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

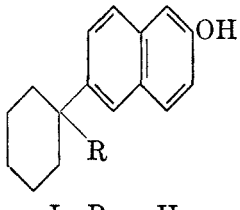
CONDENSATION OF β-NAPHTHOL WITH CYCLOHEXANOL AND ITS METHYL AND ETHYL HOMOLOGS

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

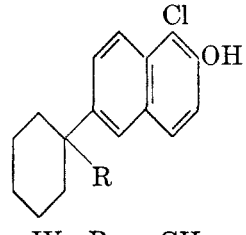
Received August 7, 1950

In continuation of our research work upon derivatives of β-naphthol having biological interest as anthelmintics and fungicides (1), we have investigated the condensation of β-naphthol with cyclohexanol and with 2-, 3-, and 4-methylcyclohexanol. The cycloalkylation procedure most convenient for that purpose was found to be Tschitschibabin's method, in which the condensing agent was phosphoric acid of high concentration (2).

In the case of cyclohexanol, we thus obtained in low yield 6-cyclohexyl-2-naphthol (I), a compound previously prepared in a different way by Alberti (3). Quite unexpectedly, replacement of cyclohexanol by its methyl homologs resulted in excellent yields of a monocycloalkylation-product which was the same in the three cases. There is thus close analogy with the cycloalkylation of phenol by means of 1-methyl-, 3-methyl-, and 4-methyl-cyclohexene (*i.e.* the dehydratation-products 2-, 3-, and 4-methylcyclohexanol) in the presence of sulfuric acid. Schrauth and Quasebarth (4) found that in all three cases a single methylcyclohexylphenol, m.p. 112.5°, was obtained, which Skraup and Binder (5)



I R = H
II R = CH_3
III R = C_2H_5

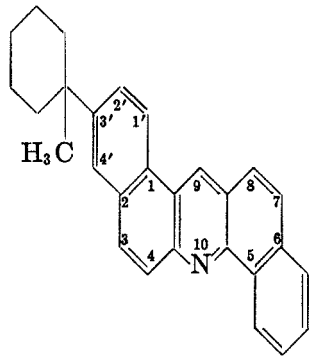


IV R = CH_3
V R = C_2H_5

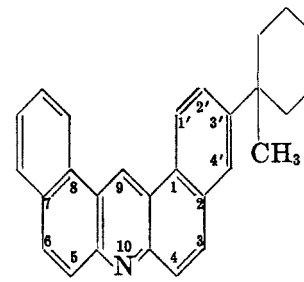
showed later by degradation experiments to be 4-(1-methylcyclohexyl)phenol (XIII). As the latter work is in line with a recent observation of Ipatieff, Meisinger, and Pines (6) that condensation of benzene with isomeric methylcyclohexenes (including the 4-isomer) resulted in 1-methyl-1-phenylcyclohexane, there is little doubt that our methylcyclohexyl-β-naphthol is a 1-methyl-1-arylcyclohexane too. This would explain well why better yields of condensation-product were obtained with methylcyclohexanols than with cyclohexanol itself, as alkylations involving tertiary cycloalkyl groups are known to be easier than those involving secondary ones. This was further substantiated by the ready condensation of 1-ethyl-1-cyclohexanol with β-naphthol to give excellent yields of ethylcyclohexyl-β-naphthol (III).

In reactions such as the present ones, the two sites of substitution to be considered on the naphthalene nucleus are the 6- and the 1-position (1), and this

