was formed by a Michael addition of ethanolamine to 3-butenonitrile.

Biology.[§] The 11 amino alcohols showing significant antifertility activity are listed in Table I in decreasing order of potency. These compounds appear to affect fertility in at least two ways: through an arrest in development of the preimplantation embryo and by prevention of postimplantation development. Although all the active members of the series are probably capable of both actions, rather surprising differences in the antifertility profiles were observed. At lower dose levels the isopropylamino (**2**) and pyrrolidino (**7**) derivatives did not alter the number of implantation sites but did prevent postimplantation embryonic development. At higher doses the isopropylamino (**2**), but not the pyrrolidino (**7**), compound had a deleterious effect on preimplantation development and thus prevented the appearance of implantation sites. The cycloalkylamino analogs **1** and **3–5** produced only the latter effect, that of preventing the appearance of implantation sites. Further studies on the biological actions of these compounds, which are described in a separate report,[8] suggest that the active members of this series of compounds possess, to varying degrees, rather specific embryotoxic effects and an action on the endometrium which precludes effective support for fetal development.

These amino alcohols represent the simplest structural type yet found which possesses significant antifertility activity. Their complete lack of estrogenic or other hormonal action and the apparent duality of the antifertility effects make them attractive candidates for further study.

Experimental Section[#]

Preparation of Amino Alcohols. Method A. Reductive Alkylation. A solution of 0.70 mol of the appropriate primary amine and 0.80 mol of the desired ketone in 100 ml of absolute EtOH was treated with 0.50 g of PtO_2 and hydrogenated at 2 atm at room temperature until hydrogen uptake ceased (1 equiv). The catalyst was removed by filtration and the product isolated by distillation through a Vigreux column at reduced pressure.

Method B. Reduction of Ethyl Oxalamides. A solution of 0.13 mol of the desired primary amine and 30 g of Et_3N in 500 ml of Et_2O was added over a 20-min period to a cooled, stirred solution of 19.1 g (0.14 mol) of ethyloxalyl chloride in 300 ml of ether. The stirred mixture was allowed to warm to room temperature over the next 45 min, and the salts were then removed by filtration. The Et_2O was removed under reduced pressure, and the residual oil, the ethyl oxalamide, was used directly for reduction. A solution of this oil in 300 ml of dry THF was dripped slowly into a mixture of 11.7 g (0.33 mol) of $LiAlH_4$ (AlH_3, prepared from $LiAlH_4$ and one-third of an equivalent of $AlCl_3$, was used in some cases, especially those containing a double bond conjugated with the nitrogen atom) in 300 ml of THF, and the mixture was stirred and refluxed overnight. The reaction mixture was worked up in the usual manner, and the pure amino alcohol was obtained by distillation under reduced pressure.

2-(Isopropylamino)ethyl Hydrogen Sulfate. A cooled solution of 10.3 g of 2-(isopropylamino)ethanol (**2**) in 50 ml of CCl_4 was treated slowly with 11.6 g of chlorosulfonic acid, keeping the temperature below 10°. After addition was complete, the mixture was allowed to warm to room temperature and kept there for 2 hr. The precipitate was collected and recrystallized twice from 95% EtOH, affording 8.9 g of product, mp 261.5–262.5°.

2-(3-Tetrahydrothienylamino)ethanol. A solution of 8.25 g of tetrahydrothiophen-3-one[9] and 4.71 g of 2-aminoethanol in 175 ml of absolute EtOH was treated with 5.07 g of sodium cyanoborohydride and 6.58 ml of 12 *N* HCl. The mixture was stirred at room temperature for 40 hr and then concentrated under reduced pressure. The residue was treated with K_2CO_3 solution and extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated. The residue was distilled twice under reduced pressure, affording 3.0 g of product, bp 87–88° (0.10 mm), which later solidified to a waxy solid, mp 41.5–46°.

