TABLE II

Cpd., Pentanoic acids	Yield, %[a]	Acid·HCl M.p., °C.	Acid·HCl Cl Anal., % Calcd.	Acid·HCl Cl Anal., % Found	Ethyl ester·HCl M.p., °C.	Ethyl ester·HCl Cl Anal., % Calcd.	Ethyl ester·HCl Cl Anal., % Found
5-Ethylamino-	72				129–132	16.91	16.86
5-Isopropylamino-	76	129–133	18.12	17.84	119–122	15.85	15.72[b]
5-*n*-Butylamino-		124.5–126[c]	16.91	16.85			
5-*s*-Butylamino-		121–122	16.91	16.87			
5-Cyclohexylamino-	71	190–192	14.98	14.98	163–166	13.44	13.47
5-Dimethylamino-	84	160–163.5	19.52	20.00			
5-Diethylamino-	70	198–201	16.91	16.74[d]			
5-Piperidino-	72	204–207[e]	15.99	15.88			

[a] As the hydrochloride of the acid. [b] Calcd. for $C_{10}H_{22}ClO_2N$: C, 53.68; H, 9.91. Found: C, 53.74; H, 9.65. [c] E. Ochiai, K. Tsuda and J. Yokoyama, *Ber.*, **68B**, 2296 (1935), report the hydrochloride, m.p. 124.5° (from acetone–ether). [d] Calcd. for $C_9H_{20}ClNO_2$: C, 51.54; H, 9.61. Found: C, 51.97; H, 9.63. [e] Recrystallized from acetone; m.p. 202–204° from ethanol–ether. W. B. Thomas and S. M. McElvain, THIS JOURNAL, **56**, 1809 (1934), report the hydrochloride of the acid, m.p. 198–200°.

step yields of 5-substituted-aminopentanenitriles much improved over the yields obtained when direct distillation of the 5-substituted-amino-3-pentenenitriles was followed by low pressure hydrogenation.

The unsaturated addition products were hydrogenated at low pressure to 5-substituted-aminopentanenitriles. These compounds in turn were hydrogenated at high pressure in the presence of ammonia. In the high pressure hydrogenations if the amine grouping was tertiary, high yields of only 5-dialkylamino-1-aminopentanes were obtained. However, when the amine grouping was secondary, an intramolecular reductive alkylation took place to a large extent to give N-substituted piperidines in addition to 5-alkylamino-1-aminopentanes. Thus, from the 5-ethylamino-, 5-isopropylamino-, 5-*n*-butylamino-, 5-*s*-butylamino- and 5-cyclohexylaminopentanenitriles were obtained the N-ethyl-, N-isopropyl-, N-*n*-butyl-, N-*s*-butyl- and N-cyclohexylpiperidines. A similar reductive cyclization has been reported recently by Boekelheide, *et al.*,[9] in the reduction of 4-(2-pyridyl)-butanenitriles.

The 5-substituted-aminopentanenitriles were also hydrolyzed to 5-substituted-aminopentanoic acids, which were isolated as their hydrochloride salts. The ethyl esters of these acids usually formed rather easily on heating the acid hydrochlorides in absolute ethanol.

Experimental

Carbon, hydrogen and nitrogen analyses reported were performed by the Clark Microanalytical Laboratory, Urbana, Illinois.

Melting points are uncorrected.

2,4-Pentadienenitrile and Amine Addition Reactions. (5-Substituted-amino-3-pentenenitriles).—The 2,4-pentadienenitrile[6] was added to a slight molar excess of amine in a pressure bottle, and the bottle was flushed out with argon before sealing. If no immediate exothermic reaction ensued, the mixture was warmed at 50° for one-half hour and then allowed to stand at room temperature for 18 hours. Unreacted starting materials were stripped under vacuum and the crude product was either purified by vacuum distillation or directly hydrogenated at low pressure.

Yields, physical constants and analyses of the 5-substituted amino-3-pentenenitriles are listed in Table I. In addition to the compounds listed in Table I, the adducts of piperidine and diethylamine also were prepared and converted to the various types of derivatives described below. These compounds have been well characterized by Frankel, *et al.*[4]

5-Substituted-aminopentanenitriles.—Low pressure hydrogenation of the 5-substituted amino-3-pentenenitriles in ether solution over 7% palladium-on-charcoal catalyst resulted in quantitative conversions to 5-substituted-aminopentanenitriles. Table I lists physical constants and analyses for these compounds.

