L-pipecolic acid and fluoresced cherry red under ultraviolet light as reported by Morrison.[2] An assay of the pipecolic acid hydrochloride showed that it had a specific activity of $1.21 \times 10^5$ disintegrations/min./mmole. Part of the pipecolic acid hydrochloride was converted to the hydantoin[4] and this derivative had a specific activity of $1.23 \times 10^5$ disintegrations/min./mmole. These observations afford strong evidence that pipecolic acid is a catabolite of L-lysine in the rat.

The high specific activity obtained suggests that pipecolic acid is involved in the conversion of L-lysine to $\alpha$-aminoadipic acid, a view in keeping with the finding that under similar experimental conditions, L-lysine, via $\alpha$-aminoadipic acid, yields glutaric acid with a specific activity of $6.45 \times 10^4$ disintegrations/min./mmole.[5]

(4) W. Leithe, *Ber.*, **65**, 927 (1932).
(5) M. Rothstein and L. L. Miller, unpublished results.

DEPARTMENT OF RADIATION BIOLOGY
UNIVERSITY OF ROCHESTER MORTON ROTHSTEIN
SCHOOL OF MEDICINE AND DENTISTRY LEON L. MILLER
ROCHESTER, NEW YORK

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## THE MINOR ALKALOIDS OF *GELSEMIUM SEMPERVIRENS*[1]

*Sir:*

In the course of our work with gelsemine the isolation of the alkaloids of *Gelsemium sempervirens* Ait. has been reinvestigated. The alkaloidal residue obtained from the combined mother liquors left after removal of all the gelsemine and sempervirine was benzoylated to separate the secondary from the tertiary amines. The neutral fraction, after purification by chromatography, crystallized readily. It was hydrolyzed and the recovered base converted to a perchlorate which on repeated recrystallization from methanol–water was separated into a very sparingly soluble crystalline perchlorate and a readily soluble one. The readily soluble perchlorate yielded alkaloid A, m.p. 171–172°, $[\alpha]^{25}D$ −142° (*c*, 0.945 in $CHCl_3$). *Anal.* Found: C, 66.89, 67.27; H, 7.00, 7.31; N, 7.78; $OCH_3$, 16.47; $NCH_3$, 3.96. Calcd. for $C_{20}H_{26}O_4N_2$: C, 67.02; H, 7.31; N, 7.82; 2 $OCH_3$, 17.30; 1$NCH_3$, 4.18. The base which contains one C-methyl and one active hydrogen (Zerewitinow) forms a neutral benzoyl derivative, m.p. 235–236°, $[\alpha]^{25}D$ −107° (*c*, 0.97 in $CHCl_3$). *Anal.* Found: C, 70.02; H, 6.50; N, 6.21. Calcd. for $C_{27}H_{30}O_5N_2$: C, 70.11; H, 6.54; N, 6.06. These properties are in agreement with those reported by Chou[2] and by Forsyth, Marrian and Stevens[3] for gelsemicine. Furthermore, the ultraviolet and infrared absorption spectra of alkaloid A were identical with the corresponding spectra determined on a sample of Chou's gelsemicine.[4] In admixture with Chou's gelsemicine (m.p. 164–167°), alkaloid A melted at 168–170°. Alkaloid A, therefore, is identical with gelsemicine.

(1) Issued as N.R.C. Bull. No. 0000.
(2) T. Q. Cohu, *Chinese J. Physiol.*, **5**, 131 (1931).
(3) W. G. C. Forsyth, S. F. Marrian and T. S. Stevens, *J. Chem. Soc.*, 579 (1945).
(4) We are indebted to Dr. Raymond-Hamet of Paris for supplying us with a sample of gelsemicine that he had received from Dr. T. Q. Chou.

