The methods of preparation are illustrated by the following examples.

4-(*p*-Methylphenacyl)-morpholine Hydrobromide.—Heat was evolved when 3.5 g. of morpholine and 5.4 g. *p*-methylphenacyl bromide were mixed without any solvent. The reddish-brown sticky paste recrystallized from ethanol yielded 5.35 g. (45%) of white crystals, m.p. 200–202°.

4-Methyl-4-(5,6,7,8-tetrahydro-β-naphthacyl)-morpholinium Iodide.—5,6,7,8-Tetrahydro-β-naphthacyl bromide was prepared in 43% yield by dropwise addition of a mixture of 204 g. of bromoacetyl bromide (1.01 moles) and 120 g. of tetralin (0.91 mole) in 600 ml. of carbon disulfide to 150 g. of aluminum chloride (1.13 moles) in 1200 ml. of carbon disulfide at 0–10°, stirring 2 hours, and decomposing with ice and dilute hydrochloric acid, m.p. 69° after recrystallization from isopropyl alcohol to constant melting point. This product was also obtained in approximately the same yield by bromination of 5,6,7,8-tetrahydro-2-acetonaphthone in acetic acid. Thirty grams of the bromide dissolved in 150 ml. of acetone, mixed with 25 g. of sodium iodide, the sodium bromide filtered off, the acetone solution evaporated and the residue recrystallized from hot methanol yielded 18 g. (49%) of 5,6,7,8-tetrahydro-β-naphthacyl iodide, m.p. 58–59°. A mixture of 7.80 g. of this iodide (0.026 mole) and 2.36 g. of 4-methylmorpholine (0.026 mole) in 50 ml. of chloroform produced a large quantity of white crystals within 36 hours. After standing several days the salt was filtered off and purified by repeatedly dissolving in hot methanol and adding ether until a constant melting point of 192–193° was reached; yield of pure product 2.38 g. (23%).

Acknowledgments.—We wish to express our appreciation to Dr. M. J. Shear and Dr. J. L. Hartwell of the National Cancer Institute and Dr. W. M. Hoehn and Dr. L. H. Goodson of Midwest Research Institute for their interest and arranging screening tests against tumors in mice, to the National Cancer Institute Analytical Laboratory for carbon and hydrogen analyses, and to Miss Betty Gay Walden, Miss Marguerite Close, Mr. George Biggerstaff, Mr. Gene Moore, Mr. Hugh Jenkins, Mr. Tom Fuller, Mr. Lilburn Norton and Mr. Harold Lyons for Volhard and Kjeldahl analyses and assistance in preparation of intermediates and purification of some of the products.

JEFFERSON CITY, TENN. RECEIVED MARCH 7, 1951

Oximes of β-Naphthacyl Halides and their Pyridinium Salts[1]

BY CARL T. BAHNER, PAUL T. SCOTT, CAROLYN CATE, BETTY GAY WALDEN AND H. DAVID BALDRIDGE, JR.

An oxime of β-naphthacylpyridinium iodide has been reported to damage sarcoma cells *in vivo*,[2] but the configuration of the oxime was not specified. In order to settle this point we have prepared the antiform of the oximes of β-naphthacyl bromide and iodide and their pyridinium salts and have submitted samples of the salts to the National Cancer Institute for screening. The 3-bromopyridinium salt has been reported in another article.[3]

Experimental

Anti-β-naphthacyl Bromide Oxime (I).—A saturated solution of 13.95 g. of hydroxylamine hydrochloride in water was added to 50 g. of β-naphthacyl bromide in 1800 ml. of methanol at room temperature, the mixture allowed to stand 6 hours at room temperature, a part of the methanol removed by vacuum distillation, the liquid cooled and filtered to recover one crop of crystals, the removal of solvent and chilling repeated to obtain a second and a third crop of crystals which were then subjected to systematic fractional crystallization from methanol. There were obtained 15.4 g. of crystals melting at 172.5°, 9.30 g. melting at 170° and 8.0 g. melting at 169°. Repeated recrystallization produced a fraction melting at 174°. A sample of the less soluble, high melting crystals was subjected to Beckmann rearrangement followed by hydrolysis and a 61% yield of β-naphthylamine was isolated, but no β-naphthoic acid could be detected.

Anti-β-naphthacylpyridinium Bromide Oxime.—The pyridinium salt, white crystals, m.p. 245°, was obtained in 83% yield by reaction of I with pyridine in alcohol. It was purified by recrystallization from ethanol and water.

Anal. Calcd. for $C_{17}H_{15}BrN_2O$: Br, 23.25. Found: Br, 23.21, 23.31.

