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# THE SYNTHESIS OF RACEMIC TREMETONE

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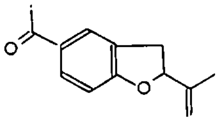
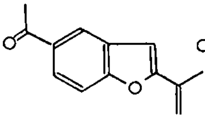
**Abstract**—Tremetone (I), the principal toxic ketone from *Eupatorium urticaefolium*, has been synthesized in its racemic form by the following sequence of reactions: 2-acetyl-2,3-dihydrobenzofuran (VIII)—(MeMgI)→2-(2′,3′-dihydro-2′-benzofuryl)-2-propanol (XIII)—($(F_3CCO)_2O$-HOAc)→2-(5′-acetyl-2′,3′-dihydro-2′-benzofuryl)-2-propyl acetate (XVII)—($H_2O, OH^-$)→2-(5′-acetyl-2′,3′-dihydro-2′-benzofuryl)-2-propanol (XVIII)—($-H_2O$)→I.

Recently we have undertaken an investigation of "tremetol", the crude toxin of white snakeroot (*Eupatorium urticaefolium*)[2], responsible for trembles in cattle[3] and milk sickness in humans.[4] To date we have reported the separation of tremetol into a sterol fraction and a ketone fraction, and the further separation of each of these fractions into several pure components.[5,6] The compounds isolated from the ketone fraction, being toxic to goldfish, have been investigated from a structural viewpoint by degradative techniques, with the findings that the principal toxic ketone, tremetone, possessed structure I[5,6] while the two minor ketones, dehydrotremetone and hydroxytremetone, possessed structures II and III, respectively.[5,7] In addition, we have synthesized racemic dihydrotremetone (IV)[5,8] and found it structurally equivalent to one of the hydrogenation products of tremetone, thus confirming the skeletal structures of this series of natural ketones. We now wish to report on the synthesis of tremetone (I) itself in its racemic modification.


I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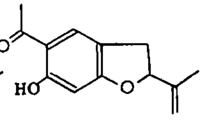

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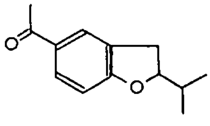
IV

The initial design for the synthesis of I is shown in Chart I, where the key steps were anticipated to be the trifluoroacetic anhydride catalyzed acetylation of VII to X, the introduction of the methylenic double bond into XI by the Wittig synthesis[9] and the final oxidation of XII to I, which might be difficult if the methylene group of XII should oxidize simultaneously with the carbonyl function.

The intermediate 2-acetyl-2,3-dihydrobenzofuran (VIII) in Chart I has been previously prepared by Stoermer *et al.*[10] as well as by Shriner and Anderson[11] by direct

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[1] The authors are grateful to the National Institutes of Health for a research grant (NIH-RG-6232) which supported this investigation.

[2] J. F. Couch, *J. Amer. Chem. Soc.* **51**, 3617 (1929).

[3] J. F. Couch, *J. Agr. Res.* **35**, 547 (1927).

[4] J. F. Couch, *J. Amer. Med. Assoc.* **91**, 234 (1928).

[5] W. A. Bonner, J. I. DeGraw, Jr., D. M. Bowen and V. R. Shah, *Tetrahedron Letters* No. 12, 417 (1961).

[6] W. A. Bonner and J. I. DeGraw, Jr., *Tetrahedron* In Press.

[7] J. I. DeGraw, Jr. and W. A. Bonner, *J. Org. Chem.* In Press.

[8] J. I. DeGraw, Jr. and W. A. Bonner, *Tetrahedron* In Press.

[9] G. Wittig and U. Schollkopf, *Chem. Ber.* **87**, 1318 (1954).

[10] R. Stoermer, C. Chydenius and E. Schinn, *Ber. Dtsch. Chem. Ges.* **57**, 72 (1924).

