TABLE I[a]

N-(ω-BROMOALKYL)SACCHARINS

N-ω-Bromoalkyl Substituent	Yield,[b] %	M.P., °C.	Formula	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
2-Bromoethyl	97	96[c]	$C_9H_8BrNO_3S$				
3-Bromopropyl	61	92.5	$C_{10}H_{10}BrNO_3S$	39.49	39.68	3.31	3.16
4-Bromobutyl	70	71–72	$C_{11}H_{12}BrNO_3S$	41.53	41.81	3.80	3.87
5-Bromopentyl	33	53.5	$C_{12}H_{14}BrNO_3S$	43.38	43.67	4.25	4.58
6-Bromohexyl	46	70.5–71	$C_{13}H_{16}BrNO_3S$	45.11	45.56	4.65	4.86
7-Bromoheptyl	64	47.5–48	$C_{14}H_{18}BrNO_3S$	46.67	47.04	5.04	5.19
8-Bromooctyl	59	54	$C_{15}H_{20}BrNO_3S$	48.13	48.18	5.39	5.54
9-Bromononyl	62	28	$C_{16}H_{22}BrNO_3S$	49.49	49.43	5.71	5.66
10-Bromodecyl	83	43–44	$C_{17}H_{24}BrNO_3S$	50.74	51.02	6.01	5.99

[a] All melting points are corrected. [b] Yield after recrystallization based on sodium saccharin. [c] H. Eckenroth, *Ber.*, **29**, 1951 (1896) reported m.p. 96°.

filtrate then was poured into 50 ml. of water. The product separated as an oil and was recovered by decanting the water layer. The crude material was alternately recrystallized from acetone and ethyl alcohol to a constant melting point of 68°. Yield, 42% (after recrystallization based on the dibromide).

Anal. Calc'd for $C_{25}H_{30}N_2O_6S_2$: C, 57.90; H, 5.83. Found: C, 57.73; H, 5.61.

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3-*tert*-Butylthianaphthene

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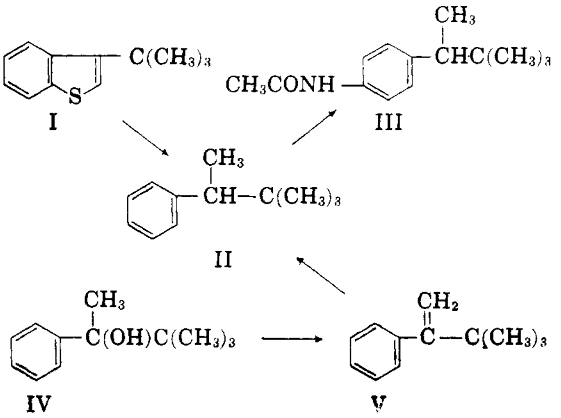
3-*tert*-Butylthianaphthene (I) was prepared in 77% yield by the alkylation of thianaphthene at 125° with isobutylene in the presence of 100% phosphoric acid. Desulfurization of compound I by means of Raney nickel[2] gave hydrocarbon II, whose acetamino derivative (III) was identical with the acetamino derivative of authentic α-*tert*-butylethylbenzene (II), prepared *via* IV and V. In the desulfurization there was a 10% survival of olefin V, although the mole ratio of hydrogen adsorbed on the Raney nickel to 3-*tert*-butylthianaphthene was 9/1. α-*tert*-Butylethylbenzene (II) and its acetamino derivative (III) are new compounds.