The sparingly soluble perchlorate yielded alkaloid B, m.p. 172.6–174°, $[\alpha]^{25}D$ −158° (*c*, 1.35 in $CHCl_3$). *Anal.* Found: C, 69.77, 69.69; H, 7.52, 7.30; N, 8.57; $OCH_3$, 9.18; $NCH_3$, 4.22. Calcd. for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37; N, 8.53; 1 $OCH_3$, 9.43; 1 $NCH_3$, 4.57. Alkaloid B contained one C-methyl and one active hydrogen (Zerewitinow); it gave a neutral benzoyl derivative, m.p. 251–252°, $[\alpha]^{25}D$ −116° (*c*, 0.99 in $CHCl_3$). *Anal.* Found: C, 72.23; H, 6.55; N, 6.54. Calcd. for $C_{26}H_{28}O_4N_2$: C, 72.20; H, 6.53; N, 6.48. The properties of alkaloid B are quite different from those of gelsemine and of gelsemicine and the infrared absorption spectra of these three bases are quite distinct. Alkaloid B thus appears to be new and it is proposed to designate it as gelsedine. Recently Janot, Goutarel and Friedrich[5] isolated from *G. sempervirens* an alkaloid (m.p. 171°, $[\alpha]D$ −160°) which gave rise to a benzoyl derivative, m.p. 262°, $[\alpha]D$ −117°. They claimed their base to be gelsemicine and assigned to it the empirical formula $C_{19}H_{24}O_3N_2$ which is the same as that now assigned to gelsedine. The properties of gelsedine were the same as those of Janot and co-workers' gelsemicine except for the ten-degree difference in the reported melting point of the benzoyl derivatives. The ultraviolet absorption spectrum of Janot and co-workers' alkaloid resembled that of gelsemine and was the same as that of gelsedine so that the two are probably identical and both are certainly different from gelsemicine.

The basic fraction obtained from the benzoylation yielded a further base (alkaloid C) which was an oil (*Anal.* Found: C, 71.18; H, 7.00. Calcd. for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.87), but formed a crystalline perchlorate, m.p. 250–252°. *Anal.* Found: C, 55.75; H, 5.66; N, 6.34. Calcd. for $C_{21}H_{24}O_3N_2 \cdot HClO_4$: C, 55.69; H, 5.56; N, 6.19. This base, which has an empirical formula differing from that of gelsemine by $CH_2O$, appears to be new.

(5) M. M. Janot, R. Goutarel and W. Friedrich, *Ann. pharm. franc.*, **9**, 305 (1951).

DIVISION OF PURE CHEMISTRY
NATIONAL RESEARCH COUNCIL H. SCHWARZ
OTTAWA, CANADA LÉO MARION

RECEIVED JUNE 25, 1953

## A SYNTHESIS OF HYDROPEROXIDES FROM GRIGNARD REAGENTS

*Sir:*

The reaction of aryl and alkyl Grignard reagents with oxygen is well known and has been found to give poor yields of phenols,[1] and good yields of alcohols.[2,3] The sequence

$$RMgX + O_2 \longrightarrow ROOMgX$$
$$ROOMgX + RMgX \longrightarrow 2ROMgX$$

has been proposed[4] for this reaction and is supported by small, but significant peroxide titration values.[5]

We have found that by slow addition of alkyl Grignard reagents to oxygen-saturated ether at −75°, the intermediate ROOMgX can be ob-

(1) F. Bodroux, *Compt. rend.*, **136**, 158 (1903).
(2) L. Bouveault, *Bull. soc. chim.*, [3] **29**, 1051 (1903).
(3) M. T. Goebel and C. S. Marvel, THIS JOURNAL, **55**, 1693 (1933).
(4) C. W. Porter and C. Steele, THIS JOURNAL, **42**, 2650 (1920).
(5) H. Wuyts, *Bull. soc. chim. Belg.*, **36**, 222 (1927).

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.

CHANDLER LABORATORY
COLUMBIA UNIVERSITY
NEW YORK 27, N. Y.

CHEVES WALLING
SHELDON A. BUCKLER

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## 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).