[11] R. Shriner and J. Anderson, *J. Amer. Chem. Soc.* **61**, 2705 (1939).

sodium amalgam reduction of 2-acetylbenzofuran (V). Shriner and Anderson state that a very large excess of sodium amalgam is necessary to obtain pure dihydroketone VIII, the semi-carbazone of which they found to have m.p. 168–169°, in contrast to the m.p. 192° reported by Stoermer. Shriner and Anderson found, moreover, that admixture of the semicarbazone of V, m.p. 217°, with that of VIII gave a sample having m.p. about 192°, and accordingly suggested that Stoermer's compound was an incompletely reduced mixture of V and VIII. For purposes of anticipated large scale preparation of VIII it was therefore felt that sodium amalgam was an impractical reagent. Shriner and Anderson have also investigated the possibility of selective hydrogenation of the double bond in the benzofuran ring of V, but found that the usual catalysts led to prior reduction of the carbonyl group.[11] This difficulty was circumvented in our work by preparation of the dimethyl ketal (VI) of 2-acetylbenzofuran, which could be smoothly reduced using Raney nickel to the 2,3-dihydro analog VII. Hydrolysis of the latter produced the desired dihydroketone VIII in good yield.

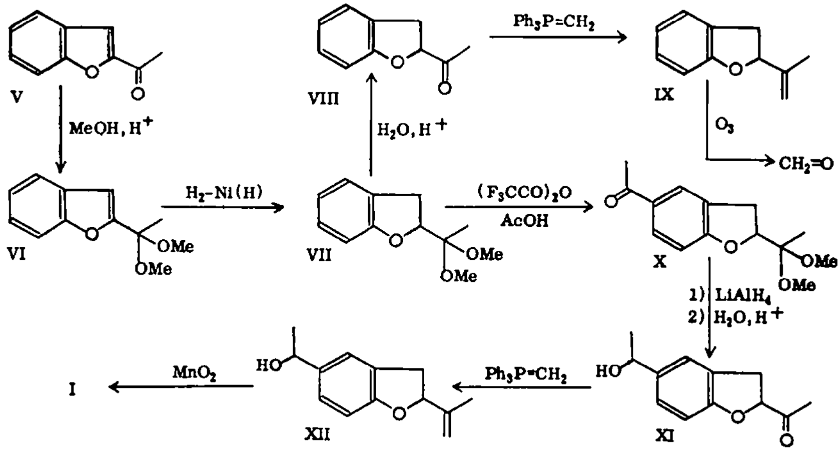


Chart I. Attempted synthesis of tremetone

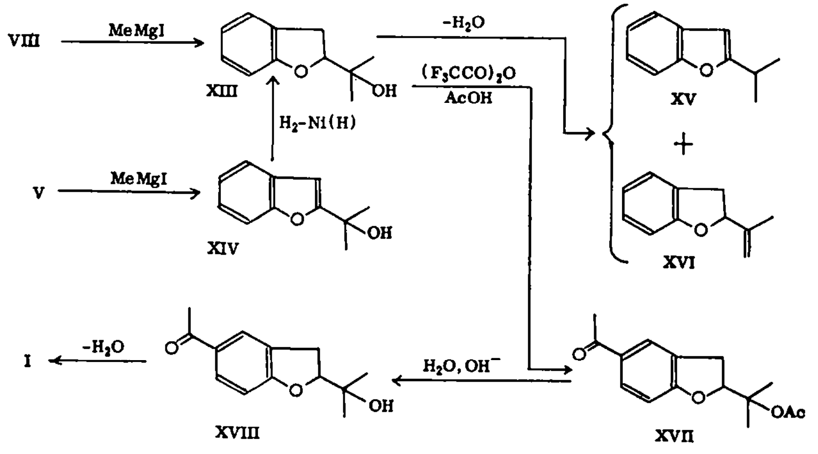
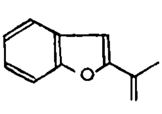


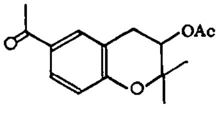
Chart II. Synthesis of racemic tremetone