2-[(2,2,2-Trifluoro-1-methylethyl)amino]ethanol. A solution of 38.5 ml of 2-aminoethanol in 1000 ml of CH_2Cl_2 was cooled to −30° and stirred while 77.2 g of trifluoroacetone was added, followed by 80 g of 4A molecular sieves. The mixture was stirred at −30° for 3 hr and then allowed to warm to room temperature and left ovenight. The filtered solution was concentrated and distilled under reduced pressure, affording 29.6 g of 2-methyl-2-trifluoromethyloxazolidine, bp 58–59° (5 mm).

A solution of this oxazolidine in 50 ml of Et_2O was added to a cooled solution of 7.6 g of $LiAlH_4$ in 250 ml of Et_2O, and the mixture was stirred overnight at room temperature. After work-up in the usual manner, the product was distilled, affording 18.0 g of amino alcohol, bp 94–95.5° (43 mm).

2-(2-Cyano-1-methylethylamino)ethanol. A solution of 40.0 g of 3-butenonitrile in 100 ml of dioxane was treated with 0.30 g of KO-*t*-Bu and then with 45.0 g of 2-aminoethanol. The mixture was left at room temperature for 0.5 hr and then refluxed for 15 hr. The mixture was distilled under reduced pressure, affording 52.6 g of crude product, bp 122–127° (2 mm).

2-(2,2-Dimethylhydrazino)ethanol. A cooled solution of 50 ml of *unsym*-dimethylhydrazine in 150 ml of EtOH was treated with 9.9 g of glycolaldehyde and 0.3 g of *p*-TSA. The solution was stirred with some 4A molecular sieves for 28 hr under an atmosphere of nitrogen. The solution was then filtered, concentrated, and distilled under reduced pressure, affording 14.3 g of the dimethylhydrazone of glycolaldehyde, bp 72–73° (9 mm).

A cooled solution of this hydrazone in 500 ml of absolute EtOH was treated with 8.8 g of sodium cyanoborohydride and then with 11.7 ml of 12 *N* HCl. The mixture was stirred at room temperature for 16 hr and then treated with concentrated K_2CO_3 solution, CH_2Cl_2, and Et_2O. The organic layer was separated and dried well over Na_2SO_4 and then over $CaSO_4$. The solution was concentrated and distilled under reduced pressure, affording 4.0 g of product, bp 96–97° (45 mm).

§ Groups of ten female rats were given the test compounds orally on each of the first six days of pregnancy. Day one of pregnancy was defined as the date of mating, as verified by the presence of vaginal spermatozoa. Aqueous solutions of salts were used *per se*, while the pH of solutions of bases was adjusted to 7 with HCl. The uteri were examined between days 16–18 of pregnancy for the presence and gross appearance of the implantation sites. Animals having one or more normal fetuses were considered to be pregnant.

All compounds listed in the tables were characterized by microanalysis and nmr spectra. In all cases, except the two noted, the analytical figures (C, H, and N) were within acceptable limits (0.4%), and all nmr spectra were consistent with the structures and showed no extraneous peaks.

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Local Anesthetics. Alkylthioalkyl- and Alkylsulfinylalkylaminoacylanilides

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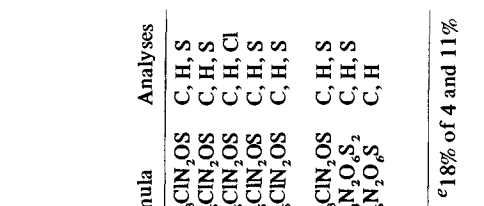
In our studies of aminoacylanilides as local anesthetics we have previously reported a few alkoxyalkylaminoacylanilides.[1] Here we present the results of experiments with some closely related thio analogs.

