[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS, AND THE RESEARCH LABORATORIES OF THE "SOCIÉTÉ BELGE DE L'AZOTE" LIÈGE]

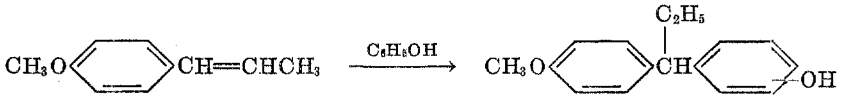
ARYLALKYLATION OF PHENOLS AND NAPHTHOLS WITH DERIVATIVES OF STYRENE

NG. PH. BUU-HOÏ, HENRI LE BIHAN, FERNAND BINON, AND PIERRE MALEYRAN

Received March 5, 1952

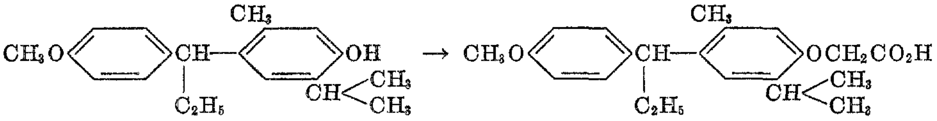
In a previous paper (1), the condensation of styrene with a series of phenols and naphthols was described, and the constitution of the various α-phenylethyl derivatives thus obtained was discussed. It was deemed of interest to investigate the behavior of some substituted derivatives of styrene in similar arylalkylation reactions.

Anethole (I), one of the most readily available derivatives, underwent a sulfuric acid-catalyzed condensation with phenol in an inert solvent such as toluene, to give a liquid (α-anisyl-*n*-propyl)phenol (II), probably a mixture of the



I II

o- and *p*-isomers. The constitution of this reaction product was proved by the chromic acid oxidation of its methyl ether to a mixture of ketones, from which 2,4′- and 4,4′-dimethoxybenzophenone were isolated. Similar condensations with *o*-, *m*-, and *p*-cresol, and with α-naphthol, also yielded liquid (α-anisyl-*n*-propyl)cresols and a liquid (α-anisyl-*n*-propyl)naphthol, but with thymol, a solid substance was obtained, apparently *p*-(α-anisyl-*n*-propyl)thymol (III). These compounds,



III IV

and the viscous liquid diphenols they yielded on demethylation with pyridine hydrochloride, are of interest as intermediates in the preparation of plasticizing agents, halogenated germicides and fungicides, and synthetic resins. The alkali salts of aryloxyacetic acids such as *p*-(α-anisyl-*n*-propyl)thymoxyacetic acid (IV) give tensioactive aqueous solutions which might be useful as wetting agents.

Cinnamic acid, another readily available derivative of styrene, was then investigated. Its condensation with phenol was first described by Liebermann and Hartmann (2), who used sulfuric acid in acetic acid solution as the condensation catalyst, and obtained 3,4-dihydro-4-phenylcoumarin; this reaction was subsequently applied by von Auwers to β-naphthol (3) for the preparation of 3,4-dihydro-4-phenyl-5,6-benzocoumarin. We have extended this condensation to a

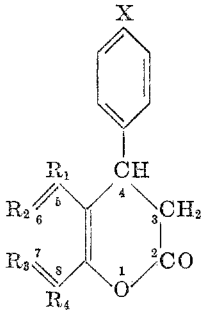
TABLE I

3,4-DIHYDRO-4-ARYLCOUMARINS (V)

