TABLE I

2-ARYLOXYALKYL-3-HYDROXY-1,4-NAPHTHOQUINONES

2-Substituent	Procedure	M. p., °C.	Solvent	Form	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R. A. A.[b]	pE[c]
$-(CH_2)_{10}OC_6H_5$	A and B	87.5–88	Methanol	Yellow needles	$C_{26}H_{30}O_4$	76.82	76.80	7.44	7.46	6.3	11.4
$-(CH_2)_{10}OC_6H_4C_6H_5$-*p*	A and B	123–124	Methanol	Yellow needles	$C_{32}H_{34}O_4$	79.63	79.62	7.10	7.40		
$-(CH_2)_{10}OC_6H_4CH_3$-*p*	A	93–94	Ligroin[a]	Yellow needles	$C_{27}H_{32}O_4$	77.11	77.12	7.67	7.96	2.7	
$-(CH_2)_{10}OC_6H_4Cl$-*p*	B	88.5–89.5	Methanol	Yellow needles	$C_{26}H_{29}O_4Cl$	70.82	71.04	6.63	6.66	6.4	11.6
$-(CH_2)_{10}OC_6H_4C_6H_{11}$-*p*	B	92.5–93.5	Methanol	Yellow powder	$C_{32}H_{40}O_4$	78.65	78.89	8.25	8.40		
$-(CH_2)_{10}OC_{10}H_7$-α	B	103–104	Methanol	Yellow powder	$C_{30}H_{32}O_4$	78.92	78.67	7.23	7.19		
$-(CH_2)_8OC_6H_5$	B	83.5–84.5	Methanol	Yellow prisms	$C_{24}H_{26}O_4$	76.16	75.98	6.93	6.96	0.47	10.4
$-(CH_2)_8OC_6H_4Cl$-*p*	B	95–96	Methanol	Yellow rosettes	$C_{24}H_{26}O_4Cl$	69.81	70.09	6.10	6.39	4.7	11.1
$-(CH_2)_8OC_6H_4CH_3$-*p*	B	89–90	Methanol	Yellow needles	$C_{25}H_{28}O_4$	76.50	76.59	7.19	7.30	3.3	11.0
$-(CH_2)_7OC_6H_5$	B	88–89	Methanol	Yellow prisms	$C_{23}H_{24}O_4$	75.86	75.87	6.64	6.84	0.34	9.1
$-(CH_2)_7OC_6H_4Cl$-*p*	B	95.5–96.5	Ligroin[a]	Yellow platelets	$C_{23}H_{23}O_4Cl$	69.25	69.17	5.81	5.91	0.6	10.2
$-(CH_2)_7OC_6H_4CH_3$-*p*	B	105.5–107	Methanol	Yellow platelets	$C_{24}H_{26}O_4$	76.16	75.93	6.92	6.84	2.1	10.1
$-(CH_2)_9OC_6H_4Cl$-*p*	C and B	95–96	Methanol	Yellow needles	$C_{25}H_{27}O_4Cl$	70.33	70.13	6.38	6.38	9.1	11.4
$-(CH_2)_9OC_6H_5$	C	87.5–88	Methanol	Yellow needles	$C_{25}H_{28}O_4$	76.50	76.84	7.36	7.70	0.66	11.1

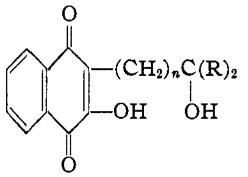
[a] B. p. 90–120°. [b] For the determination of the relative anti-respiratory activity of these quinones we are indebted to Miss Shirley Katz and Mrs. Grace Nahm. [c] Critical extraction constant ref. 12.

in the usual manner.[26] From 1 g. of XVI there was obtained 1 g. (76%) of XVII, m. p. 123–125°.

Anal. Calcd. for $C_{27}H_{26}O_7$: C, 70.12; H, 5.67. Found: C, 70.32; H, 5.84.

