(NF_2), 1230 and 1420 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 7.35 (s, 5, C_6H_5), 2.08 (m, 3, CH_3).

Anal. Calcd for $C_9H_8F_4N_2O_4S$: C, 34.18; H, 2.55; F, 24.03; N, 8.86. Found: C, 33.92; H, 3.01; F, 23.23; N, 8.77.

Registry No.—Difluoramine, 10405-27-3; sulfuric acid, 7664-93-9; 4-(3,3-dinitrobutyl)-4-difluoramino-1,3-dioxa-2-thiolane 2,2-dioxide, 18963-41-2; 4-(3,3,3-trinitropropyl)-4-difluoramino-1,3-dioxa-2-thiolane 2,2-dioxide, 18963-42-3; 4,5-dimethyl-4,5-bis(difluoramino)-1,3-dioxa-2-thiolane 2,2-dioxide, 18963-43-4; 4-phenyl-4,5-bis(difluoramino)-5-methyl-1,3-dioxa-2-thiolane 2,2-dioxide, 18963-44-5.

Ring–Chain Tautomerism of Imine–Amine or Ketone–Carbinol Systems Obtained by Condensation of Dilithio-N-Substituted Carboxamides or Sulfonamides with Benzonitrile. Synthesis of Cyclic Products[1]

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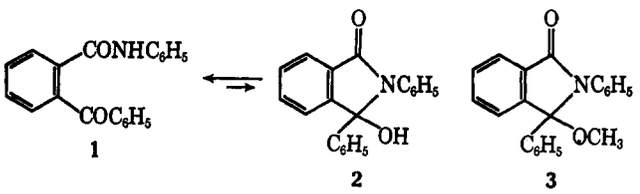
Condensations of benzonitrile at the *ortho* position of N-substituted benzamides and N-substituted benzenesulfonamides were effected by means of *n*-butyllithium to form imine–amine, ring–chain tautomeric systems; in three of the four cases studied, the equilibrium was far on the side of the cyclic primary amines. All four of the primary amines were condensed with benzaldehyde to give corresponding benzal derivatives; also, the imine–amine product from N-methylbenzenesulfonamide and benzonitrile reacted with ethanol to give a cyclic ether–sulfonamide. The imine–amine, ring–chain products from the N-substituted benzenesulfonamides were hydrolyzed to afford ketone–carbinol, ring–chain systems, the equilibrium of which was far on the side of the ketone. Condensations of benzonitrile at the 2-methyl group of N-substituted *o*-toluenesulfonamides were effected by means of *n*-butyllithium, and the resulting imines were hydrolyzed to give corresponding ketone–carbinol, ring–chain tautomeric systems. Although the equilibrium was on the side of the ketone, the cyclic carbinols were dehydrated to afford unsaturated cyclic sulfonamides, which are substituted benzothiazines. These double-bonded compounds underwent intramolecular β elimination with alkali amides in liquid ammonia to form corresponding acetylenic sulfonamides. Several new types of products were synthesized.

Ketones having acidic groups at the *ortho* positions such as *o*-benzoylbenzoic acid[2] and *o*-benzoybenzanilide (**1**)[3] are known to exhibit ring–chain tautomerism. Thus, **1** is in equilibrium with carbinol amide **2** as evidenced by polarographic measurements and by reaction with methanol in the presence of acid to form ether amide **3**.[3]

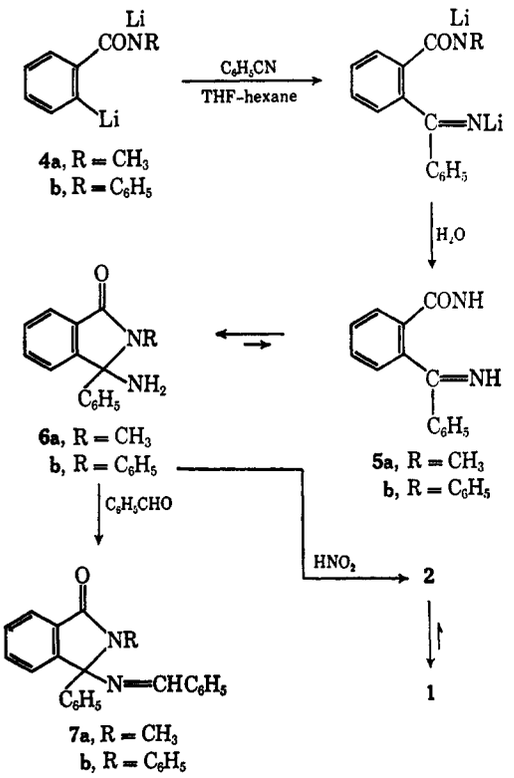


1 2 3

In the present investigation some new ring–chain systems involving imine–amine or ketone–carbinol tautomers were prepared and converted to certain new types of cyclic products.

Tautomerisms Involving Five-Membered Rings.—Dilithiocarboxamides **4a,b** were condensed with benzonitrile to form the imine carboxamides **5a,b,** which entered into equilibrium with the cyclic amine carboxamides **6a,b** as evidenced by their condensations with benzaldehyde to give the benzal derivatives **7a,b,** respectively; also cyclic amine **6b** was deaminated with nitrous acid to afford ketone **1** (Scheme I). The dilithioamides **4a,b** were prepared by dilithiation of the corresponding N-substituted benzamides by means of *n*-butyllithium in tetrahydrofuran (THF)–hexane.[4]

SCHEME I



Interestingly, the equilibrium between the imines

(1) Supported by the Army Research Office (Durham) and by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute.

(2) P. R. Jones and P. J. Desio, *J. Org. Chem.*, **30**, 4293 (1965).

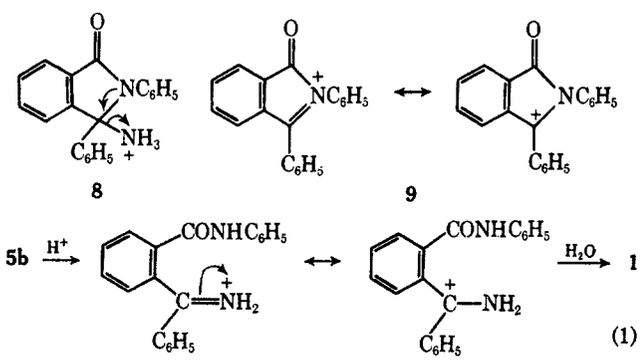
(3) S. Wawzonek, H. A. Laitinen, and S. J. Kwiatkowski, *J. Amer. Chem. Soc.*, **66**, 830 (1944); see also P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(4) See W. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

5a,b and the corresponding cyclic amines **6a,b**, especially that between **5a** and **6a**, was evidently far on the side of the latter compounds (see Scheme I); moreover, equilibration occurred rapidly. Thus, the ring–chain products obtained on neutralization of the reaction mixture from dilithioamide **4a** and benzonitrile under all conditions, and of that from dilithioamide **4b** and the nitrile under most conditions, appeared to consist largely of cyclic amine **6a** or **6b**; this was indicated by their nmr spectra which showed signals for their two amino hydrogens and by other data (see Experimental Section).

