[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

Some Derivatives of Tetrahydrothiapyran as Possible Local Anesthetics

BY CHARLES BARKENBUS AND JAMES A. WUELLNER[1]

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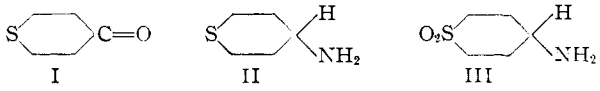
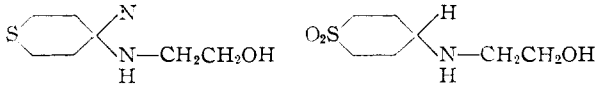
The preparation of 4-aminothiapyran is described and by it the thiapyranyl group has been incorporated into two structures widely used as local anesthetics. Conversion of these compounds to their corresponding sulfones was attempted, but this was not accomplished owing to certain interesting properties of the amino sulfones. Possible causes for these abnormal properties are suggested.

The preparation of tetrahydro-1,4-thiapyrone (I) offers a convenient way of entering the thiapyran series.[2] It was found that 4-aminotetrahydrothiapyran (II) could be made from this ketone by the reduction of its oxime with sodium and alcohol in reasonable over-all yields. Acid reducing agents failed to give the amine while catalytic reduction was impossible because of the sulfur. The Leuckart reduction using formamide caused profound decomposition with evolution of hydrogen sulfide. This amine is a weak base (K_b 1.86 × 10^{-5}) and undergoes the usual amine reactions.



I II III

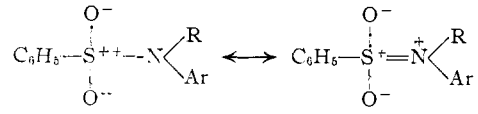


IV V

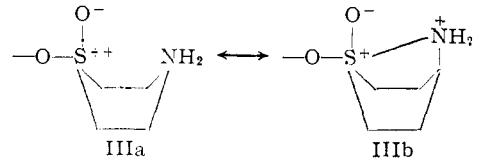
4-Aminotetrahydrothiapyran-1-dioxide (III), the sulfone of II, was prepared by the reduction of the oxime of tetrahydro-1,4-thiapyran-1-dioxide with hydrogen and Raney nickel in good yields. It was made also by the oxidation of an amide of II followed by hydrolysis. This amine is extremely soluble in water and is a weaker base than amine II (K_b 1.61 × 10^{-7}).

The amine II reacted readily with ethylene chlorohydrin to give the expected 4-(2-hydroxyethylamino)-tetrahydrothiapyran (IV). The corresponding aminosulfone III however failed to react even under drastic conditions with ethylene chlorohydrin. 4-(2-Hydroxyethylamino)-tetrahydrothiapyran-1-dioxide (V) was made, however, by reductive alkylation of a mixture of tetrahydro-1,4-thiapyrone-1-dioxide and ethanolamine using Raney nickel and hydrogen at 1200 p.s.i.

It is rather surprising that the aminosulfone III should be such a weak base in comparison to the aminosulfide II and that it could not be alkylated like II under any condition with ethylene chlorohydrin. It does not seem reasonable that these marked differences can be attributed to an inductive effect of the sulfone group. Molecular models show that in the boat form the amine group of the aminosulfone III is very close to the sulfur atom. Recently Adams and Lundstrom[3] have postulated that one reason for restricted rotation of certain amines might be resonance of the type



Owing to the closeness of the sulfone sulfur and the amino nitrogen in the boat form of III one could postulate the possibility of resonance of a similar type in this compound as shown in IIIa and IIIb.



IIIa IIIb

This resonance would at least partially utilize the unshared pair of electrons of the nitrogen atom and would account for its weak basic properties. Alkylation of amines can be explained by the formation of a transient state produced by sharing of the unshared pair of electrons of the nitrogen atom with a carbonium ion. Resonance of this type then would interfere with alkylation. It might also be reasonable to expect some hydrogen bonding since this is possible with sulfone groups.[4] However, it is doubtful whether this type of bond would cause these abnormalities. Deactivation by intermolecular reaction is also a possibility. Naller[5] has observed that the hydroxyl group of 4-tetrahydrothiapyranol is extremely difficult to replace by chlorine. The above postulations could well apply to this compound.