is supported not only by chemical evidence, but also by the theoretical determination of reactive points in the molecule of β-naphthol through calculation of π-electron densities (7). In our methyl- and ethyl-cyclohexyl-β-naphthol, the 1-position must be free, as xanthene derivatives were very readily obtained on treatment with various aldehydes in mineral acid media (8). Also, the Ullmann condensation of our methylcyclohexyl-β-naphthol with α-naphthylamine and paraformaldehyde (9) readily yielded an acridine closely related in its properties to the angular 1,2:5,6-dibenzacridine; similarly, reaction with β-naphthylamine resulted in a substance akin in its properties to 1,2:7,8-dibenzacridine. These considerations made it highly probable that the product from the condensation of β-naphthol with methylcyclohexanols in the presence of phosphoric acid is in fact 6-(1-methylcyclohexyl)-2-naphthol (II), and that with 1-ethyl-1-cyclohexanol is 6-(1-ethylcyclohexyl)-2-naphthol (III). The two above acridines, which are thus 3′-(1-methylcyclohexyl)-1,2:5,6-dibenzacridine (VI) and 3′-(1-methylcyclohexyl)-1,2:7,8-dibenzacridine (VII), are under biological investigation by Professor A. Lacassagne for possible carcinogenic or tumor growth-inhibitory properties. The substituted 1,2:7,8-dibenzoxanthenes readily ob-

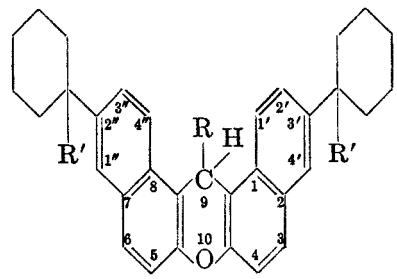


VI



VII

tained as mentioned above by condensation of the naphthols (I, II, and III) with a series of aldehydes in acetic acid medium and in the presence of hydrochloric acid, have the general formula (VIII), and are listed in Table I. They too are of biological interest as potential plant growth regulators, for the basic compound of the series, 9-phenyl-1,2:7,8-dibenzoxanthene, has been found to display such activity in spite of its unfavorable physical properties (10).



VIII

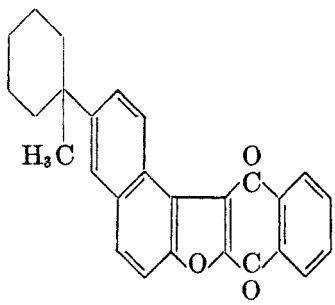
In view of the outstanding anthelmintic properties of 1-chloro-6-*tert*-butyl-2-naphthol against the tapeworm, 1-chloro-6-(1-methylcyclohexyl)-2-naphthol (IV) and 1-chloro-6-(1-ethylcyclohexyl)-2-naphthol (V) were prepared from the action of sulfuryl chloride upon compounds II and III. Apart from any potential anthelmintic properties, the chlorinated naphthols (IV) and (V), as well as their methyl and ethyl ethers, are interesting with regard to possible fungicidal properties, as 1-chloro-6-*tert*-butyl-2-naphthol and its ethers have been found potent in that respect.

TABLE I

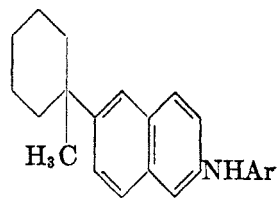
1,2:7,8-DIBENZOXANTHENES OF GENERAL FORMULA VIII

R	R'	FORMULA	M.P., °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
Phenyl	H	$C_{29}H_{38}O$	191	89.6	7.2	89.3	7.5
Phenyl	CH_3	$C_{41}H_{42}O$	214	89.4	7.6	89.1	7.5
4-Tolyl	CH_3	$C_{42}H_{44}O$	219	89.3	7.8	89.2	7.9
4-Chlorophenyl	CH_3	$C_{41}H_{41}ClO$	308	84.2	7.0	83.9	7.1
3-Nitrophenyl	CH_3	$C_{41}H_{41}NO_3$	227	82.7	6.8	82.5	7.0
4-Chlorophenyl	C_2H_5	$C_{43}H_{45}ClO$	262	84.2	7.3	84.0	7.2
4-Methoxyphenyl	CH_3	$C_{42}H_{44}O_2$	217	86.9	7.6	86.6	7.7
4-Methoxyphenyl	C_2H_5	$C_{44}H_{48}O_2$	207	86.8	7.9	86.5	8.0
3,4-Methylenedioxyphenyl	CH_3	$C_{42}H_{42}O_3$	238	84.8	7.0	84.6	7.2
3-Pyrenyl	CH_3	$C_{51}H_{46}O$	dec. >285	90.6	6.8	90.3	6.9