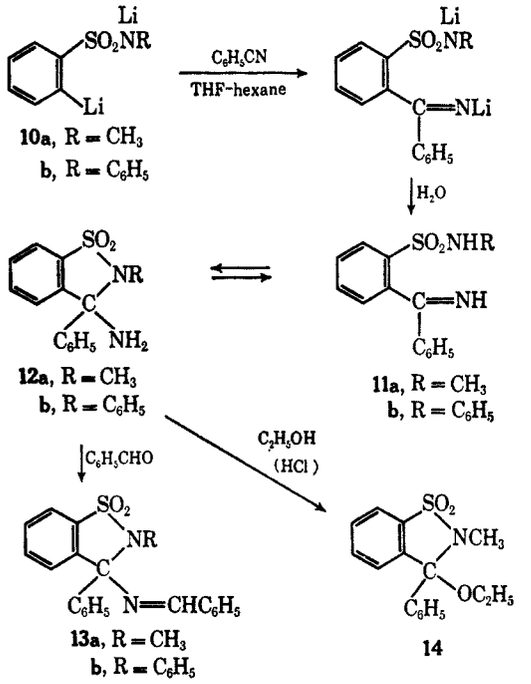
Although imine **5b** was isolated in 25% yield by inverse neutralization of the appropriate reaction mixture and careful fractionation of the product, this imine was readily converted to cyclic amine **6b** in refluxing ethanol; also, in connection with a nmr determination, imine **5b** was slowly converted to amine **6b** on standing in deuteriochloroform at room temperature. Imine **5b** was easily distinguished from amine **6b**, especially by nmr spectra; whereas the spectrum of **6b** showed a signal for the two protons of the primary amine, the spectrum of **5b** presumably exhibited absorptions for the imine and amide protons in the field of aromatic hydrogens (overlap). Since an attempt to isolate imine **5a** under similar conditions was unsuccessful, the conversion of imine **5a** to amine **6a** apparently occurred even more readily than that of imine **5b** to amine **6b**.

The ring–chain product **5b–6b** (mainly **6b**) was hydrolyzed with aqueous acetic acid containing a little sulfuric acid at 25–30° to form ketone amide **1**. The mechanism might involve either protonation of amine **6b** to form **8** which loses ammonia to give carbonium ion **9** leading to carbinol **2** and then to ketone **1**, or protonation of imine **5b** to produce the corresponding carbonium ion leading directly to ketone **1** (eq 1); the latter course would be accompanied by equilibration as the hydrolysis progressed. Some support for the latter mechanism is the observation that the corresponding ring–chain product **5a–6a**, which appeared to consist of even less of amine **5a** (see above), failed to undergo hydrolysis under similar conditions.



It should be mentioned that, in connection with an earlier study of addition reactions of dilithioamide **4a** with ketones and aldehydes,[4] **4a** was condensed with benzonitrile to form imine **5a**, but the accompanying cyclization to give the amine **6a** was not then recognized. The ring–chain product was hydrolyzed with refluxing hydrochloric acid to form *o*-benzoylbenzoic acid, which might have arisen from either imine **5a** or amine **6a**; these conditions, which effected hydrolysis of not only the imine or amine group but also that of the carboxamide group, were much more vigorous than those employed in the present investigation (see above).

SCHEME II



Similarly, dilithiosulfonamides **10a,b** were condensed with benzonitrile to form imine sulfonamides **11a,b**, which entered into equilibrium with the cyclic amine sulfonamides **12a,b** as evidenced by their condensations with benzaldehyde to give the benzal derivatives **13a,b**, respectively; also, the cyclic amine **12a** reacted with ethanol in the presence of acid to afford the ether sulfonamide **14** (Scheme II). The dilithiosulfonamides **10a,b** were prepared from the corresponding N-substituted benzenesulfonamides and *n*-butyllithium.[5]

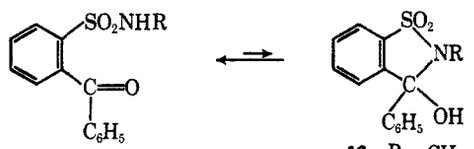
The equilibrium between the imine **11a** and the cyclic amine **12a** was evidently far on the side of the latter compound; thus the nmr spectrum of the ring–chain product showed signals for the two amino protons of **12a**; also the ir spectrum exhibited a NH_2 peak. However, the equilibrium between imine **11b** and cyclic amine **12b** appeared to be on the side of the former compound. Thus, although the nmr was somewhat equivocal, the infrared spectrum of this ring–chain product obtained under most conditions showed absorption peaks for both the primary amino and the amide imino groups. In one experiment, essentially pure cyclic amine **12b** was isolated through its hydrochloride salt but, on standing in solution in $CDCl_3$ (nmr solvent), more than half of **12b** appeared to undergo isomerization to form imine **11b** as evidenced by the changes in the ir and nmr spectra. Moreover, condensation of the ring–chain product containing **12b** with benzaldehyde occured much more slowly than that of the ring–chain product containing **12a** (see Scheme II); this is in line with the conclusion that the former equilibrium mixture consisted of relatively less of the cyclic amine.

The mechanism of conversion of amine **12a** to ether **14** may be considered to involve the formation of inter-

(5) See H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968).

mediates analogous to **8** and **9** and reaction of the analog of the carbonium ion **9** with ethanol instead of with water. There is a possibility, however, that ether **14** arose from imine **11a** by a mechanism analogous to that shown in eq 1, in which the carbonium ion reacted with ethanol and the resulting amino ether underwent protonation of the amino group followed by cyclization.

The ring–chain products **11a,b** and **12a,b** were hydrolyzed with aqueous acid to form the ring–chain systems **15a,b** and **16a,b**, the equilibrium of which was indicated by nmr and ir spectra to be far on the side of the ketones **15a,b**. The system **15a–16a** reacted with ethanol in the presence or absence of acid to form the ether. At least in the reaction catalyzed by acid, the mechanism would presumably involve the intermediate formation of a carbonium ion analogous to **9**.



15a, R = CH_3
b, R = C_6H_5 **16a**, R = CH_3
b, R = C_6H_5

The ether **14** was best prepared from the amine **12a** and commercial absolute ethanol by means of hydrogen chloride gas, with which the yield of pure **14** was 85% (see Scheme II). When a catalytic amount of 10% hydrochloric acid was used as catalyst, the ketone **15a** was mainly produced.

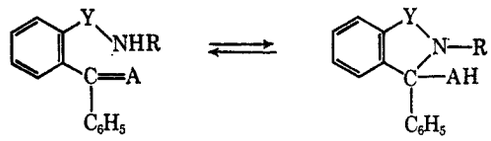
Although ether **14** was formed from ketone **15a** and commercial absolute ethanol, the product always contained an appreciable amount of the original ketone **15a**, from which **14** was difficult to separate. Relatively more of ether **14** was produced in the absence of acid than in the presence of this catalyst. Also, ether **14** underwent some cleavage in the presence of acid to regenerate the ketone **15a**, but no cleavage was observed in the absence of acid. These results are summarized in Table I in which are given the relative percentages of the ether **14** and ketone **15a** (as determined by infrared spectra) produced under various conditions.

TABLE I

PERCENTAGE COMPOSITION OF THE PRODUCT FROM KETONE **15** OR ETHER **14** WITH ETHANOL WITH AND WITHOUT ACID CATALYSTS

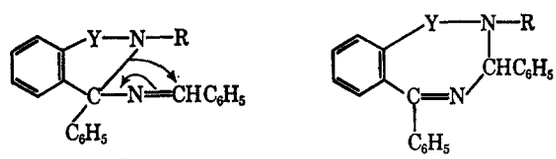
Starting compd	Catalyst	Time, hr	Temp, °C	—Product compn— % **14**	% **15a**
Ketone **15a**	10% HCl	45	25–30	67	33
Ketone **15a**	10% H_2SO_4	45	25–30	75	25
Ketone **15a**	10% H_2SO_4	0.2	78	50	50
Ketone **15a**	None	45	25–30	80	20
Ketone **15a**	None	12	8	55	45
Ether **14**	10% H_2SO_4	45	25–30	60	40
Ether **14**	None	45	25–30	100	0

It would appear from these results that the position of equilibrium in these ring–chain systems as represented by general formulas **17** and **18** is dependent on the nucleophilicity of the amide nitrogen in **17** and on the activity (acidity) of the tautomeric hydrogen in **18**. In support of the nucleophilicity factor, the equilibrium in the imine–amide system **17–18** (A = NH) was evidently farthest on the side of the cyclic amine **18** when Y was CO and R was methyl, but somewhat on the side of the open-chain imine **17** when Y was SO_2 and R was phenyl, where the nucleophilicity of the amide nitrogen would presumably be greatest and least, respectively. The equilibrium was in between these two cases when Y was CO and R was phenyl, and when Y was SO_2 and R was methyl, where the nucleophilicity of the amide nitrogen should also be intermediate. In support of the acidity factor, the equilibrium of the ketone–carbinols **17–18** (A = O) was far on the side of the ketone even when Y was CO and R was methyl where the nucleophilicity was relatively great.



