Summary

1. Thirty-two organic halides of widely varying types have been treated with mercury di-*p*-tolyl under very vigorous conditions.

2. Some of the halides have also been treated with mercury di-*n*-butyl and mercury diphenyl.

3. In general the mercury compounds are extraordinarily unreactive toward the halides studied.

4. In the cases of the five halides which gave definite reactions the behavior of the mercury compounds was analogous to that of other types of bases with the same halides.

5. It has been shown that 2,4,6-trinitrophenylmercuric compounds react normally with iodine.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

NEW PHENOLIC COMBINATIONS OBTAINED BY COUPLING CHAULMOOGRIC ACID WITH RESORCINOL[1]

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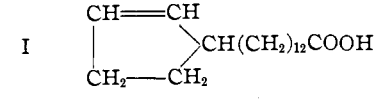
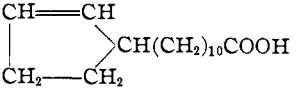
Chaulmoogric (I) and hydnocarpic (II) acids[3] in the form of their salts and esters are extensively used in leprosy therapy.[4] Notwithstanding the





fact, however, that many cures have been effected through their application, many objections have been raised to their prolonged therapeutic use, and there is still much to be desired before an ideal germicidal agent is found for the treatment of patients suffering from leprosy. New compounds of high germicidal power and low toxicity are very much desired for clinical work in the study of methods to eradicate this disease. In view of the striking bactericidal properties of alkylresorcinols and the established clinical success of hexylresorcinol[5] it seemed desirable to prepare

[1] Constructed from a dissertation presented by Wilbie S. Hinegardner to the Faculty of the Graduate School of Yale University, June, 1927, in candidacy for the degree of Doctor of Philosophy.

[2] Holder of the Richard Wrenshall Research Prize in 1925–1926.

[3] Barrowcliff and Power, *J. Chem. Soc.*, **91**, 557 (1907); Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925).

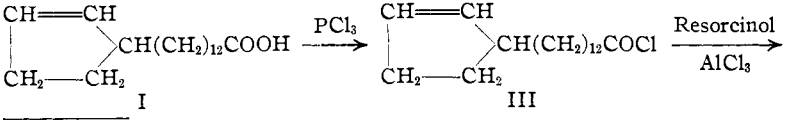
[4] Rogers, *Brit. Med. J.*, **4**, 550 (1916); **5**, 277 (1917); McDonald and Dean, *J. Am. Med. Assoc.*, **76**, 1470 (1921); Muir, *Indian J. Med. Research*, **11**, 543 (1923).

[5] Johnson and Lane, THIS JOURNAL, **43**, 348 (1921); Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926); V. Leonard, *Science*, **62**, 408 (1925); Leonard and Feirer, *Surgery Gynecol. Obstet.*, **45**, 603–611 (1927).

some resorcinol derivatives containing the cyclopentenyl group. As chaulmoogric acid was available[6] in quantity we have used it to prepare the first of this new type of compounds, namely, 1-cyclopentenyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane, V. It is a derivative of chaulmoogric acid containing no carboxyl or ester group, and thus differs structurally from those previously used in leprosy treatment. The method of synthesis reported in this paper should lend itself equally well to the preparation of lower homologs of the series; their investigation is in progress in this Laboratory.

We have introduced the chaulmoogryl group into the nucleus of resorcinol by application of the Friedel and Crafts reaction, using carbon disulfide as the solvent when the dimethyl ether of resorcinol was used, and nitrobenzene[7] when using resorcinol directly. The method developed by Nencki and others[8] of heating resorcinol and the acid in the presence of anhydrous zinc chloride was entirely inapplicable, the zinc chloride reacting with the unsaturated part of chaulmoogric acid giving resinous decomposition products. However, this latter method proved entirely satisfactory with dihydrochaulmoogric acid.[9] The preparation of resorcinol-monochaulmoograte and the rearrangement of the chaulmoogryl group into the resorcinol nucleus were not successful. The methyl group of dimethlyresorcinol para to the entering chaulmoogryl group could not be removed without complete breakdown of the compound. It has been recognized previously that methyl groups para to a ketone group are removed with difficulty, but when ortho to a ketone group they are removed with comparative ease.[10] Only those ketones in which the carbonyl is ortho to a phenol group give a red color with ferric chloride.