Some further reactions with the naphthol (II) also showed that the position 1 is free: thus, 2,3-dichloro-1,4-naphthoquinone in the presence of pyridine yielded a chlorine-free compound, apparently of formula (IX); the formation of



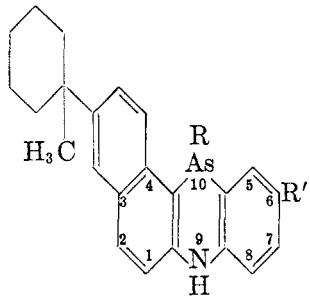
IX



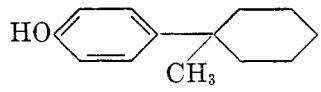
X Ar = C_6H_5
XI Ar = $C_6H_4CH_3(4)$

such derivatives of brazanquinone has recently been shown by Eistert (11) to be characteristic of phenolic compounds having a reactive hydrogen in the *ortho* position. The iodine-catalyzed Knoevenagel reaction (12) of naphthol II with aniline and *p*-toluidine readily yielded 2-phenylamino- (X) and 2-*p*-totylamino-6-(1-methylcyclohexyl)naphthalene (XI). An attempt to prepare 2-β-

naphthylamino-6-(1-methylcyclohexyl)naphthalene by means of the same reaction resulted in β,β-dinaphthylamine. The above substituted diarylamines



XII



XIII

easily underwent condensation with arsenic trichloride (13) to give 2′-(1-methylcyclohexyl)-10-chloro-9,10-dihydrophenarsazine (XII; R = Cl, R′ = H) and its 6-methyl derivative (XII; R = Cl, R′ = CH_3). These aromatic arsenicals were found to be endowed with marked fungicidal activity, less however than the organomercury compounds currently in use. These fungicidal properties are connected with the presence of the arsenic-chlorine link, since replacement of the chlorine atom by a methyl group yielded inactive products.

In view of the present work and that of Ipatieff, Meisinger, and Pines (6), some records in the literature concerning the structure of various methylcyclohexyl compounds need correction. Meyer and Bernhauer (14) described a 4-(4-methylcyclohexyl)phenol m.p. 110–111° (methyl ether m.p. 41°) obtained by cycloalkylating phenol with 4-methylcyclohexanol in the presence of sulfuric acid. That compound has now been found to be 4-(1-methylcyclohexyl)phenol (XIII). Similarly, a compound prepared by Kursanow (15) by cycloalklyation of benzene with optically active 3-methylcyclohexyl chloride and listed as pure 3-methyl-1-phenylcyclohexane should be 1-methyl-1-phenylcyclohexane. This also holds for the compound prepared by Bodroux (16) and by Hennion (17) from benzene, 3-methylcyclohexene, and aluminum chloride. As Kursanow's product remains slightly optically active, it must contain as an impurity some 3-methyl-1-phenylcyclohexane; the tertiarisation of methylcyclohexyl radicals in Friedel-Crafts reactions is therefore less complete than might be believed.

EXPERIMENTAL

6-Cyclohexyl-2-naphthol. A mixture of 150 g. of β-naphthol, 150 g. of cyclohexanol, and 300 g. of concentrated phosphoric acid (*d.* 1.85) was gently heated to the reflux, and kept at about 120–125° for 12 hours. After cooling, the mixture was poured into water, and the reaction-product taken up in benzene. The solution obtained was washed with a 10% aqueous solution of sodium carbonate, then with water, dried over sodium sulfate, and the solvent evaporated. Vacuum-fractionation of the residue gave along with some recovered β-naphthol, two portions: 129 g. b.p. 210–250° at 16 mm., and 37 g., b.p. 260–310° at 16 mm. The lower-boiling portion gave on redistillation (b.p. 225–227° at 16 mm.) and crystallization from cyclohexane, about 20 g. of a product m.p. 162° [the literature (3) gives m.p. 161–162°]. The higher-boiling fraction was composed in part of *6-cyclohexyl-2-naphthol cyclo-*

hexyl ether, since refluxing with pyridine hydrochloride gave cyclohexene and the free naphthol, m.p. 162°, along with an unsplit portion (pale yellow viscous oil, b.p. *circa* 275° at 16 mm.) which was probably a mixture of dicyclohexylnaphthols.

