solid was filtered, washed with EtOAc–$Me_2CO$ (9:1), and dried to give 64.4 g (38%) of **9**: mp 151–156.5°. Recrystallization from methyl isobutyl ketone gave 55.7 g (33%) of essentially pure **9**, mp 159.5–161°; rods from *i*-PrOH, mp 160–161.5°. Anal. ($C_{18}H_{28}BrNO$) C, H, N.

**2,5-Dimethyl-2'-hydroxy-9α-propyl-6,7-benzomorphan (10).** To 48% HBr (600 ml) was added **9**·HBr (61.4 g, 0.17 mol) and the solution refluxed 20 hr. The reaction mixture was cooled, poured onto crushed ice, and made alkaline with 12 *M* $NH_4OH$. The semisolid that resulted was dissolved in $CHCl_3$ (2.0 l), washed with $H_2O$, and dried ($Na_2SO_4$). Evaporation of the solvent left 42.8 g (96%) of tan crystalline material which was recrystallized from dioxane (400 ml) to give 25.4 g (56.8%) of **10**: mp 212–216.5°. An additional crystallization from dioxane and finally from absolute EtOH gave fine needles of pure **10**: mp 217.5–219°. Anal. ($C_{17}H_{25}NO$) C, H, N.

**2,5-Dimethyl-2'-hydroxy-9β-propyl-6,7-benzomorphan (11) Hydrochloride Dihydrate.** The filtrate from the 25.4 g of **10** above was evaporated to give a solid to which $H_2O$ (50 ml) was added. After addition of 37% HCl to pH 1–2 (Hydrion paper), the slurry was heated to solution and filtered hot (Celite), and the filter was washed with 10 ml of hot $H_2O$. The combined filtrate and washing were cooled to 0° and the resulting crystals filtered, washed with ice–$H_2O$, and air-dried to give 8.9 g (17.4%) of **11**·HCl·$2H_2O$, mp 267.5–270.5°; oblong prisms from $H_2O$, mp 270–272.5°. Anal. ($C_{17}H_{26}ClNO \cdot 2H_2O$) C, H, N.

Treatment of an aqueous solution of **11**·HCl with $NH_4OH$ gave a solid which was recrystallized twice from absolute EtOH to give cubes of **11** (base), mp 182.5–184°. Anal. ($C_{17}H_{25}NO$) C, H, N.

The filtrate from the 8.9 g of **11**·HCl above was made alkaline with $NH_4OH$ and the resulting base mixture reprocessed as described for the isolation of **10** and **11**. In this manner additional **10** (1.8 g) and **11** (1.8 g) were obtained (total isolated yield of **10** and **11**, 60.6 and 20.9%, respectively).

**Rates of Methiodide Formation of 10 and 11.** Using the procedure previously described,[8] the predominant **10** and lesser **11** isomers produced in the cyclization of **9** were shown to be converted to the corresponding methiodides to an extent of 99 and 14%, respectively, during 24 hr. The assigned relative stereochemistry of **10** and **11** is thereby confirmed.

**Acknowledgment.** We thank Mrs. L. Atwell, Medicinal Chemistry Section, for the analgesic assay data.

## References and Notes

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# Synthesis and Neuroleptic Activity of Isomeric Thieno[1,4]benzothiazines

C. J. Grol* and H. Rollema

*Department of Pharmaceutical Chemistry, State University, Groningen, The Netherlands.* *Received February 3, 1975*

To investigate the influence of electronic properties of the tricyclic thiazine system on neuroleptic activity, a series of the isomeric *N*-dimethylaminopropylthienobenzothiazines was synthesized. All compounds were screened for neuroleptic activity in mice and rats. For the active compounds lowest active doses in the antiamphetamine test were determined. Activity appeared to be dependent on the mode of annelation of the thiophene molecule: compounds bearing the same substituent and side chain with the thiophene molecule in 2,3 and 3,4 annelation were active, while those compounds with a 3,2 annelation seemed to be devoid of activity at the given dose.