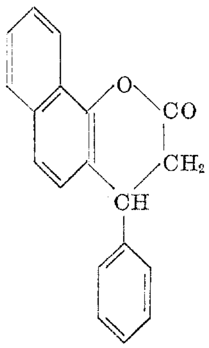
SUBSTITUENT	FORMULA	M.P., °C.	B.P., °C./MM.	ANALYSES Calc'd C	ANALYSES Calc'd H	ANALYSES Found C	ANALYSES Found H
4-Phenyl	$C_{15}H_{12}O_2$	78	217/13				
8-Methyl-4-phenyl[a]	$C_{16}H_{14}O_2$	108	220/12	80.6	5.8	80.5	5.7
7-Methyl-4-phenyl	$C_{16}H_{14}O_2$	124	225–227/12	80.6	5.8	80.9	5.9
6-Methyl-4-phenyl	$C_{16}H_{14}O_2$	83	228–230/16	80.6	5.8	80.5	5.8
6-Chloro-5-methyl-4-phenyl	$C_{16}H_{13}ClO_2$	117	247/15	70.5	4.8	70.8	4.8
6-Methyl-4-phenyl-8-isopropyl	$C_{19}H_{20}O_2$	74	225–228/13	81.4	7.3	81.6	7.2
6,7-Dimethyl-4-phenyl	$C_{17}H_{16}O_2$	111	225–230/13	81.0	6.3	80.9	6.5
5,8-Dimethyl-4-phenyl	$C_{17}H_{16}O_2$	78	225–230/13	81.0	6.3	80.9	6.2
7-Methoxy-4-phenyl	$C_{16}H_{14}O_3$	108	255–260/13	75.6	5.5	75.3	5.4
4-*p*-Anisyl	$C_{16}H_{14}O_3$	138	248–250/15	75.6	5.5	75.4	5.5
4-*p*-Anisyl-7-methyl	$C_{17}H_{16}O_3$	94	263/15	76.1	5.9	76.0	6.0
4-*p*-Anisyl-6-methyl	$C_{17}H_{16}O_3$	120	260–265/15	76.1	5.9	76.5	5.8
4-*p*-Chlorophenyl	$C_{15}H_{11}ClO_2$	116	225–235/15	69.6	4.3	69.4	4.3
6-Chloro-5-methyl-4-*p*-chlorophenyl	$C_{16}H_{12}Cl_2O_2$	140	255–275/15	62.5	3.9	62.2	4.1
6-Chloro-5-methyl-4-(4′-hydroxy-3′-methoxyphenyl)[b]	$C_{17}H_{15}ClO_4$	211		64.0	4.7	63.6	4.4

[a] All these new dihydrocoumarins formed well-crystallized colorless prisms from methanol or ethanol. [b] This compound decomposed on vacuum-distillation, unlike all the others.

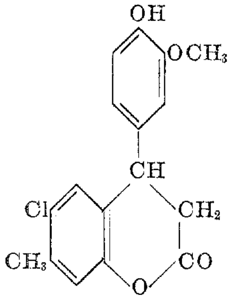
wide series of phenols, and also to substituted cinnamic acids such as 4-chloro- and 4-methoxy-cinnamic acid, and ferulic acid. The reaction was best performed in toluene or tetralin; the new 3,4-dihydro-4-arylcoumarins (V) thus obtained are listed in Table I. Condensation of cinnamic acid with α-naphthol yielded 3,4-dihydro-4-phenyl-7,8-benzocoumarin (VI); ferulic acid (4-hydroxy-3-methoxycinnamic acid) yielded with 4-chloro-*m*-cresol the dihydrocoumarin (VII). In the case of 5-hydroxyhydrindene (VIII), the