Anti-β-naphthacyl Iodide Oxime (II).—A solution of 0.92 g. of I dissolved in a minimum volume of acetone was mixed with 1.42 g. (excess) of sodium iodide in 10 ml. of acetone, the sodium bromide removed after several hours by filtration and the oxime obtained in crystalline form by cooling the solution in an ice-bath and filtering. After repeated recrystallization from ethanol the product melted at 148°. Beckmann rearrangement, followed by hydrolysis, gave a 71% yield of β-naphthylamine, m.p. 105–107°. A portion of this compound was treated with acetic anhydride to give the N-acetyl derivative, m.p. 134–135°. No β-naphthoic acid was isolated.

The oximes appeared to be stable for several days at room temperature, but after several weeks most of the samples had turned brown and showed other indications of decomposition.

Anti-β-naphthacylpyridinium Iodide Oxime.—A mixture of 2.5 g. of II (0.008 mole) and 0.63 g. of pyridine (0.008 mole) in a little acetone seemed to react completely within a few minutes. After several hours 2.6 g. of white crystals were removed by filtration and washed with chloroform; m.p. 222–223° (dec.) after recrystallization from methanol.

Anal. Calcd. for $C_{17}H_{15}IN_2O$: C, 52.34; H, 3.88. Found: C, 51.94; H, 4.02.

Acknowledgments.—The authors wish to express their thanks to Dr. M. J. Shear and Dr. J. L. Hartwell of the National Cancer Institute for their interest in this project and for obtaining carbon and hydrogen analyses on one of the compounds.

DEPARTMENT OF CHEMISTRY
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN. RECEIVED MARCH 31, 1951

Investigations in the Acetylene Series. I. The Reactions of 3-Methyl-1-butyn-3-ol with Phosphorus Trichloride and of 3-Methyl-3-buten-1-yne with Hydrochloric Acid

BY ERNST D. BERGMANN AND D. HERRMAN

Hennion, Sheehan and Maloney[1] have recently reported on the reaction of 3-methyl-1-butyn-3-ol (I) with hydrochloric acid under various conditions. The present note supplements their conclusions.

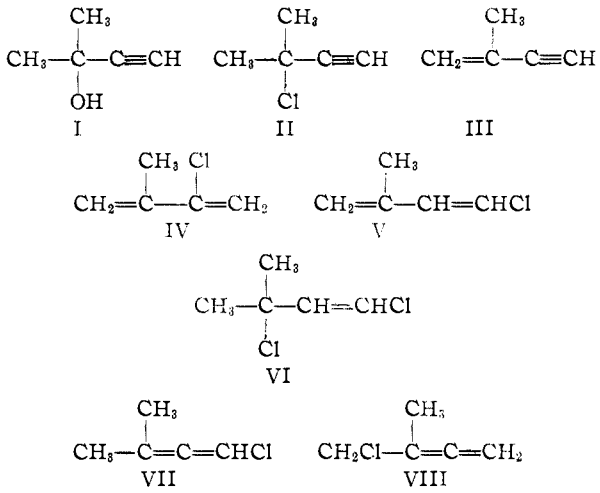
In the reaction of 3-methyl-1-butyn-3-ol (I) with phosphorus trichloride, the corresponding *t*-chloride (II) and 3-methyl-1-chloro-1,3-butadiene (V) were obtained; they were identified by their reactions. When hydrochloric acid reacted upon (I), 3-methyl-1-chloro-1,2-butadiene (VII), isolated by Hennion and co-workers[1] in their experiments,

(1) This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, Public Health Service, for which we are grateful.

(2) Albert J. Dalton, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 246; *cf.* J. L. Hartwell and S. R. L. Kornberg, THIS JOURNAL, **68**, 1131 (1946).

(3) Carl T. Bahner, Wm. K. Easley, Madge D. Pickens, Harold D. Lyons, Lilburn L. Norton, Betty Gay Walden and George E. Biggerstaff, THIS JOURNAL, **73**, 3499 (1951).

(1) Hennion, Sheehan and Maloney, THIS JOURNAL, **72**, 3542 (1950).



was not encountered, but instead the 3-methyl-4-4-chloro-1,2-butadiene (VIII) was formed (see below). Its formation—from the dehydration product (III) of (I)—is in accord with the scheme proposed by Carothers, Berchet and Collins[2] for the conversion of vinylacetylene into chloroprene.

The conditions favoring the formation of the isomers (II), (V) and (VIII), respectively, were determined. It was known[3] that (IV) is best obtained when 3-methyl-3-buten-1-yne (III) is treated with concentrated hydrochloric acid in the presence of cuprous and ammonium chlorides.

