EXPERIMENTAL

All adducts listed in Table I were prepared by the following procedure as exemplified by 1,3-di-(2-furyl)-3-(*p*-bromomercapto)-propan-1-one.

p-Bromothiophenol (5.0 g, 0.0264 mole) was added to 5.0 g (0.0265 mole) of 1,3-di-(2-furyl)-2-propen-1-one in 100 ml of ethanol, followed immediately by 5 drops of the catalyst triethylamine. After refluxing for 2 hr on a steam bath, the solution was cooled. The precipitate that formed was collected and recrystallized from ethanol–water to give a white crystalline material, mp 90–91°, in almost quantitative yield.

Anal.—Calc. for $C_{17}H_{13}BrO_3S$: C, 54.12; H, 3.47; Br, 21.18; S, 8.48. Found: C, 53.81; H, 3.42; Br, 21.02; S, 8.61.

Other intermediates used were 1-(2-furyl)-3-(2-thienyl)-2-propen-1-one, 1-(2-thienyl)-3-(2-furyl)-2-propen-1-one, and 1,3-di-(2-thienyl)-2-propen-1-one.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 13, 1974, from the *Uniroyal Chemical Company, Naugatuck, CT 06770*

Accepted for publication September 11, 1974.

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COMMUNICATIONS

Influence of Peroxide Impurities in Polyethylene Glycols on Drug Stability

Keyphrases □ Polyethylene glycols—peroxide impurity, corticosteroid stability □ Antioxidants—butylated hydroxytoluene, propyl gallate □ Colorimetric assay—peroxide concentrations

To the Editor:

The poor stability of an experimental topical corticosteroid formulated in polyethylene glycol 300 was found to be due to the high concentration of peroxides in the vehicle. Removal of the impurity from the vehicle led to an increase in stability of the steroid at elevated temperatures. Boon and Mace (1) reported that degradation of tripelennamine hydrochloride in polyethylene glycol 300 was dependent on the concentration of ethylene oxide in polyethylene glycol; when the concentration of ethylene oxide exceeded 0.1%, there was measurable loss of the active constituent.

Higher molecular weight polyethylene glycols and polyethylene glycol esters, *i.e.*, polyethylene glycol 400, polyethylene glycol 1500, and polyethylene glycol 6000 distearate, used to solubilize the steroid before its incorporation into an ointment formulation (petrolatum base), all contained peroxides as impurities and the steroid showed poor stability. Except for one sample of polyethylene glycol 1500, samples of polyethylene glycols from different manufacturers all contained peroxides. In one instance, a small quantity of hydrogen peroxide had been added by the manufacturer to maintain a water-clear product.

Although the identities of the peroxides present as impurities were not determined, they are believed to consist of various organic peroxides rather than hydrogen peroxide *per se*. The concentrations of peroxide in polyethylene glycols of different molecular weights and polyethylene glycol 6000 distearate are reported in Table I. In the colorimetric assay used, the glycol sample was added to an acidified potassium iodide solution and the iodine liberated was titrated against standard thiosulfate solution.

The level of peroxide in polyethylene glycols increased with aging. Studies in these laboratories showed that the presence of selected antioxidants and water (5–10%) in the vehicle helped to decrease the concentration of peroxides. Thus, of eight antioxidants tested, butylated hydroxytoluene and propyl gallate were the most successful in this respect, and pretreatment of the vehicle with 0.005–0.05% of either agent was effective. The decomposition of peroxides under the influence of water or antioxidants was slow at room temperature but was accelerated by heating. Both the concentration of antioxidant and the duration of heating (60–80°) required for the removal of peroxide were dependent on the initial con-

Table I—Peroxide Concentrations in Polyethylene Glycols

Manufacturer	Polyethylene Glycol 300[a]	Polyethylene Glycol 400[a]	Polyethylene Glycol 1500[b]	Polyethylene Glycol 6000 Distearate[b]
I	1.4	3.24	<0.01	1.97
II	4.86	3.95	4.26	N.T.[c]
III	9.3	5.7	N.T.	1.92[d]

[a] Microequivalents of thiosulfate per milliliter of glycol. [b] Microequivalents of thiosulfate per gram of glycol. [c] N.T. = not tested. [d] Additional vendor.

centration of peroxide. The presence of water in the formulation helped prevent any further production of peroxide.