In previous papers we described the synthesis of some isomers of the dithienothiazine system.[1] Attempts to synthesize promazine analogs, however, were unsuccessful due to oxidation of the intermediate N-unsubstituted dithienothiazines.

As was shown in some preliminary experiments the thienobenzothiazines, in which one thiophene molecule is replaced by the less reactive benzene nucleus, were more stable compounds. In addition, we have a tool to enhance the stability of the thiazine system by the introduction of electron-withdrawing groups. These groups hamper the formation of the radical cation,[2] the first step in disproportionation and decay reactions.[3,4] In our studies we investigate to what extent the electronic structure of thiazines influences their neuroleptic activity.

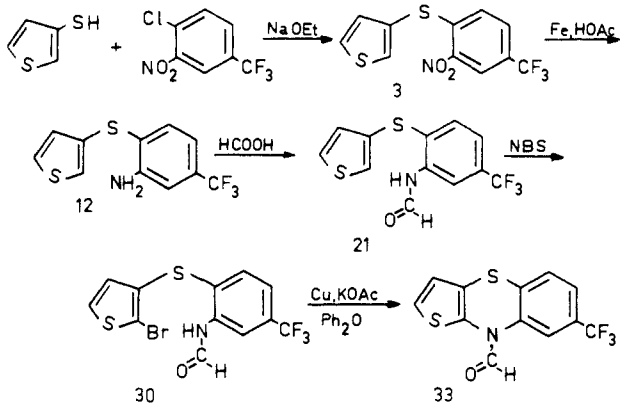
Differences in electronic properties can be achieved by preparing isomeric thienobenzothiazines, varying in the mode of annelation of the thiophene molecule. In order to reduce the physicochemical differences to a minimum, all isomers should bear the same substituent and side chain.

In this paper the synthesis and preliminary pharmacology of thienobenzothiazine analogs of promazine, chlorpromazine, and triflupromazine are reported.

**Chemistry.** For the synthesis of isomeric thienobenzothiazine systems we used the reaction scheme developed in our previous investigations. All isomers were prepared using a synthetic sequence as outlined for the thieno[3,2-*b*][1,4]benzothiazine substituted with a trifluoromethyl group in the benzene ring (Scheme I).

*Address correspondence to the Laboratorium voor Farmaceutische en Analytische Chemie, Ant. Deusinglaan 2, Groningen.

**Scheme I**



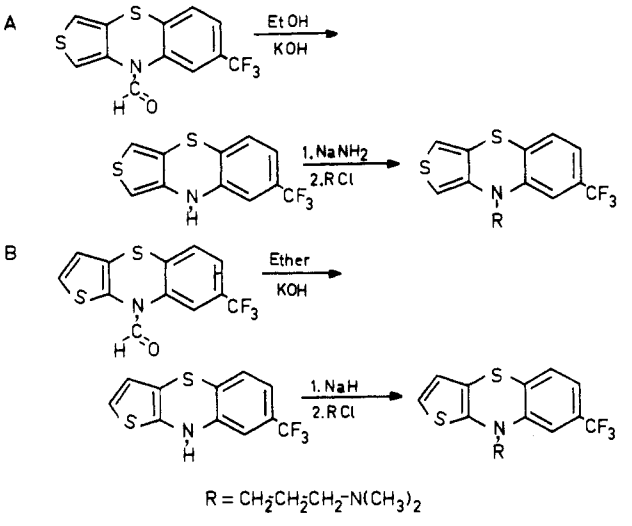
Substitution of 3-thiophenethiol with 2-nitro-3-chloro-$\alpha,\alpha,\alpha$-trifluorotoluene was accomplished with a freshly prepared solution of NaOEt in absolute ethanol. Depending upon the various compounds different reaction conditions were employed for this substitution reaction to obtain optimum yields (Table I).