The next step in the synthesis of the Procaine type of structure consisted in the esterification of the above alcohols with *p*-nitrobenzoyl chloride. This esterification proceeded normally with the hydrochloride of IV and the resulting *p*-nitro ester (VI) as its hydrochloride was reduced smoothly to β-(4-tetrahydrothiapyranylamino)-ethyl *p*-aminobenzoate hydrochloride (VII). By using the hydrochloride as suggested by Cope[6] no amide formation was observed.

When V was used as its hydrochloride no esterification took place with *p*-nitrobenzoyl chloride even under extreme conditions. However, if its free base was used the amide, N-(*p*-nitrobenzoyl)-N-(2-hydroxyethyl)-4-aminotetrahydrothiapyran-1-dioxide (VIII) was formed readily. This amide VIII could be reduced with stannous chloride to the amino amide IX. Some amides of this type rearrange to the ester in an acid medium[7] but this

(1) Abstracted from a portion of a dissertation submitted by James A. Wuellner to the Graduate School of the University of Kentucky in partial fulfillment of the requirements for the Ph.D. Degree, 1952.

(2) E. Fehnel and M. Carmack, THIS JOURNAL, **70**, 1813 (1948); C. Barkenbus and V. Midkiff, *J. Org. Chem.*, **16**, 232 (1951).

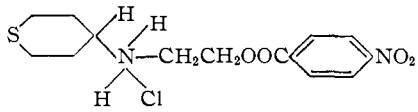
(3) R. Adams and K. Lundstrom, THIS JOURNAL, **76**, 5474 (1954).

(4) D. Barnard, J. Fabian and H. Koch, *J. Chem. Soc.*, 2442 (1949).

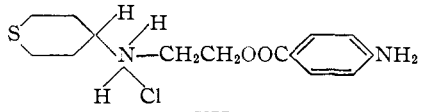
(5) R. Naller, *ibid.*, 2749 (1949).

(6) A. Cope and E. Hancock, THIS JOURNAL, **66**, 1448 (1944).

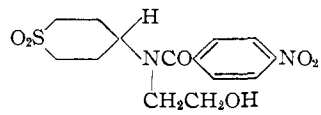
(7) T. Immediata and A. Day, *J. Org. Chem.*, **5**, 512 (1940).



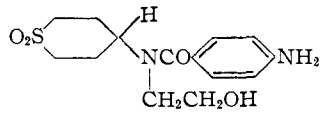
VI



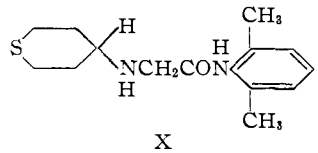
VII



VIII



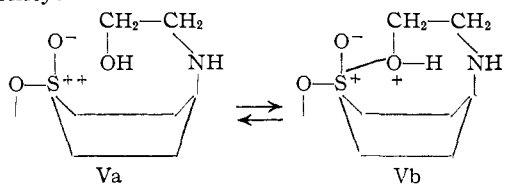
IX



X

amide failed to rearrange. No method was found to prepare the sulfone of VII.

The failure of V to be esterified with *p*-nitrobenzoyl chloride in contrast to its corresponding aminosulfide alcohol IV again shows the abnormal behavior of the aminosulfones. The fact that this aminosulfone alcohol forms an amide would indicate that the unshared pair of electrons of the nitrogen are reasonably active and, even though the explanation for the deactivation of the amino group in IX is valid, it would be hard to conceive how this would apply to the hydroxyl group of the alcohol. Molecular models of V show that the hydroxyethyl group can be very close to the sulfone sulfur atom. This could lead to resonance as postulated for the amino sulfone as shown in Va and Vb. The resonance form of the amino group also might contribute some to the over-all stability.