Table I



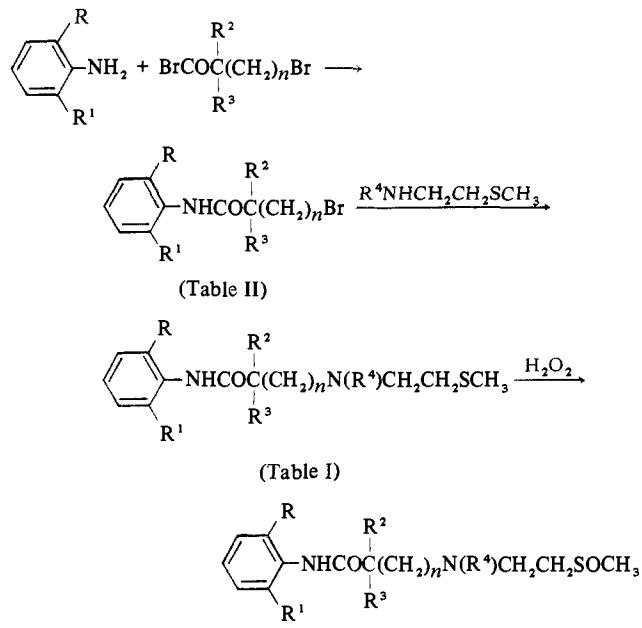
No.	R	R^1	R^2	R^3	n	R^4	Y	X	Yield,[a] %	Mp, °C	Recrystn solvent	pK_a[b]	Distr[b,c] coeff	Formula	Analyses
1	H	C_2H_5	H	CH_3	0	H	S	Cl	58	153–154	EtOH–Et_2O	6.8	38	$C_{14}H_{23}ClN_2OS$	C, H, S
2	H	C_2H_5	H	CH_3	0	CH_3	S	Cl	89[d]	153–154	EtOH–Et_2O, MeCN		590	$C_{15}H_{25}ClN_2OS$	C, H, S
3	H	C_2H_5	H	H	1	CH_3	S	Cl	58	121–122	EtOH–Et_2O	7.7	33	$C_{15}H_{25}ClN_2OS$	C, H, Cl
4	H	C_2H_5	CH_3	CH_3	0	H	S	Cl	18[e]	145–147[f]	Me_2CO	7.0	163	$C_{15}H_{25}ClN_2OS$	C, H, S
5	H	C_2H_5	H	CH_3	1	H	S	Cl	11[e]	140–142[f]	Me_2CO–95% EtOH	7.7	25	$C_{15}H_{25}ClN_2OS$	C, H, S
									61[g]						
6	CH_3	CH_3	H	CH_3	0	H	S	Cl	100[d]	173–174	MeCN–EtOH–Et_2O, *i*-PrOH	6.7	5.5	$C_{14}H_{23}ClN_2OS$	C, H, S
7	H	C_2H_5	H	CH_3	0	H	SO	HSO_4	100[d]	162.5–163	MeOH–Et_2O	<6	1	$C_{14}H_{24}N_2O_6S_2$	C, H, S
8	H	C_2H_5	H	CH_3	0	CH_3	SO	CO_2 —CO_2H	81	91–93	MeOH–Et_2O, MeCN	<6	0.55	$C_{17}H_{26}N_2O_6S$	C, H

[a] Pure compound. [b] A. Brändström, AB Hässle, Göteborg, Sweden, personal communication. [c] Cod liver oil (Oleum Jecoris aselli, Pharmacop. Nord.)–water method. [d] Uncrystallized. [e] 18% of 4 and 11% of 5 obtained in same reaction batch. [f] Mixture melting point of 4 and 5: 115–140°. [g] 61% of 5 obtained in the addition reaction.

Local anesthetics containing open-chain thioether groups on the ultimate alkyls of the aliphatic amine moiety have been synthesized in the procaine series[2-4] and among cocaine-related agents.[4] The thioether function has also been incorporated in rings (thiomorpholine) in the same relative position in local anesthetics of various types.[5,6] Open-chain sulfoxides have also been described[3,4,7] in this context.

Chemistry. The compounds (Tables I[8] and II) were produced as shown in Scheme I. The bromoacylanilides were

Scheme I



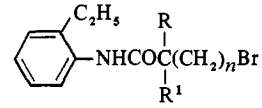
obtained by Löfgren's acetate buffer method.[9] In the case of the β-bromo derivative **10**, we observed in one run a depression of the melting point caused by admixture of the corresponding acrylanilide. This elimination product forms easily from the somewhat thermally unstable **10**.

