypentanone-4, could not be obtained, an observation which is in harmony with the findings of Lewis, Spiegel and Sabbath[6] who also found it impossible to prepare the *t*-butyl and *t*-amyl phenyl ethers.

In these condensations the following by-products were found: (1) acetone, (2) mesityl oxide, (3) condensation products of mesityl oxide with phenols, such as: (a) alkali insoluble (non-phenolic) condensation products: chromanols and polymeric chromenes (from molar mixtures of mesityl oxide and phenol or a phenol with both ortho positions free (*m*- and *p*-cresol)[7]) (b) alkali soluble (phenolic condensation products: 2,4,4-trimethyl-2-(*p*-hydroxy)phenyl chromane (m. p. 165°) (from 1 mole of mesityl oxide and two moles of phenol) and phenolic polymers (from molar mixtures[8] of mesityl oxide and an ortho substituted phenol (*o*-cresol, guaiacol)[9]) (4) *p*-*t*-butyl-

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(1) Presented before the Division of Organic Chemistry at the New York meeting of the American Chemical Society, April 23, 1935.

(2) Several parts were taken from the thesis of S. Reznek presented to the Graduate School of New York University, in partial fulfilment of the requirements for the degree of Master of Science, 1936.

(3) O. Blum-Bergmann, *J. Chem. Soc.*, 1020 (1935); *Ber.*, **65**, 109 (1932); Cook and Hewett, *Chem. and Ind.*, **52**, 451 (1933); *J. Chem. Soc.*, 1098 (1933); 365, 653 (1934); Kon and co-workers, *ibid.*, 1081 (1933); 124 (1934); M. T. Bogert, *Science*, **77**, 289 (1933); Bogert and Davidson, THIS JOURNAL, **58**, 185 (1934).

(4) A. Liebmann, *Ber.*, **14**, 1842 (1881); **15**, 150 (1882); Fischer and Gruetzner, *ibid.*, **26**, 1646 (1893).

(5) Weissgerber, *ibid.*, **44**, 1438 (1911); Weger and Billmann, *ibid.*, **36**, 644 (1903); Kramer and Spilker, *ibid.*, **29**, 561 (1896); **33**, 2260 (1900); **23**, 3278 (1890); Moschner, *ibid.*, **33**, 737 (1900); Stoermer and Boes, *ibid.*, **33**, 3016 (1900).

(6) Lewis, *J. Chem. Soc.*, **83**, 329 (1903); Spiegel and Sabbath, *Ber.*, **34**, 1946 (1901).

(7) J. B. Niederl, THIS JOURNAL, **51**, 2426 (1929); McIntosh, U. S. Patent 1,448,556 (1923).

(8) Dianin, *J. Russ. Phys. Chem. Soc.*, **46**, 1313 (1914).

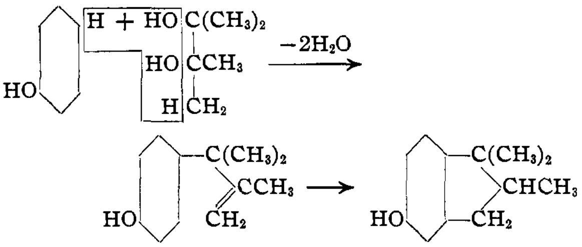
(9) B. Greenblat, B.Sc., Thesis, New York University, 1935.

TABLE I

	Condensation products from diacetone alcohol	Formula	M. p., °C.	B. p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	1,3,3-Trimethyl-6-hydroxyindane	$C_{12}H_{16}O$	119	263–267	81.81	9.10		81.83	9.38	
	(a) Dinitro derivative	$C_{12}H_{14}N_2O_5$	112		54.14	5.26	10.52	54.54	5.58	10.14
	(b) Dibromo derivative	$C_{12}H_{14}Br_2O$	190		43.11	4.19		43.08	4.39	
	(c) Monobromo deriv. methyl ether	$C_{13}H_{17}BrO$	69		58.20	6.30		58.54	6.45	
II	1,3,3-Trimethyl-6-hydroxyindene polymer	$(C_{12}H_{14}O)x$	80–90	250–255 (3 mm.)	82.75	8.00		82.15	7.96	
III	1,3,3-Trimethyl-x-methoxy-6-hydroxyindane	$C_{13}H_{18}O_2$		258–265	75.72	8.73		75.95	9.00	
IV	From pinacol: 1,1,2-trimethyl-5-hydroxyindane	$C_{12}H_{16}O$	121	240–250	81.81	9.10		81.41	9.25	