These ketones were readily reduced to the corresponding alkylresorcinols by the Clemmensen method.[11] The synthesis and reduction of chaulmoogryl resorcinol, IV, is represented by the following steps



I III

[6] We wish to thank Dr. Richard Wrenshall of the University of Hawaii for supplying a large portion of the chaulmoogric acid used in this research. The remainder was obtained from chaulmoogra oil purchased in the market.

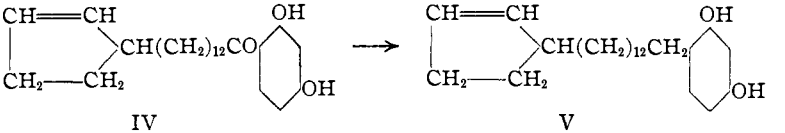
[7] Behn, *Chem. Zentr.*, I, 1223 (1898); German patent 95,901, *Friedländer*, **5**, 143 (1900); Klarmann, THIS JOURNAL, **48**, 2358 (1926); Bartlett and Garland, *ibid.*, **49**, 2098 (1927).

[8] Nencki and Sieber, *J. prakt. Chem.*, **23**, 147 (1881); Nencki and Schmid, *ibid.*, **23**, 546 (1881); Nencki, *Monatsh.*, **10**, 906 (1889).

[9] The dihydrochaulmoogric acid was kindly supplied to us by Dr. Richard Wrenshall.

[10] Auwers and Rietz, *Ber.*, **40**, 3514 (1907).

[11] Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 51, 681 (1914); Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913); Majima and Nakamura, *Ber.*, **46**, 4089 (1913).



IV V

The double bond in the cyclopentenyl group is not reduced in this process since after reduction both the mono- and di-methyl ether of IV show optical activity. The non-optical activity of the 1-cyclopentenyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane, V, is probably due to internal compensation of the type shown by bromodihydrochaulmoogric acid, which is practically inactive though its esters show a decided optical activity.[12] The ketones which we have prepared show decreasing optical activity with decrease in methylation, and further decrease in optical activity upon reduction of the ketone group; thus it might be expected that V would show no measurable activity since the ketone IV is only slightly active.

1-Cyclopentyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane has been prepared and found to differ from 1-cyclopentenyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane, V, thus proving conclusively that the double bond in this compound is not reduced when it is treated according to the Clemmensen procedure. The great stability of the asymmetric carbon atom in chaulmoogric acid argues against racemization, and especially is this supported by the observation that the mono- and dimethyl ethers of the ketone, IV, show optical activity after reduction.

Experimental Part

Chaulmoogric Acid.—The chaulmoogric acid, which was brownish-yellow from slight oxidation, was distilled under 2–3 mm. pressure and crystallized once from ethyl acetate. Glistening white flakes melting at 68° were obtained. A 20-g. portion recrystallized repeatedly from ethyl acetate melted at 68–68.5° and gave $[\alpha]_D^{25°} = +62.2°$ in chloroform.

Anal. Subs., 0.0940: CO_2, 0.2656; H_2O, 0.0983. Calcd. for $C_{18}H_{32}O_2$: C, 77.07; H, 11.51. Found: C, 77.07; H, 11.67.

Fusion of Chaulmoogric Acid with Resorcinol and Zinc Chloride.—Eleven grams of chaulmoogric acid, 3.9 g. of resorcinol and 4.9 g. of anhydrous zinc chloride were heated at 100–105° with constant stirring for one hour. Resorcinol and zinc chloride were removed and the residue distilled at 2 mm. pressure, but only 0.8 g. (6% yield) of very impure chaulmoogrylresorcinol was obtained. After several crystallizations from an ether–petroleum ether mixture a few tenths of a gram of material remained which melted at 68–71°. It was soluble in 10% sodium hydroxide solution, very soluble in ether, alcohol and acetone. When dissolved in alcohol a deep red color resulted upon the addition of a drop of ferric chloride solution.