The reactions between the halogenoacylanilides and the methylthioethylamines were carried out by refluxing a solution of the two reagents in the ratio 1:2.6 when the amine was primary and 1:4 in the case of secondary amines. As mentioned above, the β-bromo derivative **10** could be expected to eliminate HBr on heating; the resulting acrylanilide, however, would react[10] with the primary amine forming derivative **3**. Thus, the same β-amino compound will be formed regardless of whether the reaction path involves a substitution or an elimination-addition sequence.

The α-bromo compound **9**, like other α-bromopropionanilides, reacted with the amines almost completely by an SN2 mechanism (no elimination reaction was observed). The α-bromoisobutyryl derivative **11** reacts quite differently, however. The presence of two methyl groups adjacent to the α-bromine promotes elimination, such that, if the amine is of suitable geometry and strength, an addition reaction will follow resulting in the formation of a mixture of α- and β-aminoacylanilides (in the present case **4** and **5**, respectively) and some acrylanilide. The β-aminoacylanilide is obviously formed by addition of the primary amine to the acrylanilide. This was confirmed by a separate synthesis of **5** from 2′-ethylmethacrylanilide and methylthioethylamine.

The separation of the α- and β-aminoacylanilides **4** and **5** was performed according to a simple, convenient, four-funnel countercurrent method.[11] It should be pointed out that β-aminoacylanilides as a rule cannot be purified by distillation because of elimination of aliphatic amine

Table II



No.	R	R^1	n	Yield,[a] %	Mp, °C	Recrystn solvent	Formula	Analyses
9	H	CH_3	0	63	129.5–130	95% EtOH	$C_{11}H_{14}BrNO$	H; C[b]
10	H	H	1	75[c]	87.5–88	Cyclohexane	$C_{11}H_{14}BrNO$	H; C,[d] Br[e]
11	CH_3	CH_3	0	84	62–63	Petroleum ether (30–60°)	$C_{12}H_{16}BrNO$	C, H

[a]Pure compound. [b]C: calcd, 51.6; found, 51.0. [c]Uncrystallized. [d]C: calcd, 51.6; found, 53.0. [e]Br: calcd, 31.2; found, 32.2.

leading to formation of the corresponding acrylanilide.

The two sulfoxides **7** and **8** were prepared as described in the Experimental Section.[12] The *N*-methyl-2-methylthioethylamine, previously described,[2] was synthesized from 1-methylaziridine and methanethiol.

Pharmacology and Toxicology. The compounds were tested for their local anesthetic properties on the sciatic nerve of the rat *in vivo*[13] and the sciatic nerve of the frog *in vitro*.[13] Acute single-dose intraperitoneal and intravenous toxicity was determined in mice, and local tissue irritating effects were evaluated following intradermal injection into rabbits[14] (see Experimental Section).

The data in Table III summarize the result of these experiments. The anesthetic properties of the new compounds indicate that they are all inferior to lidocaine: their latency is longer, their duration is shorter, and the frequency of anesthesia obtained with them is lower.

The two sulfoxides **7** and **8** closely related to **1** and **2**, respectively, deviate from the latter ones in their slow rate of block on the isolated frog nerve, a slowness that is paralleled by their long latencies in the *in vivo* blocks. The durations of **7** and **8** are close to those of **1** and **2**. Thus, this property is not appreciably altered by oxidizing the thio compounds to the corresponding sulfoxides. This structural change decreases the lipophilicity of the parent compounds. This explains their longer onset times and indicates that lipophilicity in itself is of limited importance for the duration of block. This is further illustrated by the fact that compound **6**, a 2,6-xylidide, which is isomeric to **1**, a 2-ethylanilide, shows increased durations at 1 and 2% over **1**, although the distribution coefficient of **1** is seven times that of **6** and their pK_a values are nearly equal.

