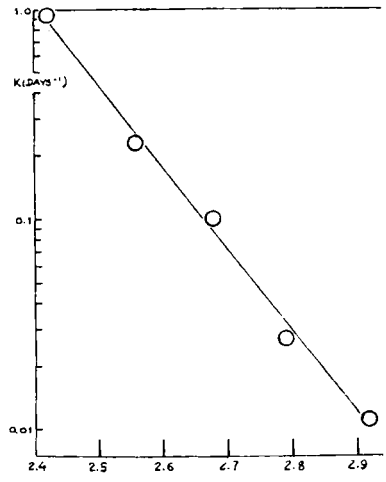

Fig. 2.—Vitamin A alcohol in Tween-Drew oil base. Plot shows pseudo first-order rate constants as a function of reciprocal absolute temperature (reciprocal °Kelvin).

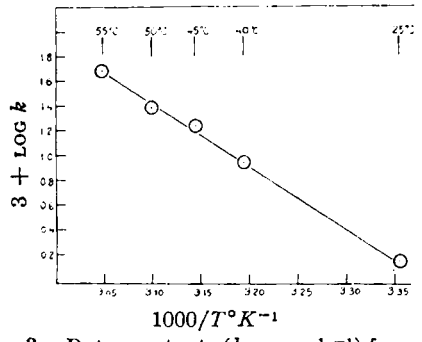

Fig. 3.—Rate constants (k = week^{-1}) for pseudo first-order rate constants of vitamin A palmitate beadlets in dry-slugged, mannitol-base, multivitamin chewable tablet. Log k is plotted against reciprocal absolute temperature.

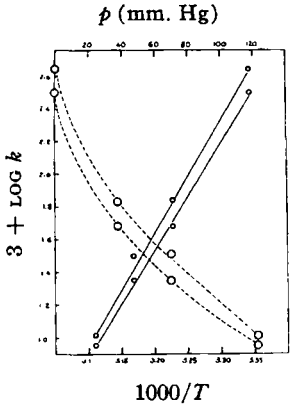

Fig. 4.—Plots of the pseudo first-order rate constant (k = month^{-1}) for vitamin A palmitate beadlets in sugar - coated tablets. Dotted lines are regular Arrhenius plots ($1/T$ scale); full lines are log k *vs.* water vapor pressure (p-scale).

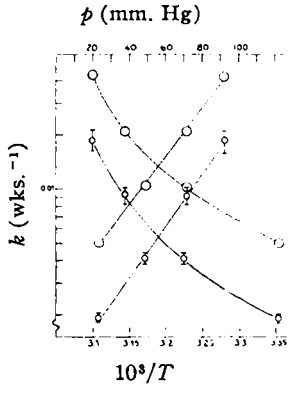

Fig. 5.—Plots of the pseudo first-order rate constants (k) for vitamin A palmitate oil in a multivitamin drop (Tween, micelle, glycerin, water). Dotted lines are regular Arrhenius plots ($1/T$-scale); full lines are log k *vs.* water vapor pressure (p-scale). Two different formulations (same vitamin A raw material) are shown.

tion for this. Attempts to relate (a) the absolute temperature to the water vapor pressure in the Arrhenius equation or (b) relate the water activity to the water vapor pressure lead to equations proportionalizing log k to log p not p.

The more deep rooted explanations to this will be the subject of subsequent publications.

REFERENCE

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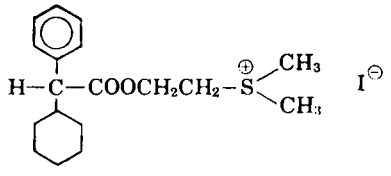
β-(α-Phenyl-α-3-thenylacetoxy) Ethyldimethylsulfonium Bromide as a Potential Antispasmodic

By HEINO A. LUTS*, W. A. ZUCCARELLO‡, J. F. GRATTAN‡, and W. LEWIS NOBLES

A comparative structure-activity evaluation was made to determine the potentiality of 3-methylthiophene as a possible active isoster of an agent which has demonstrated marked antispasmodic activity.

In 1953, Protiva and Exner (1) reported on the spasmolytic activity of the sulfonium compound, thiospasmin.



Since that time, several structural modifications have been made. Neesby and his associates (2) in this country, utilizing the same sulfonium moiety in several model compounds, found more favorable therapeutic ratios for these derivatives. It has been suggested that a structure-activity study involving thiophene analogs should include the 3-substituted

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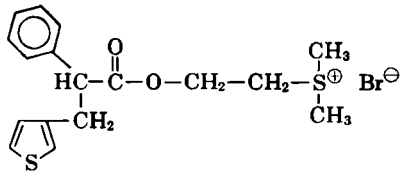
‡ Pharmacological studies were made by these authors at Smith, Miller and Patch, Inc., New York, N. Y.

thiophene analog (3, 4). It is the purpose of this paper to present data on the synthesis of the latter compound and an evaluation of its biological activity.

