ity is quite favorable. It is interesting to note that when a tertiary amine is quaternized, its antifibrillatory activity is lost. For example, the methiodide of N-3,4-dimethoxybenzyl-N-methyl-4-methoxyphenethylamine shows no antifibrillatory activity.

Experimental[3]

Preparation of Secondary Amines (Table II) General Procedure.—A mixture of equimolecular quantities of the appropriate benzaldehyde and phenethylamine was allowed to stand at room temperature for twenty hours or heated *in vacuo* for one hour on a steam-bath. The mixture was dissolved in ethanol and reduced catalytically in the presence of palladium–charcoal. After filtering off the catalyst, alcoholic hydrogen chloride solution was added followed by ether where necessary. The solid hydrochloride which precipitated was filtered off, washed with ether, dried and recrystallized from water or isopropyl alcohol.

Preparation of Tertiary Amines (Table II) General Procedure.—A mixture of the secondary amine base (1 mole), 35–40% formaldehyde (1.1 mole) and formic acid (2.5 mole) was heated on the steam-bath for eight to twelve hours. An excess of sodium hydroxide solution was added to the reaction mixture and the base was extracted with ether. Addition of alcoholic hydrogen chloride solution to the dried ether extract yielded the desired tertiary amine hydrochloride. The products were purified by recrystallization either from isopropyl alcohol or a mixture of ethanol and ether.

N-(3,4-Dimethoxybenzyl)-N-ethyl-4-methoxyphenethylamine Hydrochloride.—Twenty grams of 3,4-dimethoxybenzyl-4-methoxyphenethylamine was added to a mixture of 8.1 g. of potassium hydroxide in 60 ml. of water and 120 ml. of acetone and the resulting mixture was refluxed to effect dissolution. Ethyl sulfate (11.5 g.) was added and the mixture refluxed for eight hours, acidified with dilute hydrochloric acid, and the acetone removed by distillation. The residual mixture was diluted with water and extracted with ether to remove a small amount of insoluble oil. The aqueous solution was made basic with sodium hydroxide solution. After ether extracting, the extract was dried and the ether removed by distillation. The residual material (17.5 g.) was dissolved in ethanol, alcoholic hydrogen chloride was added, and the solution was seeded with the hydrochloride of the starting material. On standing, 2 g. of this hydrochloride separated and was filtered off. The filtrate was diluted with ether to yield 16.5 g. of product, melting at 132–135°. After recrystallization from isopropyl alcohol it melted at 134.8–136.6° cor.

Anal. Calcd. for $C_{20}H_{27}NO_3 \cdot HCl$: C, 65.65; H, 7.71; N, 3.83. Found: C, 65.77; H, 7.57; N, 3.70.

N-3,4-Dimethoxybenzyl-N-methyl-4-methoxyphenethylamine Methiodide.—The base from 5 g. of N-3,4-dimethoxybenzyl-N-methyl-4-methoxyphenethylamine hydrochloride was dissolved in 75 ml. of acetone and to it was added 12 ml. of methyl iodide. The mixture was refluxed for two hours, cooled and filtered. The solid (6.2 g.) was triturated with hot acetone, filtered off and washed with acetone and then with ether. After being dried *in vacuo* the product melted at 206–207.2° cor.

Anal. Calcd. for $C_{20}H_{28}INO_3$: I, 27.75; OCH_3, 20.36. Found: I, 28.26; OCH_3, 20.12.

Acknowledgment.—The authors are indebted to M. E. Auerbach and K. D. Fleischer and coworkers for the analyses reported.

Summary

The preparation of a series of N-benzyl-N-methylphenethylamines which has been found to possess antifibrillatory activity in varying degree is described.

The preparation of N-ethyl-N-(3,4-dimethoxybenzyl)-4-methoxyphenethylamine is also reported.

RENSSELAER, NEW YORK RECEIVED FEBRUARY 2, 1949

(3) Melting points are uncorrected unless otherwise specified.

