[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE UNIVERSITY OF SOUTHERN CALIFORNIA]

SUBSTITUTED α-DIALKYLAMINOALKYL-1-NAPHTHALENEMETHANOLS. V. THE PREPARATION OF SOME α-DIALKYLAMINOMETHYL-2-CHLORO- AND BROMO-1-NAPHTHALENEMETHANOLS[1]

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This article describes the preparation of several α-dialkylaminomethyl-2-halo-1-naphthalenemethanols, which was carried out as part of a program of synthesis of amino alcohols containing substituted naphthalene nuclei (1). Since such ethanolamines could be prepared readily from the 2-halo-1-acetonaphthones IV, the practical synthesis of the latter materials was our main problem. Several approaches were examined.

The most direct approach to the substances would appear at first to involve the Friedel-Crafts reaction on 2-halonaphthalene, just as we found it to be in the case of the 4-halo-1-acetonaphthones (2). We explored this first with 2-bromonaphthalene. Acetyl chloride and aluminum chloride gave rise in 66% yield to a mixture of the 1- and 6-acetylbromonaphthones as previously reported by Dziewonski and Sternbach (3) who accomplished the difficult separation of isomers through the phenylhydrazones. However, we found it preferable to add phenylhydrazine roughly equivalent to the 1-isomer which reacts more rapidly than the 1-isomer in acetic acid solution. After the precipitation of the 2-bromo-6-acetonaphthone phenylhydrazone was complete the 2-bromo-1-acetonaphthone IV (X = Br) was obtained with a 38% recovery of crude material and a 26% recovery of pure material after recrystallization. Since β-bromonaphthalene was obtained in 50–55% yield from β-naphthylamine, the over-all yield of 2-bromo-1-acetonaphthone was approximately 9% from β-naphthylamine.

The Friedel-Crafts reaction on 2-chloronaphthalene gave rise to a mixture of ketones from which the 2-chloro-1-acetonaphthone IV (X = Cl) was isolated rather easily by simple crystallization. The over-all yield of pure product from β-naphthylamine was 32%.

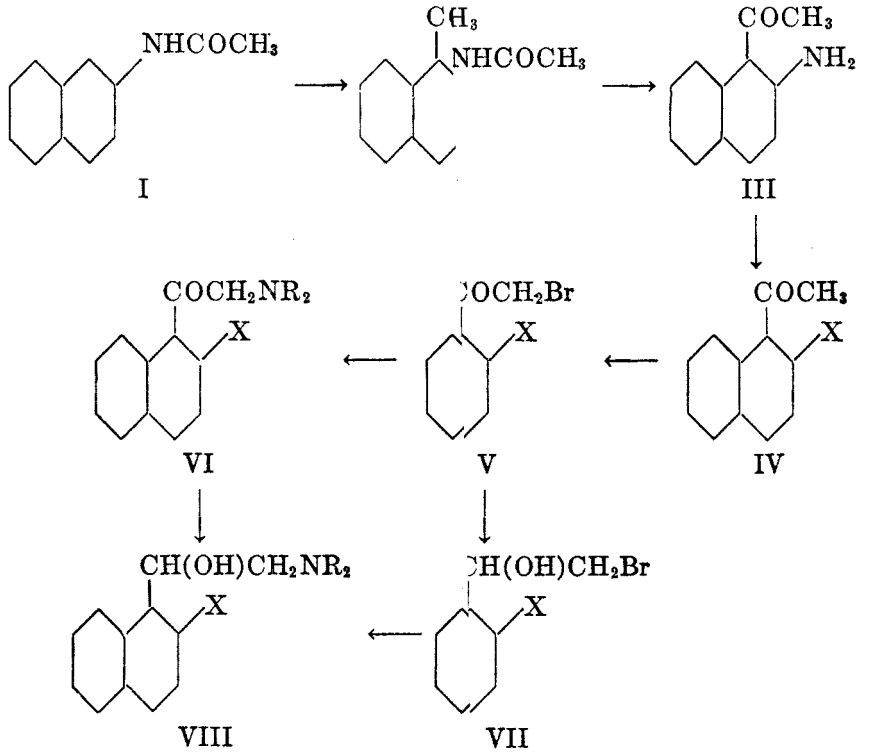
A preliminary attempt at chloromethylation (4) of β-bromonaphthalene to produce 2-bromo-1-chloromethylnaphthalene was discouraging. The latter substance was to be oxidized to 2-bromo-1-naphthoic acid which was to be built up to the bromomethyl ketone by way of the diazoketone (5).