17 **18**

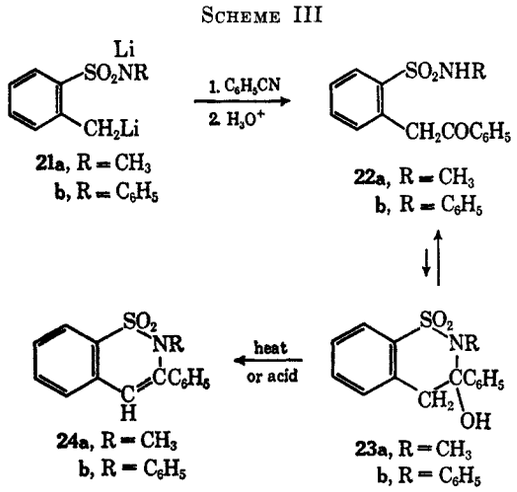
The cyclic primary amines **6a,b** and **12a,b** and the ether sulfonamide **14** appear to be new types of compounds; their straight-chain analogs would presumably be too unstable to be isolated. The benzal derivatives **7a,b** and **13a,b**, which may be represented by general formula **19**, also seem to be new types of products. There was a possibility that these derivatives might isomerize through a four-atom transition state to form the seven-atom ring **20**; the compounds isolated, however, apparently had the five-membered-ring structure **19**, since the nmr spectra showed a signal that may be attributed to the benzal proton in **19** but not one which might be ascribed to the methinyl proton in **20**.



19 **20**

Tautomerism Involving a Six-Membered Ring.—The dilithiosulfonamides **21a,b** were condensed with benzonitrile to form, on hydrolysis of the intermediate imine sulfonamides, the ketone sulfonamides **22a,b**, which entered into equilibrium with the carbinol sulfonamides **23a,b**, respectively; this was indicated by thermal dehydrations to give the unsaturated sulfonamides **24a,b**, respectively. Also the ring–chain products were dehydrated at lower temperatures by means of acid (Scheme III). The dilithiosulfonamides **21a,b**

SCHEME III

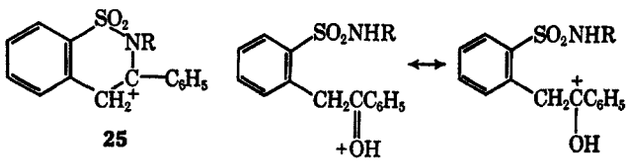


21a, R = CH_3
b, R = C_6H_5 **22a**, R = CH_3
b, R = C_6H_5

24a, R = CH_3
b, R = C_6H_5 **23a**, R = CH_3
b, R = C_6H_5

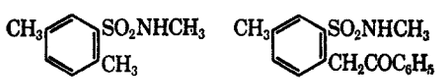
were prepared from the corresponding N-substituted *o*-toluenesulfonamides and *n*-butyllithium.[6]

The ring–chain products **22a–23a** and **22b–23b** were indicated by infrared spectra to consist almost entirely of the ketones **22a,b.** Although the thermal cyclization appears to require the presence of the carbinols **23a,b** in equilibrium, the acid-catalyzed cyclization might be explained, not only by protonation of the carbinol to form the carbonium ion **25** which loses a β proton, but also by protonation of the ketone to form the carbonium ion **26** which undergoes cyclization and proton-catalyzed dehydration. In the latter mechanism, the carbinols **23a,b** may be formed as intermediates.

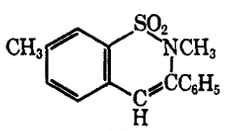


25 **26**

Similarly, the dilithio salt of sulfonamide **27** (prepared by means of *n*-butyllithium) was condensed with benzonitrile to form ketone sulfonamide **28,** which was cyclized by means of sulfuric acid to give the unsaturated sulfonamide **29.**

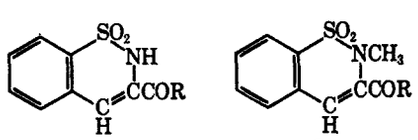


27 **28**



29

The unsaturated sulfonamides **24a,b** and **29,** which are 2,3-disubstituted 2H-1,2-benzothiazine 1,1-dioxides, appear to be the first examples of such benzothiazines having an aryl group at the 3 position and an alkyl or aryl group at the 2 position. The only earlier examples of this type of compound having a double bond at the 3,4 position have had an acyl group at the 3 position and hydrogen or a methyl group at the 2 position, as in **30** and **31,** respectively.[7]



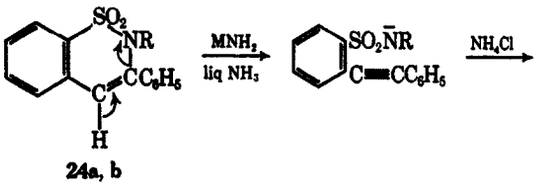
30 **31**

Interestingly, benzothiazines **24a,b** underwent intramolecular β elimination with potassium amide or sodium amide in liquid ammonia to form the acetylenic sulfonamides **32a,b,** respectively (eq 2, M = K or Na). Also, **24b** afforded a little of the ketone **22b** as by-product.

However, benzothiazine **29** failed to afford an appreciable amount of the corresponding acetylenic sulfonamide under similar conditions; instead polymeric material appeared to be produced.

(6) See H. Watanabe and C. R. Hauser, *J. Org. Chem.*, **33,** 4278 (1968).

(7) See H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, Jr. *ibid.*, **30,** 2241 (1965).



24a, b

(2)

32a, R = CH_3
b, R = C_6H_5

Experimental Section[8]

Condensation of Dilithio-N-methylbenzamide (4a) with Benzonitrile to Form Ring–Chain Product 5a–6a.—Dilithioamide **4a** was prepared under nitrogen atmosphere at 0° during 30 min from 0.05 mol of N-methylbenzamide in 80 ml of tetrahydrofuran (THF)[9] and 0.12 mol of *n*-butyllithium in 80 ml of hexane[10] and treated, after 30 min, with 0.10 mol of benzonitrile in 20 ml of THF by a modification of an earlier procedure.[4] After stirring for 30 min at 0° and for 30 min at room temperature, the reaction mixture was poured into stirred ice water. The mixture was filtered. The solid was collected, washed with 30 ml of ether, and dried to give 5.9 g of the ring–chain product **5a–6a,** mp 185–187°. The two layers of the filtrate were separated, and the organic layer was combined with ethereal extracts of the aqueous layer. The ethereal solution was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from benzene to give 2.5 g (total 7.4 g, 62%) of the ring–chain product **5a–6a,** mp 185–187° (lit.[4] mp 183–185°). This product appeared to consist almost exclusively of cyclic amine amide **6a:** ir ($CHCl_3$), 3700, 3620 (NH_2), and 1675 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.16 (s, 2, NH_2), 2.82 (s, 3, CH_3), and 7.38 ppm (m, 9.2, aromatic).

In a separate experiment, the reaction mixture was poured into a stirred aqueous ammonium chloride solution to give the ring–chain product in 50% yield.

Condensation of primary amine **6a** (1.0 g) with benzaldehyde (2.0 g) was effected in 20 ml of 95% ethanol by heating the solution on the steam bath for 3 hr. After concentrating and cooling, the product was collected and recrystallized from acetonitrile to give 1.2 g (87%) of benzalimine **7a:** mp 167–170°; ir (KBr), 1700 (C=O) and 1650 cm^{-1} (C=N); nmr ($CDCl_3$), δ 2.81 (s, 3, NCH_3), 7.4 (m, 14.4, aromatic), and 8.2 ppm (s, 1, =CH).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.95; H, 5.53; N, 8.58. Found: C, 81.26; H, 5.45; N, 8.41.