[CONTRIBUTION FROM ROHM & HAAS COMPANY]

Condensation of Acetylenes with Esters. Acetylene and Phenylacetylene with Methyl Benzoate[1]

BY W. J. CROXALL AND J. O. VAN HOOK

The ease with which acetylene[2] and mono substituted acetylenes[1] may be acylated with alkyl carbonates in the presence of quaternary ammonium alkoxides suggested that esters other than alkyl carbonates might also be suitable acylating agents. Accordingly, a number of attempts were made to condense acetylene and phenylacetylene with alkyl acetates in the presence of quaternary ammonium alkoxides. However, it was soon evident that self condensation of these esters in the presence of this base occurred to the exclusion of reaction with the alkyne. We have been able, however, to effect condensation with an ester having no active hydrogen atom, namely, methyl benzoate.

Similar condensations have been effected with esters of this general category. Ethyl benzoate[3] and ethyl cinnamate[4] have been reported to condense with sodium phenylacetylide to give phenylbenzoylacetylene and phenylcinnamoylacetylene, respectively. However, Nightingale and Wadsworth[5] have proven the latter product to be bis-phenylethynylstyrylcarbinol rather than phenylcinnamoylacetylene. Ethyl propiolate[6] has been shown to undergo a Claisen-type condensation with ethyl benzoate in the presence of metallic sodium. The use of quaternary ammonium alkoxides as condensation bases for reaction between alkyl benzoates and alkynes does not appear to have been tried before.

(1) For the second paper of this series see, Croxall and Fegley, THIS JOURNAL, **71**, 1261 (1949).

(2) Croxall and Schneider, *ibid.*, **71**, 1257 (1949).

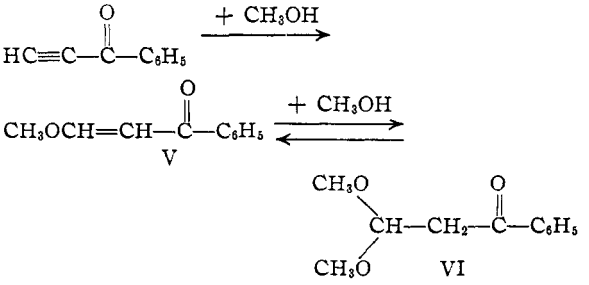
(3) Moureu and De Lange, *Compt. rend.*, **134**, 45 (1902).

(4) Worrall, THIS JOURNAL, **60**, 1266 (1938).

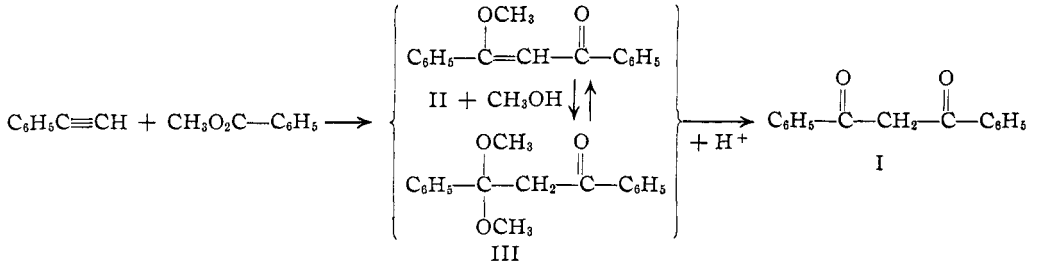
(5) Nightingale and Wadsworth, *ibid.*, **69**, 1181 (1947).

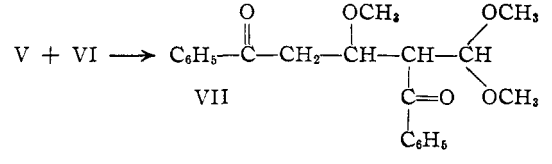
(6) Ingold, *J. Chem. Soc.*, **127**, 1199 (1925).