Whereas 2% solutions of all compounds produced low local irritation, **1**, **2**, and **4–6** were very irritating at 4% concentration. This may be a reflection of the water solubilities of the base forms.[15] The aforesaid bases are much less water soluble than **3**, **7**, and **8**.

A comparison of the thioether compounds **1–6** with their oxygen ether analogs† indicates that the former generally are somewhat weaker bases and much more lipophilic. On the isolated frog nerve the sulfur compounds showed a more rapid onset of blocking activity, whereas no definite trend in this respect was observed in the *in vivo* experiments. The durations of block in the rat sciatic nerve were the same or longer for the oxygen ethers which were also systemically more toxic but less irritating.

Experimental Section

A Thomas-Hoover capillary melting point apparatus was employed for all melting point determinations, and the melting points reported are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The microanalyses were provided by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

2-Bromo-2'-ethylpropionanilide (9). A solution of 2-ethylaniline (101.4 g, 0.837 mol) in glacial AcOH (711 ml) was cooled to 5–10° and 2-bromopropionyl bromide (201.3 g, 0.932 mol) was added in one portion, mixed, and was *immediately* followed by a cold solution of $NaOAc \cdot 3H_2O$ (276 g) in H_2O (1433 ml). After shaking for 0.5 hr, the precipitate was filtered, washed (H_2O), and dried.

3-Bromo-2'-ethylpropionanilide (10) and 2-Bromo-2'-ethyl-2-methylpropionanilide (11). The compounds were produced in the same manner as described for 9 (Table II).

2'-Ethylmethacrylanilide (12). The compound was prepared according to Bieber[16] (Bodroux reaction). The Grignard reagent was obtained by standard procedure from Mg (2.90 g, 0.119 g-atom) and EtBr (11.9 g, 0.109 mol) in anhydrous Et_2O (50 ml). A solution of *o*-ethylaniline (12.1 g, 0.0998 mol) in Et_2O (10 ml) was slowly added to it, refluxed for 0.5 hr, followed by addition of a solution of Me methacrylate (10.0 g, 0.0957 mol) in Et_2O (20 ml) over 0.5 hr, and again refluxed for 0.5 hr. After cooling (10°) and careful hydrolysis with 4 *M* HCl (30 ml) under vigorous agitation, the Et_2O solution was successively washed (dilute HCl, dilute $NaHCO_3$, H_2O) and dried ($MgSO_4$), and the solvent evaporated: yield 10.0 g (0.0528 mol, 55%) of colorless needles; mp 71.5–72° [petroleum ether (bp 60–110°)]. *Anal.* ($C_{12}H_{15}NO$) C, H, N; mol wt: calcd, 189; found, 197.

N-Methyl-2-methylthioethylamine (13).[2] A mixture of 1-methylaziridine (Chemirad) (8.30 g, 0.145 mol) and MeSH (25.0 g, 0.520 mol) in EtOH (50 ml) was heated in an autoclave at 60° for 96 hr. Anhydrous HCl was passed through the reaction mixture for 0.5 hr, followed by a stream of argon (the escaping gases were passed through caustic traps). The precipitated hydrochloride (13.7 g, mp 131–132°; reported[2] mp 128–130°) was filtered, washed (Et_2O), and dried. From the mother liquor another 4.0 g was obtained by evaporation and recrystallization (*i*-PrOH): mp 126–128°; total yield 17.7 g (0.125 mol, 86%). The salt was dissolved (concentrated NH_4OH) and salted out, and the freed base was extracted several times (Et_2O). After the Et_2O extracts were dried (Na_2SO_4) and evaporated, the residue could be used without further purification.