Condensation of Dilithiobenzanilide (4b) with Benzonitrile to Form Ring–Chain Product 5b–6b. A. Direct Neutralization of Reaction Mixture.—To a stirred solution of 0.05 mol of benzanilide in 80 ml of THF[9] was added 0.11 mol of *n*-butyllithium in 73 ml of hexane[10] at 0° to form dilithioamide **4b,** which was treated after 30 min with 0.05 mol of benzonitrile in 20 ml of THF.[9] The resulting, dark red solution was stirred for 30 min at 0°, and then neutralized by addition of aqueous ammonium chloride solution. The product was worked up as described above for **6a** to give 9.82 g (65%) of ring–chain product **5b–6b,** which appeared to consist largely of cyclic amine amide **6b:** mp 152–154°; ir (Nujol), 3360, 3300 (NH_2), and 1690 cm^{-1} (C=O); nmr ($CDCl_3$), δ 2.24 (s, 1.9,[11] NH_2), 7.35 ppm (m, 14.3, aromatic).

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.08; H, 5.31; N, 9.27.

Condensation of primary amine **6b** (1.0 g) with benzaldehyde (1.2 g) in 20 ml of 95% ethanol was effected essentially as described above for **6a** to give 1.1 g (85%) of benzalimine **7b:** mp 183–185°; ir (KBr), 1710 (C=O) and 1650 cm^{-1} (C=N);

(8) Melting points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and M-H-W Laboratories, Garden City, Mich. Ir spectra were produced on a Perkin-Elmer Infracord Model 137 and 237. Nmr spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane (δ = 0 ppm) as an internal standard.

(9) Freshly distilled from lithium aluminum hydride.

(10) Used as supplied by Foote Mineral Co., Exton, Pa.

(11) Determined with acetophenone (methyl protons) as internal standard.

nmr ($CDCl_3$), δ 7.3 (m, 19, aromatic) and 8.3 ppm (s, 1, CH=).

Anal. Calcd for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21. Found: C, 83.51; H, 5.15; N, 7.25.

Deamination of primary amine **6b** was effected by adding solution of 0.38 g (0.0055 mol) of sodium nitrite in 10 ml of water to a suspension of 1.5 g (0.005 mol) of finely powdered **6b** in 30 ml of 5 *N* hydrochloric acid at 0°. After allowing the suspension to warm to room temperature during 1 hr, the solid was collected, washed, dried, and recrystallized from acetonitrile–ethanol to give (on chilling for several days) 0.92 g (61%) of ketone amide **1**: mp 196.5–197.5° (lit.[3] mp 195°); ir (KBr), 3250 (broad, NH) and 1670 cm^{-1} (CO).

Hydrolysis of amine **6b** (or of imine **5b** in equilibrium) was effected by stirring a solution of 1 g of it in 30 ml of 50% aqueous acetic acid containing a few drops of concentrated sulfuric acid at 25–30° for 12 hr. Water (50 ml) was added and, after cooling, the resulting mixture was filtered. The solid was washed with 5% sodium bicarbonate solution, followed by water, and recrystallized from acetone–ethanol to give 0.65 g (65%) of ketone amide **1**, mp 194–196°, undepressed on admixture with **1** obtained from the deamination of **6b**.

B. Inverse Neutralization of the Reaction Mixture.—Dilithioamide **4b** was prepared and treated with benzonitrile as described under A. After stirring for 30 min at 0°, the reaction mixture was poured into stirred cold water and the layers were separated. The dark yellow organic layer was combined with an ethereal extract of the aqueous layer and, after drying (Drierite), the solution was allowed to evaporate at room temperature. The residue (grayish brown oil) was dissolved in 100 ml of dry ether, and the solution again was allowed to evaporate at room temperature. The residue, which consisted of a solid and an oil, was filtered. The solid was washed with 30 ml of ether to give, after recrystallization from cyclohexane–benzene, 3.69 g (25%) of imine amide **5b**: mp 128.5–129.5°; ir (Nujol), 3310–3190 (NH) and 1695 cm^{-1} (C=O); nmr ($CDCl_3$), δ 7.0–7.6 ppm (m, aromatic and NH).

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.03; H, 5.62; N, 9.26.

The filtrate and ethereal washing (see above) were combined and the solution was evaporated to give a thick oil. This oil was dissolved in ether, the solution was evaporated, and the process was repeated twice, but no more of imine **5b** was isolated. Instead, there was obtained, on recrystallization of the resulting solid from cyclohexane–benzene, 3.45 g (23%) of amine amide **6b**, mp 152–154° after recrystallization from acetonitrile.

On repeating the experiment and directly crystallizing the original grayish brown oil from hot ethanol, there was isolated only amine amide **6b**.

A 1.0-g sample of the isolated imine amide **5b** was dissolved in 20 ml of 95% ethanol and the solution was refluxed for 30 min. The solvent was removed, and the residue was recrystallized from acetonitrile to give 0.9 g (90%) of amine amide **6b**, mp and mmp 152–154°.

Also, the sample of imine amide **5b** in deuteriochloroform used in the nmr determination given above was allowed to stand at room temperature for several weeks, after which the nmr spectrum showed a peak at 2.24 ppm, which is ascribed to the primary amine hydrogen (see above).

Condensation of Dilithio-N-methylbenzenesulfonamide (10a) with Benzonitrile to Form Ring–Chain Product 11a–12a.—Dilithiosulfonamide **10a** was prepared under nitrogen at 0° from 0.025 mol of N-methylbenzenesulfonamide in 50 ml of THF[9] and 40 ml of 1.6 *M* *n*-butyllithium (0.0625 mole) in hexane[10] essentially as described previously. To the stirred, cold suspension was added, during 5 min, a solution of 4.13 g (0.04 mol) of benzonitrile in 20 ml of THF[9] to give a red-orange suspension. After 1 hr, 50 ml of 10–15% hydrochloric acid was added, and the two layers were separated. The acidic aqueous layer was combined with three acid extracts of the organic layer. The aqueous solution was carefully made basic with powdered potassium carbonate, and then saturated with sodium chloride. The resulting mixture was extracted three times with ether, and the extracts were combined. The ethereal solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure on the steam bath. The brown, viscous, liquid residue was stirred with a little ethanol, and the mixture was allowed to stand for 3 days. The resulting, large prismatic crystals of the ring–chain product **11a–12a** were collected, washed with a little ether, and dried in air. The filtrate (containing the ethereal washings) was evaporated and the process was repeated, to give more crystals (total 4.39 g, 64%) of **11a–12a**, mp 93.5–97° and 95–96.5° after recrystallization from ethanol. This product appeared to consist almost exclusively of the cyclic amine sulfonamide **12a**: ir (KBr), 3410 and 3340 (NH_2), 1300 and/or 1265 (SO_2), and 1150 cm^{-1} (SO_2); ir ($CHCl_3$), 3410 and 3335[12] cm^{-1} (NH_2); nmr ($CDCl_3$), δ 7.95–7.18 (m, 9.0, aromatic), 2.63 (s, A, NCH_3), and 2.48 ppm (broad, B, NH_2) (A + B = 4.8).

Anal. Calcd for $C_{14}H_{14}N_2SO_2$: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.38; H, 5.32; N, 9.82; S, 11.76.

The filtrate obtained after isolation of the ring–chain product (see above) was evaporated. The red-brown, viscous liquid residue was heated on the steam bath with 20 ml of 10% hydrochloric acid for 10 min. The resulting solid was collected, washed with water, and recrystallized from 95% ethanol to give 1.31 g (17%) of ether sulfonamide **14** (colorless prismatic cluster), mp 133–135.5° and 135.5–136° after further recrystallization. This by-product, which was shown to be identical (by mixture melting point, ir, and nmr) with ether **14** obtained on etherification of amine **12a** as described below, evidently arose on recrystallization of **12a** from ethanol.