The best synthesis we found for 2-halo-1-acetonaphthones IV involved 2-amino-1-acetonaphthone which was easily diazotized and converted to IV.

[1] This work was done under contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California, Los Angeles, and the University of Southern California. The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity of those compounds to which such numbers have been assigned will be tabulated in a forthcoming monograph.

Attempts to prepare 2-amino-1-acetonthone by a Bucherer reaction (6) on 2-hydroxy-1-acetonaphthone or by a ss-type rearrangement (7) of 2-acetamidonaphthalene I were unsuccessful; but satisfactory conditions were found for the Friedel and Crafts reaction on II; hydrolysis of the product (II to III).

A number of satisfactory Friedel and Crafts reactions on acetanilide and substituted acetanilides have been reported in the literature (8). Also, Dziewonski and co-workers (9) obtained 2-benzamido-1-benzoylnaphthalene in 30–40% yield from treatment of β-naphthylamine with benzoyl chloride and zinc chloride. Similarly we eventually obtained satisfactory acetylation of 2-acetamidonaphthalene I by regulation of experimental conditions. The proportion of alumi-



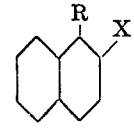
num chloride catalyst was crucial, no product being obtained in carbon disulfide or benzene with mole ratios of aluminum chloride to acetic anhydride to acetamidonaphthalene of 2.5:1.25:1. Also, other starting material was obtained with acetyl chloride in carbon disulfide where corresponding mole ratios were 1.25:1.25:1. When, with acetic anhydride in carbon disulfide, the above mole ratios were 8:2:1, a product was obtained which had the correct composition for the 2-acetamido-1-acetonaphthone II (Table I), yielded a 2,4-dinitrophenylhydrazone, gave an iodoform test, and failed to give a test for a primary amine. The yield in this step was improved to 4 and with approximately an 80% yield on the hydrolysis of II to the 2-amino-1-acetonaphthone III (Table I) the over-all yield of III from acet-β-naphthalide I was about 38%.

The over-all yield of III from I was improved to 45% by avoiding isolation of II and further improved by use of acetyl chloride instead of acetic anhydride, acetyl chloride being added to a suspension of the amide and aluminum chloride in carbon disulfide. This modified procedure gave rise to yields of III of 60–70%.

The structure of the 2-amino-1-acetonaphthone III was clear from the subsequent diazotization and conversions to the 2-halo-1-acetonaphthones IV. The bromo compound was identical with the material prepared from β-bromonaphthalene by Dziewonski and Sternbach's method (3). In addition to the 2-amino-1-acetonaphthone III, m.p. 110–111°, from the modified procedure in which the 2-acetamido-1-acetonaphthone was not isolated, there was obtained a