TABLE II

2-DIALKYLCARBINOLALKYL-3-HYDROXY-1,4-NAPHTHOQUINONES



n[a]	R	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	R. A. A.[b]
9	C_4H_9-*n*	$C_{28}H_{42}O_4$	75.98	75.70	9.57	9.77	2.7
9	C_5H_{11}-*n*	$C_{30}H_{46}O_4$	76.55	76.66	9.85	9.93	2.9
9	C_5H_{11}-*i*	$C_{30}H_{46}O_4$	76.55	76.33	9.85	9.94	2.9
9	C_4H_9-*i*	$C_{28}H_{42}O_4$	75.98	75.82	9.57	9.40	1.25
9	C_3H_7-*n*	$C_{26}H_{38}O_4$	75.32	75.20	9.48	9.32	1.3
8	C_5H_{11}-*i*	$C_{29}H_{44}O_4$	76.28	76.08	9.71	9.82	1.9
8	C_4H_9-*i*	$C_{27}H_{40}O_4$	75.65	75.60	9.53	9.60	0.77

[a] All of these compounds were obtained as viscous oils. [b] The relative antirespiratory activity of quinone XV (n = 8, R = C_5H_{11}-*n*) (lapinone) is 3.4.

2-(5′,5′-Diphenylpentene-4′)-3-hydroxy-1,4-naphthoquinone (XIX).—A solution of 0.39 g. of XVII in 75 cc. of dry benzene was added dropwise over a period of twenty minutes to a stirred solution of phenylmagnesium bromide, prepared from 3.14 g. (0.02 mole) of freshly distilled bromobenzene and 0.48 g. (0.02 mole) of magnesium in 75 cc. of dry ether. The light orange solution was refluxed for four hours and then decomposed with 50 cc. of 20% sulfuric acid. The ether layer was separated, and the ether was removed. All attempts at crystallization from ligroin (b. p. 90–100°) or methanol gave only an oil. When the product stood in aqueous acetic acid in the cold room there was obtained 0.1 g. of thick yellow needles, m. p. 132–134°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.20; H, 5.87.

Summary

A number of 2-alkyl-3-hydroxy-1,4-naphthoquinones have been synthesized with oxygen in the side chain (either hydroxyl oxygen or ether oxygen) to be tested as antimalarial agents. Several of the aryloxy ethers possess high activity on the basis of *in vitro* assay.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. XIV. Isopropyl Derivatives of Dibenzenesulfonamidomesitylene

BY ROGER ADAMS AND NILS K. NELSON[1]

The synthesis of various N,N′-alkylated dibenzenesulfonamidomesitylenes and separation of *cis* and *trans* forms have been previously described.[2] All of the compounds reported are *n*-alkyl derivatives. The synthesis of the mono- and diisopropyl homologs has now been undertaken. Steric factors not existent in the preparation of the *n*-alkyl derivatives were encountered.

Mono-isopropylation of diaminomesitylene was accomplished by prolonged boiling of an ethanolic solution of diaminomesitylene with a large excess of isopropyl bromide. More drastic conditions were required to prepare the diisopropyl derivative. When an ethanolic solution of diaminomesitylene and isopropyl bromide was heated in a bomb at 100° for forty-eight hours, a mixture of the mono- and diisopropyl derivatives resulted. When this mixture was subjected to similar treatment, the diisopropyl derivative was formed in 44% yield. At temperatures as high as 180°, a large amount of propylene was evolved and no

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[2] Adams and Tjepkema, THIS JOURNAL, **70**, 4204 (1948); Adams, *et al.*, *ibid.*, **71**, 1620 (1949); **72**, 128, 132, 135, 2454, 2458, 4606 (1950).

alkylation took place. The diisopropyldiaminomesitylene was purified through the dinitroso derivative followed by reduction with urea.

Benezenesulfonation of N,N′-diisopropylaminomesitylene in pyridine on a steam-cone for five hours gave a mixture of the *cis* and *trans* N,N′-diisopropyldibenzenesulfonamido isomers. Shorter reaction periods and lower temperatures gave only the monobenzenesulfonation derivative or a mixture of mono- and dibenzenesulfonation product which, however, could be further benzenesulfonated to the disubstituted derivatives. The isomeric disubstituted derivatives could be separated by crystallization only with great difficulty in contrast to the ease of separation of the stereoisomeric *n*-alkyl homologs. By chromatography, the two forms were readily isolated in a pure state.