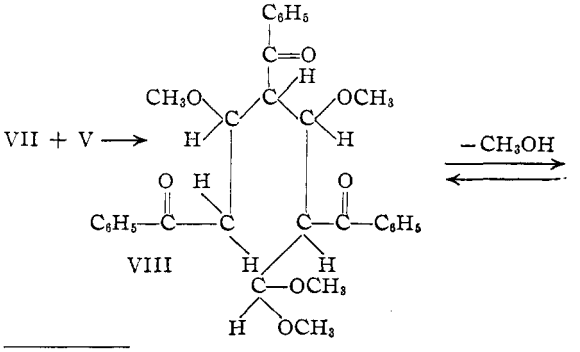
In the present work phenylacetylene has been added to methyl benzoate at room temperature in the presence of benzyltrimethylammonium methoxide[1,2] which contained an equivalent of methanol. There was obtained from this reaction mixture a distillate which on standing deposited crystals of dibenzoylmethane (I). Extraction of the distillate with a solution of copper acetate in methanol yielded a further quantity of the diketone (I) in the form of the copper salt. The remaining oil was shown by methoxyl determination to be a mixture of β-methoxychalcone (II) and 1,3-diphenyl-3,3-dimethoxy-1-propanone (III). Both these compounds yielded dibenzoylmethane (I) when hydrolyzed with aqueous hydrochloric acid. The over-all reaction of methyl benzoate with phenylacetylene may be represented as



A possible explanation of the transformations responsible for the production of the tribenzoylbenzene (IV) may be arrived at by assuming a series of condensations of the Michael type. The diketone (VII) which would be formed from (V) and (VI) could condense with (V) to yield a triketone (VIII). Under the influence of the quaternary ammonium base, VIII might be expected to lose one molecule of methanol to yield the unsaturated triketone (IX). This in turn may undergo an internal Michael condensation to give a six-membered ring with the resultant loss of methanol to produce tribenzoylbenzene (IV). It is possible, of course, that some of these changes occur during distillation. This type of mechanism is similar to that advanced by Fuson and McKeever for the trimerization of vinyl mesityl ketone.[8]





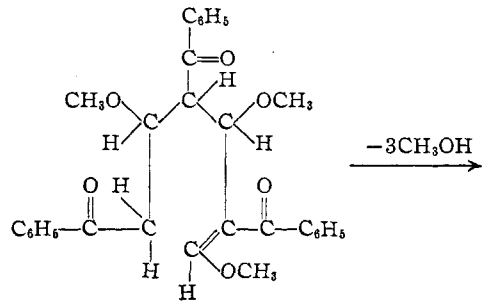


When methyl benzoate in the presence of the above quaternary ammonium base was contacted with acetylene there was obtained an orange solid which could not be purified by crystallization. Analysis showed it to have the composition of a benzyl trimethylammonium salt of a reaction product consisting of approximately two molecules of acetylene and two molecules of methyl benzoate. Treatment of this substance with hydrochloric acid yielded a viscous oil which could not be crystallized. On forced distillation under reduced pressure the oil gave after considerable decomposition a crystalline compound which was identified as tribenzoylbenzene (IV). The belief that the orange colored substance was a quaternary ammonium salt received support from the fact that it reacted with methyl iodide to yield benzyltrimethylammonium iodide and a compound which from analytical data corresponded to 1-methoxy-2,4-dibenzoyl-1,3-pentadiene (X).

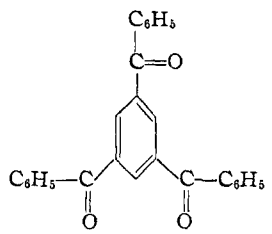
It is thought that both phenylacetylene and acetylene react with methyl benzoate according to a mechanism similar to that outlined for alkyl carbonates and alkynes.[1,2] In the case of the former, phenylbenzoylacetylene would be the expected intermediate. However, the observed products appear to be the result of addition of methanol to the intermediate phenylbenzoylacetylene[7] to produce the chalcone (II) and propanone (III). With acetylene one might likewise expect the formation of mono (V) and dimethoxy (VI) ketones.[7]

(7) Bowden, Braude and Jones, *ibid.*, 945-948 (1946).

(8) Fuson and McKeever, THIS JOURNAL, **62**, 2088 (1940).