6-(1-Methylcyclohexyl)-2-naphthol (II). A mixture of 150 g. of β-naphthol and 175 g. of 2-methylcyclohexanol was treated with 300 g. of phosphoric acid (*d* 1.85) as in the case of cyclohexanol. After the usual treatment, there was obtained 155 g. of a portion boiling within a range of 227–270° at 15 mm.; after redistillation under the same pressure and crystallization of the fraction, b.p. 235–237° (120 g.), in cyclohexane, *6-(1-methylcyclohexyl)-2-naphthol* was obtained in the form of long silky colorless needles, m.p. 141°, very soluble in ethanol and benzene.

Anal. Calc'd for $C_{17}H_{20}O$: C, 85.0; H, 8.3.
Found: C, 84.9; H 8.5.

The corresponding *picrate* formed long silky bright orange needles, m.p. 135–136° from ethanol. A small amount of the same naphthol was obtained (along with 1-methylcyclohexene) on pyridine hydrochloride treatment of the oily portion, b.p. 280–320° at 15 mm. (50 g.), which was therefore partly made up of *6-(1-methylcyclohexyl)-2-naphthol methylcyclohexyl ether*. Replacement of 2-methylcyclohexanol by the 3- and 4-isomers gave the same naphthol (II), with slightly lower yields.

6-(1-Methylcyclohexyl)-2-naphthol ethers. The *methyl* ether, obtained from naphthol II in alkaline solution with methyl sulfate, formed shiny colorless leaflets, m.p. 99°, from methanol.

Anal. Calc'd for $C_{18}H_{22}O$: C, 85.0; H, 8.6.
Found: C, 84.8; H, 8.6.

The *ethyl* ether, similarly prepared with ethyl sulfate, crystallized from methanol in shiny colorless leaflets m.p. 80°.

Anal. Calc'd for $C_{19}H_{24}O$: C, 85.1; H, 8.9.
Found: C, 85.0; H, 9.0.

1-Chloro-6-(1-methylcyclohexyl)-2-naphthol (IV). Sulfuryl chloride (11 g.) was stirred dropwise into a cold solution of 20 g. of naphthol II in 100 ml. of dry chloroform. After removal of the solvent, the residue was vacuum-distilled; the main fraction, b.p. *circa* 240° at 16 mm., gave after recrystallization from ligroin long silky colorless needles m.p. 83°.

Anal. Calc'd for $C_{17}H_{19}ClO$: C, 74.3; H, 6.9.
Found: C, 74.1; H, 7.0.

The corresponding *methyl ether* formed shiny colorless leaflets, m.p. 87° from methanol.

Anal. Calc'd for $C_{18}H_{21}ClO$: C, 74.9; H, 7.3.
Found: C 74.8; H, 7.5.

The *ethyl ether* crystallized from methanol in similar colorless leaflets, m.p. 90°.

2-Phenylamino-6-(1-methylcyclohexyl)naphthalene (X). A mixture of 5 g. of naphthol II and 5 g. of aniline was refluxed with 0.02 g. of iodine for two hours; the reaction product was poured into water and taken up in benzene, and the benzene solution washed with dilute sodium hydroxide, and dried over sodium sulfate. The residue from evaporation of the solvent gave on vacuum-distillation 5 g. of product, b.p. 302–305° at 20 mm., which crystallized from ligroin in colorless needles, m.p. 82°.

Anal. Calc'd for $C_{23}H_{25}N$: N, 4.4. Found: N, 4.2.

2-p-Tolylamino-6-(1-methylcyclohexyl)naphthalene (XI). Similarly prepared from 5 g. of naphthol II, 5 g. of *p*-toluidine, and 0.02 g. of iodine, it crystallized from ligroin as shiny colorless needles, m.p. 102°, b.p. 314–316° at 20 mm.

Anal. Calc'd for $C_{24}H_{27}N$: N, 4.2. Found: N, 4.2.