(II) is formed in 47% yield when (I) reacts at 0–5° with phosphorus trichloride in presence of cuprous and ammonium chlorides. It is easily recognized by its instantaneous response to silver nitrate solution.

(V) is obtained as by-product of (II) in 23% yield in the above reaction; the two isomers are separated by fractional distillation.

(VIII) is prepared from 3-methyl-3-buten-1-yne (III) by treatment with concentrated hydrochloric acid and calcium chloride. At a conversion of 49%, the ratio of (VIII) and (IV) formed in this reaction, was 7:10; the boiling points of the two isomers at atmospheric pressure differ by 14°.

TABLE I

PHYSICAL CONSTANTS OF COMPOUNDS C_5H_7Cl

H, Hennion, *et al.*[1]; F, Favorskaja[4]; C, Carothers and Coffman[3]; B, present authors

No.		Boiling point °C.	Mm.	d^{20}_4 (H, 25°)	$n^{20}D$ (H, 25°)
II	H	75–76	760	H 0.9035	H 1.4155
	F	74–76		B .9080	B 1.4172
	B	76–76.5	765		
IV	H	93		H .9523	H 1.4640
	C	93	760	C .9593	C 1.4689
	B	92–92.5	765	B .9580	B 1.4678
V	F	97.5–98		F .9543	F 1.47189
	B	101.5–102.5	765	B .9527	B 1.4768
VII	H	100–103		H .9435	H 1.4738
	F	101–104		F .9515	F α1.46697
VIII	B	106–107	765	B .9599	B 1.4752

(2) Carothers, Berchet and Collins, THIS JOURNAL, **54**, 4066 (1932).

(3) Carothers and Coffman, *ibid.*, **54**, 4071 (1932). Compare du Pont, U. S. Patent 1,950,441 (*Chem. Zentr.*, **105**, II, 1037 (1934)).

(4) Favorskaja, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 386 (1939) (*C. A.*, **33**, 9281 (1939)).

In Table I the physical constants of the various compounds are summarized.

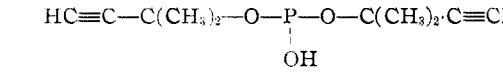
As toward maleic anhydride,[1] the 1,3-dienes (IV) and (V) show a characteristic difference in their reaction with 1,4-naphthoquinone; (IV) gives a chlorinated hydro-anthraquinone,[3] whilst (V) reacts with evolution of hydrogen chloride and loss of hydrogen, 2-methylanthraquinone being obtained.

The structure of (VIII) is supported by its vigorous response to silver nitrate. It is differentiated from the tertiary chloride (II) by its positive reaction with sodium iodide. (II), as tertiary chloride, is naturally refractory.[5]

Experimental

1-Chloro-3-methyl-1,3-butadiene (V) and 3-Chloro-3-methyl-butyne (II).—At a temperature not exceeding 5° and with stirring, phosphorus trichloride (150 cc.) was added during four hours to 3-methylbutyn-3-ol (I) (420 g.), containing 25 g. of cuprous chloride, 12.5 g. of ammonium chloride and a trace of *t*-butyl-catechol. The product was fractionated under 100 mm. pressure, giving two main cuts: (a) b.p. 25–35°, b.p. 76–76.5° (765 mm.), 239 g. (47%), (II); (b) b.p. 35–50°, b.p. 101–102.5° (765 mm.), 115 g. (23%), (V). *Anal.* Calcd. for C_5H_7Cl (V): C, 58.8; H, 6.8; Cl, 34.4; available Cl, 0. Found: C, 58.6; H, 7.0; Cl, 34.4; available Cl, 0.2. ("Available" Cl: titratable after digestion with alcoholic potassium hydroxide solution for two hours.)

The residues of a number of such batches were fractionated *in vacuo*. Two additional products were thus obtained: (a) b.p. 66–67° (80 mm.), consisting of a dichloro compound (possibly (VI)). *Anal.* Calcd. for $C_5H_8Cl_2$: Cl, 51.1; available Cl, 25.5. Found: Cl, 50.9; available Cl, 25.4). (b) b.p. 100° (5 mm.). This fraction, secured only in very small quantities, contained phosphorus, but no chlorine; it is, perhaps, a diester of (I) and phosphorous acid (calcd. for $C_{10}H_{15}O_3P$: P, 14.5. Found: P, 15.2).