EXPERIMENTAL[3]

Purification of thianaphthene. The commercial sample[4] was 99.5 mole-% pure (t_f 31.07 ± 0.01°).[5] It was purified to 99.99 mole-% purity (t_f 31.309° ± 0.005°). The freezing point of pure thianaphthene is estimated to be 31.314° ± 0.07°.[6]

3-tert-Butylthianaphthene (I). Into a stirred mixture of 201 g. (1.5 moles) of thianaphthene and 50 g. of 100% phosphoric acid at 125° was passed 2.4 cu. ft. (3.0 moles) of isobutylene. The organic layer was dissolved in 600 ml. of ether; the solution was washed with aqueous carbonate followed by water, and dried. The ether was evaporated and the residue was fractionated to give 219 g. (75% yield based on thianaphthene) of product; b.p. 149°/20 mm.[7] n_D^{25} 1.5871, d_4^{25} 1.0578. The compound solidified to a glassy material when cooled in Dry Ice-acetone or liquid nitrogen.

Anal. Calc'd for $C_{12}H_{14}S$: C, 75.71; H, 7.41. Found: C, 75.81; H, 7.41.

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(1) Present address: Verona Research Center, Koppers Co., Inc., Verona, Pa.

(2) Mozingo, Wolf, Harris, and Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(3) All melting and boiling points are uncorrected; t_f is corrected.

(4) Jefferson Chemical Co., Inc., N. Y. 16, N. Y.

(5) t_f = freezing temperature determined by extrapolation of freezing curve; temperatures measured by platinum resistance thermometer and G-2 Mueller bridge which had been certified by National Bureau of Standards and checked prior to the thianaphthene measurements at the triple point of water and with a National Bureau of Standard benzoic acid cell.

(6) The equilibrium temperature of the 99.99% sample was 0.005° ± 0.002° lower than t_f when half frozen; hence t_{f0} is estimated to be 31.314° ± 0.007°.

(7) Conary and McCleary, U. S. Patent 2,652,405 (1953), reported b.p. 132°/10 mm.

Desulfurization of 3-tert-butylthianaphthene (I). 3-*tert*-Butylthianaphthene (16 g., 0.08 mole) was refluxed for 1 hour with a slurry of 180 g. of Raney nickel[8] in 500 ml. of absolute ethanol. The mixture was filtered hot, and the nickel was washed with ethanol. The combined filtrate-wash was fractionated to give 11.5 g. (85% yield) of hydrocarbon II; b.p. 91–94°/20 mm., n_D^{25} 1.4915, d_4^{25} 0.8667. Infrared analysis revealed the presence of 5–10% of olefin V; analytical hydrogenation indicated 11%. The olefin-contaminated material was hydrogenated, and the product was converted to its acetamino derivative by the method of Ipatieff and Schmerling;[9] m.p. 146–147°, mixture m.p. with an authentic sample 146–147°. The same acetamino derivative was obtained from the olefin-contaminated hydrocarbon.

2-Phenyl-3,3-dimethyl-2-butanol (IV). *Preparation A*. Acetophenone (120 g., 1.0 mole) in 100 ml. of ether was slowly added with stirring to an ether solution of *tert*-butylmagnesium chloride (prepared from 92.6 g. (1.0 mole) of *tert*-butyl chloride in 500 ml. of ether and 24.3 g. (1.0 mole) of magnesium turnings) and the reaction product was hydrolyzed with saturated aqueous ammonium chloride. The ether layer was concentrated and the residue was distilled to give 17 g. of IV;[10] b.p. 124–125°/20 mm., n_D^{25} 1.5142, d_4^{25} 0.9691 (9% yield based on acetophenone). Attempts to prepare the *p*-nitro- and 3,5-dinitrobenzoates of IV failed.

2-Phenyl-3,3-dimethyl-2-butanol (IV). *Preparation B*. A solution of 70 g. (0.70 mole) of pinacolone in 100 ml. of dry ether was added during 1 hour to a stirred, refluxing 150-ml. ether solution of phenyllithium prepared from 10.5 g. (1.5 moles) of lithium and 120 g. (0.77 mole) of bromobenzene. The mixture was stirred for an additional hour. After 65 hours, 25 ml. of ethanol was added to dissolve the residual lithium, followed by 175 ml. of water. The ether layer, after washing with water, and drying, was concentrated on a steam-bath to give a 134-g. residue. The latter was distilled through a 27-plate column at 5/1 reflux ratio to give 97.6 g. (78% yield based on pinacolone) of carbinol IV, b.p. 120–128°/20 mm. Redistillation at 10/1 reflux ratio gave 75.5 g. (61% over-all yield) of IV with the following constants: b.p. 128°/20 mm., n_D^{25} 1.5157, d_4^{25} 0.9705.