phenol, *p-t*-butylcresols [the 2-methyl-4-*t*-butylphenol was identified through its trinitro derivative (m. p. 85°) and the 2-methyl-4-*t*-butylphenoxyacetic acid; (m. p. 117°); the 4-methyl-2-*t*-butylphenol as the 4-methyl-2-*t*-butylphenoxy acetic acid (m. p. 121°)] and *p-t*-butylguaiacol; all of which were evidently formed by pyrolytic cleavage ("cracking") of the six-carbon-atom side chain, as already observed in related reaction systems;[10] (5) amorphous resins (m. p. 80–90°, b. p. 200–210° at 3 mm.) which were not further identified.

Substituting diacetone glycol (2-methylpentadiol-2,4, b. p. 190–194°) for diacetone alcohol in these condensations did not lead to crystalline condensation products, whereas the condensation of pinacol yielded the crystalline 1,1,2-trimethyl-5-hydroxyindane (IV) involving a reaction mechanism similar to the formation of 2-phenyl-3-methylindene from acetophenone pinacol.[11]



1,1,2-Trimethyl-5-hydroxyindane (m. p. 121°)

Treatment of the above 1,1,2-trimethyl-5-hydroxyindane with concd. nitric acid resulted in the formation of picric acid.

Experimental Part

Condensation Method.—One mole (94 g.) of phenol and one mole (116 g.) of diacetone alcohol (b. p. 63–66° at 22 mm.) were placed in a 1-liter Erlenmeyer flask and heated to about 150°. Two moles (272 g.) of fused zinc chloride, crushed to small pieces, was added quickly and the whole boiled rapidly for several minutes with vigorous stirring or repeated shaking. The flask was then attached to a reflux condenser and placed in an oil-bath, which previously had been heated to 180°, and the reaction mixture refluxed for thirty minutes; after that it was removed from the oil-bath and shaken well for a minute or two. The refluxing was then continued for ninety minutes, but the oil-bath gradually heated to 210°, at which temperature the reaction mixture slowly refluxed. The hot condensation product was then poured into about 1 liter of warm, acidified water, stirred well and as soon as cool transferred to a separatory funnel, the water drawn off and the remaining oil taken up in about 400 cc. of toluene. The toluene solution was washed repeatedly with warm, weakly acidified water and finally filtered to remove the last traces of the tarry mass which remained undissolved. The toluene was shaken out well with 250 cc. of Claisen solution (50% potassium hydroxide and an equal volume of methyl alcohol).[12]

The Claisen solution extract separated after several hours, and was then washed with benzene and finally acidified with dilute hydrochloric acid. A dark brown oil separated out (about 140 g.) which was again washed with water, then taken up in ether (or ethyl acetate), dried over calcium chloride and the ether evaporated off. The residue was distilled at atmospheric pressure and the following fractions collected: (1) 225–255°, 14.5 g.; (2) 255–285°, 12 g.; (3) 285–300°, 10 g. Fraction 1 was a light colored oil with no definite boiling point. Fraction 2 crystallized upon cooling and scratching the side wall of the receiver, but remained saturated with an oil. It was centrifuged, the oil decanted and added to fraction 3; upon redistillation more of the crystalline material was obtained. Further, very slow distillation of the polymerized residue in the distilling flask yielded an oil up to 350°, but above 300° formation of water was observed. The main portion of this oil, when dried and redistilled, again boiled between 260–285° and also crystallized. The crystalline material was dried completely on porous tile and recrystallized from diisobutylene. In the condensations of the cresols and of guaiacol with diacetone alcohol a similar procedure was followed. When diacetone glycol or pinacol was used in these condensations, the heating of the reaction mixture had to be prolonged considerably (two hours for the diacetone glycol, twenty-four hours for the pinacol).

I. Phenol Coefficient.—23 (30% alcoholic solution, 37°, *Staphylococcus aureus*).—This compound appears to

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[10] McGreal and Niederl, THIS JOURNAL, **57**, 2625 (1935).

[11] Salmon and Legagneur, *Bull. soc. chim.*, [4] **45**, 718 (1929).