Condensation of primary amine **12a** (1.10 g) with benzaldehyde (0.85 g) was effected in 24 ml of ethanol (refluxed for 3 hr). The solvent was removed under reduced pressure on the steam bath, and the residue (pale yellow solid) was dissolved in 40 ml of benzene. The solution was washed with saturated sodium bisulfite solution, followed by water, and dried ($MgSO_4$). The solvent was removed and the residue (fine crystals) was washed with ethanol and dried in air to give 1.25 g (86%) of benzalimine **13a**: mp 213–215° and 214–215.5° after recrystallization from acetone–ethanol; ir (KBr), 1635 (C=N), 1285 (SO_2), and 1195 and/or 1160 cm^{-1} (SO_2).

Anal. Calcd for $C_{21}H_{18}N_2SO_2$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.69; H, 4.92; N, 7.41.

Etherification of cyclic amine **12a** (0.30 g) with commercial absolute ethanol (30 ml) was effected by saturating the solution (cooled in an ice bath) with dry hydrogen chloride gas, and allowing the clear solution to stand in a stoppered flask at room temperature (25–30°) for 45 hr. The solvent was evaporated in a current of air under the hood. The residue (crystalline solid) was washed with water, dried, and recrystallized from 95% ethanol to give 0.28 g (85%) of ether sulfonamide **14**: mp 134–136° and 135.5–136.5° after another recrystallization; ir (KBr), 1300 (SO_2), 1165 and/or 1150 (SO_2), 1210 and/or 1055 cm^{-1} (C–O–C); nmr ($CDCl_3$), δ 8.03–7.08 (m, 9.0, aromatic), 3.85–2.73 (m, 2.1, CH_2), 2.64 (s, 2.9, NCH_3), and 1.52 ppm (t, 2.9, J = 7.0 cps, CCH_3); mol wt 305 (Rast) (calcd, 303).

Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62; S, 10.56. Found: C, 63.48; H, 5.61; N, 4.56; S, 10.41.

Hydrolysis of amine **12a** (or of imine **11a** in equilibrium) was effected by heating 0.50 g of it with 6 ml of 10% hydrochloric acid on the steam bath for 10 min. The resulting solid was collected, washed with water, and dried to give 0.49 g (96%) of ketone sulfonamide **15a** (leaflets): mp 116.5–117.5° and 119.5–120.5° after recrystallization from ethanol; ir (KBr), 3300 (NH), 1665 (CO), 1330 and/or 1267 (SO_2), and 1167 cm^{-1} (SO_2); ir ($CHCl_3$), 3320 cm^{-1} (NH); nmr ($CDCl_3$), δ 8.28–7.15 (m, 9.0, aromatic), 5.16 (broad, 0.9, NH), and 2.64 ppm (d, 2.8, J = 4.8 cps, NCH_3).

Anal. Calcd for $C_{14}H_{13}NSO_3$: C, 61.07; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.95; H, 4.79; N, 5.21; S, 12.19.

This ketone sulfonamide **15a** (mp 120–121.5°) was obtained in 86% yield from N-methylbenzenesulfonamide (0.025 mol) by condensing its dilithio derivative **10a** with benzonitrile and hydrolyzing the crude reaction product with hydrochloric acid. The two samples were shown to be identical.

Interconversion of Ketone 15a and Ether 14.—First, ten standard chloroform solutions were prepared employing authentic samples of **15a** and **14**. These solutions contained 10 mg/ml (in total) of the two components; the percentage composition of the two components in these solutions ranged from 0 to 100%. In order to obtain the calibration lines from these solutions,

(12) Calcd value, 3333 cm^{-1} $\nu_s = 345.53 + 0.876\nu_{as}$); see K. Nakanishi, "Infrared Absorption Spectroscopy" Holden-Day, Inc., San Francisco, Calif., 1962; L. J. Bellamy and R. L. Williams, *Spectrochim. Acta.*, **9**, 341 (1957).

the absorbance of peaks at 3320 and 1088 and/or 980 cm^{-1} (0.5–0.6-mm sodium chloride window cells being employed) were used for **15a** and **14**, respectively; the Lambert–Beer's law was satisfactory for these concentrations.

A sample of ketone sulfonamide **15a** or ether **14** was treated with ethanol in the presence or absence of acid to give a mixture consisting of **15a** and **14**. A chloroform solution (10 mg/ml) of the product mixture was prepared and the percentage composition of **15a** and **14** was determined by comparison of the absorbance at the indicated peaks with that of the calibration lines. In Table I are summarized the results obtained under various conditions. The details are described below.

Cyclization of ketone sulfonamide **15a** (0.50–0.75 g) with ethanol (20–30 ml) was effected in the presence of 10% hydrochloric or sulfuric acid (0.1 ml), or absence of the acid, by allowing the clear solution to stand for 45 hr at room temperature in a stoppered flask, or by refluxing for 0.2–12 hr (see Table I) The solvent was evaporated in a current of air under a hood. The solid residue was collected, washed with water, and dried to give a mixture (0.49–0.76 g) of **15a** and **14**, mp 93–120°; the percentage composition was determined as described above.

Attempt to cyclize ketone sulfonamide **15a** (0.5 g) with ethanol (100 ml) in the presence of hydrogen chloride (45 hr) was unsuccessful, and 76% of the starting compound was recovered.

Ring opening of ether sulfonamide **14** (0.30 g) was effected with ethanol (10 ml) containing 10% sulfuric acid (0.1 ml). After standing at room temperature for 45 hr, the reaction mixture was worked up to give a crystalline mixture (0.28 g) of **15a** and **14**, mp 94–120°; the percentage composition was determined as described above.

An attempt to open the ring of **14** (0.30 g) in 88% aqueous ethanol (10 ml) without acid was unsuccessful and 93% of the starting compound was recovered.

Ring opening and etherification of cyclic amine **12a** (0.30 g) was effected with ethanol (10 ml) in the presence of 10% hydrochloric acid (2.4 ml) by heating on the steam bath for 10 min. The mixture gave, on work-up, a crystalline mixture of ketone sulfonamide **15a** and ether sulfonamide **14**, the percentage composition of which was 67 and 33%, respectively (see above method).

Condensation of Dilithio-N-phenylbenzenesulfonamide (10b) with Benzonitrile to Form Ring–Chain Product 11b–12b.—Dilithiosulfonamide **10b** was prepared from 0.025 mol of N-phenylbenzenesulfonamide in 100 ml of THF[9] and 40 ml (0.0625 mol) of 1.6 *M* *n*-butyllithium in hexane,[10] and condensed with 0.04 mol of benzonitrile in 40 ml of THF[9] essentially as described above for dilithiosulfonamide **10a**. The viscous, liquid residue obtained on evaporation of the solvent from the ethereal solution of the product was stirred with a little ether and the mixture was allowed to stand overnight. The resulting prismatic crystals were collected, washed with a little ether, dried in air, and combined with more crystals isolated from the filtrate. The crude product was triturated with hot ether to remove yellow material and to give 5.36 g (64%) of the ring–chain product **11b–12b**, mp 142–143.5° and 141.5–143° after recrystallization from methanol. The product appeared to consist mainly of imine **11b** but also of some amine **12b**: ir (KBr), 3395 and 3325 (NH_2), 3260 (NH), 1275 (SO_2), and 1170 and/or 1150 cm^{-1} (SO_2); ir ($CHCl_3$), 3420 and 3340[13] (NH_2), and 3280 cm^{-1} (NH); nmr ($CDCl_3$), δ 8.10–7.00 ppm (m, aromatic and NH); another nmr of the same sample ($CDCl_3$) showed δ 8.10–6.55 (m, A = 15.3, aromatic and NH) and 2.31 ppm (broad, B = 0.7, NH_2) (A + B = 16.0).