Before continuing with the proposed sequence in Chart I it was decided to investigate the Wittig reaction of the dihydroketone VIII in order to check the feasibility of the penultimate conversion of XI to XII by this reaction. When VIII was heated with methylene triphenylphosphine in refluxing tetrahydrofuran, a 50% yield of crude product resulted. Distillation and chromatography, however, afforded only a 6% yield of material identified as 2-isopropenyl-2,3-dihydrobenzofuran (IX) by its IR spectrum (methylenic bands at 6·05 and 11·05 $\mu$), its UV spectrum (peaks at 225, 280 and 288 m$\mu$ indicative of the dihydrobenzofuran system) and the fact that its ozonization produced formaldehyde. The very poor yield obtained during the above Wittig synthesis made it appear inadvisable to continue the proposed synthetic sequence in Chart I, and the alternative route illustrated in Chart II was developed.

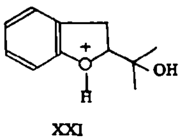
The preparation of 2-(2′,3′-dihydro-2′-benzofuryl)-2-propanol (XIII) was accomplished either by reaction of methylmagnesium iodide with the above dihydroketone VIII, or by reaction of this Grignard reagent with 2-acetylbenzofuran (V), followed by Raney nickel reduction of the resulting tertiary alcohol XIV. The behavior of XIII towards dehydrating media was next investigated to determine whether reasonable yields of the methylenic olefin XVI (analogous to the desired I) could be obtained. Stoermer *et al.*[10] claim to have prepared olefin XVI by merely distilling the tertiary alcohol XIII at reduced pressure. In our hands this procedure proved ineffectual, as did also dehydration attempts involving heating XIII in refluxing acetic acid or distilling it from *p*-toluenesulfonic acid. It thus appeared likely that Stoermer had actually dehydrated a mixture of the tertiary alcohols XIII and XIV, since the crude product which they employed was prepared by action of methylmagnesium halide on a sample of dihydroketone VIII suspected of containing significant amounts of the non-reduced analog V.[11] Thus they most likely obtained the diene, 2-isopropenylbenzofuran (XIX) instead of the expected XVI. We subsequently found that the powerful dehydrating action of phosphoryl chloride in pyridene[12] would effect dehydration of the carbinol XIII, yielding (90%) an hydroxyl-free product which appeared by its IR spectrum to be an approximately equal mixture of the desired 2-isopropenyl-2,3-dihydrobenzofuran (XVI) and 2-isopropylbenzofuran (XV). These data were considered encouraging with respect to the last step in Chart II, since it was anticipated that chromatography would effectively separate any olefin mixture obtained.



XIX



XX



XXI

The action of a mixture of trifluoroacetic anhydride and acetic acid on the tertiary alcohol XIII led smoothly to the formation of 2-(5-acetyl-2′,3′-dihydro-2′-benzofuryl)-2-propyl acetate (XVII), m.p. 95–96°, which in turn could be readily saponified to the 5-acetyl tertiary alcohol XVIII, m.p. 75·5–76·5°. To show that rearrangement to the isomeric secondary acetate XX had not occurred during the above acetylation of XIII, the deacetylated product XVIII was treated overnight with acetic anhydride in pyridine. As expected for a tertiary alcohol under these conditions, no acetylation occurred.

[11] B. Koechlin and T. Reichstein, *Helv. Chim. Acta* 27, 549 (1944).

It has previously been observed that O-acetylation by the trifluoroacetic anhydride-acetic acid reagent is a rapid reaction, but that ring acetylation requires longer time.[13] This observation was verified in our experience in that interruption of the acetylation of XIII after a brief period afforded a product whose IR spectrum showed strong ester carbonyl absorption but only a weak band in the IR region of conjugated carbonyl absorption.

Final conversion of XVIII into tremetone by dehydration was attempted again by the various procedures applied above to XIII. Ordinary dehydrating conditions again failed, however, and it was necessary to employ phosphoryl chloride and pyridine at 75° in order to effect this step. Chromatography of the dehydration product led to several substances which were not identified, as well as to a fraction whose IR spectrum was superimposible on that of tremetone (I). The synthetic I was also converted to its 2,4-dinitrophenylhydrazone, m.p. 186–190°, the IR spectrum of which was again identical with that of the corresponding derivative of the natural ketone.