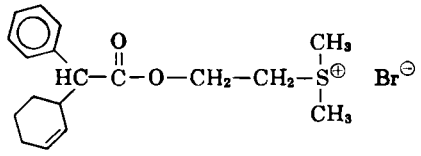
The sulfonium salt which serves as the basis for this paper was prepared by reacting phenyldiethylmalonate (I) with 3-thenylbromide (II) in ethanol in the presence of sodium. The compound thus formed (III) was then decarboxylated to yield a substance (IV); this was subsequently reacted with β-chloroethylmethylsulfide (5) (V), yielding the compound (VI). The quaternary salt of this agent was formed with methyl bromide to yield the compound (VII).

PHARMACOLOGY

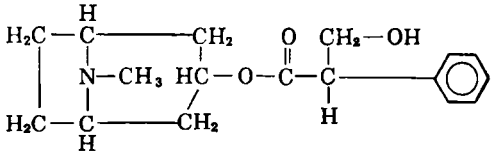
The antispasmodic activity of the 3-methylthiophene analog was compared with that of the cyclohexenyl derivative and of atropine. The findings, together with the formulas of each, are presented below.



Compound VII.—β-(α-Phenyl-α-3-thenylacetoxy) Ethyldimethyl sulfonium Bromide



CDS-216.—Dimethylsulfonium Ethyl-α-phenyl-α-(2,3-cyclohexenyl) Acetic Acid Bromide (2)

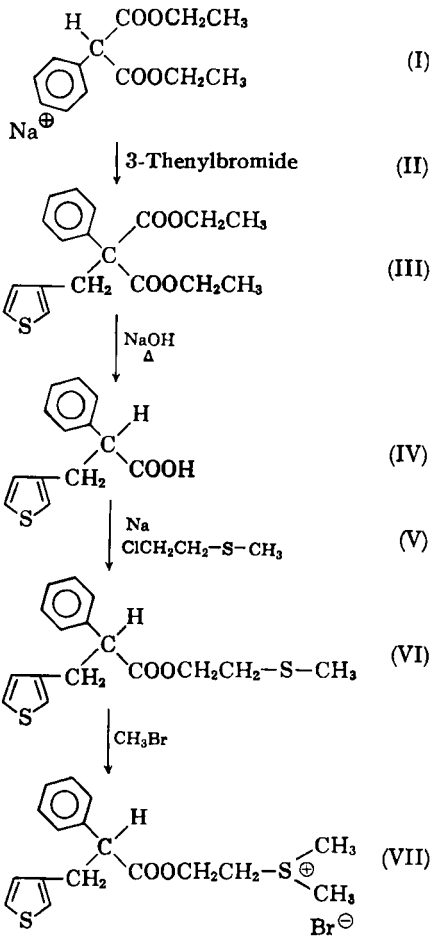


Atropine

PHARMACOLOGIC STUDIES

Acute Toxicity.—The median lethal dose (LD_{50}) of compound VII, when administered intraperitoneally in mice, was estimated to be 93 mg./Kg. The LD_{50} of dimethylsulfonium ethyl-α-phenyl-α-(2,3-cyclohexenyl) acetic acid bromide (hereafter designated CDS-216) was 72 mg./Kg. Mice receiving toxic doses of compound VII exhibited tremors, mydriasis, increased respiratory rate, and clonic convulsions. Death appeared to result from respiratory arrest.

In Vitro Spasmolytic Action—Isolated Rabbit Ileal Segment.—The ability of compound VII to antagonize the spasmogenic effect of acetylcholine was only one-twentieth that of CDS-216 or atropine. It would appear that substitution of the cyclohexenyl group of CDS-216 with methylthiophene was followed by a marked reduction in antispasmodic activity. Like atropine, compound VII reduced both the tonus and amplitude of contraction of normal smooth muscle.



General Scheme of Synthesis

Antagonism of the Effects of Carbaminoylcholine (Carbachol) or Faradization of the Peripheral End of the Sectioned Right Vagus Nerve.—Compound VII, when administered intravenously in pentobarbitalized rabbits at dose levels of 0.5 to 1.0 mg./Kg., affected a slight, transient reduction in the hypermotility of the ileum, *in situ*, induced by carbachol (6). These dose levels of compound VII prevented the cardiac slowing following stimulation of the vagus nerve. Again, the effect was evanescent in nature. In the main, compound VII possessed only one-tenth to one-twentieth the activity of either CDS-216 or atropine in these tests.

Tremorine Antagonism.—Since the antitremorine activity of many compounds parallels their cholinolytic action, the ability of compound VII to prevent the tremors and/or lacrimation following tremorine administration was examined (7). Whereas atropine and CDS-216 prevented both the tremors and the lacrimation at dose levels below 1 mg./Kg., compound VII did not have effect on the tremors when given at dose levels as high as 40 mg./Kg., although lacrimation could be prevented at dose levels of 10 mg./Kg. and above. Substitution of the methylthiophene with the cyclohexenyl moiety was fol-

lowed by increased ability to antagonize tremors and lacrimation induced by tremorine.