High Pressure Hydrogenation of 5-Substituted-aminopentanenitriles.—These hydrogenations were carried out in ethanol solution saturated with ammonia over Raney nickel catalyst at initial pressures of 800–1400 p.s.i. and temperatures of 90–100°. The products were separated by vacuum distillation.

Table I lists the physical constants and analyses for the 5-substituted-amino-1-aminopentanes.

Hydrolyses of 5-Substituted-aminopentanenitriles (5-Substituted-aminopentanoic Acids).—Hydrolyses were carried out in concd. hydrochloric acid—heating the mixtures on a steam-bath for 2–3 hours. The resulting solution was then carefully evaporated to dryness, and the solid residue was extracted twice with hot acetone or with cold absolute ethanol. Acetone proved more satisfactory, since it did not dissolve the by-product ammonium chloride as readily as did the ethanol. In addition, in some cases in which ethanol was used and the mixtures were warmed, the acids were at least partly converted to their ethyl esters. The hydrochlorides of the 5-substituted-aminopentanoic acids were precipitated by addition of ether to the acetone or ethanol solutions and could be recrystallized from either acetone or ethanol–ether mixtures. Acetone recrystallization appeared to give crystals of somewhat higher melting point. Table II lists the physical constants and analyses for these compounds.

TABLE III

ADDITION PRODUCTS OF 2,4-PENTADIENENITRILE WITH TWO MOLES OF AMINE

Cpd., pentanenitriles	B.p., °C.	Mm.	Ref. index, n_D^{20}	°C.	Neut. equiv., Calcd.	Found
3,5-Di-(ethylamino)-	82–85	1	1.4635	20	81.61	83.9
3,5-Di-(*n*-butylamino)-	142–143	3	1.4612	20	112.7	111.0
3,5-Di-(dimethylamino)-	105–115[a]	5	1.4549	25		

[a] P. Kurtz[3] reports a b.p. 120–122° (10 mm.).

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Diels–Alder Reactions with Arylethenesulfonyl Fluorides

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Although several aromatic and saturated aliphatic sulfonyl fluorides have been prepared by treating the corresponding sulfonyl chlorides with boiling potassium fluoride solution,[2] no unsaturated aliphatic sulfonyl fluorides are reported. 2-Phenyl-

(9) V. Boekelheide, W. J. Linn, P. O. Grady and M. Lamberg, THIS JOURNAL, **75**, 3215 (1953).

(1) This work is taken from Mr. Hoerger's M.S. thesis.

(2) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2193 (1931).

ethenesulfonyl fluoride and 2-*p*-nitrophenylethenesulfonyl fluoride were readily obtained from the corresponding sulfonyl chlorides by refluxing with an aqueous solution of potassium fluoride. The sulfonyl fluorides are more resistant to hydrolysis than the corresponding sulfonyl chlorides; in fact, 2-phenylethenesulfonyl fluoride, melting at 96–97°, can be steam distilled without appreciable hydrolysis. When ethenesulfonyl chloride was treated with boiling aqueous potassium fluoride, no ethenesulfonyl fluoride could be obtained because of hydrolysis and polymerization reactions.

Several recent reports[3–5] concern the use of unsaturated sulfonic acid derivatives as dienophiles in the Diels–Alder reaction. These derivatives include sulfonyl chlorides, methyl sulfonates and sulfonamides. Since fluorine is more electronegative than any of the atoms attached to sulfur in the preceding derivatives, it was expected that unsaturated sulfonyl fluorides should be active dienophiles.

2-*p*-Nitrophenylethenesulfonyl fluoride and cyclopentadiene gave 6-*p*-nitrophenyl-2,5-endomethano-1,2,5,6-tetrahydrobenzenesulfonyl fluoride in yields ranging from 77% at 45° to 27% at 155°. The structure was assigned on the basis of analysis, saponification equivalent and conversion of the hydrolyzed adduct to the known[4] *p*-toluidine and S-benzylthiouronium salts. The adduct appears to be a mixture of stereoisomers, since repeated recrystallization (of adduct having the calculated saponification equivalent) was necessary to obtain a sample with a constant melting point. This conclusion is supported by the work of Rondestvedt[4] who found that the adduct from cyclopentadiene and 2-*p*-nitrophenylethenesulfonyl chloride, m.p. 105–116°, can be converted into a bromosultone in 74% yield; but, after the adduct is recrystallized five times to m.p. 116–121.5°, it can be converted to the bromosultone in 85% yield, indicating that the recrystallizations remove some of the isomer in which the sulfo group lies in the exo-position and is thus unable to undergo cyclization.