V

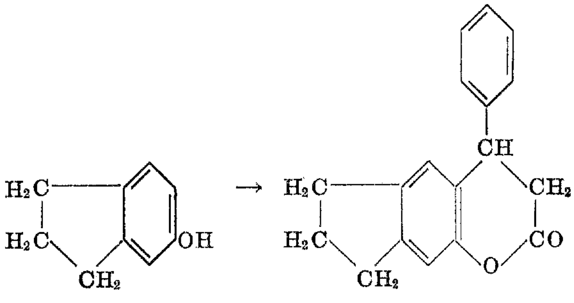


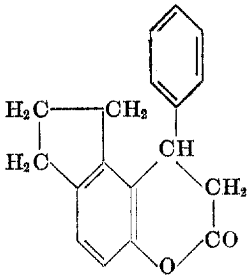
VI



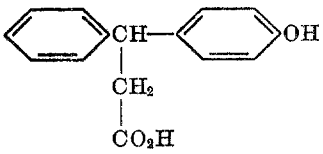
VII

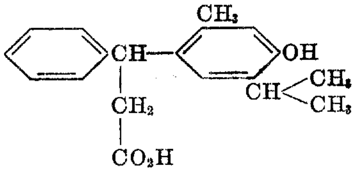
condensation product with cinnamic acid should be represented as 3,4-dihydro-4-phenyl-6,7-trimethylenecoumarin (IX) rather than as 3,4-dihydro-4-phenyl-5,6-trimethylenecoumarin (X), in view of the general tendency of 5-substituted hydrindene derivatives to undergo reactions at the 6- position, according to the Mills-Nixon rule (4). It should be mentioned that no coumarin derivative was obtained from salicylic acid and vanillin with cinnamic acid. All these new substances are under biological investigation for potential germination-inhibitory activity and as potential anticoagulants and insecticides; they might also serve as intermediates for the synthesis of iodinated compounds to be used in x-ray photography.



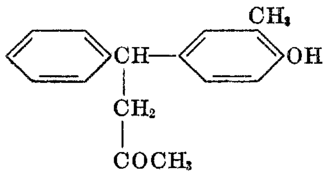

X

In the condensation of cinnamic acid with phenol, Liebermann and Hartmann (2) isolated β-phenyl-β-4-hydroxyphenylpropionic acid (XI) as a by-product; it has now been found that this acid is readily obtained when the reaction is performed in tetralin; with thymol, β-phenyl-β-(2-methyl-5-isopropyl-4-hydroxyphenyl)propionic acid (XII) was prepared in the same way.

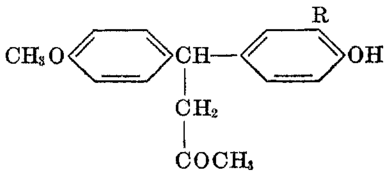

XI


XII

Further derivatives of styrene investigated in the course of this study were the α,β-ethylenic aromatic ketones. Benzalacetone was found to condense readily with o-cresol to give (3-methyl-4-hydroxybenzhydryl)acetone (XIII). Similarly, from 4-anisalacetone, (4-hydroxy-4′-methoxybenzhydryl)acetone (XIV) was prepared with phenol, and (3-methyl-4-hydroxy-4′-methoxybenzhydryl)acetone (XV) with o-cresol. The structure of these substances makes them



XIII



XIV; R = H
XV; R = CH_3

interesting intermediates for the synthesis of amidone-like analgesics; this work will be reported later.

Biological examination showed the condensation product (II) of anethole with phenol to be estrogenic in mice in the Allen-Doisy test, at 20 mg.

EXPERIMENTAL

Condensation of anethole with phenol. To a warm mixture of 94 g. of phenol and 10 g. of sulfuric acid, a solution of 74 g. of redistilled anethole in 100 ml. of toluene was added in small portions. The mixture was refluxed for two hours, washed after cooling with an aqueous solution of sodium carbonate, then with water, and dried over sodium sulfate. After evaporation of the solvent, the residue was vacuum-fractionated, giving 72 g. (60% yield) of crude *(α-anisyl-n-propyl)phenol* (II), boiling at 200–240°/13 mm.; after redistillation, the product formed a pale yellow, viscous oil, b.p. 212–217°/13 mm., n^{17}_{D} 1.58545.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4.
Found: C, 78.9; H, 7.5.

The methyl ether yielded on chromic acid oxidation in acetic acid a ketonic product which, after vacuum-distillation and fractional recrystallization from ethanol, yielded a less soluble fraction [colorless needles, m.p. 145°; no depression in the m.p. was observed on admixture with 4,4′-dimethoxybenzophenone (5)], and a more soluble fraction [colorless needles, m.p. 101°, alone or on admixture with 2,4′-dimethoxybenzophenone (6)].

Demethylation of (α-anisyl-*n*-propyl)phenol by brief heating with pyridine hydrochloride yielded a yellow resin, b.p. 240–242°/13 mm., which did not crystallize.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.0.
Found: C, 78.6; H, 7.0.

Condensation of anethole with the cresols. (*a*). The reaction between 192 g. of *m*-cresol and 133 g. of anethole in toluene with 18 g. of sulfuric acid gave 147 g. of *(α-anisyl-n-propyl)-m-cresol,* a pale yellow viscous oil, boiling at 230–235°/23 mm., n^{18}_{D} 1.57837.