When dibenzenesulfonamidomesitylene was alkylated with ethanolic isopropyl bromide, the reaction proceeded very slowly and only the higher melting isomer of N,N′-diisopropyldibenzenesulfonamidomesitylene resulted. The conversion was only 9%, the balance consisting of monoalkylated and unchanged material.

Benzenesulfonation of monoisopropyldiaminomesitylene gave monoisopropyldibenzenesulfonamidomesitylene which was identical with the product from monoisopropylation of dibenzenesulfonamidomesitylene.

Experimental

N-Isopropyldiaminomesitylene.—A solution of 5 g. of diaminomesitylene in 100 ml. of isopropyl alcohol and 20 g. of isopropyl bromide was allowed to reflux on a steam-cone for thirty-six hours. During the course of the reaction, two 5-ml. portions of isopropyl bromide were added. After standing overnight at room temperature the alcohol and excess isopropyl bromide were removed by evaporation. After making the mixture alkaline with 5% potassium hydroxide, it was extracted with six 100-ml. portions of ether. These were combined, 75 ml. of dry benzene was added, and the ether and benzene were removed by distillation under reduced pressure. The product remaining was distilled *in vacuo* to give a light yellow oil, b. p. 114–115° (4 mm.); $n^{20}\text{D}$ 1.5442. The yield was 3.25 g. (50%).

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48. Found: C, 74.75; H, 10.46.

N,N′-Diisopropyldiaminomesitylene.—A solution of 30 g. of diaminomesitylene in 50 ml. of 95% ethanol and 65 g. of isopropyl bromide was heated in a glass-lined iron bomb for forty-eight hours at 100°. The heating was not continuous, but was in four twelve-hour periods over a span of four days. The ethanol and excess isopropyl bromide were removed by distillation. The residue was made basic with 5% potassium hydroxide and extracted with ether. To the ether was added 100 ml. of dry benzene, and the ether and benzene were removed by distillation under reduced pressure. The residue was distilled *in vacuo* yielding 27 g. of a yellow liquid, b. p. 114–117° (2 mm.); $n^{20}\text{D}$ 1.5338–1.5348. This product was dissolved in a solution of 50 ml. of ethanol and 30 ml. of isopropyl bromide and the process repeated. The product was distilled *in vacuo* and formed a light yellow liquid, b. p. 115–117° (2 mm.); $n^{20}\text{D}$ 1.5227–1.5229. The yield was 19 g. (44.5%).

The product contained minute amounts of unalkylated product as shown by solution in concentrated hydrochloric acid, treatment with cold sodium nitrite solution and addition of an alkaline solution of β-naphthol which resulted in the formation of a small amount of red dye. The compound was purified further by converting it to the dinitroso derivative followed by reduction.

N,N′-Dinitroso-N,N′-diisopropyldiaminomesitylene.—To a solution of 15.3 g. of crude N,N′-diisopropyldiaminomesitylene ($n^{20}\text{D}$ 1.5228) in 21 ml. of concentrated hydrochloric acid was added dropwise with constant stirring a solution of 9 g. of sodium nitrite in 25 ml. of water. The mixture was cooled with an ice–salt-bath. The addition was completed in thirty minutes. The mixture was extracted with three 200-ml. portions of ether. This ethereal solution was extracted once with 5% hydrochloric acid, once with water, twice with 5% potassium hydroxide, and once more with water. The solution was then evaporated to dryness on a steam-cone. There remained 15 g. (80%) of a yellow, semi-crystalline wax.

One gram of this product was recrystallized once from petroleum ether (b. p. 80–110°), once from 50% ethanol, and three times from absolute ethanol. Long white prisms were formed, m. p. 101.5–103° (cor.).

Anal. Calcd. for $C_{15}H_{24}N_4O_2$: C, 61.62; H, 8.27. Found: C, 61.71; H, 8.18.