Anal. Calcd for $C_{19}H_{16}N_2SO_2$: C, 67.83; H, 4.79; N, 8.33; S, (9.53. Found: C, 67.51; H, 4.90; N, 8.45; S, 9.81.

A sample of this product (mp 141.5–143°) was dissolved in ethanol, and the solution (cooled in an ice bath) was treated with concentrated hydrochloric acid. The mixture was evaporated overnight in a current of air under a hood. The solid residue was collected, washed with a little water, and dried to give prismatic crystals of apparently the hydrochloride salt of cyclic amine **12b**: mp 195–198° dec; ir (KBr), 3070 and 2850 (broad, primary ammonium salt), 1660 and 1530 (NH_3), 1350 and/or 1325 (SO_2), and 1155 cm^{-1} (SO_2).

Anal. Calcd for $C_{19}H_{17}N_2SO_2Cl$: N, 7.51; Cl, 9.51. Found: N, 7.44; Cl, 9.43.

(13) Calcd value, 3341 cm^{-1}; see ref 12.

When a solution of this salt in ethanol was made basic with sodium carbonate solution and the solvent was removed, the residue apparently consisted of cyclic amine **12b**; the sample melted at 127–128°, solidified at 129–130°, and then melted again at 141.5–143.5°; ir (KBr), 3400 and 3330 (NH_2), 1280 (SO_2), and 1177 and/or 1157 cm^{-1} (SO_2); ir ($CHCl_3$), 3415 and 3340[13] cm^{-1} (NH_2); nmr ($CDCl_3$), δ 8.10–6.92 (m, A = 14.7, aromatic) and 2.42 ppm (broad, B = 1.3, NH_2) (A + B = 16.0).

Anal. Calcd for $C_{19}H_{16}N_2SO_2$: N, 8.33. Found: N, 8.17.

After standing for 1 week, again the nmr spectrum of this solution was taken, but the 2.42-ppm signal had disappeared. The solution was then evaporated to give imine **11b**: mp 140–143°; ir (KBr), 3270 (NH), 1340 and/or 1320 (SO_2), and 1150 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 8.00–7.00 ppm (m, aromatic and NH).

Condensation of imine–amine **11b-12b** (1.01 g) with benzaldehyde (0.74 g) was effected in 24 ml of ethanol (refluxed for 24 hr). The solvent was removed under reduced pressure on the steam bath, and the residue (yellow viscous liquid) was stirred with a little ether and left to stand in a current of air under a hood. The separated solid was collected, washed with a little ether, and dried in air. The filtrate (and the ethereal washings) was evaporated to give more of the solid which was collected to give a total of 0.91 g (71%) of benzalimine **13b**, mp 145–148°, and 0.86 g (67%) of fine prismatic crystals: mp 147–149° after recrystallization from acetone–ethanol; ir (KBr), 1638 (C=N), 1304 (SO_2), and 1175 cm^{-1} (SO_2); nmr (acetone-d_6), δ 8.59 (s, 0.9, =CH) and 8.20–6.34 ppm (m, 19.0, aromatic).

Anal. Calcd for $C_{26}H_{20}N_2SO_2$: C, 73.56; H, 4.75; N, 6.60. Found: C, 73.37; H, 4.92; N, 6.51.

When a mixture of the same composition of the reactants was refluxed for 3 hr and then worked up, only the starting ring–chain compound **11b–12b** was recovered (72% recovery).

Hydrolysis of imine–amine **11b-12b** (0.5 g) was effected by refluxing with 20 ml of 10% hydrochloric acid for 1.5 hr. The resulting solid was collected, washed with water, and dried to give 0.48 g (96%) of ketone sulfonamide **15b** (fine prismatic crystals): mp 144–145.5° after recrystallization from ethanol (lit.[14] mp 143–145°); ir (KBr), 3240 (NH), 1620 (CO), 1335 and/or 1227 (SO_2), and 1160 cm^{-1} (SO_2); ir ($CHCl_3$), 3285 cm^{-1} (NH); nmr ($CDCl_3$), δ 8.05–6.92 ppm (m, aromatic and NH).

Anal. Calcd for $C_{19}H_{15}NSO_3$: C, 67.64; H, 4.48; N, 4.15; S, 9.50. Found: C, 67.37; H, 4.56; N, 4.17; S, 9.84.

This ketone sulfonamide **15b** (recrystallized from 95% ethanol), mp 145–147°, was obtained in 58% yield from N-phenylbenzenesulfonamide (0.025 mol) by condensing its dilithio derivative **10b** with benzonitrile and hydrolyzing the crude reaction product with hydrochloric acid. This product was shown to be identical with that obtained from hydrolysis of the imine–amine **11b–12b** (see above).

Condensation of Dilithio-N-methyl-*o*-toluenesulfonamide (21a) with Benzonitrile to Form Ketone Sulfonamide 23a. Cyclodehydration to Give Benzothiazine 24a.—Dilithiosulfonamide **21a** was prepared under nitrogen at 0° from 0.02 mol of N-methyl-*o*-toluenesulfonamide in 70 ml of THF[9] and 0.046 mol (30 ml) of 1.6 *M* *n*-butyllithium in hexane[10] essentially as described previously and treated with 0.026 mol of benzonitrile in 30 ml of THF.[9] After stirring for 1 hr, the red-orange reaction mixture was hydrolyzed with dilute hydrochloric acid.[15] The resulting mixture was worked up to give, after recrystallization from methanol, a total of 4.08 g (71%) of ring–chain product **22a–23a** (prismatic crystals), mp 149–150.5°; the analytical sample (glittering leaflets) melted at 150–151°. This product appeared to consist almost exclusively of *o*-benzoylmethyl-N-methylbenzenesulfonamide (**22a**): ir (KBr), 3290 (NH), 1680 (CO), 1420 and/or 1410 (SO_2), and 1150 cm^{-1} (SO_2); nmr (acetone-d_6), δ 8.20–7.30 (m, 9.0, aromatic), 6.20 (broad, NH), 4.90 (s, 1.6, CH_2), and 2.55 ppm (d, 2.4, J = 5.4 cps, NCH_3).

Anal. Calcd for $C_{15}H_{15}NSO_3$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.39; H, 5.51; N, 4.83.

Thermal cyclodehydration of **22a** (1.0 g) was effected by heating it under nitrogen in a round-bottomed flask on a Wood's

(14) I. Remsen and A. P. Saunders, *Am. Chem. J.*, **17**, 359 (1895).

(15) An attempt to isolate the intermediate imine–sulfonamide by careful decomposition of the reaction mixture with water was unsuccessful, the ketone-sulfonamide **22a** being obtained.

metal bath at 220–230° for 7 hr. The molten mass was allowed to stand at room temperature for a few days. The resulting solid was recrystallized from methanol to give 0.87 g (92%) of 2-methyl-3-phenyl-2H-1,2-benzothiazine 1,1-dioxide (**24a**): mp 120.5–122°; ir (KBr), 1610 (C=C), 1340 and/or 1330 (SO_2), 1190 and/or 1170 (SO_2), 854 and 831 cm^{-1} (=CH); nmr ($CDCl_3$), δ 8.10–7.20 (m, 9.4, aromatic), 6.70 (s, 0.7, vinyl), and 2.96 ppm (s, 3.0, NCH_3).

Anal. Calcd for $C_{15}H_{13}NSO_2$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.41; H, 4.79; N, 5.04.

Acid-catalyzed cyclodehydration of **22a** (3.0 g) was effected was dissolving it in 30 ml of concentrated sulfuric acid at 0°. After 30 min, the solution was poured onto 100 g of crushed ice. The resulting white precipitate was collected, washed with water, dried, and recrystallized from methanol to give 2.72 g (97%) of benzothiazine **24a**, mp 120.5–122°.

