CONCLUSIONS

The analyses of the data of Patel, Banker, and DeKay by means of theory demonstrates the possible usefulness of the quantitative theory in future studies. Simple relations could be employed to help evaluate the proposed mechanisms. It would be of interest to investigate experimentally other types of ointments, e. g., the water-in-oil type, suspension type, bound drug type, etc., and compare results with appropriate theoretical relationships (1, 2).

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Synthesis of Some Monoamino Alkynes

By JOHN L. NEUMEYER† and JOSEPH G. CANNON‡

The preparation of a series of monoamino alkynes has been undertaken. A method of reduction of the substituted and unsubstituted quinolines to their corresponding tetrahydro derivatives is presented. Some of the monoamino alkynes showed weak fungicidal activity against *T. mentagrophytes*.

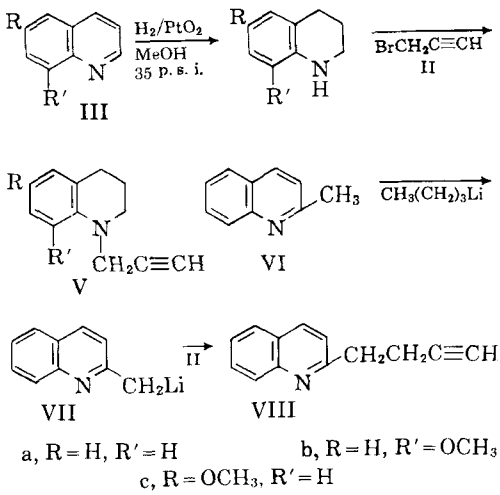
DURING THE COURSE of the investigation of a series of unsymmetrically alkylated acetylenic bis-quaternary ammonium compounds, it was necessary to prepare a series of monoamino alkynes (I)

$$RCH_2C{\equiv}CH$$
I

R = Pyrrolidino, diethylamino, 1,2,3,4-tetrahydroquinolino, 6-methoxy-1,2,3,4-tetrahydroquinolino, 8-methoxy - 1,2,3,4 - tetrahydroquinolino, 2 - quinolyl methyl

The structural similarity of certain of these intermediates to a series of 8-hydroxy-2-quinoline acrylic acids, prepared by Vaidya and Cannon (1), exhibiting fungicidal activity, prompted us to screen these compounds as potential fungicides. Preliminary screening against *T. mentagrophytes*, and *C. albicans* revealed that some of these compounds showed fungicidal activity against *T. mentagrophytes* at concentrations of 100–500 mcg./ml.

Propargyl bromide (II) was employed as the alkylating agent for the preparation of these compounds by the following routes.



a, R = H, R′ = H b, R = H, R′ = OCH_3

c, R = OCH_3, R′ = H

The catalytic reduction of quinoline and of the 6- and 8-methoxy-quinolines (III a, b, and c) was based on a method of Skita and Meyer (2) who reduced quinoline to decahydro- and tetrahydroquinoline with platinum chloride in glacial acetic acid. Employing platinum oxide (Adams) in methanol at 35 p.s.i., we successfully reduced the quinolines III a, b, and c to their respective tetrahydro derivatives in 80–96% yields. Propargyl bromide (II) was then treated with a 1-molar excess of the appropriate tetrahydroquinoline in isopropyl alcohol. The formation of quaternary propargyl halide salts was prevented by adding the propargyl bromide slowly to the amine. The alkynyl amines could be readily purified by fractional distillation

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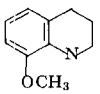
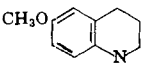
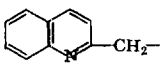
TABLE I.—MONOAMINE ALKYNES
R—$CH_2C{\equiv}CH$

