tained in good yield. This not only supports the proposed reaction sequence, but also offers an attractive new synthesis of hydroperoxides. Table I shows the effect on yield of some systematic variations in conditions in the oxidation of *t*-butyl MgCl.

TABLE I

EFFECT OF VARYING CONDITIONS ON THE YIELD OF *t*-BUTYL HYDROPEROXIDE FROM *t*-BUTYLMAGNESIUM CHLORIDE

| Run | Normality of reagent | Temp., °C. | Time of addition, min.[a] | Yield,[b] % |
|---|---|---|---|---|
| 1 | 1.62 | −65 | 40 | 34.4 |
| 2 | 1.62 | −71 | 120 | 78.4 |
| 3 | 0.56 | −71 | 40 | 85.7 |
| 4 | 1.74 | −69 | 70 | 45.9 |
| 5 | 0.53 | −74 | 80 | 91.4 |
| 6 | 0.53 | −7 | 80 | 27.9 |

[a] Of 50 ml. of RMgCl solution to 50 ml. of oxygen-saturated ether. [b] By titration.

TABLE II

YIELDS OF HYDROPEROXIDES BY ADDITION OF VARIOUS GRIGNARD REAGENTS TO OXYGEN-SATURATED ETHER

| Grignard reagent | Normality | Yield of hydroperoxide[a] |
|---|---|---|
| *t*-Butyl MgCl | 0.56 | 85.7 |
| *t*-Amyl MgCl | .35 | 91.9 |
| 2-Octyl MgCl | .50 | 91.4[c] |
| Cyclohexyl MgCl | .52 | 66.2 |
| Cyclohexyl MgBr | .69 | 30.0 |
| Ethyl MgCl | .48 | 57.0 |
| Ethyl MgBr | .54 | 28.2 |
| Benzyl MgCl | .50 | 30.0[b] |

[a] By titration. [b] B.p. 53.5/0.09 min., $n^{25}D$ 1.5352, $d^{20}_4$ 1.120, *Anal.* 90.0%. [c] B.p. 58–59 (0.5 min.), $n^{25}D$ 1.4269, $d^{20}_4$ 0.868, *Anal.* 91.4%.

We have investigated the scope of the reaction using optimum conditions based on experience with *t*-butyl MgCl. Table II summarizes the yields of hydroperoxides obtained from various Grignard reagents under the same conditions used for run 3 of Table I. The reaction seems general for the synthesis of primary, secondary and tertiary hydroperoxides, with alkylmagnesium chlorides giving better yields than the corresponding bromides. All the hydroperoxides were isolated and characterized with the exception of ethyl hydroperoxide, the explosive character of which is well known.

Large scale runs with several of the Grignard reagents gave similar results, and yields of isolated hydroperoxide approach the quantities indicated by titration. Treatment of *t*-butyl OOMgCl with acid chlorides and alkyl halides gave peresters and peroxides, respectively. The reaction of benzyl MgCl is especially interesting since attempts to prepare benzyl hydroperoxide by autoxidation of toluene have proved unsuccessful. This hydroperoxide is fairly stable on isolation, but is converted to benzaldehyde by short treatment with alkali.

Further work continues on aromatic and acetylenic Grignard reagents, but we are reporting these preliminary results in the hope that this synthetic method will be useful to other workers in this active field.

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RECEIVED JULY 30, 1953

## THE STRUCTURE OF METOPON

*Sir:*

Ever since the realization that metopon (methyldihydromorphinone) has properties which make it more valuable in some respects than morphine,[1] considerable interest has attached to the elucidation of its structure, a problem related to that of the structures of the two methyldihydrothebainone isomers which are formed in the reaction of enolic derivatives of dihydrocodeinone with methylmagnesium halides.[2] One of the isomers, the sole product when the enol acetate is used, leads eventually to metopon.

It was recognized by Small[2] that the methyl group which has entered the molecule must be either in position 5 or 7 of dihydrothebainone, but repeated efforts to settle this point by studying the properties of the substances formed,[2] by degradative and synthetic studies[3] and by work on model compounds[4] have failed to give the desired answer.