α-tert-Butylstyrene (V). 2-Phenyl-3,3-dimethyl-2-butanol (71 g., 0.40 mole) was passed over activated alumina at 275°, 150 mm., and 1 liquid hourly space velocity. Distillation of the catalyzate gave 45 g. (70% yield) of olefin V;[11] b.p. 75°/10 mm., n_D^{25} 1.4992, d_4^{25} 0.8733, t_f −21.16°, 98.9–99.5 mole-% pure. Analytical hydrogenation indicated the presence of 1.01 double bonds.

α-tert-Butylethylbenzene (II). Olefin (V) (50 g., 0.31 mole) was hydrogenated at atmospheric pressure in the presence of 0.5 g. of Adams' platinum catalyst. The catalyzate was filtered and distilled through 27-plate column at 10/1 reflux ratio to give 40 g. (80% yield) of distillate; b.p. 79–80°/10 mm., n_D^{25} 1.4928, d_4^{25} 0.8700. The compound solidified to a

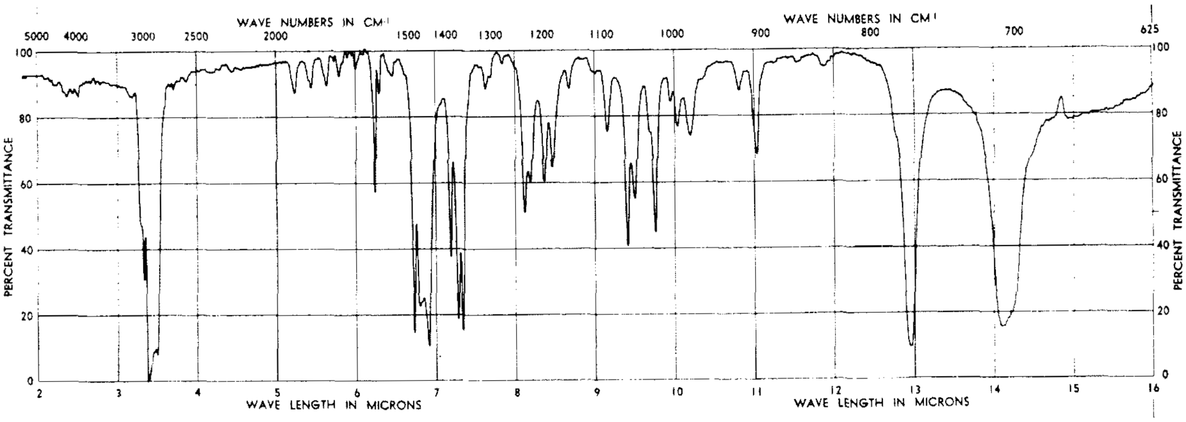

FIG. 1.—INFRARED SPECTRUM OF *α-tert*-BUTYLETHYLBENZENE (II).