2'-Ethyl-2-(2-methylthioethylamino)propionanilide (1). A mixture of 9 (12.8 g, 0.0500 mol) and $MeSC_2H_4NH_2$[17] (17.2 g, 0.189 mol) in EtOH (25 ml) was allowed to reflux for 8 hr. After removal of solvent and excess amine *in vacuo*, the residue was dissolved ($CHCl_3$) and extracted with 1 *M* HCl, the combined acid extracts were washed (Et_2O), the cold aqueous phase was based out to pH 7–7.5 (7 *M* NaOH), and the freed base was taken up in $CHCl_3$. After drying (Na_2SO_4) and evaporating the solvent, the residue was converted to the hydrochloride.

2'-Ethyl-2-(*N*-methyl-2-methylthioethylamino)propionanilide (2). A mixture of 9 (9.08 g, 0.0354 mol) and 13 (9.70 g, 0.0922 mol) in C_6H_6 (19 ml) was allowed to reflux under argon for 5 hr. The precipitated hydrobromide of 13 was filtered: wt 5.84 g (0.0314 mol, 89%); mp 77–78° (EtOH–Et_2O). The residue obtained by evaporating the filtrate was worked up as described for compound 1.

2'-Ethyl-3-(*N*-methyl-2-methylthioethylamino)propionanilide (3). The compound was made using the procedure described for 2 from 10 (13.8 g, 0.0539 mol), 13 (14.7 g, 0.140 mol), and C_6H_6 (30 ml). The reaction product in $CHCl_3$ (25 ml total volume) was washed with phosphate buffer (five 25-ml portions, 0.067 *M*, pH 7.8). The $CHCl_3$ solution was evaporated, and from the residue the hydrochloride was prepared.

2'-Ethyl-2-methyl-2-(2-methylthioethylamino)propionanilide (4)

†A. Brändström, *et al.*, unpublished results.

Table III. Local Anesthesia and Toxicity[a]

No.	Isolated frog nerve,[b] rate of block	Latency, min[c]	Sciatic nerve block in rat: Duration,[d] min (frequency, %)[e] 0.5%	1.0%	2.0%	3.0%	4.0%	Acute toxicity in mouse, mg/kg ip	iv	Intradermal irritation in rabbit[f] 2%	4%
1	1.4	3–4	12 ± 4 (50)	24 ± 8 (67)	45 ± 11 (86)	54 (100)	86 ± 20 (95)	450–500	60	0–1	1–3
2	1.2	3–4		0	29 ± 9 (77)		70 ± 10 (83)	650	75	2	3
3	0.7	5			81 ± 12 (100)			340	100	0–sl	sl–1
4	1.4	4–7		36 ± 6 (83)	78 ± 9 (71)			500	35	sl–1	1–3
5	0.8	4–6		53 ± 9 (67)	103 ± 13 (67)			150	25	sl–1	1–3
6	1.3	5–7	18 ± 5 (67)	39 ± 8 (92)	88 ± 8 (100)			185–200	30	sl–1	1–3
7	0	12–15		38 ± 10 (50)	76 ± 12 (100)		74 ± 12 (100)	>1400	500	0	sl
8	0	6–8			54 ± 11 (83)		87 ± 9 (67)	500	55	sl	1–2
Lid.[g]	1.0	1	71 ± 8 (100)	96 ± 10 (100)	115 ± 16 (100)			105	19.5	0–sl	sl–1

[a] Technique, see Experimental Section. [b] Relative values, lidocaine = 1. [c] 2% solution. [d] ±1 standard deviation. [e] Indicated in parentheses. [f] 0, no irritation; sl, very slight irritation; 1, moderate irritation; 2, obvious irritation; 3, strong irritation, necrosis. [g] Lidocaine hydrochloride.