In contrast to the above sulfonyl fluoride, 2-phenylethenesulfonyl fluoride did not give an adduct with cyclopentadiene at several temperatures in the range 25–150°. This lack of reactivity is surprising since 2-phenylethenesulfonyl chloride forms an adduct with cyclopentadiene in 63% yield at 45°.[4] A possible explanation for the inertness of 2-phenylethenesulfonyl fluoride may be that the temperatures employed were not favorable for shifting the equilibrium in the desired direction. The importance of temperature is shown by Rondestvedt's work with sulfonic acid derivatives,[4] *e.g.*, methyl 2-*p*-nitrophenylethenesulfonate reacts with cyclopentadiene to form an adduct in 68% yield at 155°, but fails to react at temperatures below 130°, whereas N,N-diethyl-2-*p*-nitrophenylethenesulfonamide reacts with cyclopentadiene in 87% yield at 45°, but fails to react at 155°.

(3) H. R. Snyder, H. V. Anderson and D. P. Hallada, THIS JOURNAL, **73**, 3258 (1951).

(4) C. S. Rondestvedt and J. C. Wygant, *J. Org. Chem.*, **17**, 975 (1952).

(5) C. S. Rondestvedt and J. C. Wygant, THIS JOURNAL, **73**, 5785 (1951).

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Experimental

2-Phenylethenesulfonyl Fluoride.—To a solution of 24.9 g. (0.123 mole) of 2-phenylethenesulfonyl chloride[6] in 30 ml. of xylene was added a solution containing 16 g. of potassium fluoride in 15 ml. of water. The mixture was stirred and refluxed for 2.5 hours, during which time the less soluble potassium chloride precipitated as it was formed. The reaction mixture was steam distilled, the distillate extracted with ether, dried with calcium sulfate and the ether was evaporated. Upon recrystallization from petroleum ether (90–100°), there was obtained 11.7 g. (51.4% yield) of product, m.p. 96–97°. (Attempts to purify the crude reaction mixture by crystallization from several solvents, instead of steam distillation, failed to remove unreacted sulfonyl chloride.)

Anal. Calcd. for $C_8H_7FO_2S$: C, 51.61; H, 3.78; sapon. equiv., 93.1. Found: C, 51.75; H, 3.86; sapon. equiv., 91.4.

2-*p*-Nitrophenylethenesulfonyl Fluoride.—To 10.0 g. (0.040 mole) of 2-*p*-nitrophenylethenesulfonyl chloride[7] in 25 ml. of xylene was added a solution containing 5 g. (0.086 mole) of potassium fluoride in 6 ml. of water. The mixture was stirred and refluxed for 2.5 hours and then poured into 300 ml. of ice-water. After filtering the crude yellow product and recrystallizing three times from benzene–petroleum ether mixtures, there was obtained a 57% yield of the sulfonyl fluoride, m.p. 155–158°.

Anal. Calcd. for $C_8H_6FNO_4S$: C, 41.56; H, 2.62; N, 6.06; sapon. equiv., 115.5. Found: C, 41.63; H, 2.86; N, 6.37; sapon. equiv., 114.6.

6-*p*-Nitrophenyl-2,5-endomethano-1,2,5,6-tetrahydrobenzenesulfonyl Fluoride.—To 2.03 g. of 2-*p*-nitrophenylethenesulfonyl fluoride dissolved in 200 ml. of toluene was added 1.2 g. of freshly distilled cyclopentadiene. The solution was kept at 45° for 3.5 days and then the solvent and excess cyclopentadiene were removed in an air jet. The resulting oil solidified upon standing at room temperature for a day. The residue weighed 2.54 g. (97%), m.p., 65–76°. Recrystallization of the residue from ethanol gave the following fractions: I, 0.42 g., m.p. 92–96°; II, 1.05 g., m.p. 76–94°; III, 0.53 g., m.p. 74–91°; combined yield of I, II and III, 77%. Evaporation of the filtrate left an oil which could not be crystallized. The saponification equiv. of fraction II was found to be 145.4 (calculated, 148.6). After repeated recrystallizations from petroleum ether, the adduct melted at 102–104°.