To a warm (50°), vigorously stirred solution of 14.2 g. of urea in 150 ml. of 50% sulfuric acid was slowly added 15 g. of N,N′-dinitroso-N,N′-diisopropyldiaminomesitylene. After the addition and the nitroso compound had dissolved completely, the mixture was heated to 100° and stirred for fifteen minutes. It was now cooled to room temperature, diluted with 150 ml. of water, made basic with aqueous ammonia, and extracted with four 300-ml. portions of ether. A 50-ml. portion of benzene was added to the ether extract. The ether and benzene were removed by distillation. The residue was distilled *in vacuo*. The yield was 9.4 g. (78%) of a light yellow oil, b. p. 115–116° (3 mm.); $n^{20}\text{D}$ 1.5229.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18. Found: C, 77.03; H, 11.02.

This product gave no dye with sodium nitrite and β-naphthol. The Liebermann nitroso test was negative.

N,N′-Diisopropyldibenzenesulfonamidomesitylene.

(I) (One Isomer).—To a solution of 5 g. of dibenzenesulfonamidomesitylene in 100 ml. of absolute ethanol was added 0.54 g. of sodium. The mixture was evaporated to dryness and dried over calcium chloride in a desiccator. The dry powder was suspended in 200 ml. of dioxane (which had been dried by refluxing several days with sodium and distilling) and allowed to reflux for one week on a hot-plate. After cooling, the suspension was filtered. The filtrate was evaporated to dryness. Recrystallization from benzene, methanol and ethanol yielded 0.6 g. of white prisms (9.5%). The compound melted immediately when the melting point tube was immersed in the bath at 188° (cor.). However, when the compound was heated slowly, it merely softened at 188° (cor.) and melted at 194° (cor.). Although this product had the correct analysis, it was probably contaminated with traces of the other isomer since chromatography permitted isolation of a product which melted sharply at 194–195° (cor.).

Anal. Calcd. for $C_{27}H_{34}N_2O_4S_2$: C, 63.00; H, 6.68. Found: C, 63.18; H, 6.71.

(II). **(Two Isomers)**.—To a solution of 9.4 g. of N,N′-diisopropyldiaminomesitylene (prepared from N,N′-dinitroso-N,N′-diisopropyldiaminomesitylene) in 10 ml. of pyridine was added 28.2 g. of benzenesulfonyl chloride. The mixture was heated on a steam-cone for five and one-half hours and allowed to stand at room temperature for thirty-six hours. It was poured with stirring into 1500 ml. of cracked ice and water. After standing for a day, a dark brown product was removed by filtration. It was digested with 1300 ml. of 10% sodium hydroxide for ten minutes, filtered, washed and dried in a desiccator. The product was dissolved in ethanol, treated with Norit and allowed to stand. Light cream colored crystals precipitated slowly from the solvent. The yield was 12 g. A second crop of 4 g. melting in the same region was obtained by concentrating the mother liquor. The over-all yield was 78%, m. p. 154–165°.

When N,N′-diisopropyldiaminomesitylene in pyridine was heated on a steam-bath for fifteen minutes with excess of benzenesulfonyl chloride, an impure benzenesulfonated product was formed, presumably a mixture of the mono- and dibenzenesulfonated derivatives. The crude material could be converted into a mixture of the two disubstituted isomers by the procedure just described.

After extracting the product, m. p. 154–165°, four times with hot methanol, white prisms separated from the fourth extract which had an appreciably higher melting point. The crystals were recrystallized once from ethanol and once from a mixture of ethanol and methanol, m. p. 188–189° (cor.). When immersed in a bath preheated to 180°, the m. p. was 194° (cor.).

Anal. Calcd. for $C_{27}H_{24}N_2O_4S_2$: C, 63.00; H, 6.68. Found: C, 63.31; H, 6.60.