TABLE I

PROPERTIES AND ANALYSES OF COMPOUNDS



SN	X	R	M.P. °C	ANALYSIS			
				%C		%H	
				Calc'd	Found	Calc'd	Found
	$NHCOCH_3$	$COCH_3$	151	73.99	73.58	5.76	5.77
	NH_2	$COCH_3$	110–111	77.81	77.60	5.99	6.21
	Cl	$COCH_3$	64–65	70.42	69.95	4.43	4.55
	Cl	$COCH_2Br$	97–98	50.83	50.35	2.84	2.94
	Br	$COCH_2Br$	116–117	43.94	43.94	2.46	2.51
	Cl	$CH(OH)CH_2Br$	80–81	50.47	50.30	3.53	3.51
	Br	$CH(OH)CH_2Br$	78.5–79.5	43.67	43.70	3.05	3.10
5905	Cl	$CH(OH)CH_2N(C_2H_5)_2$	64–64.5	69.18	69.12	7.26	7.21
6620	Cl	$CH(OH)CH_2N(C_4H_9)_2 \cdot HCl$	136.5–137[a]	64.86	65.08	7.89	7.76
			124.5–125[a]		64.71		7.99
8100	Cl	$CH(OH)CH_2N(C_5H_{11})_2 \cdot HCl$	121–126	66.32	66.60	8.35	8.38
7936	Cl	$CH(OH)CH_2N(C_6H_{13})_2 \cdot HCl$	121–122	67.59	67.46	8.75	8.64
8681	Br	$CH(OH)CH_2N(C_4H_9)_2 \cdot HCl$	134–135	57.90	57.78	7.05	7.13

[a] Two crystalline modifications.

small amount of a material, m.p. 163–164°, with the correct composition of an isomer of III, probably 2-amino-6-acetonaphthone.

The 2-chloro-1-acetonaphthone IV (X = Cl, Table I) was prepared in yields of 65–70% from the amino ketone III by the Sandmeyer reaction. Thus the over-all yield from β-naphthylamine by this approach was 41%. For the 2-bromo-1-acetonaphthone IV (X = Br, Table I) the yield was low, but, since only one amino alcohol VIII corresponding to it was needed, the preparation was not further investigated. Bromination of the 2-halo-1-acetonaphthones IV to bromo ketones V (Table I) was easily accomplished.

The bromo ketones V were converted to amino alcohols VIII (Table I) by routes already described (1, 10).

EXPERIMENTAL

Melting points are uncorrected. Analyses by Jack W. Ralls and Bruce Day.

β-Bromonaphthalene. This material, m.p. 56.0–56.5°, was prepared in 50–55% yield from β-naphthylamine following directions of Geissman and Tulagin (11) and recrystallized from aqueous methanol.

Preparation of 2-bromo-1-acetonaphthone from β-bromonaphthalene. The mixture of ketones was prepared in 66% yield from β-bromonaphthalene, acetyl chloride, and aluminum chloride in carbon disulfide essentially by the method of Dziewonski and Sternbach (3). Since hydrolysis of the phenylhydrazones was accompanied by formation of considerable tarry material, the separation of the ketones was carried out by converting most of the 6-isomer to phenylhydrazone, leaving the 1-acetonaphthone unreacted. It is difficult to judge the composition of the mixed ketone. Anderson and Johnston (12) estimate the ketone mixture is approximately one-tenth 6-bromo-2-acetonaphthone. However, treatment of the crude ketone with the equivalent amount of phenylhydrazine in glacial acetic acid precipitated about one-third of the ketone and we proceeded on this basis.

The ketone mixture (73.7 g., 0.296 mole) was dissolved in 150 ml. of glacial acetic acid and into this solution was washed 12.8 g. (0.118 mole) of phenylhydrazine with the aid of 50 ml. of glacial acetic acid. In about one minute a yellow precipitate began to form. When precipitation appeared complete, the phenylhydrazone was collected on a filter and washed with ether. The phenylhydrazone weighed 34.8 g. (0.103 mole). The combined filtrate and washings were diluted with 500 ml. of water and extracted with ether. The ether extract was washed in turn with carbonate solution, twice with 5% hydrochloric acid, and twice with water. After the ether solution was dried over potassium carbonate and the ether removed on the steam-bath, the residue was distilled at 1 mm. The fraction of b.p. 145–155° weighed 27.7 g. (0.111 mole), 37%. Recrystallization from a petroleum ether-ligroin mixture yielded 19.2 g. of 2-bromo-1-acetonaphthone, m.p. 63–64° [literature (3) 64–65°].