We have now shown that isomethyldihydrocodeinone which is formed, by reclosure of the oxide bridge, from isomethyl dihydrothebainone is 7-methyldihydrocodeinone: Formylation of dihydrocodeinone with ethyl formate and sodium ethoxide in benzene solution gave 7-hydroxymethylene dihydrocodeinone as an amorphous amphoteric solid, m.p. 179°, $[\alpha]^{25}D$ −256.5° (water), characterized as its yellow aniline derivative, m.p. 249°, dec. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.69; H, 6.75; N, 7.14. Several attempts at direct reduction of the free hydroxymethylene compound or its esters to a methyldihydrocodeinone were unsuccessful. Reduction in acetic acid with 5% palladium on charcoal gave a phenolic substance shown to be 7-hydroxymethyldihydrothebainone, m.p. 206–206.5°, $[\alpha]^{25}D$ −39° (ethanol). Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.00; H, 7.73; N, 4.69. The desired reduction of the hydroxymethylene group was finally effected in the following manner: Transformation into the ethylenedithioacetal by treatment with ethanedithiol and anhydrous hydrogen chloride gave the anticipated compound as an amorphous solid, m.p. 75–78°, which could be purified by chromatography. Calcd. for $C_{21}H_{25}O_3NS_2$: C, 62.51; H, 6.24. Found: C, 62.02; H, 6.63. The ethylenedithioacetal was desulfurized by refluxing in acetone with Raney nickel and the product was isolated by chromatography, yielding needles, m.p. 164°, *undepressed on admixture with an authentic specimen of isomethyldihydrothebainone*, kindly supplied by Dr. L. F. Small. The infrared spectra of the two substances were also identical. Isomethyldihydrocodeinone, agreeing in melting point and ro-

(1) See for instance L. E. Lee, *J. Pharm. Exp. Ther.*, **75**, 161 (1942); T. A. Henry, "The Plant Alkaloids," J. & A. Churchill, Ltd., London, 1949, p. 262.

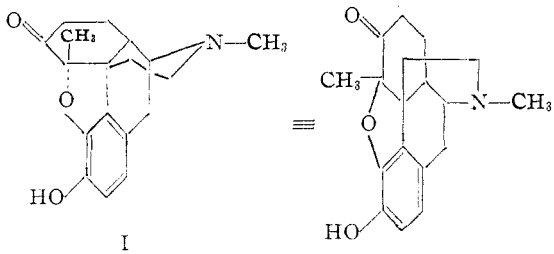
(2) L. F. Small, H. M. Fitch and W. E. Smith, THIS JOURNAL, **58**, 1457 (1936); L. F. Small, S. G. Turnbull and H. M. Fitch, *J. Org. Chem.*, **3**, 204 (1938); L. F. Small and H. M. Fitch, U. S. Patent 1,178,-010 (Oct. 31, 1939).

(3) L. J. Sargent and L. F. Small, *Science*, **112**, 473 (1950); L. J. Sargent and L. F. Small, Abstracts of Papers, 118th Meeting A.C.S., Sept., 1950, p. 53N.

(4) R. I. Meltzer and J. A. King, THIS JOURNAL, **75**, 1355 (1953).

tation with the literature values, was also isolated after the desulfurization.

With the demonstration that isomethyldihydrothebainone and isomethyldihydrocodeinone have the additional methyl group at position 7, methyldihydrocodeinone and metopon are proved to be 5-methyl compounds since the isomerism of the two methyldihydrocodeinones cannot be the result of epimerism at $C_7$ (the two isomers are stable to base and give rise to two different enol acetates[2] and metopon can be represented by structure I.