Va Vb

In preparing the Xylocaine type of structure 4-aminotetrahydrothiapyran was condensed with ω-chloro 2,6-dimethylacetanilide. This was accomplished with reasonable yields to give ω-(4-tetrahydrothiapyranylamino)-2,6-dimethylacetanilide hydrochloride (X).

The abnormal activity of 4-aminotetrahydrothiapyran-1-dioxide (X) toward alkylation prevented the preparation of the sulfone of X.

ω-(4-Tetrahydrothiapyranylamino)-2,6-dimethylacetanilide·HCl (X) produced local anesthesia of about the same duration and degree as Procaine but was somewhat more irritating. β-(4-Tetrahydrothiapyranylamino)-ethyl *p*-aminobenzoate·HCl (VII) was less active than Procaine and definitely more irritating. Neither one showed any anticonvulsant activity.[8]

Experimental[9]

4-Aminotetrahydrothiapyran (I).—A solution of 20 g. (0.152 mole) of tetrahydro-1,4-thiapyrone oxime in 500 ml. of absolute ethanol was heated to boiling in a two-liter round-bottomed flask on a water-bath. The flask was equipped with a 150-cm. reflux condenser of very wide bore (2.5 cm.). When the alcohol solution was boiling the water-bath was removed and 50 g. (2.2 gram atoms) of sodium cut in small pieces was added through the condenser as fast as possible and while still keeping the material in the flask.

When all the sodium had dissolved the mixture was cooled thoroughly in an ice–salt-bath and cautiously acidified with concentrated hydrochloric acid. About 300 ml. of acid was required. After acidification the solvent mixture was distilled with occasional additions of water to facilitate the distillation of ethanol. When all the ethanol had been removed the mixture was transferred to the flask of a continuous extract apparatus, made basic with concentrated alkali, and extracted with ether for a period of 24 hours. The ether extract was dried over anhydrous magnesium sulfate and the ether distilled. The crude brown residue was distilled under reduced pressure, the distillate being received directly in a second distilling flask cooled under a stream of cold water. The amine boiled at 51.8 to 53° (2 mm.). It crystallized in the receiver as white crystals melting at 33–34°, and weighed 6 g. (30%). It is very soluble in ether and water and darkens on prolonged standing even in the dark. *Anal.* Calcd. for $C_5H_{11}NS$: S, 27.35. Found: S, 27.41; K_b, 1.86×10^{-5}.

4-Acetamidotetrahydrothiapyran, m.p. 159.6°. *Anal.* Calcd. for $C_7H_{13}NOS$: S, 20.13. Found: S, 20.28.

4-Benzamidotetrahydrothiapyran, m.p. 119°. *Anal.* Calcd. for $C_{12}H_{15}NOS$: S, 14.49. Found: S, 14.55.

4-Benzenesulfonamidotetrahydrothiapyran, m.p. 94.4°. *Anal.* Calcd. for $C_{11}H_{15}NO_2S_2$: S, 24.90. Found: S, 24.97.

4-Acetamidotetrahydrothiapyran-1-dioxide.—To 8.5 g. (0.033 mole) of 30% hydrogen peroxide was added 5 g. (0.032 mole) of 4-acetamidotetrahydrothiapyran in 1-g. portions. The flask and its contents were shaken after each addition while cooling under running water. After all the amide had been added the mixture was shaken for five to ten minutes and then allowed to stand at room temperature for 2 hours. It was then evaporated to dryness on a steam-bath under a current of air. The residue was crystallized from a mixture of acetic acid and ether. The white crystalline solid melted with decomposition at 201.6–203.6°. The yield was 5.9 g. (65%). *Anal.* Calcd. for $C_7H_{13}NO_3S$: S, 16.77. Found: S, 16.75.