Preparation of 2-chloro-1-acetonaphthone from β-chloronaphthalene. The Friedel-Crafts reaction at 0° between β-chloronaphthalene (13), acetyl chloride, and aluminum chloride in carbon disulfide was carried out similarly to the conversion of the β-bromonaphthalene, an 84% yield of the mixture of isomeric ketones being obtained. Distillation at reduced pressure was not necessary in this case, the product crystallizing soon after the removal of solvent. Recrystallization of 12.5 g. of the mixed ketone from 140 ml. of 80% ethanol yielded 6.3 g. of 2-chloro-1-acetonaphthone, m.p. 62.5–64.0°.

2-Acetamidonaphthalene. This material, m.p. 131–132° was prepared in 90–97% yield by the method of Kaufmann (14).

2-Acetamido-1-acetonaphthone. In a one-liter 3-necked flask in a good hood were placed 18.5 g. (0.10 mole) of 2-acetamidonaphthalene, 20.4 g. of acetic anhydride, and 200 ml. of anhydrous carbon disulfide. The flask was equipped with an efficient stirrer, an efficient reflux condenser protected with a drying tube, and a short length of ¾-inch rubber tubing connected to a conical flask for addition of 107 g. (0.80 mole) of aluminum chloride.

The contents of the flask were warmed to the reflux temperature with a pan of warm water. Then the aluminum chloride was added in small portions over a two-hour period to the well-stirred mixture. Refluxing was continued for two more hours and then the flask was allowed to stand for three hours.

The reflux condenser and the addition tube were removed and the flask was fitted with a dropping-funnel and a condenser for downward distillation. Dropwise addition of 250 ml. of water with stirring caused rapid distillation of carbon disulfide. Residual traces of carbon disulfide were distilled by warming the flask in warm water. Then, 200 ml. of 1.5 *N* hydrochloric acid was added rapidly and the flask was allowed to cool. The brown solid was removed by filtration and air-dried. A solution of this solid in hot 50% by vol. ethyl alcohol was filtered, treated with Norit, and cooled slowly. Two more recrystallizations of the deposited crystals yielded 10.9 g., 48%, of white crystalline product, m.p. 151°. The material yielded a 2,4-dinitrophenylhydrazone, m.p. 244° and gave a positive iodoform test.

2-Amino-1-acetonaphthone. (*a*) *From 2-acetamido-1-acetonaphthone.* The latter material was mixed with 5 times its weight of glacial acetic acid and 10 ml. of 18 *N* sulfuric acid per gram of amide and the mixture was held under reflux for two hours. The mixture was then chilled and neutralized with concentrated sodium hydroxide. The precipitated amine was dissolved in ether and the solution was dried over potassium carbonate. Bubbling hydrogen chloride gas into the ether solution precipitated the hydrochloride, which was filtered, dissolved in warm water, decolorized with Norit, and reprecipitated by dropwise addition of 10% sodium hydroxide until the solution was basic. The amine was dissolved in dilute acid, decolorized again, and reprecipitated. One recrystallization from water containing about 10% methanol yielded light golden platelets, m.p. 110–111°, in 80% yield.

(*b*) *Directly from 2-acetamidonaphthalene.* In a one-liter 3-necked flask were placed 18.5 g. (0.10 mole) of 2-acetamidonaphthalene, 67 g. (0.50 mole) of aluminum chloride, and 400 ml. of carbon disulfide. The flask was equipped with a powerful mercury-sealed stirrer, an efficient reflux condenser, and a dropping-funnel protected by a drying tube. The reflux condenser was fitted with a drying tube followed by a hydrogen chloride trap. The flask was cooled with an ice-bath and 9.3 g. (0.125 mole) of redistilled acetyl chloride was added in twenty minutes to the well-stirred mixture. Stirring was continued for three hours, at the end of which a gummy complex was formed. The flask and contents were allowed to come to room temperature and stand overnight. The next day, the mixture was heated to reflux in warm water and stirring was carried on as well as possible for one hour. Hydrogen chloride was copiously evolved at this point.

