above gave an almost quantitative yield of II which was recrystallized from benzene to yield slightly yellow crystals melting at 138–140°, which was the melting point recorded for II prepared by reduction of acetyl *p*-coumaric acid phenylimidochloride with stannous chloride.[4]

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APPLETON, WIS.

Urethanes of Tropine and Phenylmethylpyrazolone

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Some years ago, when these laboratories were engaged in the synthesis of cholinergic drugs, it became desirable to prepare the dimethylurethanes of tropine and of phenylmethylpyrazolone and to study pharmacologically these substances and some of their quaternary salts.

EXPERIMENTAL

Tropine, m.p. 63–64°, could be obtained from atropine in 85–95% yield by refluxing 20–25 min. with alcoholic potassium hydroxide, followed by rapid ethereal extraction of the cooled diluted solution (Tropic acid, m.p. 105–106°, could be isolated from the acidified alkaline solution).

Dimethylcarbamoyltropine. Equal weights of tropine and dimethylcarbamoyl chloride were rapidly heated to 150–160°. The color of the mixture changed to reddish brown and on cooling the mixture solidified. The pulverized solid was extracted with benzene and then dissolved in water. The aqueous solution was made basic with sodium carbonate, extracted with chloroform, and the solvent stripped from the extract to leave the crude product. This could be purified *via* the picrate (chromatographed on alumina) but this procedure offered little advantage over direct distillation. The pure product distilled at 105–120° (1 mm.) without decomposition and was obtained in 38 to 46% yield. It was a colorless liquid, soluble in water, benzene, alcohol, and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.26; H, 9.43; N, 13.20. Found: C, 62.52; H, 9.62; N, 12.89.

The *picrate* was prepared in the usual manner and melted at 210–212° after recrystallization from alcohol.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot C_6H_3N_3O_7$: C, 46.26; H, 5.25; N, 15.80. Found: C, 46.09; H, 4.88; N, 16.33.

The methiodide was prepared by interaction of the urethane and methyl iodide in methanol. It melted at 250–252° after recrystallization from methanol and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot CH_3I$: C, 40.67; H, 6.49; N, 7.90. Found: C, 40.86; H, 6.77; N, 7.74.

The *methobromide* was prepared by the addition of a dry benzene solution of the urethane to a solution of an excess of methyl bromide in benzene. It melted at 280–283° after recrystallization from methanol and ether.

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Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot CH_3Br$: C, 46.89; H, 7.55; N, 9.11. Found: C, 46.61; H, 7.58; N, 9.13.

The *benzochloride* was so hygroscopic that it could not be obtained pure. The *benzobromide* was prepared by the interaction of the urethane and benzyl bromide in boiling benzene. It melted at 250–252° after recrystallization from ethanol and ether.

Anal. Calcd. for $C_{11}H_{20}N_2O_2 \cdot C_7H_7Br$: C, 56.39; H, 7.10; N, 7.31. Found: C, 55.61; H, 7.28; N, 7.01.

1-Phenyl-3-methyl-5-dimethylcarbamoyloxypyrazole. Equal weights of the dry potassium salt of 1-phenyl-3-methyl-5-pyrazolone and dimethylcarbamoyl chloride were heated on the steam bath for 15 min. and the mixture was then leached with chloroform. The chloroform solution was washed with aqueous sodium carbonate, dried, and distilled to give 45–50% yields of product, b.p. 167–172° (2–3 mm.).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.67; H, 6.12. Found: C, 63.98; H, 6.40.

This material did not give a picrate, methiodide, or benzochloride (no picrate or quaternary salts of phenylmethylpyrazolone are reported in the literature).

The methiodide and benzobromide of dimethylcarbamoyltropine showed no cholinergic effect on isolated guinea pig intestine at a concentration of 100 γ/cc. (determined by Dr. R. J. Schachter).

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Reaction of NBS with Allylic Alcohols

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In connection with previous studies[2] on selective oxidations of secondary alcohols with *N*-bromosuccinimide, the oxidation of the steroid allylic alcohols was investigated. Δ^4-Cholestene-3β,6β-diol was oxidized mainly to 3,6-cholestanedione (42% yield), presumably through the intermediate formation of Δ^4-cholestene-6β-ol-3-one, which was indeed isolated also but in low yield (17%). The results contrast with those obtained with the corresponding saturated 3β,6β-diol,[2] where only the 6β-hydroxyl group is affected, but are understandable in terms of a half-chair conformation for Ring A in the unsaturated diol.[3]

In the reaction of *N*-bromosuccinimide with 7β-hydroxycholesterol, neither of the hydroxyl groups is oxidized; instead a bromohydrin is obtained (57% yield). This is converted into an oxide when treated with base. This oxide and the isomeric oxide were both obtained by oxidation of Δ^5-cholestene-3β,7β-diol with perphthalic acid. The

(1) This investigation was carried out during 1954 in the Department of Chemistry, Harvard University, under a grant from the Camille and Henry Dreyfus Foundation. Present address: Productos Esteroides S.A., México City.

(2) L. F. Fieser, H. Heymann, and S. Rajagopalan, *J. Am. Chem. Soc.*, **72**, 2306 (1950); L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3935 (1949); **71**, 3938 (1950); **72**, 5530 (1950).