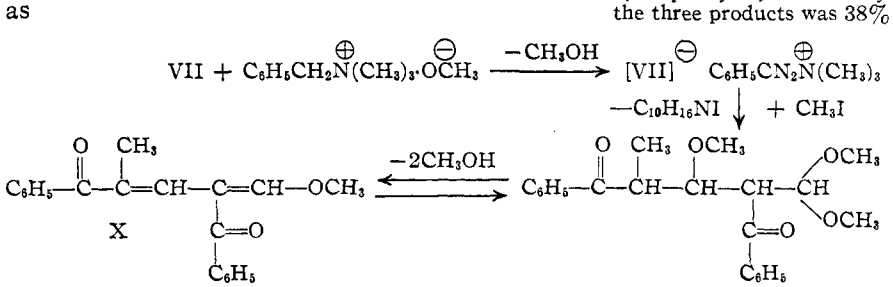


IX



IV

The condensation of V and VI to give the diketone (VII) is substantiated by the alkylation experiment with methyl iodide from which the diene (X) was obtained. This may be represented as



Acknowledgment.—We wish to thank Dr. R. C. Fuson for his helpful suggestions in preparing this paper. The analyses were carried out under the direction of Dr. E. L. Stanley and Mr. C. W. Nash. Miss R. Lookabaugh prepared the phenylacetylene.

Experimental

The condensations were all conducted in apparatus which was thoroughly dry and swept free of air with dry nitrogen. Special care was maintained during the preparation of the benzyltrimethylammonium methoxide[1,2] so as to avoid all contact with air and moisture. This procedure was necessary for the proper functioning of this type condensation base. The general procedures were the same as those outlined previously.[1,2]

Phenylacetylene with Methyl Benzoate.—In a 1-liter, 3-necked flask was placed 86 g. (0.4 mole) of benzyltrimethylammonium methoxide containing an equivalent of methanol,[1] 45 g. (0.33 mole) of methyl benzoate and 34 g. (0.33 mole) of phenylacetylene. The temperature during these additions was maintained below 40° and the mixture was stirred for twenty hours after which time the color was dark brown. The mixture was poured on cracked ice, acidified with concentrated hydrochloric acid and extracted three times with ethyl ether. The ether extracts were washed with a sodium bicarbonate solution and dried over Drierite. The aqueous sodium bicarbonate extract upon acidification with hydrochloric acid gave 6 g. of benzoic acid, m. p. 120–122°. Distillation of the ether extracts gave, after removing ether, 6 g. of material, b. p. 60–90° (1 mm.); $n^{20}D$ 1.5240 (gave a precipitate with 2,4-dinitrophenylhydrazine reagent, m. p. 117–119°; but was not characterized) and 30 g. of an amber-colored oil, b. p. 150–160° (1.5 mm.). Upon standing overnight the oil deposited 0.5 g. of crude dibenzoylmethane which was collected on a filter and recrystallized from petroleum ether (b. p. 90–100°), m. p. 77–79°.[9] The copper salt of the dibenzoylmethane after crystallization from chloroform melted at 293–299°, dec.[9] Treatment of the diketone with phenylhydrazine gave 1,3,5-triphenylpyrazole, m. p. 139–140°.[10] The corresponding 1-(2,4-dinitrophenyl)-3,5-diphenylpyrazole which was prepared from 2,4-dinitrophenylhydrazine and recrystallized from ethanol melted at 151–153°. *Anal.* Calcd. for $C_{21}H_{14}O_4N_4$: C, 65.29; H, 3.65; N, 14.53. Found: C, 65.14; H, 3.76; N, 14.44.

The amber oily filtrate from above was shaken with a solution of copper acetate (7 g. of hydrated copper acetate in 150 ml. methanol) and filtered to give 6 g. of the copper salt of dibenzoylmethane, m. p. 293–299° dec.