[12] Claisen, *Ann.*, **418**, 96 (1919).

show physiological properties resembling slight oestrogenic activity[13] when tested according to the method of Dodds and co-workers.[14] (Ia) Two g. of 1,3,3-trimethyl-6-hydroxyindane was dropped in small portions into 25 cc. of concentrated nitric acid at room temperature. A very vigorous reaction took place. Upon standing overnight yellow needles separated out which were dried on porous tile and recrystallized from 75% alcohol. (Ib) Prepared by the addition of bromine water to an aqueous solution of 1,3,3-trimethyl-6-hydroxyindane. (Ic) The methyl ether was prepared by refluxing 2 g. of the sodium salt of 1,3,3-trimethyl-6-hydroxyindane and the calculated amount of methyl iodide for six hours in absolute ethyl alcohol. The methyl ether was obtained as an oil and treated with bromine in carbon tetrachloride. The crystals obtained were recrystallized from 75% alcohol.

Summary

Recent investigation as to the formation of indene and hydrindene (indane) compounds have been extended to include the formation of such compounds by the condensation of β-hydroxy ketones and α- and β-glycols with phenols.

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[13] Wm. F. Hart, Ph.D. Thesis, New York University, April 1, 1936.

[14] Allan, Dickens and Dodds, *J. Physiol.*, **68**, 348 (1930).

[CONTRIBUTION NO. 579 FROM THE KODAK RESEARCH LABORATORIES]

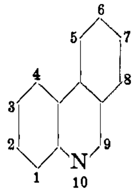
Studies in the Cyanine Dye Series. V. Dyes Derived from 9-Methylphenanthridine

BY L. G. S. BROOKER AND G. H. KEYES

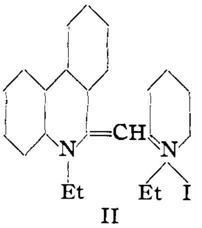
Many cyanines derived from quinoline are good photographic sensitizers, but it was found by one of us that certain cyanine dyes containing the isoquinoline nucleus, such as that obtained by condensing isoquinoline ethiodide with quinaldine ethiodide, were weak in their sensitizing action, and this observation has found confirmation and extension in the independent work of Fisher and Hamer,[1] who have devised a much improved method for the synthesis of isoquinoline dyes of this type.

In view of the fact that phenanthridine (I) may be considered as a derivative of quinoline and also of isoquinoline it seemed of interest to investigate the properties of cyanine dyes derived from this base.

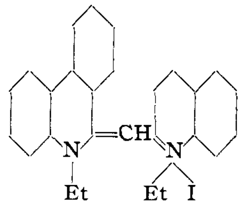
I



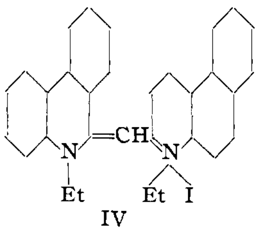
For the synthesis of these dyes 9-methylphenanthridine proved to be a convenient starting point. This base was originally prepared by Pictet and Hubert[2] and their method has been improved by Morgan and Walls.[3] The ethiodide of the base, which has not been described hitherto, was prepared by heating the base with ethyl p-toluenesulfonate, followed by conversion of the quaternary p-toluenesulfonate into the iodide. When treated with 2-iodoquinoline ethiodide in the presence of triethylamine,[4] the ethiodide readily yielded 1,1′-diethyl-3,4-benzo-2,2′-cyanine iodide (III), whilst condensation of the etho-p-toluenesulfonate with 2-iodopyridine ethiodide and with 2-iodo-β-naphthoquinoline ethiodide furnished 1,1′-diethyl-3′,4′-benzo-2-pyrido-2′-cyanine iodide (II) and 1,1′-diethyl-3,4,5′,6′-dibenzo-2,2′-cyanine iodide (IV), respectively. (For the sake of uniformity the phenanthridine nucleus in each formula is shown as containing the ternary nitrogen atom.)



II



III



IV

If the dyes II, III and IV are compared with the simpler dyes 1,1′-diethyl-2-pyrido-2′-cyanine iodide (V),[4,5] 1,1′-diethyl-2,2′-cyanine iodide

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[1] Fisher and Hamer, *J. Chem. Soc.*, 1905 (1934).

[2] Pictet and Hubert, *Ber.*, **29**, 1182 (1896).

[3] Morgan and Walls, *J. Chem. Soc.*, 2447 (1931).

[4] Brooker and Keyes, THIS JOURNAL, **57**, 2488 (1935).

[5] Hamer and Kelly, *J. Chem. Soc.*, 777 (1931).