Compound	M.p. or B.p., °C.	n_D^{25}	Method	Yield, %	Formula	Analysis, % Calcd.	Analysis, % Found
$(CH_3CH_2)_2N$—	52/70 mm.	1.4291	B	75	...	...	...
Hydrochloride	194–195[a]	...	..	..	$C_7H_{14}ClN$	N, 9.50 Cl, 24.10	N, 9.18 Cl, 24.04
	92–94/150 mm.[b]	1.4622	B	78	...	...	...
Hydrochloride	151–151.5[c,d]	...	..	..	$C_7H_{12}ClN$	N, 9.63 Cl, 24.41	N, 9.43 Cl, 24.48
	92–94/0.3 mm.	1.5822	C	86	$C_{12}H_{13}N$	C, 84.20 H, 7.65 N, 8.17	C, 83.84 H, 7.60 N, 8.66
Hydrochloride	154–156[c,e]	...	..	..	$C_{12}H_{14}ClN$	N, 6.74 Cl, 17.08	N, 6.48 Cl, 16.90
	94–98/0.07 mm. 48–49[f]	... ...	C ..	75 ..	$C_{13}H_{15}NO$ ...	C, 77.60 H, 7.46 N, 6.97	C, 77.61 H, 7.34 N, 7.00
Hydrochloride	155–157[e]	...	..	..	$C_{13}H_{16}ClNO$	N, 5.89 Cl, 14.92	N, 5.56 Cl, 14.59
	100–102/0.01 mm. 45–46[g]	... ...	C ..	78 ..	$C_{13}H_{15}NO$ ...	C, 77.60 H, 7.46 N, 6.97	C, 77.41 H, 7.20 N, 7.58
Hydrochloride	156–158[e,f]	...	..	..	$C_{13}H_{16}ClNO$	N, 5.89 Cl, 14.92	N, 5.61 Cl, 14.57
	100–102/0.08 mm.	1.6042	D	33	$C_{13}H_{11}N$	C, 86.28 H, 6.08 N, 7.74	C, 86.61 H, 6.07 N, 8.52
Hydrochloride	144.5–146[g]	...	..	..	$C_{13}H_{12}ClN$	N, 6.47 Cl, 16.29	N, 6.77 Cl, 16.50

[a] Recrystallized from absolute ethanol-ether. [b] Biel (7) reports 74–77° (85 mm.). [c] Hygroscopic. [d] Recrystallized from *n*-butanol-Skelly B. [e] Recrystallized from isopropyl alcohol. [f] Recrystallized from Skelly A. [g] Recrystallized from ethanol-water. [h] Recrystallized from ethanol-Skelly B.

at reduced pressure. A 2-quinolyl derivative was prepared by treating *n*-butyl lithium with quinaldine (VI); the resulting 2-(lithio methyl) quinoline (VII) was condensed with an equimolar quantity of propargyl bromide, to yield 2-(3-butynyl) quinoline (VIII).

EXPERIMENTAL

All melting points were obtained in a Hershberg-type, silicone filled melting point apparatus equipped with Anschutz immersion thermometers. The samples were placed in the circulating silicone bath 10° below the melting points and heated at the rate of 1–2° per minute. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England, and Huffman Microanalytical Laboratories, Wheatridge, Colo. Infrared spectra were determined on a Beckman IR-5 double-beam infrared recording spectrophotometer.

A. Substituted 1,2,3,4-tetrahydroquinolines

8 - Methoxy - 1,2,3,4 - tetrahydroquinoline.—8-Hydroxyquinoline was converted to 8-methoxyquinoline with dimethyl sulfate in 53% yield by the method of Vogel (3) m.p. 45–46° [Kaufman and Rothlin (4) reported 46–47°]. Eight grams (0.05 mole) of 8-methoxyquinoline in 100 ml. of methanol was hydrogenated in a Parr hydrogenation apparatus using 0.4 Gm. of platinum oxide as the catalyst; the calculated amount of hydrogen was absorbed in 50 minutes. The product was isolated by removing the catalyst by filtration, evaporating the solvent under reduced pressure, and fractionally distilling the residue, b.p. 94–98° (0.75 mm.), yield 7 Gm. (87%); n_D^{26} 1.5846.

Anal.—Calcd. for $C_{10}H_{13}NO$: C, 73.60; H, 7.98; N, 8.60. Found: C, 73.82; H, 7.83; N, 9.02.

The benzenesulfonamide of this secondary amine was prepared by shaking 0.5 Gm. of the amine in 25 ml. of 5% solution of sodium hydroxide and 1 Gm. of benzenesulfonyl chloride. An oil separated which, after standing for several days, crystallized. The yellow needles were recrystallized several times from 95% ethanol to yield a white crystalline product, m.p. 91.8–92.4°.

Anal.—Calcd. for $C_{16}H_{17}NO_3S$: C, 63.29; H, 5.65; N, 4.62. Found: C, 63.07; H, 5.30; N, 4.90.

6-Methoxy-1,2,3,4-tetrahydroquinoline (Thalline).—Twenty-five grams (0.157 mole) of 6-methoxyquinoline (Eastman white label) in 100 ml. of methanol was hydrogenated in a Parr hydrogenation apparatus using 0.4 Gm. of platinum oxide as the catalyst. The calculated amount of hydrogen was absorbed in 19 hours. The product was purified by vacuum distillation to give 24 Gm. (96% yield) of a pale yellow oil b.p. 84–85° (0.01 mm.). The oil solidified on cooling and the compound was recrystallized from 95% ethanol, m.p. 40–42°. [Cromwell (5) using a copper chromite catalyst under a pressure of 1800 lbs./sq. in. at 180° reported a product with a m.p. 42–43° in 93% yield.]