and 2'-Ethyl-2-methyl-3-(2-methylthioethylamino)propionanilide (5). A mixture of 11 (13.5 g, 0.0500 mol) and $MeSC_2H_4NH_2$[17] (17.2 g, 0.189 mol) in 95% EtOH (25 ml) was allowed to reflux for 8 hr under argon. Solvent and excess amine were evaporated *in vacuo*; the residue was dissolved in 1 *M* HCl and washed (Et_2O). The acid solution was alkalinized (7 *M* NaOH), extracted ($CHCl_3$), and evaporated. The residue (5.5 g, 0.196 mol, 39%) was partitioned between Et_2O and phosphate buffer (0.067 *M*, pH 7.0).[11,18] A determination of distribution coefficients[18] (*K*) for the two components, brought about by extracting a buffer solution (30 ml) of a small amount of the residue with consecutive volumes of Et_2O (10-ml portions), gave $K_4 = 23$ and $K_5 = 2.9$. The remainder of the residue was separated into its components by a four-funnel countercurrent procedure, using Et_2O (50 ml) and buffer (400 ml) in each extraction. The resulting two fractions were each reextracted according to the same pattern. Thus was obtained pure 4 (2.50 g, 8.90 mmol, 18%) and pure 5 (1.55 g, 5.52 mmol, 11%). Each fraction was converted to its hydrochloride.

Compound 5 was also prepared in the following way. A mixture of 12 (7.24 g, 0.0383 mol) and $MeSC_2H_4NH_2$[17] (5.00 g, 0.0548 mol) in MeOH (21 ml) and water (8 ml) was allowed to reflux under argon for 96 hr. After evaporation of solvent and excess amine, the residue was dissolved (1 *M* HCl) and thoroughly washed (Et_2O). The acid solution was made alkaline (7 *M* NaOH) and exhaustively extracted (Et_2O). After drying (Na_2SO_4) and evaporation, an oil was obtained from which a hydrogen sulfate was derived. A hydrochloride was also prepared and found identical with the one described above (mixture melting point).

2-(2-Methylthioethylamino)-2',6'-propionoxylidide (6). This compound was obtained by the method used for 1 from 2-bromo-2',6'-propionoxylidide[19] and $MeSC_2H_4NH_2$.[17]

The method of Karrer, *et al.*,[12] for the oxidation of sulfides to the corresponding sulfoxides was utilized for the following compounds. 2'-Ethyl-2-(2-methylsulfinylethylamino)propionanilide (7). Prepared from 1, a hydrogen sulfate was obtained. 2'Ethyl-2-(*N*-methylsulfinylethylamino)propionanilide (8). Prepared from 2, a hydrogen oxalate was obtained.

Rat Sciatic Nerve Block. Solutions (0.20 ml) containing 5, 10, 20, 30, or 40 mg/ml of the hydrochloride or an equivalent amount of another salt in saline were injected around the sciatic nerve at the midpoint of the femur of female Wistar rats.[13]

Isolated Frog Sciatic Nerve Block. The compounds, in 0.02 *M* concentration in a frog Ringer-type solution (*cf.* Takman, *et al.*[20]), were tested on isolated sciatic-peroneal nerve preparations of *Rana pipiens* by means of the action potential technique.[13] The rate of nerve block was estimated by determining the exposure time necessary to produce a 50% reduction in the height of the action potential, and this was compared to the corresponding value for lidocaine (=1).

Acute Intraperitoneal and Intravenous Toxicities. Saline solutions of the hydrochlorides (20 mg/ml) or equivalent amounts of other salts were administered to female albino mice (Charles River CD random-bred). The results are estimated and should only be looked upon as approximate LD_{50} values.

Local Irritating Effect. Solutions, 20 and 40 mg/ml as above, were injected intradermally in female, New Zealand, white rabbits and the irritation effects were estimated from gross examination of the sites 24 hr after injection.[14]

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Book Reviews

The Pathology of Transcription and Translation. (Biochemistry of Disease Series, Vol. 2, 1972). Edited by Emmanuel Farber with seven contributors. Marcel Dekker, New York, N. Y. 1972. x + 176 pp. 16 × 23 cm. $10.50.

The first chapter of the book, a brief examination of clearly defined lesions produced by alterations in DNA, asks more questions than it answers. However, it is a stimulating discussion of the pathology of DNA. Acidic nuclear proteins and their role in gene expression in eukaryotic cells are discussed in the next chapter together with diseases where gene expression appears to be implicated. This is followed by an analysis of the relationship between DNA damage and cell death.