The remarkable stability of the tertiary alcohols XIII and XVIII toward dehydration, particularly by acid, is noteworthy. Several similar cases of pyrolitically and dehydratively stable $\beta$-phenoxy tertiary alcohols have been previously reported. Stoermer prepared[14] 1-phenoxy-2-methyl-2-propanol and 1-phenoxy-2-ethyl-2-butanol and found them stable upon distillation at 231° and 260°, respectively. Hurd and Perletz[15] found that the former compound was undecomposed even on vacuum distillation over iodine, while Behal and Sommelet attempted[16] dehydration of the latter with oxalic acid. None of these authors has offered a rationale for the stability of such $\beta$-aryloxy alcohols. We would like to suggest that the stability of such alcohols to acid catalyzed dehydration is due to protonation of the ether oxygen (as in XXI), with the resulting oxonium center deterring formation of the adjacent carbonium ion involved in such dehydrations.

## EXPERIMENTAL

*2-Acetyl-2,3-dihydrobenzofuran* (VIII). A solution of 2-acetylbenzofuran (20·0 g), trimethyl orthoformate (40 ml) and *p*-toluenesulfonic acid (5 mg) in absolute methanol (60 ml) was heated under reflux for 1 hr, cooled to room temp and then treated with 5% methanolic sodium methoxide (10 ml) in one portion with stirring. The solution was evaporated to dryness at red. press. and the residue was dissolved in ether (200 ml), the precipitated salts were filtered and the ether filtrate was stripped of solvent. The resulting crude 2-acetylbenzofuran dimethylketal (VI) was purified by distillation, 20·0 g (77·5%), b.p. 94–97° (0·5 mm). Its IR spectrum showed no carbonyl band, weak bands at 6·2–6·3 $\mu$ (benzofuran system) and a quartet of ketal bands at 8·5–9·5 $\mu$. The UV spectrum in ethanol showed a strong peak at 245 m$\mu$, also indicative of the benzofuran system.[17]

A mixture of the above dimethylketal VI (47·0 g) and Raney nickel slurry (5 teaspoons; wet with ethanol) in absolute ethanol (175 ml) was hydrogenated in a Parr apparatus at a pressure of 3 atm. After 2 hr 0·84 equivalent of hydrogen was absorbed, but it proved necessary to continue the hydrogenation overnight for complete reduction. The catalyst was filtered and the filtrate was evaporated at red. press., yielding 47·0 g of VII, a clear liquid which was used below without further purification. Its IR spectrum showed no carbonyl absorption and indicated that reduction had occurred, since the strong 6·2 $\mu$ band characteristic of the dihydrobenzofuran system was present.

The above 2-acetyl-2,3-dihydrobenzofuran dimethylketal (VII; 20·0 g) was stirred vigorously for 2·5 hr with 1 N HCl (100 ml), and the mixture was extracted twice with ether. The extracts were

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[13] J. Tedder, *Chem. Rev.* **55**, 787 (1955).

[14] R. Stoermer, *Ber. Dtsch. Chem. Ges.* **39**, 2296 (1906).

[15] C. D. Hurd and P. Perletz, *J. Amer. Chem. Soc.* **68**, 38 (1946).

[16] A. Behal and M. Sommelet, *Bull. Soc. Chim.* **31**, 300 (1904).

[17] J. Jones and A. Lindsey, *J. Chem. Soc.* 1836 (1950).

washed with saturated sodium bicarbonate solution, dried and stripped of solvent at red. press. affording crude 2-acetyl-2,3-dihydrobenzofuran (VIII). This was distilled at red. press., 12·0 g (77%), b.p. 60–62° (0·5 mm). The IR spectrum of the product showed carbonyl absorption at 5·83 $\mu$.