Anal. Calc'd for $C_{17}H_{20}O_2$: C, 79.3; H, 8.1.
Found: C, 79.0; H, 8.0.

Demethylation with pyridine hydrochloride yielded a deep yellow viscous oil, boiling at 248–250°/13 mm.

(*b*). *p*-Cresol gave a 67% yield of *(α-anisyl-n-propyl)-p-cresol* as a pale yellow oil, boiling at 225–228°/13 mm., n^{18}_{D} 1.57340.

Anal. Calc'd for $C_{17}H_{20}O_2$: C, 79.3; H, 8.1.
Found: C, 79.1; H, 8.4.

The demethylation product formed a viscous yellow oil, boiling at 238–240°/13 mm., which could readily be chlorinated by sulfuryl chloride.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.0; H, 7.4.
Found: C, 79.0; H, 7.8.

Similar liquid condensation products were obtained from anethole with *o*-cresol, the xylenols, and 4-chloro-3-methylphenol, but these were not investigated further.

p-(α-Anisyl-n-propyl)thymol (III). Condensation of 160 g. of thymol with 74 g. of anethole, performed in the usual way, yielded 102 g. (66% yield) of a product boiling at 232–233°/12 mm., which crystallized from ligroin as colorless prisms, m.p. 99°.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.7.

Found: C, 80.2; H, 8.6.

The reaction yielded also 26 g. of a higher-boiling portion (265–270°/12 mm.) as a viscous orange oil. The demethylation product of III was a viscous yellow oil, boiling at 245–255°/12 mm.; *p-(α-anisyl-n-propyl)thymoxyacetic acid* (IV), prepared by addition of a solution of 5.2 g. of sodium hydroxide in 20 ml. of water to a molten mixture of 15.4 g. of III and 5 g. of chloroacetic acid, crystallized from ligroin as fine colorless needles, m.p. 106°.

Anal. Calc'd for $C_{22}H_{28}O_4$: C, 74.1; H, 7.5.

Found: C, 74.3; H, 7.8.

Condensation of anethole with the naphthols. (*a*). From 202 g. of α-naphthol and 104 g. of anethole, 153 g. (57% yield) of a viscous liquid *(α-anisyl-n-propyl)-1-naphthol*, boiling at 262–264°/13 mm., $n_D^{17.5}$ 1.63929, was obtained.

Anal. Calc'd for $C_{20}H_{20}O_2$: C, 82.2; H, 6.8.

Found: C, 82.4; H, 6.9.

The *methyl ether* was a pale yellow oil, b.p. 255–256°/13 mm., n_D^{19} 1.62531.

Anal. Calc'd for $C_{21}H_{22}O_2$: C, 82.3; H, 7.1.

Found: C, 82.5; H, 7.0.

There was also obtained in the condensation reaction 24 g. of a portion b.p. >290°/13 mm.

(*b*). From β-naphthol, 125 g. (61% yield) of *(α-anisyl-n-propyl)-2-naphthol* boiling at 275–276°/13 mm. was obtained; its *methyl ether* was a pale yellow viscous oil, b.p. 264–265°/13 mm., n_D^{19} 1.62632.

Anal. Calc'd for $C_{21}H_{22}O_2$: C, 82.3; H, 7.1.

Found: C, 82.3; H, 7.0.

(3-Methyl-4-hydroxybenzhydryl)acetone (XIII). A mixture of 41 g. of redistilled benzalacetone, 43 g. of *o*-cresol, 2 ml. of sulfuric acid, and 20 g. of benzoyl peroxide dissolved in 150 ml. of toluene was refluxed for 12 hours. After cooling, the mixture was washed with an aqueous solution of sodium carbonate, then with dilute hydrochloric acid and with water, and dried over sodium sulfate. After evaporation of the toluene, the residue gave on vacuum-fractionation 25 g. of a thick orange-yellow oil, b.p. 260–290°/16 mm., which solidified. After recrystallization from a mixture of benzene and cyclohexane, colorless needles were obtained, m.p. 133°, giving a yellow coloration with sulfuric acid. The presence of a —CH_2CO— group in this ketone and the two following ones was ascertained by positive Pfitzinger reactions with isatin, and by the formation of amines in the Leuckhardt reaction.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.