Tetrahydro-1,4-thiapyrone-1-dioxide Oxime.—Ten grams (0.086 mole) of tetrahydro-1,4-thiapyrone (I) was dissolved in 25 ml. of acetone and 25 ml. (0.22 mole) of 30% hydrogen peroxide was added in portions with shaking and cooling of the reaction mixture. After all the hydrogen peroxide had been added, the reaction mixture was shaken until it no longer evolved heat. It was then allowed to stand for at least 24 hours. The mixture was then evaporated to dryness on a steam-bath under a current of air. The crude sulfone which remained as a residue was dissolved in 200 ml. of water, 10 g. (0.144 mole) of hydroxylamine hydrochloride and 20 g. (0.147 mole) of sodium acetate trihydrate were added and the mixture refluxed for two hours. The solvent was removed by evaporation and the residue extracted repeatedly with hot acetone. The extracts were evaporated to dryness and the oxime recrystallized from methanol. The yield was 11 g. (80%) and the purified product melted with decomposition at 197.8°. *Anal.* Calcd. for $C_5H_9NO_3S$: S, 19.53. Found: S, 19.59.

4-Aminotetrahydrothiapyran-1-dioxide (III). **Procedure A.**—Five grams (0.055 mole) of 4-acetamidotetrahydrothiapyran-1-dioxide was hydrolyzed for five hours with 30 ml. of concentrated hydrochloric acid and 90 ml. of water. The mixture then was evaporated to dryness and the hydro-

(8) We are indebted to Dr. M. G. VanCampen of the Wm. S. Merrell Co. for evaluating the anesthetic activity of these compounds.

(9) All melting points are corrected.

chloride, which remained as residue, was purified by crystallization from a water–acetone mixture at 20°. The yield was 2.7 g. (70%) and the salt did not melt below 250°.

Ten grams (0.054 mole) of 4-aminotetrahydrothiapyran-1-dioxide hydrochloride was treated with an equivalent amount (3.02 g.) of potassium hydroxide in the minimum amount of water in order to liberate the free amine. The mixture then was evaporated nearly to dryness on a steam-bath and the drying completed in a vacuum desiccator. The dry residue was transferred to the thimble of a Soxhlet extractor and extracted with chloroform for 24 hours. After the chloroform extract had been dried over anhydrous magnesium sulfate and filtered from the drying agent, it was concentrated to a small volume (5–10 ml.), to which was added sufficient Skellysolve A to throw out the amine. The product then was purified by crystallization from a mixture of chloroform and Skellysolve A at −20°. The yield was 6.4 g. (80%). The purified amine melted at 85–86°. *Anal.* Calcd. for $C_5H_{11}NO_2S$: S, 21.64. Found: S, 21.70; K_b, 1.61×10^{-7}.

4-Aminotetrahydrothiapyran-1-dioxide. Procedure B.—Ten grams (0.061 mole) of tetrahydro-1,4-thiapyrone-1-dioxide oxime in 100 ml. of commercial absolute alcohol was hydrogenated over 1 g. of Raney nickel at a pressure of 1200 p.s.i. and a temperature of 40°. The duration of the hydrogenation was three hours. After filtering from the catalyst the solution containing the amine was saturated with hydrogen chloride gas. One hundred ml. of ether then was added and the mixture cooled to −20° to complete the precipitation of the hydrochloride. The salt was filtered and the amine obtained from it as under procedure A. The yield by this method was 5.4 g. (60%).

4-(2-Hydroxyethylamino)-tetrahydrothiapyran (IV).—Ten grams (0.086 mole) of 4-aminotetrahydrothiapyran (II) and 3.5 g. (0.043 mole) of ethylene chlorohydrin were refluxed in 150 ml. of dry benzene. The 4-aminotetrahydrothiapyran hydrochloride which formed during the reaction was filtered about every eight hours, dried and weighed, until 90% of the theoretical amount was obtained. The total time consumed was about 80 hours. The benzene then was distilled and any unreacted 4-aminotetrahydrothiapyran recovered by distillation under reduced pressure. The bath temperature then was raised to 180–200° and the product distilled under reduced pressure. The compound distilled at 132–135° (1 mm.), as a viscous, colorless liquid which always crystallized upon standing, but more rapidly when strongly cooled. The solid melted at 46.1° and the yield was 5.2 g. (75%). *Anal.* Calcd. for $C_7H_{15}NOS$: S, 19.89. Found: S, 20.09; K_b, 6.04×10^{-7}.