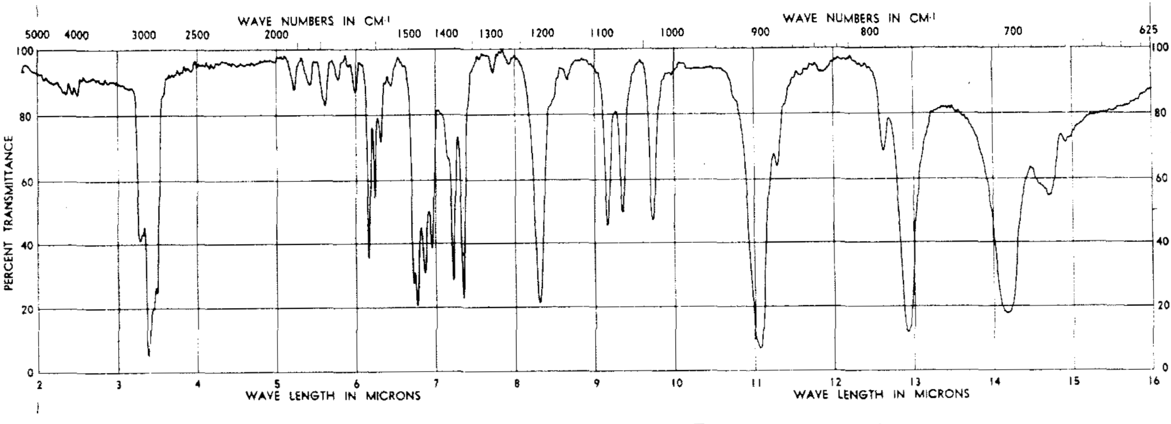

FIG. 2.—INFRARED SPECTRUM OF *α-tert*-BUTYLSTYRENE (V).

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(8) The Raney nickel was prepared by the method of Mozingo; *Org. Syntheses*, **22**, 15 (1941); the final heating temperature was 50°; the nickel contained 0.9 mole of adsorbed hydrogen.

(9) Ipatieff and Schmerling, *J. Am. Chem. Soc.*, **59**, 1056 (1937).

(10) Ramart-Lucas, *Ann. chim.*, (8) **30**, 349 (1913) reported b.p. 116–117°/15 mm., n_D^{25} 1.5135, d_4^{25} 0.9708; also, that its phenylurethan could not be prepared.

(11) Ramart-Lucas, *Ann. chim.*, (8) **30**, 349 (1913) reported b.p. 88–90°/15 mm., n_D^{25} 1.5013, d_4^{25} 0.8839.

glass when cooled to −70°. The infrared spectrum (Fig. 1) revealed the absence of characteristic olefinic unsaturation noted with compound (V) (Fig. 2).

Anal. Calc'd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.65; H, 11.08.

Its *acetamino* derivative melted at 146.5–147.5° after crystallization from aqueous methanol.

Anal. Calc'd for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.59.

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Derivatives at C_{20} of 17(α)-Hydroxy 20-Ketosteroid 21-Acylates

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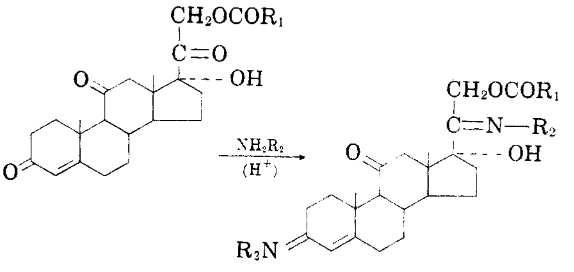
In 1954, H. Reich and B. K. Samuels[1] reported the isolation, in high yield, of the *20*-2,4-dinitrophenylhydrazone and the 20-semicarbazone of 21-acetoxypregnenolone. These results were of interest in view of reports[2-6] on the inertness of the 20-keto 21-acylate grouping towards carbonyl derivatization. Reich did not, however, describe the direct formation of derivatives, such as the semicarbazone, at position 20 in the presence of both 17(α)-hydroxyl and 21-acylates. This might be presumed a still more hindered case with respect to difficulty of formation of such derivatives.

We report here the formation of 20-semicarbazones and oximes of steroids in the presence of both 17(α)-hydroxyl and 21-acylate functions without loss of the 21 acyl group. The yields are generally good and real doubt is cast on the importance of "steric hindrance" in view of two factors. First, the 20-semicarbazones are obtained by careful buffering of the reaction mixture into the pH range described for the case of simpler unhindered ketones.[7] Second, in the case of cortisone, 3,20-disemicarbazones of several "hindered" esters were formed without undue difficulty. Models of such esters, in accord with the above observations, do not show extensive hindrance about the 20-carbonyl position.