Four-hours heating at 200–220° of an equimolecular mixture of β-naphthylamine and naphthol II with a little iodine gave, after vacuum-distillation and crystallization of the reaction-product from methanol, *β,β-dinaphthylamine*, m.p. 171°; the literature gives m.p. 170°.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.0.

8-(1-Methylcyclohexyl)dinaphtho[2,1,2',3']furan-8,13-dione (IX). A solution of equimolecular amounts of naphthol II and 2,3-dichloro-1,4-naphthoquinone in pyridine was refluxed for 12 hours; the precipitate obtained on dilution with methanol formed bright yellow needles, m.p. 242°, from benzene giving with sulfuric acid an intense blue coloration. Yield, 50%.

Anal. Calc'd for $C_{27}H_{22}O_2$: C, 82.2; H, 5.6.
Found: C, 82.0; H, 5.8.

3'-(1-Methylcyclohexyl)-1,2:5,6-dibenzacridine (VI). To a boiling mixture of 5 g. of naphthol II and 2.5 g. of α-naphthylamine was cautiously added in small portions 0.5 g. of paraformaldehyde. The reaction product was brought to the boil for five minutes and then vacuum-distilled. The sticky orange jelly boiling above 300° at 13 mm. crystallized on standing with ethanol and was recrystallized, from a mixture of ethanol and benzene as pale yellow prisms, m.p. 205°, giving with sulfuric acid an intense orange-yellow coloration and a green fluorescence.

Anal. Calc'd for $C_{28}H_{25}N$: C, 89.6; H, 6.6.
Found: C, 89.5; H, 6.8.

The corresponding *picrate* separated from chlorobenzene as fine orange-yellow needles, decomposed by heating over 225°.

3'-(1-Methylcyclohexyl)-1,2:7,8-dibenzacridine (VII). Obtained from naphthol II and β-naphthylamine as for the above isomer, it separated from a mixture of ethanol and benzene as fine shiny pale yellow needles, m.p. 169°, giving with sulfuric acid an intense orange-yellow coloration and a green fluorescence.

Anal. Calc'd for $C_{28}H_{25}N$: C, 89.6; H, 6.6.
Found: C, 89.4; H, 6.6.

Its *picrate* crystallized from nitrobenzene as shiny orange-yellow needles, melting with decomposition above 286–290°.

2'-(1-Methylcyclohexyl)-10-chloro-9,10-dihydrophenarsazine. A solution of 4 g. of diarylamine X and 2.5 g. of arsenic trichloride in 10 ml. of dry *o*-dichlorobenzene was refluxed for 12 hours. The precipitate obtained after cooling gave on recrystallization from chlorobenzene shiny yellow prisms, melting with decomposition above 270°. The sternutatory properties were not very pronounced; tested upon *Fusarium graminearum*, this compound showed a strong fungistatic activity.

Anal. Calc'd for $C_{23}H_{23}AsClN$: C, 65.1; H, 5.4.
Found: C, 64.9; H, 5.4.

The corresponding 10-methyl compound was completely inactive.

2'-(1-Methylcyclohexyl)-6-methyl-10-chloro-9,10-dihydrophenarsazine. Obtained from diarylamine XI and arsenic trichloride, it separated from chlorobenzene as shiny bright yellow needles, melting with decomposition above 275°. It showed the same biological properties as the lower homolog.

Anal. Calc'd for $C_{24}H_{25}AsClN$: C, 65.8; H, 5.7.
Found: C, 65.5; H, 5.8.

The 10-methyl compound (XV; R = R' = CH_3) was similarly biologically inactive.

6-(1-Ethylcyclohexyl)-2-naphthol (III). The 1-ethyl-1-cyclohexanol used in this work was prepared by a Grignard reaction between cyclohexanone and ethylmagnesium bromide. The condensation of 63 g. of that alcohol with 77 g. of β-naphthol by 150 g. of phosphoric acid was effected as indicated for the lower homolog. After recrystallization from ligroin, the fraction b.p. 235–255° at 16 mm. (50 g.) gave colorless needles, m.p. 115°, very soluble in cyclohexane and ethanol.