Some of these observations were substantiated by McKenzie (2), who studied peroxide formation and decomposition in triethylene glycol. Azaz *et al.* (3) employed antioxidants to stabilize benzocaine hydrochloride in cetomacrogol solutions containing peroxide impurities.

The reaction of trace metals in the polyethylene glycols with propyl gallate to form colored reactants was prevented by the inclusion of a small quantity of a chelating agent, *e.g.*, 20 ppm of ethylenediaminetetraacetic acid. Since all polyethylene glycols used in these studies contained less than 0.01% ethylene oxide, it is suggested that the reported (1) instability of tripelennamine hydrochloride in polyethylene glycol 300 may have been due not only to the presence of ethylene oxide in the formulation but also the presence of peroxides.

We recommend the use of only the highest quality polyethylene glycols in formulations, a determination of the stability of the active constituent in glycols under elevated temperature conditions (to assess the effect of pretreating the vehicle with antioxidants at elevated temperatures), and, finally, the incorporation of a small percent of water in the formulation.

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Received September 19, 1974.

Accepted for publication November 4, 1974.

The authors thank Mr. Peter Valatin of the Squibb Institute for Medical Research, New Brunswick, N.J., for the peroxide evaluation.

[x] To whom inquiries should be directed.

Constituents of *Cannabis sativa* L. IX: Stability of Synthetic and Naturally Occurring Cannabinoids in Chloroform

Keyphrases □ *Cannabis sativa* L.—stability of synthetic and naturally occurring cannabinoids in chloroform □ Cannabinoids—stability in chloroform □ Marijuana—stability of synthetic and naturally occurring cannabinoids in chloroform □ Stability—synthetic and naturally occurring cannabinoids in chloroform

To the Editor:

A report from these laboratories demonstrated that chloroform was a more efficient solvent for extracting cannabinoids from *Cannabis sativa* L. than benzene, pentane, hexane, petroleum ether, ethanol, acetone, and ether. Moreover, cannabinoids[1] extracted with chloroform were stable at ambient temperature for 144 hr (1).

Recently, Parker *et al.* (2) reported that synthetic cannabidiol was unstable in spectrograde chloroform over an 8-day period. The authors stated that: "caution should be exercised in the use of chloroform as a solvent for prolonged extraction and storage of cannabidiol." Since members of this research group (3–6) and others (7) have employed chloroform as an extracting solvent and since a working group, sponsored by the United Nations[2], on the chemistry of *Cannabis* and its components recently recommended that the procedure developed in these laboratories be used worldwide, it seemed imperative that additional data be presented in support of chloroform as the solvent of choice for extracting cannabinoids from *Cannabis*.

The basic procedure utilized in these laboratories is as follows. Samples of *Cannabis* are extracted at ambient temperature with nanograde chloroform[3] for 1 hr[4]. After that time, the chloroform is removed *in vacuo* and an ethanolic solution containing a known amount of the internal standard, androst-4-ene-3,17-dione, is added. Therefore, by allowing 15 min for workup, each sample is exposed to chloroform for a maximum of 75 min. Thus, if synthetic and naturally occurring cannabinoids are stable in chloroform for 75 min, chloroform, as previously recommended (1, 7), would be the solvent of choice for extraction of naturally occurring cannabinoids found in crude drug preparations from *C. sativa* L.

We wish to report results of a 3-month stability study using chloroform as the solvent for the following: (*a*) synthetic cannabidiol, (−)-Δ^8- and Δ^9-*trans*-tetrahydrocannabinols, $\Delta^{9,11}$-tetrahydrocannabinol (exocyclic), and cannabinol; (*b*) an extract of female Mexican *Cannabis* grown in Mississippi (coded CMEF-71, ME-A); and (*c*) a synthetic mix-

[1] Combination cannabidiol–cannabichromene, (−)-Δ^9-*trans*-tetrahydrocannabinol, and cannabinol.

[2] United Nations Document MNAR/9/1974.

[3] Mallinckrodt Chemical. One-gallon amber bottles are kept at ambient temperature, opened one at a time as needed, and used with minimum exposure to air, *etc.*

[4] For details, see Refs. 1 and 4–6. Androst-4-ene-3,17-dione was first used as an internal standard by Davis *et al.*, *Lloydia*, **33**, 453(1970).