Reduction of the nitro compounds with iron powder in aqueous acetic acid gave the amines (Table I) which were converted to their *N*-formyl analogs by treatment with formic acid in benzene (Table II).

Bromination of the amide **21** with NBS in chloroform–acetic acid gave the expected product **30**. The bromination reaction was obviously unnecessary for the two other isomers where the synthesis was started with 3-bromo-2-thiophenethiol or 3-bromo-4-thiophenethiol. The ring closure of the bromoamides was performed in diphenyl ether with activated copper bronze and potassium acetate (Table III).

In the next step the *N*-formylthienobenzothiazines should be hydrolyzed to form the unsubstituted thiazine systems. For the more stable compounds it was possible to hydrolyze in ethanol–water with base (Scheme II, A). It appeared that for compounds **40**, **41**, and **45** this route was not successful due to rapid decomposition of the formed thiazines.

**Scheme II**



We developed for these compounds the heterogeneous hydrolysis (Scheme II, B). The compound was dissolved in ether to which a solution of potassium hydroxide in water was added. Then sufficient ethanol was added to obtain a reasonable reaction rate, which was followed by TLC analysis. In this way the thiazines were obtained (Table III). Even under this mild condition we were not able to isolate the thiazine from the hydrolysis reaction of **31**, a clear demonstration of the absence of stabilizing influences of the electron-withdrawing $CF_3$ and Cl substituents in this isomer. The thiazines were purified by recrystallization and appeared to be stable if protected from light. The structure was established by spectroscopic evidence and elemental analysis (Table III).

The thiazines were converted to their promazine analogs by alkylation with sodium amide or sodium hydride and 3-chloropropionyldimethylamine in refluxing toluene or xylene (Scheme II). The crude bases that were isolated were purified by vacuum distillation and treated in ether with ether–HCl whereby the HCl salts precipitated, which were recrystallized twice from ethanol–ether (Table IV).

Comparison of the uv spectra of the isomers shows the differences in aromatic character between the 3,4 annelated and the other two isomers. The dienophilic character of the thiophene molecule in the 3,4 isomer is shown by the position of the longest wavelength absorption band being 20 nm lower than that for the 3,2 and 2,3 isomers. In the latter compounds the diene part of the thiophene molecule is directly conjugated over the sulfur atom (2,3 isomer) and over the nitrogen atom (3,2 isomer) with the benzene ring, resulting in a more delocalized system.

The $^1H$ NMR spectrum of the thiazines shows absorptions for the side chain at 2.12–2.20 ($CH_3$), 2.30–2.34 [$-CH_2N(CH_3)_2$], 1.78–1.90 ($CH_2$), and 3.70–3.78 ($-CH_2N$), while the aromatic protons absorb at 6.0–7.4 ppm. In contrast to the uv spectra a substituent effect is recognized in the $^1H$ NMR spectra where the electron-withdrawing $CF_3$ group has caused a deshielding of the aromatic hydrogen atoms and the protons of the methylene group on the thiazine nitrogen atom.

**Pharmacology and Discussion.** Injections were prepared by dissolving appropriate amounts of the HCl salts (no. **53** as fumarate) in saline. All compounds were screened for neuroleptic activity, which was indicated by palpebral ptosis, sedation, and catalepsy in rats and mice after intraperitoneal injection of 40 mg/kg.

Compounds that showed some activity (no. **48**, **49**, and **53** appeared to lack activity at these doses) were examined for antagonism to amphetamine-induced stereotypy and agitation according to Janssen et al.;[5] male wistar rats (±250 g) were given a sc dose of the drug under investigation, immediately followed by 5 mg/kg of amphetamine iv and occurrence of agitation, chewing, and sniffing was scored. The results are shown in Table IV as lowest active doses in mg/kg.