The residue after evaporation of the first three methanol extracts was extracted with methanol repeatedly and each extract evaporated to dryness. The residues gradually decreased in melting point from 185–190° to 145–155°, each lower than the preceding. The material with the lowest melting point on extraction with methanol yielded a product, m. p. 153–170°. After recrystallization from ethyl acetate and then from ethanol, the product melted at 171–173° (cor.). This material probably contained traces of the higher melting isomer for from the chromatographic procedure a product, m. p. 181–182°, resulted. The melting point was depressed by admixture with the product, m. p. 188–189°. The infrared absorption in chloroform indicated that the two substances were different.

Anal. Calcd. for $C_{27}H_{34}N_2O_4S_2$: C, 63.00; H, 6.68. Found: C, 62.92; H, 6.57.

This procedure for separation of the isomers was quite unsatisfactory. A simple chromatographic separation, however, was found.

A solution of 1 g. of the mixture of isomers (m. p. 155–165°) in 10 ml. of chloroform was poured onto 24 g. of alumina in a 24 × 1.2 cm. column. The alumina was washed with 50 ml. of chloroform.

first 20 ml.	5 ml.	15 ml.	5 ml.	5 ml.
nil	0.3 g.	0.4 g.	0.1 g.	0.1 g.
	155–177°	155–165°	170–173°	173–174°
	(A)			(B)

Fraction (A) was dissolved in 10 ml. of chloroform and subjected to a second similar operation.

first 25 ml.	5 ml.		
nil	0.1 g.	5 ml.	15 ml.
	188–190°	188–189°	155–165°
	(C)		

Fraction (C) upon recrystallization, once from methanol and once from ethyl acetate, gave white crystals, m. p. 194–195° (cor.).

Fraction (B) upon recrystallization, twice from methanol and twice from ethyl acetate, gave white crystals, m. p. 181–182° (cor.).

N-Isopropyldibenzenesulfonamidomesitylene. (A).—A mixture of 4 g. of dibenzenesulfonamidomesitylene, 50 ml. of acetone, 40 ml. of methanol, 1.04 g. of potassium hydroxide and 4.6 g. of isopropyl bromide was allowed to reflux on the steam-cone for forty-eight hours. During the course of the reaction 4 g. more of isopropyl bromide was added. The mixture was evaporated to dryness. The residue was washed twice with 5% potassium hydroxide solution, extracted twice with carbon disulfide, recrystallized once from methanol and twice from ethyl acetate. The yield was 0.1 g. of small white crystals, m. p. 196–197° (cor.).

Anal. Calcd. for $C_{22}H_{28}N_2O_4S_2$: C, 60.99; H, 5.97. Found: C, 60.79; H, 6.21.

(B).—A solution of 9.79 g. of N-isopropyldiaminomesitylene in 25 ml. of pyridine and 18 g. of benzenesulfonyl chloride was heated on the steam-cone for twenty minutes. The warm mixture was poured slowly onto 300 g. of ice in 700 ml. of water. The ice-water was stirred vigorously for several minutes. The water was removed by decantation, and the brown gum on the bottom of the beaker was dissolved in ethanol and allowed to stand for several weeks. Fine white crystals formed which were recrystallized several times from ethanol. The yield was 1.5 g. (8.5%), m. p. 195.5–196.5° (cor.).

Anal. Calcd. for $C_{22}H_{22}N_2O_4S_2$: C, 60.99; H, 5.97. Found: C, 61.17; H, 6.20.

Summary

1. Diaminomesitylene reacts stepwise with isopropyl bromide to form first N-isopropyldiaminomesitylene and then N,N′-diisopropyldiaminomesitylene. The second step of the alkylation must be carried out under pressure.

2. N,N′-Diisopropyldiaminomesitylene reacts stepwise with benzenesulfonyl chloride to form first N,N′-diisopropylmonobenzenesulfonamidomesitylene and then N,N′-diisopropyldibenzenesulfonamidomesitylene. *cis-* and *trans*-modifications of the latter compound formed and were separated.

3. Isopropylation of the disodium salt of dibenzenesulfonamidomesitylene with isopropyl bromide gave only the higher melting, presumably the *trans*, diisopropyl isomer.

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