Anal. Calcd. for $C_{13}H_{12}FNO_4S$: C, 52.52; H, 4.07; N, 4.71. Found: C, 52.41; H, 4.12; N, 4.50.

When 5.6 g. of cyclopentadiene and 2.0 g. of 2-*p*-nitrophenylethenesulfonyl fluoride were refluxed in bromobenzene (about 155°) for three hours, considerable tar formation occurred and the adduct, m.p. 87–93°, was obtained in only 27.3% yield. After five recrystallizations, the m.p. was 102–104°. Refluxing a toluene solution of 2-*p*-nitrophenylethenesulfonyl fluoride and cyclopentadiene for six hours gave the adduct in 72% yield.

The adduct was hydrolyzed to the sodium sulfonate in sodium hydroxide solution, the excess base was neutralized, and the S-benzylthiuronium salt was prepared, m.p. 231–234° with decomposition (lit.[5] 235° dec.). The *p*-toluidine salt of the hydrolyzed adduct was also prepared, m.p. 216–218.5° (lit.[5] 217.5–219°).

Attempted Reaction of 2-Phenylethenesulfonyl Fluoride with Cyclopentadiene.—In a typical reaction, 4.00 g. of the sulfonyl fluoride was dissolved in 200 ml. of toluene containing 2.75 g. of freshly distilled cyclopentadiene and the solution maintained at 45° for 3.5 days. There was recovered 82% of unchanged sulfonyl fluoride. There was also obtained 0.41 g. of an oil which could not be crystallized from benzene, ethanol, acetone or chloroform. Attempts to hydrolyze this oil to the sodium sulfonate with dilute base resulted only in tar formation.

Similar results were obtained when the reactants were

(6) F. G. Bordwell, *et al.*, *ibid.*, **68**, 139 (1946).

(7) F. G. Bordwell, A. B. Colbert and B. Alan, *ibid.*, **69**, 1778 (1947).

kept at room temperature for 8 days, at 60° for 2.5 days and at 80° for 21 hours. When the reactants were refluxed in toluene at 110° for 12 hours, or in bromobenzene at 155° for 11 hours, there was considerable tar formation, less than 5% of the original sulfonyl fluoride could be recovered, and no adduct could be isolated.

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Autoxidation of Cholesterol during Purification *via* the Dibromide[1]

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Recent investigation of cholesterol biogenesis using carbon-14 has accentuated the problem of obtaining pure sterol preparations from animal tissues. Isolation as the sterol digitonide followed by conversion to the dibromide and subsequent reduction to the sterol have been advocated as reliable procedures for radiochemically pure cholesterol obtained from isolated organ perfusion and from intact animal experiments.[2] These procedures are not without objection in that artifacts may arise during decomposition of the digitonides and during bromination–debromination.[3]

In addition to these difficulties autoxidation of cholesterol may occur during the debromination reaction. In the routine use of the modified zinc–acetic acid debromination procedure of Schwenk and Werthessen[2a] the presence of several unidentified Liebermann–Burchard positive materials was discovered in supposedly pure preparations. These materials manifested themselves as characteristic patterns of spots on paper chromatograms, as recorded in Table I. In every instance spots corresponding to cholesterol and to the epimeric 7-hydroxycholesterols were found. Of the unidentified spots spot IV (system A) and spot III (system B) appeared in most of the chromatograms and were intense in some. Spot I in both systems occurred in most of the patterns and must correspond to higher oxygenated sterols. It is likely that spots I, IV and II of system A correspond to spots I, III and IV of system B, respectively.

The identities of Table I are assigned on evidence of relative migration on the chromatograms of the known and the suspect sterol, separately and in admixture, and on evidence of color behavior with the Liebermann–Burchard and antimony trichloride reagents. It should be emphasized that these evidences are from two independent paper chromatographic systems; the system of Neher and Wettstein[4] (system B) involves partition between two liquid phases, while the simple ascending system (system A, *o*-dichlorobenzene) does not. By examination of the debromination products in the two systems several sterols of possible implication are eliminated from consideration. Mobility data for related sterols are presented in Table II.[5]