Acid-catalyzed cyclodehydration of **22a** (1.0 g) was also accomplished by refluxing a solution of it in 50 ml of benzene with 0.05 g of *p*-toluenesulfonic acid (hydrate) for 24 hr. The cooled reaction mixture was shaken with sodium carbonate solution and then with saturated sodium chloride solution. The benzene solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure (steam bath). The solid residue was recrystallized from methanol to give 0.88 g (94%) of benzothiazine **24a**, mp 118–120°.

Samples of **24a** obtained as fine needles by these three methods of cyclodehydration were shown to be identical by mixture melting points and ir spectra.

Condensation of Dilithio-N-phenyl-*o*-toluenesulfonamide (21b) with Benzonitrile to Form Ketone Sulfonamide 23b. Cyclodehydration to Give Benzothiazine 24b.—Dilithiosulfonamide **21b** was prepared from 0.02 mole of N-phenyl-*o*-toluenesulfonamide and 0.046 mol of *n*-butyllithium and treated with 0.026 mol of benzonitrile as indicated above for **21a**. The reaction mixture was hydrolyzed with dilute hydrochloric acid[15] and worked up to give, after recrystallization from acetone–methanol, a total of 5.30 g (76%) of ring–chain product **22b–23b**, mp 169.5–171°. This product appeared to consist almost exclusively of *o*-benzoylmethyl-N-phenylbenzenesulfonamide (**22b**): ir (KBr), 3265 (NH), 1675 (CO), 1320 (SO_2), and 1145 cm^{-1} (SO_2); nmr (acetone-d_6), δ 8.27–7.00 (m, 15.0, aromatic and NH) and 4.88 ppm (broad, 2.0, CH_2).

Anal. Calcd for $C_{20}H_{17}NSO_3$: C, 68.35; H, 4.88; N, 3.99. Found: C, 68.67; H, 4.80; N, 3.92.

Thermal cyclodehydration of **22b** (1.0 g) was effected by heating it at 240–250° for 4 hr as described above for **22a** to give, after recrystallization of the product from benzene (decolorized with activated charcoal), 0.92 g (97%) of 2,3-diphenyl-2H-1,2-benzothiazine 1,1-dioxide (**24b**): mp 240–241°; ir (KBr), 1610 (C=C), 1340 (SO_2), 1170 (SO_2), 850 and 832 cm^{-1} (=CH).

Anal. Calcd for $C_{20}H_{15}NSO_2$: C, 72.05; H, 4.54; N, 4.20. Found: C, 72.21; H, 4.50; N, 4.10.

Acid-catalyzed cyclodehydration of **22b** (1.0 g) was accomplished in refluxing benzene with a catalytic amount of *p*-toluenesulfonic acid as described above for **22a** to give, after recrystallization from benzene, 0.89 g (94%) of **24b**, mp 238–239.5°.

Samples of **24b** obtained as fine crystals by these two methods of cyclodehydration were shown to be identical by mixture melting points and ir spectra.

N-Methyl-2,5-dimethylbenzenesulfonamide (**27**) (mp 90–91°) was prepared in 88% yield from *p*-xylenesulfonyl chloride and methylamine (gas) in ether: ir (KBr), 3335 (NH), 1305 and 1155 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 7.79 (s, 1.0, 6-H), 7.21 (s, 2.0, 3- and 4-H), 5.10 (broad, 0.8, NH), 2.62 (d, A, J = 3.6 cps, NCH_3), 2.59 (s, B, 2-CH_3) (A + B = 6.0), and 2.36 ppm (s, 3.0, 5-CH_3).

Condensation of the Dilithio Salt of Sulfonamide 27 with Benzonitrile to Form Ketone 28. Cyclodehydration to Give Benzothianine 29.—N-Methyl-2,5-dimethylbenzenesulfonamide (**27**) (0.05 mol) was converted to its dilithio salt with *n*-butyllithium (0.11 mol), and this salt was condensed with benzonitrile (0.06 mol) essentially as indicated above for the condensation of dilithiosulfonamide **21a** with this nitrile. The product obtained on hydrolysis of the reaction mixture with hydrochloric acid was recrystallized from acetone–methanol to give 14.0 g (92%) of 2-benzoylmethyl-5-methyl-N-methylbenzenesulfonamide (**28**): mp 150–151.5°; ir (KBr), 3300 (NH), 1675 (CO), 1310 (SO_2), and 1150 cm^{-1} (SO_2).

Anal. Calcd for $C_{16}H_{17}NSO_3$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.13; H, 5.64; N, 4.55.

Cyclodehydration of **28** (14.0 g) was effected by means of cold sulfuric acid (70 ml) as described above for **22a**. The product was recrystallized from acetone–methanol to give 12.93 g (98%) of 2,7-dimethyl-3-phenyl-2H-1,2-benzothiazine 1,1-dioxide (**29**) (fine prismatic crystals): mp 183–184°; ir (KBr), 1600 (C=C), 1340 and/or 1330 (SO_2), and 1155 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 7.85–7.33 (m, 8.0, aromatic), 6.70 (s, 1.1, vinyl), 2.98 (s, 3.0, NCH_3), and 2.45 ppm (s, 2.9, 7-CH_3).

Anal. Calcd for $C_{16}H_{15}NSO_2$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.29; H, 5.30; N, 4.86.

β Elimination of Benzothiazines with Alkali Amides to Form Acetylenic Products. A. Conversion of 24a to 32a.—To a stirred suspension of 0.018 mol of potassium amide, prepared from 0.7 g (0.018 g-atom) of potassium in 250 ml of liquid ammonia, was added 1.62 g (0.006 mole) of benzothiazine **24a** through a rubber tubing from an erlenmayer flask (under anhydrous condition). After 3 hr, the orange-brown suspension was decomposed with 1.0 g of ammonium chloride. The liquid ammonia was evaporated, and 200 ml of ether was added. The mixture was refluxed for several minutes, then cooled and filtered to remove some solid. After the solid was washed with ether, the ethereal filtrate containing the washings was dried ($MgSO_4$), and the solvent was removed. The residue (yellow sticky liquid) was dissolved in a little chloroform, chromatographed on alumina packed with chloroform, and then eluted with this solvent. The first fraction gave, on evaporation of the solvent, 0.04 g of unidentified material. The second fraction gave 0.93 g (57%) of *o*-(N-methylsulfamyl)tolane (**32a**) as a faint yellow sticky liquid: ir (neat), 3340 (NH), 2210 (C≡C), 1425 and 1162 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 8.15–7.20 (m, 9.2, aromatic), 5.10 (broad, 0.9, NH), and 2.59 ppm (d, 3.0, J = 5.3 cps, NCH_3).

Anal. Calcd for $C_{15}H_{13}NSO_2$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.66; H, 5.07; N, 5.05.

The third fraction gave 0.05 g of a mixture of **32a** and unidentified compound by ir.

Similarly, the reaction was effected employing 0.006 mol of benzothiazine **24a** and 0.009 mol of potassium amide. After 2 hr, the reaction mixture was worked up to give 0.60 g (38%) of the recovered starting compound of **24a** and 0.77 g (48%) of tolane **32a**. Also, 0.05 g of a mixture of **32a** and unidentified compound was obtained.

Likewise, the reaction was effected with 0.002 mol of **24a** and 0.004 mol of sodium amide (stirred for 1 hr). The crude product was indicated by ir to contain acetylenic compound **32a** and recovered starting compound of **24a**.

B. Conversion of 24b to 32b.—This reaction was effected essentially as described above under A employing 0.005 mol of benzothiazine **24b** and 0.015 mol of sodium amide. After 2 hr, the reaction mixture was decomposed with ammonium chloride and worked up. The ethereal solution of the product was washed with water and dried ($MgSO_4$). The solvent was removed. The solid residue was recrystallized from methanol to give 1.30 g (78%) of *o*-(N-phenylsulfamyl)tolane (**32b**, fine prismatic crystals): mp 103–106.5° and 105–106.5° as rhombic plates after another recrystallization from methanol; ir (KBr), 3280 (NH), 2205 (C≡C), 1335 and/or 1325 (SO_2), 1165 and/or 1155 cm^{-1} (SO_2); nmr ($CDCl_3$), δ 8.20–6.95 ppm (m, aromatic and NH).