Anal. Calc'd for $C_{18}H_{22}O$: C, 85.0; H, 8.6.
Found: C, 84.9; H, 8.7.

Some of the same naphthol could be obtained by splitting the higher-boiling fraction (13 g., b.p. 270–300° at 16 mm.) with pyridine hydrochloride.

1-Chloro-6-(1-ethylcyclohexyl)-2-naphthol (V). A solution of 10 g. of the above naphthol in 50 ml. of dry chloroform was treated with 5.4 g. of sulfuryl chloride in the usual way.

Yield, 10 g. of a product b.p. *circa* 240–245° at 16 mm., crystallizing from ligroin in long colorless silky needles, m.p. 79°.

Anal. Calc'd for $C_{18}H_{21}ClO$: C, 74.8; H, 7.2.
Found: C, 74.5; H, 7.2.

Preparation of the dibenzoxanthenes (VIII). A solution of an aromatic aldehyde (1.2 moles) and of the required naphthol (2 moles) in the minimum quantity of acetic acid was refluxed for five minutes with some drops of hydrochloric acid; the mixture rapidly solidified after cooling and was recrystallized from ethanol, except for the pyrene derivative which had to be recrystallized from toluene.

4-(1-Methylcyclohexyl)phenol methyl ether. The treatment with aqueous sodium hydroxide and methyl sulfate of 4-(1-methylcyclohexyl)phenol prepared according to Schrauth and Quasebarth (4), gave an ether crystallizing from ligroin in colorless prisms, m.p. 40–41°. Meyer and Bernhauer (14) gave m.p. 41° for their compound.

SUMMARY

1. The cycloalkylation of β-naphthol with cyclohexanol and four of its homologs has been investigated.

2. The reaction with 2-, 3-, and 4-methylcyclohexanol has been found to yield the same product, apparently 6-(1-methylcyclohexyl)-2-naphthol. The reaction with 1-ethyl-1-cyclohexanol gave similarly 6-(1-ethylcyclohexyl)-2-naphthol.

3. Several derivatives of the substituted naphthols thus prepared have been synthesized for biological testing.

PARIS V^e^, FRANCE
RENORY—LEIGE, BELGIUM

REFERENCES

(1) BUU-HOÏ, LE BIHAN, BINON, AND RAYET, *J. Org. Chem.*, **15**, 1060 (1950).
(2) TSCHITSCHIBABIN, *Bull. soc. chim.*, [5] **2**, 515 (1935).
(3) ALBERTI, *Ann.*, **450**, 309 (1926).
(4) SCHRAUTH AND QUASEBARTH, *Ber.*, **57**, 854 (1924).
(5) SKRAUP AND BINDER, *Ber.*, **62**, 1129 (1929).
(6) IPATIEFF, MEISINGER, AND PINES, *J. Am. Chem. Soc.*, **72**, 2772 (1950); see also PINES, STREHLAU, AND IPATIEFF, *J. Am. Chem. Soc.*, **72**, 1564 (1950).
(7) DAUDEL, BUU-HOÏ, AND MARTIN, *Bull. soc. chim.*, [5] **15**, 1202 (1948).
(8) CLAISEN, *Ann.*, **237**, 265 (1887).
(9) ULLMANN AND FETTVADJIAN, *Ber.*, **36**, 1029 (1903).
(10) THOMPSON, SWANSON, AND NORMAN, *Botan. Gaz.*, **107**, 476 (1946).
(11) EISTERT, *Ber.*, **80**, 52 (1947).
(12) KNOEVENAGEL, *J. prakt. Chem.*, **89**, 17 (1914).
(13) WIELAND AND RHEINHEIMER, *Ann.*, **423**, 1 (1929).
(14) MEYER AND BERNHAUER, *Monatsh.*, **53/54**, 734 (1929).
(15) KURSANOW, *J. Russ. Phys.-Chem. Soc.*, **38**, 1304 (1907).
(16) BODROUX, *Ann. chim.*, [10] **11**, 511 (1929).
(17) HENNION, *J. Am. Chem. Soc.*, **66**, 1801 (1944).