Dihydrochaulmoogrylresorcinol was prepared from dihydrochaulmoogric acid by the preceding method except that the temperature and time of heating were identical with those used in the preparation of hexylresorcinol. This gave a 50% yield of the desired ketone and 20% of the acid was recovered. After several crystallizations from 95% acetone it melted at 89.5°.

[12] Shriner and Adams, THIS JOURNAL, **47**, 2731 (1925).

This ketone was also prepared from dihydrochaulmoogryl chloride and resorcinol by application of a Friedel and Crafts reaction in nitrobenzene. A 70% yield was obtained, the product melting at 89.5° after repeated recrystallizations from acetone. Both ketone preparations gave the same oxime.

Anal. Subs., 0.0947: CO_2, 0.2665; H_2O, 0.0877. Calcd. for $C_{24}H_{38}O_3$: C, 76.94; H, 10.23. Found: C, 76.74; H, 10.36.

The oxime of dihydrochaulmoogrylresorcinol was prepared according to the method used by Hill and Evans.[13] Two grams of dihydrochaulmoogrylresorcinol and 0.5 g. of hydroxylamine hydrochloride were added to 8 cc. of anhydrous pyridine and the solution heated on the steam-bath for ten hours. The oxime was obtained as an oil which crystallized on cooling. After several recrystallizations from benzene, it melted at 169–170°. The crystals were in the form of silvery flakes that turned yellow on exposure to light.

Anal. Calcd. for $C_{24}H_{39}O_3N$: N, 3.60. Found (Kjeldahl): N, 3.57, 3.49.

Chaulmoogryl chloride[14] was prepared most satisfactorily by the action of an excess of phosphorus trichloride on chaulmoogric acid at room temperature for twenty-four to thirty hours. The excess of trichloride was removed by vacuum distillation, when the acid chloride was obtained as a colorless liquid that could not be purified by distillation.

Phosphorus pentachloride and thionyl chloride partly decomposed chaulmoogric acid. The potassium salt of chaulmoogric acid and thionyl chloride can be used satisfactorily for preparing the acid chloride except for the difficulty of preparing the anhydrous potassium salt.

Dimethyl and Monomethyl Ethers of Chaulmoogrylresorcinol.—Chaulmoogryl chloride from 26.0 g. of chaulmoogric acid and 12.5 g. of dimethylresorcinol were dissolved in 50 cc. of carbon disulfide and slowly added in small portions to 35 g. of powdered aluminum chloride covered with 25 cc. of carbon disulfide. The reaction was completed within two hours and water was then added to decompose any addition products formed. After extraction with ether and drying, the solvent was removed and the reaction product distilled under 2–3 mm. pressure. At 230–238° (uncorr.) 8.4 g. of a clear brownish-yellow oil was obtained (23% yield). Traces of chaulmoogric acid were removed from this and upon redistillation a bright yellow oil was collected that partially solidified on standing. By fractional crystallization from acetone silky needles were first obtained melting at 56–58° and a second more soluble fraction also crystallizing in needles melting at 34–36°. The two products were finally obtained in pure form by recrystallization from alcohol and acetone and melted at 65 and 46°, respectively. The higher-melting compound was less soluble, gave a red color when dissolved in alcohol and treated with a drop of ferric chloride solution, and gave a positive Millon's reaction. It was insoluble in sodium hydroxide solution and slowly developed a reddish color when exposed to the air. It was identified as **1-chaulmoogryl-2-hydroxy-4-methoxybenzene.**

Anal. 1.2967 g. made up to 50.1 cc. in chloroform at 25° gave a rotation of +0.722° in a 4-dcm. tube; $[\alpha]_D^{25°} = +6.98°$. Subs., 0.1770: CO_2, 0.5001; H_2O, 0.1640. Calcd. for $C_{25}H_{38}O_3$: C, 77.66; H, 9.91. Found: C, 77.07; H, 10.34.