The alcoholic filtrate was distilled to remove methanol, the residue taken up in ether, washed with water, dried over Drierite and distilled. After removing ether, there was obtained 25 g. of a straw-colored liquid, b. p. 145–155° (1 mm.); $n^{20}D$ 1.6350. A methoxyl determination indicated 16.40% methoxyl. Treatment of the oil with concentrated hydrochloric acid gave dibenzoylmethane, m. p. 77–79°. The oil on treatment with phenylhydrazine and acetic acid gave 1,3,5-triphenylpyrazole, m. p. 139–140°.[10] Therefore, from the methoxyl determination the oil consisted of 66% β-methoxychalcone and 34% 1,3-diphenyl-3,3-dimethoxy-1-propanone. The yield of the three products was 38% based on the phenylacetylene and methyl benzoate and 31% on the benzyltrimethylammonium methoxide.

Acetylene with Methyl Benzoate.—At five p. s. i. gage pressure, acetylene was pressed into a stirred mixture of 213 g. (1.0 mole) of benzyltrimethylammonium methoxide containing an equivalent of methanol[1] and 260 g. (2.0 moles) of redistilled methyl benzoate. The initial acetylene absorption was rapid and it was necessary to cool the mixture with an ice-bath in order to maintain the temperature below 45°. After the initial exothermic reaction the acetylene absorption became slower. At the end of five hours 18 g. (0.69 mole) of acetylene had been absorbed. The mixture consisted of an orange solid suspended in a dark brown liquid. One liter of anhydrous ether was added, the mixture stirred for ten minutes, the orange solid collected on a filter and washed with ether. The orange solid (180 g.) was dissolved in methanol and precipitated by the addition of ether. Two ether precipitations gave a material which melted at 161–164°, dec.; sintering from 147°. *Anal.* Calcd. for $C_{31}H_{40}O_5N$: N, 2.76. Found: N, 3.00.

The filtrate, the ether washings and the methanol–ether precipitation liquors were combined and washed with water. The ether layer was separated, dried over Drierite and distilled. After removing ether there was collected 140 g. (1.03 moles) of unreacted methyl benzoate, b. p. 50–65°; $n^{20}D$ 1.5150. The aqueous layer, after acidification with hydrochloric acid, gave 6 g. of benzoic acid, m. p. 118–121° (from ethanol–water).

Tribenzoylbenzene.—Thirty grams of the orange solid was stirred with a cracked ice–hydrochloric acid mixture and the organic layer removed. The aqueous layer was extracted with ether, the ether extracts combined with the organic layer, dried over Drierite and distilled. After

(9) Pond, York and Moore, THIS JOURNAL, **23**, 789 (1901).

(10) Knorr and Laubmann, *Ber.*, **21**, 1206 (1888).

considerable decomposition, there was obtained a viscous distillate, b. p. 260 (1 mm.), which partially solidified. Crystallization from methanol gave 4 g. of tribenzoylbenzene, m. p. 120–121°. A mixture of this with tribenzoylbenzene prepared from the sodium salt of α-formylacetophenone according to the method of Claisen[11] melted at 120.5–122°. *Anal.* Calcd. for $C_{27}H_{18}O_3$: C, 83.05; H, 4.65. Found: C, 83.36; H, 5.00.

The trioxime melted at 210–211°.

1-Methoxy-2,4-dibenzoyl-1,3-pentadiene.—To a stirred suspension of 45 g. of the orange solid in 100 ml. of methanol, maintained at 10°, there was added 72 g. (0.5 mole) of methyl iodide. The mixture was allowed to gradually warm to room temperature and stand overnight. It was diluted with 500 ml. of ether and the benzyltrimethylammonium iodide allowed to settle. The liquid phase was separated by decantation, the quaternary ammonium iodide transferred to a filter with the aid of ether and washed with additional ether. After drying at 60° there was obtained 34 g. of the quaternary ammonium iodide. *Anal.* Calcd. for $C_{10}H_{16}NI$: N, 5.05. Found: N, 4.72.