Such diesters are normally formed from phosphorus trichloride and primary and secondary alcohols[6]; however, tertiary acetylenic alcohols of type (I) are known to form esters which appear to be somewhat more stable than esters of tertiary alcohols normally are.[7]

1,4-Naphthoquinone and (V).—A mixture of 1 g. of 1,4-naphthoquinone and 2 cc. of (V) was heated for 30 minutes at 100°; after this period, the evolution of hydrogen chloride had ceased. The product, 2-methylanthraquinone, was triturated with methanol and recrystallized from acetone; m.p. and mixed m.p. 172°. (*Anal.* Calcd. for $C_{15}H_{10}O_2$: C, 81.1; H, 4.5. Found: C, 80.9; H, 4.6.)

3-Methyl-4-chloro-1,2-butadiene (VIII) and 3-Methyl-2-chloro-1,3-butadiene (IV).—At a temperature of 10° and with vigorous agitation, 3-methyl-3-buten-1-yne (III)[2,8] (233 g.) was treated with concentrated hydrochloric acid (800 cc.), containing calcium chloride (25 g.). After five hours, the organic layer was separated, washed with water, dried and fractionated. After unchanged starting material (119.8 g., 51%), a wide cut was secured (30–70° (100 mm.), 142.5 g.) and refractionated: (a) b.p. 92–92.5° (760 mm.) 70 g. (40%, calcd. on (III) entered into reaction): (IV); (b) b.p. 106–107° (760 mm.) 50 g. (29%, calcd. on (III) entered into reaction): (VIII).

Rearrangement of (VIII) to (IV).—When 20 g. of (VIII) was shaken at 20° for four hours with 5 cc. of concd. hydrochloric acid, 0.5 g. of cuprous chloride and 0.25 g. of ammonium chloride, 5.5 g. of (IV), b.p. 90–93°, $n^{20}D$ 1.4680, was obtained upon fractional distillation of the reaction

(5) Conant and co-workers, THIS JOURNAL, **46**, 232 (1924); **47**, 476, 488 (1925); E. Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **B20**, 161 (1933).

(6) McCombie, Saunders and Stacey, *J. Chem. Soc.*, 380 (1945).

(7) Rupe and Vonaesch, *Ann.*, **442**, 74 (1925). See Nazarov, *C. A.*, **33**, 5682 (1939).

(8) E. Bergmann and Zimkin, *J. Chem. Soc.*, 3455 (1950).

product (36.4%). 3.0 g. of the starting material, b.p. 104–106°; $n^{20}D$ 1.4732, was recovered; the intermediary fraction, boiling between 93 and 104°, amounted to 10.8 g.

The greater part of this investigation was carried out in the Research Laboratories of Publicker Industries, Inc., Philadelphia, Pa.

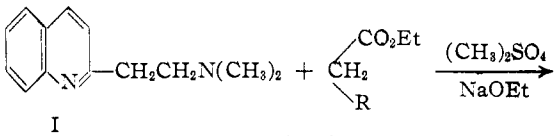
DANIEL SIEFF RESEARCH INSTITUTE
WEIZMANN INSTITUTE OF SCIENCE
REHOVOTH, ISRAEL RECEIVED DECEMBER 11, 1950

A Study of the Alkylation of Active Methylene Compounds Using 2-(β-Dimethylaminoethyl)-quinoline[1,2]

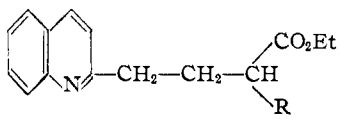
BY V. BOEKELHEIDE AND G. MARINETTI

In previous publications,[3,4] we have reported on the synthesis of various quinolizidine derivatives by the condensation of 2-vinylpyridine with active methylene compounds followed by reductive cyclization. Because some of the compounds prepared in this work showed activity as muscular relaxant agents,[5,6] it seemed of value to examine some of the corresponding compounds in the quinoline series.

For the synthesis of the quinoline derivatives, it was necessary to modify the previous approach due to difficulties experienced in the laboratory preparation of 2-vinylquinoline. Thus, instead of attempting to convert 2-(β-dimethylaminoethyl)-quinoline (I) to 2-vinylquinoline by a Hofmann decomposition, the base was employed directly as an alkylating agent using the procedure developed by Albertson, Archer and Suter for similar alkylations with other Mannich bases.[7] As is shown below, the alkylation of diethyl malonate, ethyl acetoacetate and ethyl benzoylacetate proceeded smoothly to give the corresponding γ-(2-quinolyl)-butyric esters in yields of 33 to 44%.