2-Acetyl-2,3-dihydrobenzofuran semicarbazone was prepared in the usual way and recrystallized twice from dil ethanol, m.p. 173–174°. A m.p. of 168–169° has been recorded for this compound, prepared *via* the sodium amalgam reduction of 2-acetylbenzofuran.[11] 2-Acetyl-2,3-dihydrobenzofuran oxime was also prepared for characterization. After recrystallization from 20% ethanol the product showed m.p. 112·5–113·5°, in agreement with the m.p. 111–112° previously reported for this oxime.[10]

2-(2′,3′-*Dihydro-2′-benzofuryl*)-2-*propanol* (XIII). A Grignard solution prepared from magnesium (7·8 g) and methyl iodide (46·8 g) in anhydrous ether (240 ml) was treated with rapid stirring over 45 min with a solution of the above 2-acetyl-2,3-dihydrobenzofuran (25·2 g) in ether (60 ml), after which the mixture was poured upon ice (500 g) and acidified with 3 N HCl (120 ml). The aqueous layer was reextracted with ether, and the combined extracts were washed with sodium bicarbonate solution, dried and stripped of solvent at red. press. The oily residue was distilled, b.p. 78–80° (1 mm), to produce 20·0 g (72%) of clear, viscous 2-(2′,3′-dihydro-2′-benzofuryl)-2-propanol (XIII), whose IR spectrum showed strong hydroxyl and no carbonyl absorption. (Found: C, 73·59; H, 7·94; O, 18·33. $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92; O, 17·96%).

The above 2,3-dihydro tertiary alcohol XIII could be prepared equally well by Raney nickel reduction of the previously described[8] 2-(2′-benzofuryl)-2-propanol (XIV). The latter carbinol (1·05 g) and Raney nickel slurry (0·1 teaspoon) in ethanol (10 ml) were hydrogenated at room temp and atm press. in a volumetric apparatus. After the theoretical uptake of hydrogen was absorbed, the catalyst was filtered and the filtrate was stripped of solvent, affording 1·05 g of viscous liquid whose IR spectrum was identical with that of the product described above. In larger runs, employing a Parr shaker at 3 atm press., yields of 86% were obtained after distillation of the crude product.

*Dehydration of* 2-(2′,3′-*dihydro-2′-benzofuryl*)-2-*propanol* (XIII). Pilot attempts to dehydrate compounds of this type were investigated at this stage of the synthesis. Refluxing acetic acid, as well as slow vacuum distillation from *p*-toluenesulfonic acid failed to achieve dehydration of XIII, but the following procedure[12] proved effective. A solution of the tertiary alcohol XIII (0·70 g), pyridine (7 ml) and phosphoryl chloride (1·0 g) was heated under reflux for 5 min, then cooled and diluted with water. The mixture was extracted with ether and, after acidic and alkaline washes, the extract was evaporated at red press., affording 0·60 g of oily residue. The IR spectrum of this product showed complete absence of hydroxyl absorption and appeared to be equivalent to that of an equal mixture of 2-isopropylbenzofuran (XV) and 2-isopropenyl-2,3-dihydrobenzofuran (XVI).

2-(5′-*Acetyl-2′,3′-dihydro-2′-benzofuryl*)-2-*propyl acetate* (XVII). The above 2,3-dihydro tertiary alcohol XIII (1·5 g) was added to a mixture of trifluoroacetic anhydride (4·0 g) and glacial acetic acid (1·05 g) and the resulting purple solution was allowed to stand at room temp for 3 hr, then was poured with stirring into water (50 ml) containing an excess of solid sodium bicarbonate. The mixture was extracted thrice with ether and the extracts were dried, filtered and stripped of solvent, yielding 2·15 g of residue which was crystallized from hexane–benzene (7:3; 10 ml) to produce 1·04 g of solid. This was combined with an additional 0·28 g of crystals obtained by working over the mother liquors, and the product was recrystallized from hexane (15 ml) to yield 1·03 g (47%) of the desired XVII having m.p. 95–96°. Its IR spectrum showed no hydroxyl absorption, ester carbonyl at 5·80, conjugated ketone at 6·03 and phenyl with two adjacent hydrogens absorption at 12·2–12·3 $\mu$. (Found: C, 68·64; H, 6·92; O, 24·27. $C_{15}H_{18}O_4$ requires: C, 68·68; H, 6·92; O, 24·40%).