Found: C, 79.9; H, 7.1.

(4-Hydroxy-4'-methoxybenzhydryl)acetone (XIV). Condensation of 50 g. of redistilled anisalacetone with 53 g. of phenol, performed as above, yielded 34 g. of a portion boiling at 267–270°/16 mm., which crystallized from a mixture of benzene and cyclohexane to give 20 g. of colorless prisms, m.p. 129°.

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.5; H, 6.6.

Found: C, 75.8; H, 6.5.

(3-Methyl-4-hydroxy-4'-methoxybenzhydryl)acetone (XV). From 50 g. of anisalacetone and 43 g. of *o*-cresol, 44 g. of a fraction boiling at 274–284°/16 mm. was obtained, crystallizing from benzene and cyclohexane as colorless prisms, m.p. 123°.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.0.

Found: C, 76.1; H, 7.1.

Condensation of cinnamic acid with phenol. A mixture of 57 g. (0.38 mole) of cinnamic acid, 71 g. (0.76 mole) of phenol, 15 g. of sulfuric acid, and 100 ml. of tetralin was refluxed for two hours. After cooling, the reaction mixture was extracted several times with a hot aqueous solution of sodium carbonate, then washed with water and dried over sodium sulfate; after removal of tetralin in a vacuum, the residue was fractionated, giving 25 g. of *3,4-dihydro-4-phenylcoumarin*, b.p. 218°/13 mm., m.p. 77°. The sodium carbonate extracts yielded on acidification with dilute hydrochloric acid 26 g. of *β-phenyl-β-(4-hydroxyphenyl)-propionic acid*, melting at 152° after recrystallization from toluene; the literature (2) gave m.p. 151°. When the reaction was performed in toluene, only traces of this acid were obtained. No disubstituted products could be detected in this reaction.

Condensation of cinnamic acid with thymol. In addition to a dihydrocoumarin listed in Table I, this reaction yielded *β-phenyl-β-(4-hydroxy-2-methyl-5-isopropylphenyl)propionic acid*, crystallizing from benzene as fine colorless needles, m.p. 161°.

Anal. Calc'd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.5.
Found: C, 76.4; H, 7.7.

3,4-Dihydro-4-phenyl-7,8-benzocoumarin (VI). This compound (48 g.) was obtained from 50 g. of cinnamic acid, 98 g. of α-naphthol, and 10 g. of sulfuric acid in tetralin; it formed from methanol colorless leaflets, m.p. 112°, boiling at 278–280°/20 mm.

Anal. Calc'd for $C_{19}H_{14}O_2$: C, 83.1; H, 5.1.
Found: C, 82.6; H, 4.7.

3,4-Dihydro-4-phenyl-6,7-trimethylenecoumarin (IX) formed from methanol fine colorless needles, m.p. 122°, boiling at 245–246°/16 mm. (Yield: 60%).

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H. 6.1.
Found: C, 81.5; H, 6.2.

SUMMARY

1. Several derivatives of styrene, including anethole, cinnamic acid, and arylideneacetones, have been successfully condensed with a series of phenolic compounds.

2. The constitution and practical value of the reaction products are discussed.

PARIS V^e, FRANCE
RENORY-LIÈGE, BELGIUM

REFERENCES

(1) BUU-HOÏ, LE BIHAN, AND BINON, *J. Org. Chem.*, **17,** 243 (1952).
(2) LIEBERMANN AND HARTMANN, *Ber.*, **24,** 2582 (1891); **25,** 957 (1892).
(3) VON AUWERS, *Ann.*, **439,** 132 (1924).
(4) MILLS AND NIXON, *J. Chem. Soc.*, 2510 (1930).
(5) SCHNACKENBERG AND SCHOLL, *Ber.*, **36,** 654 (1903).
(6) STOERMER, *Ber.*, **41,** 323 (1908).