The flask was cooled and the carbon disulfide layer was decanted and discarded. To the residue in the flask was added about 300 g. of chopped ice and the mixture was left in the hood with occasional stirring until the vigorous hydrolysis was complete. Concentrated hydrochloric acid (100 ml.) was added and the mixture was warmed on the steam-bath to expel carbon disulfide. Then the mixture was held under reflux until the oil disappeared and a clear red-brown solution formed. The liquid was poured into an Erlenmeyer flask and the reaction flask was rinsed with hot hydrochloric acid (100 ml. of water and 50 ml. of conc'd hydrochloric acid). The rinsings were added to the Erlenmeyer flask, and its contents cooled. The deposited hydrochloride of 2-amino-1-acetonaphthone was dissolved in the minimum amount of boiling water. The solution was filtered and added to a mixture of 20 g. of sodium hydroxide, 50 ml. of water and 300 g. of chopped ice. The precipitated amine was removed by filtration and air-dried. Recrystallization with the use of Nuchar XXX from 100 ml. benzene yielded 11.1–13.0 g. (60–70%) of product, m.p. 110–111°, including a small second crop obtained by concentration of the mother liquor to about half the volume.

Further concentration of the mother liquor yielded a small amount of material, m.p. 163–164°, probably a position isomer of the main product.

Anal. Calc'd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99.

Found: C, 78.30; H, 6.03.

Conversion of 2-amino-1-acetonaphthone to 2-chloro-1-acetonaphthone. In a 600-ml. beaker, 46.2 g. (0.25 mole) of 2-amino-1-acetonaphthone[2] and 125 ml. of concentrated hydrochloric acid were stirred into a thin paste with a motor-driven stirrer. The mixture was cooled to −5° by an ice-salt bath and the diazotization was carried out with a solution of 17.3 g. (0.25 mole) of sodium nitrite in 100 ml. of water. The diazotization required about an hour, the temperature being kept below 0° during this time and for an additional fifteen minutes, while the mixture was stirred. A test for nitrous acid at this time was usually negative. When it was positive, a little urea was added.

The diazonium chloride solution was poured rapidly into a solution of cuprous chloride in concentrated hydrochloric acid maintained at 70°. The cuprous chloride (15) was prepared from 78.2 g. of cupric sulfate pentahydrate and dissolved immediately in 110 ml. of concentrated hydrochloric acid. After refluxing the whole mixture one hour, the dark liquid was left overnight.

[2] We are indebted to Dr. Elderfield at Columbia University, Dr. Hartshorn at Dartmouth College, and their co-workers for the preparation of some of this material.

After this, the crude product, a black tar, was filtered out and washed free from acid with water. It was dried in an evaporating dish in an oven at 70° for twenty-four hours, after which, on cooling, it solidified to a crumbly black solid. This was then distilled from a Claisen flask with a wide side-arm at 5 mm. The distillate soon solidified to a nearly white solid, which was recrystallized from alcohol or a mixture of petroleum ether and ligroin, to yield 33.2–35.8 g., 65–70%, of material, m.p. 64–65°, b.p. 158–160° (4 mm.).

Conversion of 2-amino-1-acetonaphthone to 2-bromo-1-acetonaphthone. 2-Amino-1-acetonaphthone (46.2 g., 0.25 mole) suspended in 100 ml. of 48% hydrobromic acid, was diazotized in the usual manner with a solution of 17.3 g. (0.25 mole) of sodium nitrite in 100 ml. of water. A cuprous bromide solution was prepared by adding a hot solution of 16.6 g. of sodium bisulfite and 11.0 g. of sodium hydroxide to a hot solution of 78.2 g. of cupric sulfate pentahydrate and 41.6 g. of potassium bromide. The precipitated cuprous bromide was filtered, washed, and dissolved in 100 ml. of 48% hydrobromic acid. The cold diazonium bromide solution was added to the cuprous bromide solution heated to 70°. Foaming was prevented with a few drops of caprylic alcohol.