For purpose of comparison the values of promazine, chlorpromazine, and trifluopromazine are also tabulated, demonstrating the decrease in activity if one benzene nucleus in phenothiazines is replaced by thiophene.

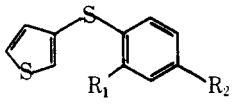
It is obvious from these results that the position of the thiophene molecule has a marked influence on biological activity. Compounds bearing the same substituent with the thiophene molecule in a 3,2 annelation showed no neuroleptic activity at the given dose, while 2,3 and 3,4 annelated compounds were active as neuroleptics. In addition, it can be seen that 2 substituents have the same influence on activity as in other neuroleptics: $-H < -Cl < -CF_3$.

To investigate whether the differences we found are due to differences in electronic properties of the isomeric thienobenzothiazine system, physicochemical parameters are now being determined, which will be published in future.

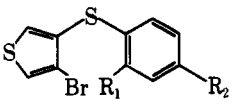
## Experimental Section

Melting points were determined with a Büchi-Tottoli apparatus and are not corrected. The $^1H$ NMR spectra were determined in

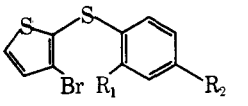
**Table I.** Nitro- and Aminophenylthienyl Sulfides



1-3,10-12



4-6,13-15

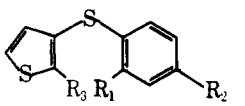


7-9,16-18

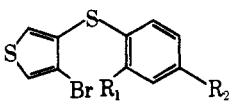
| No. | $R_2$ | Mp or bp (mm), °C | Recrystn solvent | Yield, % | Procedure | Analyses |
|---|---|---|---|---|---|---|
| | | | For $R_1 = NO_2$ | | | |
| 1 | H | 77–77.5 | MeOH | 60 | B | C, H, N, S |
| 2 | Cl | 97–98 | MeOH | 90 | B | C, H, N, S, Cl |
| 3 | $CF_3$ | 72–72.5 | Petr ether | 84 | A | C, H, N, S |
| 4 | H | 107–108 | EtOH | 80 | B | C, H, N, S, Br |
| 5 | Cl | 82–85 | MeOH | 80 | B | C, H, N, Cl; Br, S[a] |
| 6 | $CF_3$ | 79–81 | Hexane | 88 | A | C, H, N, S, Br |
| 7 | H | 94–95 | EtOH | 75 | B | C, H, N, S, Br |
| 8 | Cl | 114–116 | MeOH | 84 | B | C, H, N, S, Cl; Br[b] |
| 9 | $CF_3$ | 82–83 | Petr ether | 40 | A | C, H, N, S, Br |
| | | | For $R_1 = NH_2$ | | | |
| 10 | H | 156–160 (1) | | 80 | | C, H, N, S |
| 11 | Cl | 163–166 (0.6) | | 83 | | C, H, N, S, Cl |
| 12 | $CF_3$ | 126–128 (0.3) | | 74 | | C, H, N, S |
| 13 | H | 178–179 (0.9) | | 89 | | C, H, N, S, Br |
| 14 | Cl | 56–58 | MeOH | 85 | | C, H, N, S, Br |
| 15 | $CF_3$ | 152–154 (0.3) | | 74 | | C, H, N, S, Br |
| 16 | H | 151–154 (0.3) | | 80 | | C, H, N, S, Br |
| 17 | Cl | 52–55 | MeOH | 75 | | C, H, N, S, Br, Cl |
| 18 | $CF_3$ | 48–49 | Hexane | 83 | | C, H, N, S, Br |

[a] Br: calcd, 22.79; found, 21.7. S: calcd, 18.29; found, 18.9. [b] Br: calcd, 22.79; found, 22.3.