Inhibition of the Chromodacryorrhea Induced by Acetyl-β-methylcholine (Mecholyl).—Compound VII antagonized the action of Mecholyl on the parasympathetic effector cells of the accessory lacrimal glands in the rat. The median protective dose (PD_{50}) of compound VII was 1.4 mg./Kg., while that for atropine was shown to be 0.3 mg./Kg. In this test, compound VII was approximately one-fifth as active as atropine, but only slightly less active than CDS-216 (PD_{50} of 0.9 mg./Kg.).

Mydriatic Action.—Compound VII, when applied topically to the cornea of the rabbit, did not have effect on pupillary diameter at concentrations to 1.0%. CDS-216, at a concentration of 1.0%, caused only slight mydriasis; atropine, at a concentration of 0.5%, produced maximal pupillary dilation.

Effect on Hexobarbital Hypnosis.—When administered at several dose levels, compound VII did not alter either the time of induction or the duration of sleep produced by hexobarbital.

Other Pharmacologic Actions.—Compound VII was devoid of significant analgesic activity and possessed no local anesthetic action. It exerted neither an adrenolytic effect nor a potentiating action on the pressor response to *l*-epinephrine, and did not antagonize the vasodepressor action of histamine. At the dose levels employed, compound VII appeared to potentiate the action of serotonin on the isolated rat uterus.

EXPERIMENTAL[1]

α-Phenyl-α-3-thenylacetic Acid.—This agent was prepared by standard malonic ester synthesis, namely by refluxing 24.1 Gm. (0.1 mole) of the sodium salt of phenyldiethylmalonate with 17.6 (0.1 mole) of 3-thenylbromide (8) in ethanol. After refluxing for 12 hours, the reaction mixture was filtered and the solvent evaporated. The residue was then saponified with alcoholic KOH and the alcohol evaporated and the residue acidified with hydrochloric acid. The resulting mixture was then extracted twice with 100 ml. of benzene and dried over potassium carbonate. After filtering and evaporating the benzene, the residue was heated in high-vacuum to yield a semisolid. Recrystallization of this material from benzene-petroleum ether gave crystals melting at 93°; yield, 38%.

Anal.—Calcd. for $C_{13}H_{12}O_2S$: C, 67.25; H, 5.24; S, 13.80. Found: C, 67.32; H, 5.27; S, 13.72.

β-(α-Phenyl-α-3-thenylacetoxy) Ethyldimethylsulfonium Bromide.—Ten grams (0.04 mole) of α-phenyl-α-3-thenylacetic acid was reacted with 0.92 Gm. (0.04 mole) of sodium in 75 ml. of isopropanol. This was then refluxed for 30 minutes and 7.0 Gm. (0.06 mole) of β-chloroethylmethylsulfide added over a period of 30 minutes with good stirring. The reaction mixture was then refluxed for 24 hours; the salt formed was separated by filtration and the solvent removed by distillation. The residue was dissolved in 20 ml. of methanol and 15 Gm. (0.16 mole) of liquid methylbromide added. The reaction mixture was then allowed to stand at room temperature for 5 days in a sealed container. After boiling away both the methanol and the unreacted methylbromide, the residue was triturated with anhydrous ether. A crystalline product was formed in 72% yield; m.p. 100–101°.

Anal.—Calcd. for $C_{17}H_{21}BrO_2S_2$: C, 50.87; H, 5.27; Br, 19.19; S, 15.98. Found: C, 50.72; H, 5.36; Br, 20.10; S, 15.71.

SUMMARY AND CONCLUSIONS

Substitution of the cyclohexenyl group of compound CDS-216 with a methylthiophene grouping affected adversely the antispasmodic activity and did not alter the toxicity appreciably.

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[1] Microanalysis performed by G. Roberts, Florham Park, N. J. All melting points are uncorrected.

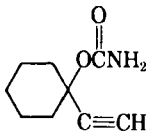
Identification of Ethinamate, Ethchlorvynol, and Methylparafynol

By W. N. FRENCH

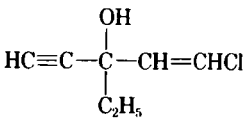
Procedures for the identification of ethinamate, ethylchlorvynol, and methylparafynol by derivative formation are described. The acid catalyzed rearrangement of ethchlorvynol gave 3-ethyl-2-penten-4-ynal.

FEW PROCEDURES are available in the literature for the identification of ethinamate (I), ethchlorvynol (II), and methylparafynol (III).

Ethinamate has been identified by general tests for unsaturation and the presence of a terminal



I



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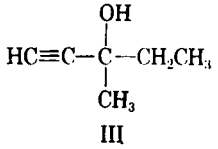

III

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