The black tarry product, obtained as in the case of the chloro analog was distilled at 3 to 4 mm. from a Claisen flask with a wide side-arm, b.p. 164–166°. Recrystallization from hexane yielded 13.4 g., 22%, of light yellow crystals, m.p. 63–64°, mixed m.p. with 2-bromo-1-acetonaphthone prepared by the Friedel-Crafts reaction on β-bromonaphthalene, 63–65°.

Preparation of ω-bromo-2-haloacetonaphthones. 2-Chloro-1-acetonaphthone (35.0 g., 0.171 mole) was dissolved in 250 ml. of anhydrous ether in a 500-ml. 3-necked flask equipped with a stirrer, a small burette, and a thermometer. Approximately 50 ml. of roughly 2 *N* ethereal hydrogen chloride was added and 27.5 g. (0.172 mole) of bromine was added from the burette in about one hour. The reaction was started at 30° and the rest of the bromination was carried out below 15°. A white precipitate began to form after about half of the bromine had been added. After the bromination, the product was removed on a Büchner funnel and washed with cold, dry ether. The ethereal solution was washed with water, dried over potassium carbonate and evaporated to yield more crude product, the total crude yield being about 95%. Recrystallization from absolute alcohol yielded 41.2 g., 85%, of needles, m.p. 97–98°.

Analogous bromination of 2-bromo-1-acetonaphthone gave rise to crude product in 97% yield and, after recrystallization from hexane to final product, m.p. 114–116.5° in 72% yield. The analytical sample, m.p. 116–117°, was obtained after two more recrystallizations from hexane.

Reduction of bromo ketones to bromohydrins. 2-Chloro-1-naphthacyl bromide and 2-bromo-1-naphthacyl bromide were reduced to bromohydrins with aluminum isopropoxide as described elsewhere (10) in crude yields of 90 and 94% respectively. Recrystallization from hexane gave rise to the pure materials in yields of 77 and 88% respectively.

Preparation of amino alcohols. (*a*) *From bromo ketones* (*1*). The reaction between 2-chloro-1-naphthacyl bromide and diethyl-, dibutyl- or dihexyl-amine[3] was carried out in benzene or ether, the yields of dialkylammonium bromide being 84–95%. The yield of acetone on reduction with aluminum isopropoxide was 81–85%. The products were isolated either as free base or as the hydrochloride. The diethylamino compound as the free base was recrystallized from pet. ether (b.p. 30–60° or 60–70°). In the other two cases, the hydrochlorides were recrystallized from acetone-ether or acetone-pet. ether. Yields of pure materials were 18–36%.

(*b*) *From bromohydrins* (*10*). The mixtures of 1 mole of bromohydrin to 4 moles of dibutyl-, diamyl- or dihexyl-amine were held at 120° for 16–24 hours. Steam distillation from basic solution removed the excess amine. The products were taken up in ether, the solutions were dried and dry ethereal hydrogen chloride was used to precipitate the products in crude yields of 73–91%. Recrystallization from ethyl acetate-ether, acetone-pet. ether, or absolute alcohol-ether gave rise to pure materials in yields of 56–70%.

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[3] The dialkylamines were supplied in some cases by Dr. Elderfield and co-workers at Columbia University.

SUMMARY

Several approaches to the 2-halo-1-acetonaphthones have been examined, the best of which appears to involve the Friedel-Crafts reaction with 2-acetamidonaphthalene followed by hydrolysis and a Sandmeyer reaction.

A number of α-dialkylaminomethyl-2-chloro- and bromo-1-naphthalenemethanols have been prepared as possible antimalarials from the 2-halo-1-acetonaphthones.

LOS ANGELES, CALIF.

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