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# BOOK REVIEWS

**The Bacteriostatic Activity of 3500 Organic Compounds for *Mycobacterium Tuberculosis Var. Hominis*.** Chemical-Biological Coördination Center Review No. 4. BY GUY P. YOUMANS, LEONARD DOUB AND ANNE S. YOUMANS, Parke, Davis and Company, Detroit, Michigan. Publications Office, National Research Council, 2101 Constitution Avenue N.W., Washington 25, D.C. 1953. v + 713 pp. 17.5 × 25 cm. Price, $5.00.

Despite the spectacular developments of the last ten years, the search for a specific chemotherapeutic agent for the treatment of tuberculosis continues. This is indicated by the list of over 3500 widely diversified organic compounds whose tuberculostatic properties have been evaluated. The assembled data speak much for the efforts of the authors who have evaluated these compounds, as well as for the originality and ingenuity of the chemists responsible for their preparation. This study underscores the importance to both chemists and biologists of a centralized coördination center which can assemble and codify data from many sources dealing with the preparation, evaluation and availability of potential chemotherapeutic agents applicable not only for the treatment and control of diseases in man but in animals and plants as well. In the absence of more precise knowledge of the metabolism of the tubercle bacillus, search for a specific chemotherapeutic agent is of necessity random in nature. The authors of this monograph clearly present the rationale of this approach to the subject and the methods employed. Their use of the virulent human type strain of tubercle bacillus, H37, a strain which has been widely studied by other investigators, increases the value of their study. The limitations of the *in vitro* and *in vivo* methods of determining the tuberculostatic value of various compounds are presented.

Some investigators, including the reviewer, are not in accord with the authors as to the value of mice in determining the chemotherapeutic action of chemicals or antibiotics. The administration of the compound in the feed makes it difficult to quantitate the results. The relation of chemical structure of some of the compounds to their tuberculostatic activity is discussed. Of the 3500 preparations that were investigated 184 were selected for *in vivo* tests on mice. Of these, 8 chemical compounds and 3 antibiotics showed some suppressive effects on the tuberculous process in mice. The method of classifying the 3500 compounds is described in detail. Despite the negative findings this monograph should serve as an excellent reference to both chemists and bacteriologists and should obviate the necessity of preparing and retesting many preparations included in this monograph. A point of minor criticism is the lack of description of Berkfeld and of Swinney filters. Although these names indicate a definite type of filter to the initiated, a brief description of the specification and uses of these filters would be helpful to the uninitiated. The formula and alphabetical indices are quite complete. The type is clear and the format is excellent.

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**Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water.** National Bureau of Standards Handbook 52. Superintendent of Documents, Washington 25, D. C. 1953. iv + 45 pp. 13 × 19.5 cm. Price 20 cents.

The National Committee on Radiation Protection sponsored by the National Bureau of Standards is made up of representatives from organizations which are concerned with the safe use of ionizing radiation and radioactive materials. These organizations include several medical societies, the U. S. Armed Forces, interested Government agencies and the National Electrical Manufacturers Association. It is the responsibility of this National Committee to make health and safety recommendations.

This particular Handbook prepared by the Subcommittee on Permissible Internal Dose under the chairmanship of Karl Z. Morgan, presents recommendations for maximal permissible levels of human exposure to those radioisotopes of greatest current interest which may gain entrance to the body by absorption, inhalation or ingestion.

The levels recommended are based largely on the principal of avoiding greater radiation than the equivalent of 0.3 roentgen per week to any organ other than the skin. Because such radiation produces no easily detectible biological effects this principal is commonly regarded as conservative, particularly for periods of exposure which do not extend over many years. However, there are still so many uncertainties with respect to the absorption, retention and distribution of inhaled or ingested radioactive materials in man, as well as with respect to the equivalent effectiveness of the particulate radiations in producing chronic injury that current estimates of permissible exposure levels to many radioisotopes cannot be made with that accuracy which would finally be desirable. Nevertheless, these recommendations, carefully considered by a competent group of experts, provide a guide for health protection which is not likely to err in the direction of permitting dangerous overexposure, particularly if the suggested factor of safety is adopted. The associated problem of whether the levels recommended can be economically achieved in industry is not discussed.