The compound melting at 46° gave no red color with ferric chloride solution and after careful purification no positive test with Millon's reagent. It was insoluble in sodium hydroxide and did not develop a red color on exposure to the air. It was identified as the methylated compound **1-chaulmoogryl-2,4-dimethoxybenzene.**

[13] Evans, Doctor of Philosophy "Dissertation," Yale University, **1926.**

[14] Powers and Gornall, *J. Chem. Soc.*, **85**, 855 (1904).

Anal. 1.2470 g. made up to 27 cc. in chloroform at 25° gave a rotation of +3.47° in a 4-dcm. tube; $[\alpha]_D^{25°}$ = +18.78°. Subs., 0.1310, 0.1174: CO_2, 0.3715, 0.3355; H_2O, 0.1207, 0.1083. Calcd. for $C_{26}H_{40}O_3$: C, 77.94; H, 10.07; Found: C, 77.34, 77.93; H, 10.30, 10.38.

Mol. wt. (in ethylene bromide). Solvent, 38.86, 38.86, 38.86; solute, 0.1213, 0.3074, 0.4090; Δt, 0.094°, 0.239°, 0.315°. Calcd. for $C_{26}H_{40}O_3$: 400.3. Found: 398, 397, 401; average, 398.

When the above procedure was modified by keeping the reaction temperature at 30–35° and adding the aluminum chloride to the chaulmoogryl chloride and resorcinol dissolved in carbon disulfide, yields of 40% were obtained, dimethylchaulmoogrylresorcinol being the only product identified. When anhydrous ferric chloride was used as the catalyst no demethylation took place by either procedure but the yields were much lower.

Esters of Resorcinol.—The anhydrous monopotassium salt of resorcinol was prepared by a procedure similar to that used by De Forcrand in preparing the monosodium salt.[15] It was a light colored, hard mass and was quite hygroscopic.

Seventeen and eight-tenths grams of this potassium salt of resorcinol was suspended in 125 cc. of dry ether and chaulmoogryl chloride (from 25 g. of chaulmoogric acid) dissolved in 75 cc. of ether slowly added. Immediate reaction occurred with the separation of potassium chloride. After this was complete water was added, the ether layer separated, washed first with water and then with sodium carbonate until free from chaulmoogric acid. The solvent was then removed, the reaction product dissolved in petroleum ether and washed with water to remove any unaltered resorcinol; it was dried and finally distilled under 2–3 mm. pressure. At 238–240° (uncorr.) 2.8 g. of a light yellow oil distilled over which immediately solidified; then at 270–281° (uncorr.), 11.7 g. of an almost colorless oil was obtained which also solidified. When crystallized from petroleum ether glistening plates were obtained melting at 51°. The compound is very soluble in hot petroleum ether, ether or acetone, but difficultly soluble in alcohol. Analysis and molecular weight determinations indicated that we were dealing with **resorcinoldichaulmoograte.**

Anal. 0.6158 g. made up to 27 cc. by chloroform at 25° gave +4.19° in a 4-dcm. tube. $[\alpha]_D^{25°}$ = +45.93°. Subs., 0.0747, 0.0948: CO_2, 0.2140, 0.2715; H_2O, 0.0703, 0.0857. Calcd. for $C_{42}H_{66}O_4$: C, 79.42; H, 10.47. Found: C, 78.13, 78.10; H, 10.53, 10.12.

Mol. wt. (in ethylene bromide). Solvent, 32.53, 32.53, 32.53; solute, 0.0815, 0.1420, 0.2406; Δt, 0.045°, 0.078°, 0.134°. Calcd. for $C_{42}H_{66}O_4$: 634.5. Found: 668, 672, 660; average, 667.