B. 3-Amino-1-propynes

To 1.0 mole of secondary amine in 150 ml. of anhydrous ethyl ether was added, with stirring,

59.5 Gm. (0.5 mole) of propargyl bromide (Aldrich Chemical Co.). The mixture was stirred at reflux for 12 hours. The ether solution was decanted from the oily amine hydrobromide layer, and the latter was extracted three times with ether. The ether was evaporated from the combined ether extracts and the residue was fractionated at reduced pressure (see Table I). The hydrochloride salts were prepared by passing dry hydrogen chloride through ether solutions of the amines. The precipitated salts were collected on a filter, washed with ether and were recrystallized (see Table I).

C. Aminoalkynyltetrahydroquinolines

To 0.18 mole of a freshly distilled 1,2,3,4-tetrahydroquinoline in 35 ml. of isopropyl alcohol was added 10.7 Gm. (0.09 mole) of propargyl bromide over a period of 30 minutes with stirring. The reaction mixture was refluxed 2 hours, then the mixture was cooled to 4° and was allowed to stand for 12 hours. The precipitate of the 1,2,3,4-tetrahydroquinoline hydrobromide was removed by filtration, and the filtrate was subjected to fractional distillation (see Table I).

The hydrochloride salts were prepared by passing dry hydrogen chloride through an ether solution of the amine. The precipitated salts were collected on a filter, washed with ether, and were recrystallized (see Table I).

D. 2-(3-Butynyl)quinoline

2-(Lithio methyl)-quinoline was synthesized by the method of Cannon (6) for the preparation of 1-(lithio methyl) isoquinoline. To the ethereal solution containing 0.1 mole of 2-(lithio methyl)-quinoline was added, in a slow stream and with stirring, a solution of 11.9 Gm. (0.1 mole) of propargyl bromide in 100 ml. of anhydrous ether. The solution turned a deep purple color and a moderate boiling ensued. As additional organic halide was added the purple color became fainter and finally disappeared. Stirring was continued overnight at room temperature, during which time a brown precipitate formed. Stirring was continued while 100 ml. of distilled water was slowly added. The aqueous layer was removed and discarded and the ethereal solution which also contained a considerable quantity of a brown precipitate was filtered and washed several times with water. After drying with anhydrous magnesium sulfate and filtering, the ether was removed from the filtrate on a steam bath and the brown-black oily residue was distilled under reduced pressure (see Table I). $\lambda_{max.\mu}^{film}$ 3.05 (=CH stretching), m 4.70 (—C≡C— stretching.)

E. Fungicidal Activity

Fungicidal activity was evaluated by a serial dilution procedure, utilizing Sabouraud's medium. The tubes were incubated at 25°; turbidimetric and growth readings were taken after 48 hours.

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Some 1,2,3,4-Benzothiatriazine 1,1-Dioxides

By SCOTT J. CHILDRESS

1,2,3,4-Benzothiatriazine 1,1-dioxide analogs of chlorothiazide have been prepared and tested for diuretic activity.

NOVELLO and Sprague (1) in 1957 reported the synthesis and diuretic activity of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (chlorothiazide). Since then numerous analogs have been described (2). There are no specific structural requirements for activity except for the presence of a sulfamyl group and even this can be substituted (3). It seemed to be of interest to prepare some substituted 1,2,3,4-benzothiatriazine 1,1-dioxides and examine them for diuretic activity.

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In order to isolate stable compounds, it was necessary to have an alkyl group in the 2-position. For convenience in synthesis, the 7-sulfamyl group was also substituted by an alkyl group. It did not seem that such substitution would destroy any potential activity in the benzothiatriazine 1,1-dioxides, for 5-chloro-2,4-bis-(methylsulfamyl)aniline, an intermediate, is reported to have diuretic properties (4). Also, methyl and isopropyl substituents in sulfamyl groups are removed metabolically in some cases (5).

The desired benzothiatriazine 1,1-dioxides were prepared by treatment of the appropriate 5-chloro-2,4-bis-(alkylsulfamyl)aniline with nitrous acid (6). The intermediates are listed in Table I and the products in Table II. The benzothiatriazine 1,1-dioxides proved to have statistically significant diuretic activity in rats (7).