The remainder (and majority) of the book deals with the pathology of RNA. The authors emphasize RNA inhibition and the response of the nucleus and nucleolus, cellular lesions produced by α-amanitin, and finally the pathology of translation. The section on the nucleus and nucleolus (Chapter 5) is the only discussion presented in what might be termed classical pathology.

The most striking aspect of the book is the relationship of fundamental biochemical lesions and the observed changes in the diseased cell. As the authors point out, this is the first systematic description of how interference with the synthesis and metabolism of DNA, RNA, and protein is related to disease in higher organisms, including man. In this book the authors have successfully presented some long overdue fresh views on the subject. Investigators in all fields of medicinal chemistry will appreciate the broad scope the authors present in this work.

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Biosynthesis. T. A. Geissman, Senior Reporter. Vol. 1. Specialist Periodical Report of the Chemical Society, London. 1972. viii + 249 pp. 13.5 × 21.5 cm. £6.50.

This book is the first volume of a series of "Specialist Periodical Reports" dealing with the synthesis of organic compounds in living organisms. The series is intended to provide systematic and comprehensive review coverage of the progress in the major areas of chemical research. This book reviews the literature on biosynthesis published during 1970 and 1971 and consists of five chapters. The first chapter discusses in a concise but adequate manner the methodology involved in modern biosynthetic experimentation with major emphasis on isotope tracer methods. Following the introductory chapter on methodology, the book is organized into four other chapters with the following headings: Biosynthesis of Terpenoids; Biosynthesis of Triterpines, Steroids and Carotenoids; Biosynthesis of Phenolic Compounds; and Biosynthesis of Alkaloids. Each individual chapter appears to represent a comprehensive and up-to-date picture of the state of knowledge in the area of biosynthesis. However, a major lack in the book is the absence of a chapter on biosynthesis of proteins, nucleic acids, and fatty acids. While the chapter on the Biosynthesis of Alkaloids does not cover all groups of alkaloids, due to lack of sufficient data published in 1971 as well as previous coverage in recently published books and monographs, the author reports per cent incorporation of various labeled substrates into alkaloids in a table form which should make this chapter a useful reference.

This book will be outstandingly useful not only to those working in the area of biosynthesis but will serve as an extremely useful introduction to those who wish to become acquainted with the current status of knowledge in this area of research.

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The Bile Acids–Chemistry, Physiology, and Metabolism. Edited by P. P. Nair and D. Kritchevsky. Vol. I: Chemistry. Plenum Press, New York and London. 1971. xi + 372 pp. 16 × 23.3 cm. $19.50.

The bile acids are the principal end products of cholesterol metabolism and perform key roles in normal and abnormal physiological processes. Volume I of "The Bile Acids" is the first reference to comprehensively review the moden chemical literature of this important class of steroids. The book discusses the chemical literature through 1970, and a second volume will discuss physiology and metabolism. Volume I includes chapters on the biosynthesis and synthesis of the bile acids; their chemical reactions, physical constants, extraction, and chromatography; mass spectra; and the solubility and micelle formation properties of the bile acids. While the coverage of a few topics is superficial, good references are given to more complete sources in the literature. Many laboratory procedures and techniques are completely described. The extensive use of trivial nomenclature and an ambiguity of drawing angular hydrogens as methyls may be a problem to some readers. However, Volume I of "The Bile Acids" will be an indispensable reference to workers in the field.

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Methods and Techniques in Clinical Chemistry. By Paul L. Wolf, Dorothy Williams, Tashiko Tsudaka, and Leticia Acosta. Wiley, New York, N. Y. 1972. xiii + 417 pp. 16 × 23.5 cm. $11.50.

Every clinical chemistry laboratory must have carefully written instructions for all of their procedures in order to minimize errors. This book represents the procedure manual for the clinical chemistry laboratory at Stanford University Medical Center. At least it represents the procedures in use at the time the manuscript was turned over to