2-(5′-*Acetyl-2′,3′-dihydro-2′-benzofuryl*)-2-*propanol* (XVIII). A solution of the above tertiary acetate XVII (12·3 g) in 5% methanolic potassium hydroxide (185 ml) was heated under reflux for 45 min then evaporated nearly dry at red. press. The residue was diluted with 10 vol water and the mixture was extracted thrice with 75 ml portions of methylene chloride. The extracts were dried, filtered and stripped of solvent to yield 8·2 g of residue which was recrystallized from hexane–benzene (2:3; 35 ml) to give 7·7 g (75%) of off-white crystals, m.p. 74–76°. An analytical sample, m.p. 75·5–76·5°, was obtained by sublimation of a portion of this product at 160° (0·5 mm), followed by recrystallization. (Found: C, 70·88; H, 7·43; O, 21·76. $C_{13}H_{16}O_3$ requires: C, 70·89; H, 7·32; O, 21·79%).

*Racemic tremetone*. Unsuccessful attempts to prepare racemic tremetone from compounds in the above series included the following: dehydration of the 5-acetyl tertiary alcohol XVIII with acetic anhydride-pyridine, pyrolysis of XVIII at 230°, heating molten XVIII with *p*-toluenesulfonic acid and pyrolysis of the above tertiary acetate XVII at 240° *in vacuo*. Again, however, only the pyridine–phosphoryl chloride reagent led to successful deyhdration.

The 5-acetyl tertiary alcohol XVIII (4·0 g), pyridine (40 ml) and phosphoryl chloride (5·7 g; slow addition) were heated at 75° in an oil bath for 20 min, then were cooled and poured into ice water. The resulting mixture was extracted thrice with ether and the extracts were washed with 1 N HCl. The aqueous layers were reextracted with ether and the combined extracts were washed with saturated sodium bicarbonate solution and water, then were dried, filtered and evaporated at red. press. The residue (2·86 g) was dissolved in ligroin (77–110°; 35 ml), whereupon the chilled solution deposited 0·8 g crystals. The mother liquors were evaporated to yield 2·0 g of syrupy residue which was chromatographed on alumina (100 g), eluting with hexane–benzene (1 : 1), benzene and finally ether. Twelve fractions were collected. The first fraction (0·48 g) was an unidentified liquid lacking carbonyl absorption in the IR. Fractions 4–8 (0·36 g) proved to be more of the crystalline material removed from the crude reaction mixture above. Fractions 10–12 (0·32 g) showed an IR spectrum identical in all respects with that of natural tremetone. The above crystalline material, m.p. 130–131°, was not identified. Its IR spectrum showed strong hydroxyl absorption at 3·07, conjugated carbonyl absorption at 6·03 and phenyl with two adjacent hydrogens absorption at 12·03 $\mu$. Its UV absorption spectrum in ethanol showed a strong peak at 234 m$\mu$, unshifted in alkali.

Fractions 10–12 from the above chromatographic separation were converted into a 2,4-dinitrophenylhydrazone in the usual manner. The product was recrystallized from a mixture of ethanol and ethyl acetate to yield dark red crystals, m.p. 186–190°. Admixture with the 2,4-dinitrophenylhydrazone of natural tremetone (m.p. 183·8–184·2°)[6] gave a slight depression, m.p. 182–187°, not unexpected for a mixture of racemic and enantiomeric modifications of optically active compounds. The IR spectra of the two derivatives of the racemic and natural ketones were significantly different only at 12·0 $\mu$, when measured in Nujol mulls. In chloroform solution the spectra of the derivatives were identical.