(3) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

configuration of the two oxides can be assigned by molecular rotation differences as compared with α- and β-cholesteryl oxides. The oxide obtained through the bromohydrin is evidently the β-oxide and therefore the bromohydrin from which it is formed is 5α-bromocholestane-3β,6β,7β-triol. The addition of hypobromous acid to the 5,6-double bond therefore is contrary to Markownikoff's rule, as has been observed in the addition of halogens[4] and hypochlorous acid,[5] and is controlled by steric factors.[6]

EXPERIMENTAL[7]

Oxidation of Δ⁴-cholestene-3β,6β-diol. Δ⁴-Cholestene-3β,6β-diol (430 mg.) in hot dioxane (75 ml.) containing 2 ml. of water was treated with *N*-bromosuccinimide (400 mg.) and the mixture was warmed on the steam bath until complete solution was effected. The solution turned yellow and then colorless. At this stage the reaction mixture was poured into water and the precipitate collected by suction. A first crystallization from benzene–petroleum ether gave 80 mg. (17% yield) of colorless needles m.p. 191–193° identified as *Δ⁴-cholestene-6β-ol-3-one* by direct comparison with an authentic sample of this compound. From a second crop of the initial solution a crystalline product, m.p. 169–170°, α_D +3.2, was obtained, which was not depressed on admixture with a pure sample of *3,6-cholestandione*. Yield, 200 mg. (42%).

5α-Bromocholestane-3β,6β,7β-triol was obtained from the reaction of Δ⁵-cholestene-3β,7β-diol (450 mg.) with NBS (280 mg.) in dioxane-water (6 ml., 0.8 ml.), 6 hr., 25°. It forms small prisms when crystallized from petroleum ether, m.p. 177–180°, α_D +28.6°.

Anal. Calcd. for $C_{27}H_{47}O_3Br$: C, 64.91; H, 9.48; Br, 15.99. Found: C, 64.99; H, 9.53; Br, 15.93.

The 3,7-dibenzoate was obtained by a similar reaction from Δ⁵-cholestene-3β,7β-diol dibenzoate; 89% yield, m.p. 142–143°, α_D −60.6°.

Anal. Calcd. for $C_{41}H_{55}O_5Br$: C, 69.57; H, 7.83. Found: C, 69.93; H, 7.53.

When refluxed with 2% potassium hydroxide for 1 hr. the bromohydrin is converted into the β-oxide of 7β-hydroxycholesterol in 92% yield; plates from petroleum ether, m.p. 166–167°, α_D +50°. The oxide is reconverted into the bromohydrin by the action of hydrogen bromide.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.45; H, 11.07. Found: C, 77.12; H, 10.99.

The 3,7-dibenzoate of the β-oxide was obtained from the corresponding bromohydrin; 64% yield, m.p. 151–153°, α_D +86°.

7β-Hydroxycholesteryl α-oxide was obtained by refluxing Δ⁵-cholestene-3β,7β-diol (800 mg.) for 6 hr. with a solution of perphthalic acid (800 mg.) in ether (40 ml.). After the usual work-up, chromatography afforded some starting material (60 mg.); the α-oxide, 250 mg., 30% yield, m.p. 153–155°, α_D +12°; intermediate nonhomogeneous fractions; and finally the β-oxide, 12% yield, m.p. 166–167° α_D +50° (no melting point depression on admixture with the oxide from the bromohydrin).

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.45; H, 11.07. Found: C, 76.86; H, 11.22.

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Reaction of Ethyl Acrylate with Methyl *n*-Hexyl Ketone

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It has been reported that the reaction of ethyl acrylate with methyl *n*-hexyl ketone in the presence of an excess of sodium ethoxide gives 1-hendecene-3,5-dione.[2] When this reaction was repeated, a product (I) with the reported melting point 69–70° and composition (corresponding to $C_{11}H_{18}O_2$) was obtained. Although examination of the infrared spectrum confirmed the presence of a 1,3-diketone by a very broad band[3] at about 1600 cm.$^{-1}$, there was no indication of the presence of a double bond. The compound did not absorb hydrogen in the presence of either Pt or Pd catalyst. The diketone had a neutralization equivalent of 178 and molecular weight (ebulliometric) of 182. It did not give a color in the ferric chloride test.

Two possible structures for the product were 2-pentyl-1,3-cyclohexanedione (II) and 4-pentyl-1,3-cyclohexanedione (III), which could be formed, respectively, by an initial Michael condensation of the two reactants at the methyl or the methylene carbon atom, followed by a cyclization reaction. Whereas II would give only one product on basic hydrolysis, 5-ketohendecanoic acid, III would give a mixture of 2-pentyl-5-ketohexanoic acid and 4-pentyl-5-ketohexanoic acid. Hydrolysis of I with barium hydroxide solution[4] gave after acidification a clear oil which resisted attempts at crystallization. This oil had a neutralization equivalent of 205 (calcd. for $C_{11}H_{20}O_3$, 200). The infrared spectrum was consistent with the keto acid structure, the carbonyl groups absorbing in a single band at about 1715 cm.$^{-1}$ A weak iodoform test was obtained, showing the presence of some material containing the CH_3CO— group. The resistance of the keto acid to crystallization and this iodoform test indicated that the original product was III, and that hydrolysis had given the mixed keto acids.

III has been prepared by the hydrogenation of 4-pentylresorcinol, in alkaline solution and in the presence of Raney nickel catalyst.[5] Repetition of

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