TABLE I

CHROMATOGRAPHIC PATTERN OF DEBROMINATION REACTION PRODUCTS

Spot	Mobility[a]	Color behavior with[b] Liebermann–Burchard	$SbCl_3$	Tentative identity
System A (*o*-dichlorobenzene)				
I	0.08	Gr-G	Bl	.....
II	.32	G	..	.....
III	.61	Rs → V → Bl	Bl	Δ^5-Cholestene-3β,7-diols
IV	.84	P → Bl-G	Bl	.....
V	.93	V → Bl-G	V	Cholesterol
System B (β-phenoxyethyl alcohol–heptane)				
I	0.01	Gr-G	Bl	.....
IIA	.11	Rs → V → Bl	Bl	Δ^5-Cholestene-3β,7β-diol
IIB	.17	Rs → V → Bl	Bl	Δ^5-Cholestene-3β,7α-diol
III	.40	P → Bl-G	Bl	.....
IV	.53	P → Bl-G	..	.....
V	1.00	V → Bl-G	V	Cholesterol

[a] The mobility in system A (*o*-dichlorobenzene) is expressed in R_f; for system B (β-phenoxyethyl alcohol–heptane) the mobility is expressed in R_c. [b] Bl = blue, Rs = rose, G = green, V = violet, Gr = gray, P = pink. These colors and sequences are reproducible.

Control chromatograms on the original cholesterol and on the cholesterol dibromide employed were run concurrently with the debromination products; in each control chromatogram only the one component was present. Cholesterol treated with zinc and acetic acid and extracted in the exact manner employed in the debromination reaction did not contain autoxidation products. Cholesteryl acetate dibromide treated in like manner also failed to give the pattern of spots expected of cholesterol dibromide; only two components were detected, corresponding to cholesterol and to cholesteryl acetate.[7]

Patterns for debromination products using other debrominating agents such as sodium iodide–ethanol,[8] potassium acetate–ethanol[9] and sodium acetate–aqueous ethanol[9,10] were also complex. Although this line was not developed further, it is likely that the 7-hydroxycholesterols contribute to these patterns.

(1) Supported in part by funds from the Texas Heart Association and by funds under contract AF 18(600-)303 with the USAF School of Aviation Medicine, Randolph Field, Texas.

(2) (a) E. Schwenk and N. T. Werthessen, *Arch. Biochem. Biophys.*, **40**, 334 (1952); (b) **42**, 91 (1953).

(3) (a) G. A. D. Haslewood, *Biochem. J.*, **33**, 709 (1939); (b) K. Tsuda and B. Umezawa, *J. Pharm. Soc. Japan*, **71**, 273 (1951); (c) K. Tsuda, R. Hayatsu, B. Umezawa and T. Nakamura, *ibid.*, **72**, 182 (1952); (d) E. Schwenk, N. T. Werthessen and H. Rosenkrantz, *Arch. Biochem. Biophys.*, **37**, 247 (1952).

(4) R. Neher and A. Wettstein, *Helv. Chim. Acta*, **35**, 275 (1952).

(5) The mobilities in the paper partition system (system B) in Table II for the epimeric pairs: 7α-hydroxycholesterol and 7β-hydroxycholesterol, Δ^4-cholestene-3β,6α-diol and Δ^4-cholestene-3β,6β-diol, afford further evidence of the relationship between mobility on paper partition chromatographic systems and structure of the steroid molecule as mentioned by Savard.[6] The greater mobilities of 7α-hydroxycholesterol and Δ^4-cholestene-3β,6β-diol over those of the 7β- and 6α-epimers, respectively, may be related to the conformation of the hydroxyl group of the sterol molecule. Thus the polar (more hindered) conformations of the 7α-hydroxyl and the 6β-hydroxyl confer greater mobility on the partition chromatograms as compared with the equatorial (less hindered) conformations of the 7β- and 6α-hydroxyls.

(6) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953).

(7) Cholesteryl acetate resists autoxidation in aqueous colloidal suspension; *cf.* S. Bergström and O. Wintersteiner, *J. Biol. Chem.*, **145**, 327 (1942).

(8) R. Schoenheimer, *Z. physiol. Chem.*, **192**, 86 (1930); *J. Biol. Chem.*, **110**, 461 (1935).

(9) V. A. Petrow, *J. Chem. Soc.*, 1077 (1937).

(10) A. Windaus and H. Lüders, *Z. physiol. Chem.*, **109**, 183 (1920).