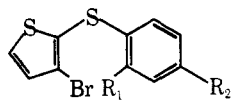
**Table II.** Amido- and Amidobromothienylphenyl Sulfides



19-21, 28-30



22-24



25-27

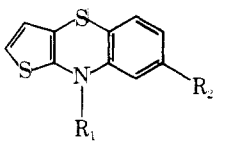
| No. | $R_2$ | Mp, °C | Recrystn solvent | Yield, % | Analyses |
|---|---|---|---|---|---|
| | | For $R_1$ = –NHCHO; $R_3$ = –H | | | |
| 19[a] | H | 62–63 | DIPE[b] | 96 | C, H, N, S |
| 20 | Cl | 76.5–77 | DIPE | 90 | C, H, N, S, Cl |
| 21 | $CF_3$ | 86–88 | $CCl_4$ | 71 | C, H, N, S |
| 22 | H | 96–97 | MeOH | 72 | C, H, N, S, Br |
| 23 | Cl | 101–102 | MeOH | 84 | C, H, N, S, Cl; Br[c] |
| 24 | $CF_3$ | 80–84 | DIPE | 74 | C, H, N, S, Br, F |
| 25 | H | 108–109 | DIPE | 86 | C, H, N, S, Br |
| 26 | Cl | 105–106 | DIPE | 83 | C, H, N, S, Br, Cl |
| 27 | $CF_3$ | 82–84 | $CCl_4$ | 93 | C, H, N, S; Br[d] |
| | | $R_1$ = –NHCHO; $R_3$ = –Br | | | |
| 28[a] | H | 69–70 | DIPE | 96 | C, H, N, S; Br[e] |
| 29 | Cl | 82–82.5 | MeOH | 70 | C, H, N, S, Cl; Br[f] |
| 30 | $CF_3$ | 79–81 | Hexane | 74 | H, N, S, Br; C[g] |

[a] $R_1$ = –NHCOCH$_3$. [b] Diisopropyl ether. [c] Br: calcd, 22.92; found, 22.2. [d] Br: calcd, 20.92; found, 20.5. [e] Br: calcd, 24.34; found, 24.9. [f] Br: calcd, 22.92; found, 22.5. [g] C: calcd, 37.71; found, 38.2.

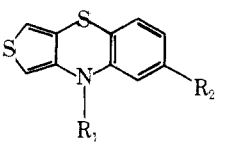
the solvent indicated ($Me_4Si$ as internal reference) with a Hitachi Perkin-Elmer Model R-24 spectrometer. The ir spectra were obtained with a Beckmann IR-33 spectrophotometer (KBr). Uv spectra were measured with a Zeiss PMQ II spectrophotometer. Microanalyses were performed by the Analytical Department of the Chemical Laboratories. Analyses for compounds reported in this paper were within ±0.4% of the theoretical values except where specifically noted.

**Nitrophenylthienyl Sulfides 1–9 (Table I). Procedure A.** To a solution of 0.05 mol of a thiophenethiol in 50 ml of EtOH was added a solution of 0.05 mol of NaOH in 10 ml of water. The mixture was stirred in a nitrogen atmosphere for 15 min and 0.05 mol of chloronitrotoluene in 25 ml of EtOH was added over a period of 10 min. The reaction mixture was refluxed for 1.5 hr and cooled. After the addition of ice water a yellow precipitate was formed which was collected, dried, and recrystallized.

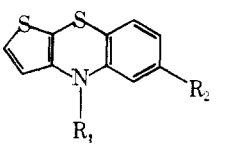
Table III. *N*-Amido- and Thieno[1,4]benzothiazines