Chaulmoogrylresorcinol.—Chaulmoogryl chloride from 50 g. of chaulmoogric acid and 26 g. of resorcinol were dissolved in 150 cc. of anhydrous nitrobenzene. The temperature was maintained at 30–35° while 29 g. of aluminum chloride was added in small portions followed by shaking. After standing for a few minutes the mixture was cooled and cold dilute hydrochloric acid and cracked ice were added. Ether extraction was then applied and the ether solution dried over anhydrous sodium sulfate. After removing all ether and nitrobenzene by vacuum distillation, the remaining oil was distilled under 2–3 mm. pressure, when we obtained thirty-eight grams of a light yellow oil which, on cooling, crystallized in long needles. On crystallization from acetone it was obtained in the form of small colorless needles melting at 83°. Removal of the nitrobenzene by vacuum distillation was more satisfactory than by steam distillation.

Anal. 1.284 g. made up to 50.8 cc. in chloroform at 25° gave a rotation of +0.14°

[15] De Forcrand, *Ann. chim. phys.*, [6] **30**, 67 (1893).

in a 4-dcm. tube. $[\alpha]_D^{25°} = +1.38$. Subs., 0.0810: CO_2, 0.2286; H_2O, 0.0728. Calcd. for $C_{24}H_{36}O_3$: C, 77.36; H, 9.74. Found: C, 76.96; H, 10.05.

The oxime of chaulmoogrylresorcinol was prepared by the method previously described. It melted at 152–154° and after three crystallizations from benzene melted sharply at 161°. In appearance it was indistinguishable from the oxime of dihydrochaulmoogrylresorcinol and, like it, turned yellow on exposure to light.

Anal. Optical activity practically within experimental error, +0.02°, in a 4-dcm. tube. Calcd. for $C_{24}H_{37}O_3N$: N, 3.61. Found (Kjeldahl): N, 3.54, 3.55.

1-Cyclopentenyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane.—Eight grams of chaulmoogrylresorcinol was reduced by the Clemmensen method, stirring constantly and keeping a small amount of an ether–benzene mixture returning to the reduction flask from a reflux condenser. When no solvent was allowed to reflux, the material soon formed a butter-like emulsion which completely prevented mixing by the stirrer. Only a few cubic centimeters of ether or ether–benzene mixture was needed to prevent emulsification. The ferric chloride test for unreduced ketone was negative after seven hours, though reduction was continued for one hour longer. The reduced material was dissolved in ether, washed with water and the solution dried over anhydrous sodium sulfate. After removal of the ether, the oil obtained was distilled under 2–3 mm. pressure. It distilled at 245–247° (uncorr.) as a colorless oil which immediately solidified on cooling. This was further purified by crystallization from a petroleum ether–ligroin mixture, separating as needles melting at 68°. It was very soluble in alcohol, acetone or ether and dissolved immediately in 10% sodium hydroxide solution. It was moderately soluble in chloroform, ligroin and petroleum ether.

Anal. 2.1038 g. made up to 27 cc. in chloroform at 25° showed very slight or no optical activity in a 4-dcm. tube. Subs., 0.1175, 0.1042, 0.0865: CO_2, 0.3458, 0.3061, 0.2551; H_2O, 0.1147, 0.1018, 0.0842. Calcd. for $C_{24}H_{38}O_2$: C, 80.38; H, 10.68. Found: C, 80.26, 80.11, 80.42; H, 10.92, 10.93, 10.89.

1-Cyclopentenyl-13-(2-hydroxy-4-methoxyphenyl)-*n*-tridecane.—Two and eight-tenths grams of the monomethyl ether of chaulmoogrylresorcinol (1-chaulmoogryl-2-hydroxy-4-methoxybenzene) was reduced by the Clemmensen method; reduction was complete in six hours. A practically pure product was obtained and after two crystallizations from petroleum ether it melted at 47.5°. It crystallized in the form of pearly flakes.

Anal. 0.3890 g. made up to 27.1 cc. with chloroform at 25° gave a rotation of +0.354° in a 4-dcm. tube; $[\alpha]_D^{25°} = +6.15°$. Subs., 0.1086: CO_2, 0.3204; H_2O, 0.1058. Calcd. for $C_{25}H_{40}O_2$: C, 80.58, H, 10.82. Found: C, 80.46; H, 10.90.