EXPERIMENTAL[8]



All derivatives were made by the following general methods:

Cortisone acetate 3,20-disemicarbazone (I). Cortisone acetate (10.0 g., 0.025 mole) was suspended in 268 cc. of methanol, and 8.6 cc. of water; the suspension was blanketed with nitrogen. To the mixture were added 13.6 g. (0.122 mole) of semicarbazide hydrochloride and 7.4 g. (0.084 mole) of sodium bicarbonate and the mixture was heated under reflux for 3½ hours. At the end of this time, the cortisone acetate had all dissolved; the temperature was reduced to 45° and heating at this temperature was continued for 21 hours. After one hour at 45°, crystallization of product took place. At the end of the 21-hour heating period, the suspension was cooled to room temperature and to it was added slowly 358 cc. of water. The resulting crystalline semicarbazone derivative (I) was cooled for 2 hours in an ice-bath, filtered, washed with water, and dried under a vacuum; wt., 12.9 g., m.p. >300°. Recrystallization was effected from pyridine-methanol.

Anal. Cf. Table I. Calc'd: Acetyl, 8.33. Found: Acetyl, 8.32.

Peaks were observed in the infrared spectrum at 5.81 μ and 7.97 μ which indicated acetoxyl. For the ultraviolet spectra, *Cf.* Table I.

Cortisone acetate 3,20-dioxime (II). A mixture of 5.0 g. (0.0124 mole) of cortisone acetate, 134 cc. of methanol, and 4.3 cc. of water was placed in a flask with stirring and the air was replaced by nitrogen. To the mixture was added 3.84 g. (0.0553 mole) of hydroxylamine hydrochloride and 5.48 g. (0.0653 mole) of sodium bicarbonate. After the reaction mixture had been heated as for the preparation of I (see above), it was concentrated *in vacuo* to 45 cc. and 50 cc. of water and 50 cc. of nearly saturated salt solution were added. The crystalline slurry was stirred for 3 hours at 0–5° and the solid was removed by filtration and washed with water. The dry wt. was 3.9 g.; m.p. soften, 150°, melted at 163–166°, dec. 188°.

After recrystallization from ethyl acetate and petroleum naphtha, the compound showed the same poorly defined melting point.

Anal. Cf. Table I.

For ultraviolet spectra, *Cf.* Table I; $[\alpha]_D^{20}$ +179.2° (*c*, 1, acetone).

3(α),17(α),21-Trihydroxypregnane-11,20-dione 20-semicarbazone 21-acetate (VIII). In 2710 cc. of methanol, 100 g. (0.246 mole) of 3(α),17(α),21-trihydroxypregnane-11,20-dione 21-acetate was dissolved. After replacing the air above the stirred solution by nitrogen, 62.3 g. (0.56 mole) of semicarbazide hydrochloride and 37.3 g. (0.45 mole) of sodium bicarbonate were added. The solution was heated under reflux for 3 hours and at 45° for an additional 20 hours; at the end of this time it was concentrated *in vacuo* to a volume of 1000 cc. The product began to crystallize at a volume of about 1500 cc. and, at the end of the concentration, crystallization was forced to completion by the addi-

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(1) H. Reich and B. K. Samuels, *J. Org. Chem.*, **19**, 1041 (1954).

(2) O. Mancera, *J. Am. Chem. Soc.*, **72**, 5752 (1950).

(3) N. L. Wendler, Huang-Minlon, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951).

(4) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951).

(5) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(6) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953).

(7) J. Conant and P. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932).

(8) Analyses by R. N. Boos and associates; ultraviolet spectra by F. A. Bacher and associates. Melting points are uncorrected.