31-33, 40, 41



34-36, 42-44

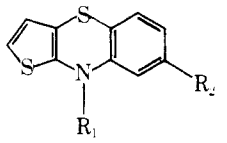


37-39, 45-47

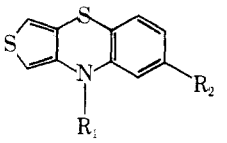
| No. | $R_2$ | Mp, °C | Recrystn solvent | Procedure | Yield, % | Analyses |
|---|---|---|---|---|---|---|
| | | | For $R_1$ = CHO | | | |
| 31[a] | H | 127–128 | EtOH | | 60 | C, H, N, S |
| 32 | Cl | 139–139.5 | EtOH | | 70 | C, H, N, S, Cl |
| 33 | $CF_3$ | 116–117 | Hexane–acetone | | 71 | C, H, N, S, F |
| 34 | H | 141–142 | EtOH | | 83 | C, H, N, S |
| 35 | Cl | 172–173 | EtOH | | 70 | C, H, N, S, Cl |
| 36 | $CF_3$ | 96–97 | Hexane–acetone | | 78 | C, H, N, S, F |
| 37 | H | 145–147 | Hexane–acetone | | 72 | C, H, N, S |
| 38 | Cl | 150–152 | EtOH | | 78 | C, H, N, S, Cl |
| 39 | $CF_3$ | 105–106 | Hexane–acetone | | 75 | C, H, N, S, F |
| | | | For $R_1$ = H | | | |
| 40 | Cl | | | B | 70 | C, H, N, Cl; S[b] |
| 41 | $CF_3$ | 170 dec | Hexane–acetone | B | 75 | C, H, N, S |
| 42 | H | 179–180 | Hexane–acetone | A | 80 | H, S; C[c] |
| 43 | Cl | 214–216 | EtOH | A | 65 | C, H, N, S, Cl |
| 44 | $CF_3$ | 176–177 | Hexane–acetone | A | 66 | C, H, N, S |
| 45 | H | 128–133 | Hexane–acetone | B | 55 | C, H, N |
| 46 | Cl | 168–170 | Hexane–acetone | A | 89 | C, H, N, S, Cl |
| 47 | $CF_3$ | 155 dec | Hexane–acetone | A | 86 | C, H, N, S |

[a] $R_1$ = $-COCH_3$. [b] S: calcd, 26.75; found, 26.3. [c] C: calcd, 58.50; found, 57.8.

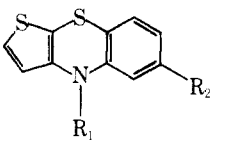
Table IV. Comparison of Activity of Salts of *N,N*-Dimethylaminopropylthieno[1,4]benzothiazines



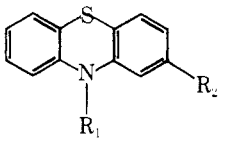
48, 49



50–52



53–55



promazines

| No. | $R_2$ | Procedure | Mp, °C | Yield, % | Analyses | Screening[d] | Amphetamine test,[e] μmol/kg |
|---|---|---|---|---|---|---|---|
| | | $R_1$ = $CH_2CH_2CH_2N(CH_3)_2 \cdot HCl$ | | | | | |
| 48 | Cl | NaH–xylene | 177–178 | 30 | H, N, Cl; C[a] | – | |
| 49 | $CF_3$ | NaH–toluene | 195–196 | 50 | C, H, N, Cl; S[b] | – | |
| 50 | H | $NaNH_2$–xylene | 167–168 | 74 | C, H, N, Cl | + | 60 |
| 51 | Cl | NaH–xylene | 198–199 | 80 | C, H, N, Cl | + | 30 |
| 52 | $CF_3$ | $NaNH_2$–toluene | 224–226 | 54 | C, H, N, S, Cl | + | 7.5 |
| 53[c] | H | $NaNH_2$–xylene | 157–158 | 50 | C, H, N, S | – | |
| 54 | Cl | NaH–xylene | 170–171 | 75 | C, H, N, Cl | + | 30 |
| 55 | $CF_3$ | NaH–toluene | 149–150 | 78 | C, H, N, S, Cl | + | 1.8 |
| Promazine | H | | | | | + | 120 |
| Chlorpromazine | Cl | | | | | + | 0.9 |
| Triflupromazine | $CF_3$ | | | | | + | 0.9 |