Anal. Calcd for $C_{20}H_{15}NSO_2$: C, 72.05; H, 4.54; N, 4.20. Found: C, 71.96; H, 4.36; N, 4.07.

The aqueous solution (water washings) was acidified with concentrated hydrochloric acid and heated on the steam bath. The resulting solid was collected, washed with water, and dried in air to give 0.04 g (2%) of *o*-benzoylmethyl-N-phenylbenzenesulfonamide (**22b**), mp 165–168° and 168–170° as fine crystals after recrystallization from acetone–methanol; admixture with a sample of ketone sulfonamide **22b** obtained as described above showed no depression (mmp 168.5–170.5°) and the ir spectra of the two samples were identical.

Similarly, the reaction was carried out with 0.005 mol of **24b** and 0.01 mol of potassium amide. After 1.5 hr, the mixture was decomposed with ammonium chloride and worked up to give 1.36 g (81%) of tolane **32b** and 0.24 g (14%) of ketone sulfonamide **22b**.

Also, the reaction was effected with 0.005 mol of **24b** and 0.0065 mol of sodium amide (stirred for 3 hr) and worked up

to give, on fractional crystallization from methanol, 0.46 g of the recovered starting compound **24b** and 0.95 g (57%) of tolane **32b**.

C. Attempted Conversion of 29 to an Acetylenic Product.—When benzothiazine **29** was treated with 3 mol equiv of sodium amide in liquid ammonia for 2 hr essentially as described above under A, a black suspension was produced, but, on work up of the reaction mixture, polymeric material was obtained and 40% of the starting compound **29** was recovered.

In an attempt to determine whether the 7-methyl hydrogen of benzothiazine **29** was ionized, 0.005 mol of **29** was treated with 0.0075 mol of potassium amide in liquid ammonia followed, after 1 hr, by 0.0065 mol of benzyl chloride. However, none of the benzyl derivative of **29** was isolated; instead, intractable polymeric material was obtained, and 37% of the **29** was recovered.

Registry No.—Benzonitrile, 100-47-0; **4b**, 18963-14-9; **5b**, 18963-15-0; **6b**, 18963-16-1; **7b**, 18963-17-2; **10a**, 18963-18-3; **10b**, 18963-19-4; **11b**, 18963-20-7; **12a**, 18963-21-8; **12b**, 18963-22-9; **12b HCl**, 18963-23-0; **13a**, 18963-24-1; **13b**, 18963-25-2; **14**, 18963-26-3; **15a**, 18963-27-4; **15b**, 18963-28-5; **21a**, 18963-29-6; **21b**, 18963-30-9; **22a**, 18963-31-0; **22b**, 18963-32-1; **24a**, 18963-33-2; **24b**, 18963-34-3; **27**, 6326-21-2; **28**, 18963-36-5; **29**, 18963-37-6; **32a**, 18963-38-7; **32b**, 18963-39-8.

Catalysis and Inhibition of the Hydrolysis of N-Methylphthalimide by Imidazole[1a]

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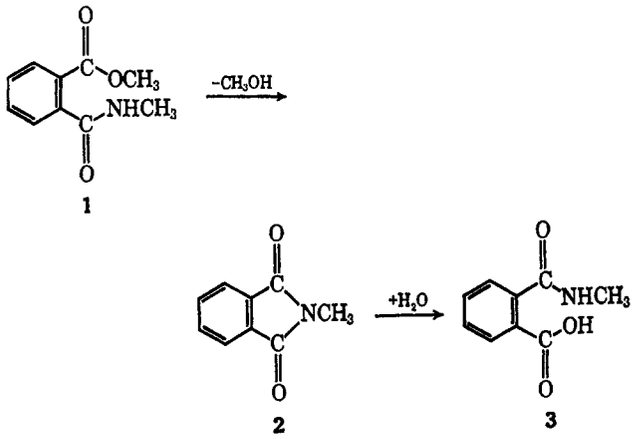
Imidazole was found to catalyze the hydrolysis of N-methylphthalimide (to N-methylphthalamic acid) at pH values of 6.4 and 7.2, and inhibit the hydrolysis of N-methylphthalimide at pH 9.7. While HPO_4^{2-} was observed to catalyze the hydrolysis of N-methylphthalimide, it did not inhibit the hydrolysis of N-methylphthalimide. The second-order rate constants (k_6) for the imidazole and HPO_4^{2-}-catalyzed hydrolysis of N-methylphthalimide were found to be 2×10^{-5} and 1.3×10^{-5} sec^{-1} M^{-1}, respectively. These results are taken as kinetic evidence for the reversible addition of imidazole to N-methylphthalimide to form a tetrahedral addition compound which is relatively unreactive toward hydroxide ion. The dissociation constant for this addition compound estimated from the inhibition of the hydrolysis of N-methylphthalimide by imidazole (1.3 M) was in reasonable agreement with the values estimated from the perturbation of the ultraviolet spectrum of N-methylphthalimide by imidazole (1.5–1.7 M). When deuterium oxide was used in place of water, imidazole and HPO_4^{2-} became less efficient catalysts. Isotope effects of 1.4 and 2.3 were observed for the imidazole and HPO_4^{2-}-catalyzed hydrolysis of N-methylphthalimide. This result and the similar catalytic efficiencies observed for imidazole and HPO_4^{2-} suggest that imidazole and HPO_4^{2-} are general base catalysts for the hydrolysis of N-methylphthalimide.

The neighboring amide group is the only functional group present in hydrolytic enzymes which has also been shown to catalyze substantially the hydrolysis of both alkyl esters and amides in low molecular weight organic compounds.[2] Alkyl esters and amides with neighboring amide groups hydrolyze through an imide intermediate. Very often the catalytic effect of the amide group is reduced, because hydrolysis of the imide intermediate is slow. For example, at 25.9°, the second-order rate constant for the hydroxide ion catalyzed cyclization of ester **1** to N-methylphthalimide (**2**) is 12,400 sec^{-1} M^{-1},[2h] while the second-order rate constant for the hydroxide ion catalyzed hydrolysis of **2** to N-methylphthalamic acid (**3**) is 24 sec^{-1} M^{-1}.[3] Because of the possible involvement of amide groups in enzymically catalyzed reactions, we have investigated the effect of



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(2) For examples of the participation of amide groups in the hydrolysis of esters and amides, see (a) J. E. H. Hancock and R. P. Linstead, *J. Chem. Soc.*, 3490 (1953); (b) E. Sondheimer and R. W. Holley, *J. Amer. Chem. Soc.*, **76**, 2467 (1954); **79**, 3767 (1957); (c) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (d) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. Soc. Chim. Belges*, **69**, 616 (1960); (e) P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); (f) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Amer. Chem. Soc.*, **84**, 2421 (1962); (g) A. J. Adler, G. D. Fasman, and E. R. Blout, *ibid.*, **85**, 90 (1963); (h) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (i) M. T. Behme and E. H. Cordes, *ibid.*, **29**, 1255 (1964); (j) J. Brown, S. C. K. Su, and J. A. Shafer, *J. Amer. Chem. Soc.*, **88**, 4468 (1966).

(3) (a) Although the rate of hydrolysis of **1** is severely limited by the hydrolysis of **2**, in alkaline solutions ester **1** hydrolyzes much faster than methyl benzoate; M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey [*J. Amer. Chem. Soc.*, **83**, 4193 (1961)] reported a value of 0.0232 sec^{-1} M^{-1} for the hydroxide ion catalyzed hydrolysis of methyl benzoate at 24.8° in 33.3% dioxane–water. (b) The value of 24 sec^{-1} M^{-1} is an average value extrapolated to zero buffer concentration at 25° in the pH range of 6.4–9.7. See Experimental Section.