Mol. wt. (in ethylene bromide). Solvent, 33.08, 33.08; solute, 0.0730, 0.1472; Δt, 0.073°, 0.147°. Calcd. for $C_{25}H_{40}O_2$: 372.3. Found: 363, 364; average, 364.

1-Cyclopentenyl-13-(2,4-dimethoxyphenyl)-*n*-tridecane.—Fourteen and seven-tenths grams of the dimethyl ether of chaulmoogrylresorcinol melting at 40° and containing a trace of the mono-methyl ether, as indicated by the ferric chloride test, was reduced by the Clemmensen method. Since no color test could be used to show the presence of unreduced ketone, the reduction was continued for eighteen hours. After three distillations the reduced material was obtained as a practically colorless oil, boiling at 250–252° (uncorr.) under 2 mm. pressure. It failed to solidify when cooled in a freezing mixture; n^{28}, 1.5414; d_{25}^{25}, 0.955.

Optical Activity.—1.070 g. made up to 10 cc. in chloroform at 25° gave a rotation of +1.02°; $[\alpha]_D^{25°} = +9.53°$.

1-Cyclopentyl-13-(2,4-dihydroxyphenyl)-*n*-tridecane.—Two and three-tenths grams of dihydrochaulmoogrylresorcinol was reduced by the Clemmensen method. The reduction required about nine hours, as the ketone reduced much less readily than the

other combinations containing the chaulmoogryl group. A light yellow product was obtained that crystallized from ligroin in hard crystalline masses melting at 73–74°.

Anal. Subs., 0.0647: CO_2, 0.1886; H_2O, 0.0649. Calcd. for $C_{24}H_{40}O_3$: C, 79.93; H, 11.19. Found: C, 79.50, H, 11.23.

Bacteriological Study

Preliminary experiments with chaulmoogrylresorcinol indicate a very low toxicity when given by mouth to rabbits or intramuscularly to rats. Tested against *B. thyphosum* the compound exerts little bactericidal or antiseptic action. It seems not improbable that this compound and lower homologs may be bactericidal for the acid-fast organisms such as leprosy and tuberculosis bacillus, through the ability of the compound to dissolve in the fat complexes of these organisms, even though the substance appears to be inert against the typhoid bacillus. Its bactericidal study is now in progress and a clinical investigation will follow.

Summary

1. The preparation of chaulmoogrylresorcinol and some of its derivatives are described.

2. The ketones prepared have been shown to be easily reduced to the corresponding alkyl resorcinols by the action of zinc amalgam.

3. The cyclopentenyl group in chaulmoogric acid is not reduced by the action of zinc amalgam.

4. The investigation of lower members of this homologous series will be continued in the Sterling Laboratory.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY]

THE ACTION OF METALLIC SODIUM ON BROMINATED CYCLIC ACETALS[1]

BY HAROLD S. HILL[2] AND G. J. C. POTTER

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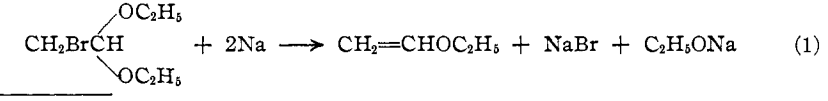
Wislicenus[3] showed that the reaction of bromo-ethylal with metallic sodium proceeded according to the following equation



$$CH_2BrCH(OC_2H_5)_2 + 2Na \longrightarrow CH_2{=}CHOC_2H_5 + NaBr + C_2H_5ONa \qquad (1)$$

[1] This paper represents one of a series of publications carried out under the joint auspices of the Canadian Pulp and Paper Association, the Pulp and Paper Division of the Forest Products Laboratories of Canada and the Department of Industrial and Cellulose Chemistry, McGill University. The authors wish to express their appreciation of the facilities placed at their disposal by the three coöperating agencies.

[2] Research Fellow, Canadian Pulp and Paper Association.

[3] Wislicenus, *Ann.*, **192**, 106 (1878).