[a] C: calcd, 49.86; found, 48.2. [b] S: calcd, 16.24; found, 15.8. [c] Fumarate. [d] Three rats were given 40 mg/kg ip. A compound was considered as active (+) when at least one rat showed symptoms of catalepsy, ptosis, or sedation and as inactive (–) if these symptoms did not occur. [e] For each compound a geometric series of successive dose levels, selected from 120, 60, ..., 1.8, 0.9 μmol/kg, was studied. Three rats were used at each dose level. Results are given as minimal effective doses for amphetamine antagonism.[5]

**Procedure B.** To a freshly prepared solution of 0.20 mol of Na in 300 ml of absolute EtOH under nitrogen was added 0.20 mol of the thiophenethiol in 45 ml of absolute EtOH. The reaction mixture was stirred for 20 min and 0.2 mol of the chloronitrobenzene compound in 100 ml of absolute EtOH was added. The solution was refluxed for 2 hr and cooled and $H_2O$ was added. The yellow precipitate was collected, washed with $H_2O$, dried, and recrystallized.

**Aminophenylthienyl Sulfides 10–18 (Table I).** To a stirred solution of 500 ml of HOAc and 300 ml of $H_2O$ the nitro com-

pounds (0.2 mol) were added. The suspension was heated to 80° and a stream of nitrogen was passed into the solution. In portions 0.4 mol of iron powder was added and the mixture was heated at reflux for 2 hr. The clear solution was poured into $H_2O$ and the oil extracted twice with $CH_2Cl_2$. The combined organic layers were washed with a $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was evaporated and the residue was distilled in vacuo.

**Amidophenylthienyl Sulfides 20–27 (Table II).** The amines 11–18 (0.1 mol) were dissolved in 300 ml of benzene and 0.15 mol of formic acid was added. The mixture was refluxed for 3 hr and poured into $H_2O$; the benzene layer was separated, washed with a $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was evaporated and the remaining solids were recrystallized.

The amide **19** was made in the same way with $Ac_2O$ (0.1 mol) and pyridine (0.1 mol) in benzene.

**Amido-3'-(2'-bromo)phenylthienyl Sulfides 28–30 (Table II).** The amides **19–21** (0.05 mol) were dissolved in a mixture of HOAc–$CHCl_3$ (1:1). To the stirred solution NBS (0.05 mol) was added in portions. After this addition the yellow solution was stirred for 2 hr and poured into $H_2O$. The $CHCl_3$ layer was washed with $H_2O$, a 10% KOH solution, and $H_2O$. The solution was dried ($MgSO_4$) and concentrated. The solid residue was recrystallized from the appropriate solvents.

**Amidothieno[1,4]benzothiazines 31–39 (Table III).** The bromoamides (10 mmol) were dissolved in 200 ml of diphenyl ether. To this solution a mixture of 2 g of KOAc and 1 g of activated copper bronze was added. The reaction mixture was stirred vigorously under nitrogen and heated to 190–200°. The reaction was followed with TLC and heating was continued until 80–90% of the starting material was converted into the thiazine. The reaction mixture was cooled and chromatographed over a silica gel column with *n*-hexane to remove the diphenyl ether and further eluted with $CHCl_3$. The $CHCl_3$ fractions were collected and concentrated leaving light-green to light-purple substances which were recrystallized.

**Thieno[1,4]benzothiazines 40–47 (Table III). Procedure A.** The formylthiazine (5 mmol) was dissolved in 60 ml of EtOH. In a nitrogen atmosphere a solution of 8 mmol of KOH in 10 ml of $H_2O$ was added. Stirring was continued until the reaction was complete, which could be followed on TLC. The colored solution was poured into a saturated NaCl solution and the precipitate was taken up in ether. The ether was washed ($H_2O$), dried ($MgSO_4$) under stirring with decolorizing carbon, and then removed, leaving a solid compound which was recrystallized.