The liquid phase and ether washings were combined and distilled under reduced pressure. After removing ether, there was obtained a yellow semisolid material which was crystallized from methanol, m. p. 103–106°; yield 6 g. After successive recrystallizations from petroleum ether–methanol it weighed 3.5 g., m. p. 108–109°, and corresponded in composition to 1-methoxy-2,4-dibenzoyl-1,3-pentadiene.

Anal. Calcd. for $C_{20}H_{18}O_3$: molecular weight, 306.4; C, 78.39; H, 5.91; $-OCH_3$, 10.13; Br No. (as cg. Br/g. sample) 52.1. Found: molecular weight (ebulliometric in acetone) 298; C, 78.49; H, 5.96; $-OCH_3$, 9.39; Br No. (as cg. Br/g. sample) 49.5.

(11) Claisen, *Ann.*, **281**, 307 (1894).

Summary

1. Phenylacetylene condenses with methyl benzoate in the presence of benzyltrimethylammonium methoxide to give β-methoxychalcone (II) and 1,3-diphenyl-3,3-dimethoxy-1-propanone (III).

2. Acetylene and methyl benzoate in the presence of this base yields a benzyltrimethylammonium complex of the reaction products from which tribenzoylbenzene is obtained.

3. A mechanism is postulated for the formation of these products.

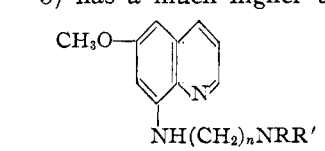
PHILADELPHIA, PA. RECEIVED JANUARY 11, 1949

[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

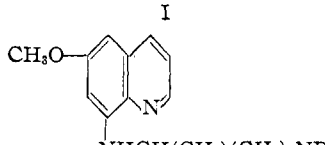
Some N¹-(6-Methoxy-8-quinolylaminoalkyl)-guanidines[1]

BY NATHAN L. DRAKE AND JOHN A. GARMAN[2]

Pentaquine (I, R = isopropyl, R′ = H, n = 5) and isopentaquine (II, R = isopropyl, R′ = H) are two 8-aminoquinoline drugs which combine curative action against vivax malaria with sufficiently low toxicity to permit their use without extreme precautions. Pamaquine (II, R = R′ = ethyl), is considerably more toxic than pentaquine or isopentaquine, and SN-12,904 (I, R = R′ = ethyl, n = 5) has a much higher toxicity than



I



II

Pentaquine. It may be concluded from this and other similar evidence that the character of the side chain in an 8-aminoquinoline is one of the units of structure whose modification may result in a decided change in toxicity.

It was, therefore, considered pertinent to investigate a series of drugs in which the terminal amino group of Pentaquine was replaced by an N¹-guanidine moiety. To this end a group of compounds of formula I, in which R is H, R′ is —NHC(=NH)NH₂, and n is 2, 3, 4 or 5 was prepared.

These new compounds are notable for their low toxicity and for the fact that the neuronal toxicity characteristic of Plasmocid[3] is absent from those homologs in which n is 2 or 3. Indeed, the toxic symptoms of these compounds[4] are referable to effects on the gastrointestinal tract and resemble those of Paludrine rather than Pamaquine.

After considerable exploratory work, the reaction of S-methylisothiourea sulfate with the appropriate 8-(amino-alkylamino)-6-methoxyquinoline in aqueous propanol was chosen for the preparation of the desired compounds. Purification was effected by precipitation of a carbonate of the drug from a butanol–ether solution by addition of solid carbon dioxide. Carbonates so prepared showed evidence of decomposition on prolonged storage, and inasmuch as their recrystallization proved impossible, they were converted to hydrochlorides by titration with dilute alcoholic hydrogen chloride. The monohydrochlorides of these bases are nearly colorless; the dihydrochlorides are highly colored. These

(1) Taken in part from a thesis submitted to the Graduate School of the University of Maryland by John A. Garman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) du Pont Predoctoral Fellow, 1946–1947.

(3) "Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, editor, J. W. Edwards, Ann Arbor, Michigan, 1946: (a) Vol. I, p. 114; (b) Vol. I, p. 458.

(4) Personal communication from L. H. Schmidt, Christ Hospital, Cincinnati.