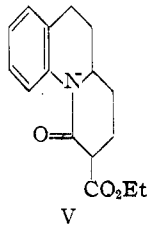
I



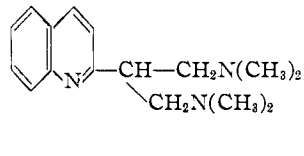
II, R = $-CO_2Et$
III, R = $-COCH_3$
IV, R = $-COC_6H_5$

As would be expected, when III and IV were boiled with 20% hydrochloric acid, hydrolysis and decarboxylation occurred to give in good yield the corresponding ketones, 1-(2′-quinolyl)-4-pentanone and γ-(2-quinolyl)-propiophenone, respectively.

Although it would be anticipated that the quinoline esters and ketones obtained in this work should undergo reductive cyclization to give benzoquinolizidine derivatives in an analogous fashion to the corresponding compounds of the pyridine series, only one example of this has thus far been studied. When II was subjected to high pressure hydrogenation using Raney nickel catalyst at 100°, approximately two molar equivalents of hydrogen were absorbed and a neutral compound, $C_{16}H_{19}NO_3$, resulted. This has been assigned structure V by analogy with the reductive cyclization of diethyl β-(2-pyridyl)-ethylmalonate.[8]



V



VI

The preparation of the starting material, 2-(β-dimethylaminoethyl)-quinoline, was accomplished by a modification of the procedure previously used by Bartholomaus.[8] The use of an excess of quinaldine in this Mannich base condensation is essential for, when equimolar quantities of quinaldine, dimethylamine hydrochloride and formaldehyde were employed, the principal product of the reaction was the di-Mannich base, VI. Since it seemed possible that VI could be used for preparing some interesting branched chain quinoline esters, we investigated the reaction of VI with diethyl malonate. Unfortunately, this alkylation proved to be rather complex in character. Provisional formulas for two of the products isolated are indicated in the experimental section.

The only compound in this series to show muscular relaxant activity was 1-(2′-quinolyl)-4-pentanone and this was much less active than previous compounds of the pyridine series.[9]

Experimental[10]

2-(β-Dimethylaminoethyl)-quinoline (I).—A solution of dimethylamine hydrochloride (28.6 g., 0.35 mole) in 30 ml. of formalin was added dropwise with stirring to quinaldine (100 g., 0.70 mole). After the heterogeneous reaction mixture was heated for one-half hour at 50°, it became homogeneous. The reaction mixture was then cooled, diluted with 50 ml. of water, and extracted with ether to remove unreacted quinaldine. When the aqueous layer was made basic, the oil which separated was taken up in ether and dried over sodium sulfate. After removal of the ether, distillation of the residue gave 27.5 g. (39%) of a light yellow oil; b.p. 120–129° at 0.7 mm., $n^{25}D$ 1.5821. The styphnate of I was obtained from acetone as yellow crystals, m.p. 148–149° (lit.,[8] 148°); the mercuric chloride double salt of I crystallized from alcohol as white needles, m.p. 160–161°, dec. (lit.,[8] m.p. 165° dec.). In our hands boiling the reaction mixture under reflux, as indicated by Bartholomaus,[8] caused considerable tar formation and resulted in very poor yields of the desired product.

1,3-Di-(dimethylamino)-2-(2′-quinolyl)-propane (VI).—To a solution of dimethylamine hydrochloride (65.2 g., 0.8 mole) in 69 ml. of a 35% formalin solution maintained at 50°, quinaldine (114 g., 0.8 mole) was added dropwise with stirring. After the mixture had been heated at 50° for two hours, it changed from an emulsion to a clear orange solu-

(1) Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

(2) Abstracted from the B.S. thesis of G. Marinetti.

(3) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(4) V. Boekelheide and E. J. Agnello, *ibid.*, **72**, 5005 (1950).

(5) V. Boekelheide and J. Mason, *ibid.*, **73**, 2356 (1951).

(6) J. F. O'Leary, D. E. Leary and I. H. Slater, *Proc. Soc. Exp. Biol. and Med.*, in press.

(7) N. F. Albertson, S. Archer and C. M. Suter, THIS JOURNAL, **67**, 6 (1945); see also W. Herz, K. Dittmer and S. J. Cristol, *ibid.*, **68**, 1698 (1947); N. J. Leonard and E. H. Burk, Jr., *ibid.*, **72**, 2543 (1950).

(8) E. Bartholomaus, German Patent 497,907, May 8, 1927.

(9) We are indebted to Dr. I. H. Slater, University of Rochester, School of Medicine and Dentistry, Rochester, New York, for the physiological testing.

(10) Analyses by Miss C. King and the Micro-tech Laboratories.