**Procedure B.** To a solution of 6.6 mmol of the thiazine in 200 ml of ether a solution of 1.6 g of KOH in 10 ml of $H_2O$ was added under vigorous stirring. A stream of nitrogen was passed into the heterogeneous mixture and sufficient EtOH was added to obtain a reasonable reaction rate (10–20 ml). After the reaction was complete, the reaction mixture was poured into a saturated NaCl solution. The ethereal layer was washed (NaCl) and dried on $MgSO_4$ under stirring with decolorizing carbon and the ether was evaporated. The isolated thiazines were then recrystallized.

***N,N*-Dimethylaminopropylthieno[1,4]benzothiazines 48–55 (Table IV).** The thiazine (4.7 mmol) was dissolved in 30 ml of dry xylene. Under nitrogen and with stirring 200 mg (5 mmol) of powdered $NaNH_2$ was added and the reaction mixture was heated for 2 hr. Then 730 mg (6 mmol) of 3-(dimethylamino)propyl chloride was added and the red-colored reaction mixture was refluxed (1–4 hr). The disappearance of the starting thiazine was followed on TLC. When the reaction was complete, the mixture was cooled and washed several times with $H_2O$. The organic layer was extracted with 15% tartaric acid and the acid layer was washed with toluene. The tartaric acid solution was rendered alkaline with a 15% NaOH solution and the oil was extracted into toluene. The organic layer was dried ($CaCl_2$) and concentrated leaving a dark-colored oil. This oil was distilled in vacuo and dissolved in absolute ether. A solution of ether saturated with dry HCl gas was added and the precipitate was collected and dried in vacuo. The HCl salts were recrystallized twice from absolute EtOH–ether.

**Acknowledgments.** The authors wish to thank Mrs. A. Westerbrink and Mr. D. Dijkstra for their valuable technical assistance. We also are indebted to the Pharmacological Department of Janssen Pharmaceutica, Beerse, Belgium, for carrying out the pharmacological tests.

## References and Notes

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# *Book Reviews*

**The Theory of Rate Processes in Biology and Medicine.** By Frank H. Johnson, Henry Eyring, and Betsy J. Stover. Wiley, New York, N.Y. 1974. 703 pp. $27.50.

The theory that any process, chemical or biological, which involves an orderly progressive change at some characteristic or definable rate follows the same fundamental laws was first proposed in 1935. During the intervening years a number of investigators have shown the application of the theory to processes ranging from simple chemical reactions to complex biological processes. According to the authors, "the purpose of this volume is to outline the conceptual basis of modern rate theory and to apply the net results of this rational quantitative theory to representative rate processes in biology and medicine in an effort to achieve a better understanding of the phenomena involved".

The book includes six chapters, a bibliography, an author index, a list of sources for the 257 illustrations presented in the text, an index to the genera and species mentioned in the book, and a concise subject index. The first chapter introduces the theory of rate processes and the application of this theory in biology and medicine. Chapter two discusses the application of the theory of rate processes to the phenomena of bioluminescence and chemiluminescence. In Chapter three, the role of temperature as an agent affecting rate processes is discussed. The next chapter discusses the influence of hydrostatic pressure and molecular volume changes on the rate process theory. Chapter five evaluates the action of inhibitors in relation to concentration, temperature, and hydrostatic pressure on rate processes. The final chapter is a highly interesting application of the theory of absolute rate processes to the complex dynamics of mammalian life. The bibliography contains 76 pages of references, providing a highly useful source of additional information. The book's value is greatly enhanced by the numerous useful illustrations provided throughout the book.

This book should prove highly interesting to biologists wishing to understand the theoretical basis of rate processes, to chemists wishing to know more about biological processes, and to physicians attempting to understand the fundamental, molecular basis of medical problems.

*Department of Life and Behavioral Sciences*
*U.S. Air Force Academy*
*Colorado 80840*
Donald F. Logsdon, Jr.