4-(2-Hydroxyethylamino)-tetrahydrothiapyran-1-dioxide (V).—A mixture of 6 g. (0.041 mole) of tetrahydro-1,4-thiapyrone-1-dioxide 3.05 ml. (0.0405 mole) of ethanolamine and 1 g. of Raney nickel in 100 ml. of commercial absolute alcohol was shaken for four hours with hydrogen at a pressure of 1200 p.s.i. and a temperature of 50°. The mixture was filtered from the catalyst and the solvent evaporated. The residue was dissolved in 100 ml. of hot chloroform, filtered from any insoluble material and cooled. If colored, the chloroform solution also was treated with activated charcoal. Ether then was added until an oil began to separate when the mixture was cooled at −20°. The supernatant liquid was decanted from the oil into a second flask and ether again added. If an oil again separated the mixture was cooled and the supernatant liquid again decanted. This procedure was repeated until a white crystalline material separated upon the addition of more ether. The product then was isolated by alternately adding portions of ether and cooling the mixture to −20° until precipitation was complete. The crystals were filtered and purified by crystallization from a mixture of chloroform and ether. The yield was 5.5 g. (70%). The purified product melted at 80.4°. *Anal.* Calcd. for $C_7H_{15}NO_3S$: S, 16.59. Found: S, 16.47; K_b, 2.10×10^{-8}.

4-(2-Hydroxyethyl)-aminotetrahydrothiapyran-1-dioxide hydrochloride was prepared by passing dry hydrogen chloride gas into a chloroform solution containing 2 g. (0.011 mole) of the amine. The salt was recrystallized from a mixture of water and ethanol and dried in a vacuum desiccator over potassium hydroxide. The yield was 1.2 g. *Anal.* Calcd. for $C_7H_{16}ClNO_3S$: S, 13.96. Found: S, 13.97.

β-(4-Tetrahydrothiapyranylamino)-ethyl *p*-Nitrobenzoate Hydrochloride (VI).—Ten grams (0.062 mole) of 4-(2-hydroxyethylamino)-tetrahydrothiapyran (IV) in 20 ml. of chloroform was saturated with dry hydrogen chloride gas. To this mixture was added 11.6 g. (0.062 mole) of *p*-nitrobenzoyl chloride dissolved in 20 ml. of chloroform, and the mixture was heated at 50–55° for 48 hours. The chloroform then was decanted, the residue washed well with dry ether to remove unreacted *p*-nitrobenzoyl chloride and the residue recrystallized from a mixture of water and alcohol. The yield was 13 g. (60%). The substance did not melt below 250°. *Anal.* Calcd. for $C_{14}H_{19}ClN_2O_4S$: S, 9.24. Found: S, 9.20.

β-(4-Tetrahydrothiapyranylamino)-ethyl *p*-Aminobenzoate Hydrochloride (VII).—Sixteen grams (0.071 mole) of stannous chloride dihydrate was dissolved in 16 ml. of C.P. concentrated hydrochloric acid and the solution cooled at 0°. To this solution was added 5 g. (0.027 mole) of β-(4-tetrahydrothiapyranylamino)-ethyl *p*-nitrobenzoate hydrochloride and the initial exothermic reaction moderated under running water in order to hold the temperature below 75°. The mixture then was allowed to stand until it cooled to room temperature. After having poured the cooled mixture into an excess of cold potassium hydroxide solution, the basic mixture was extracted well with ether and the extract dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue accurately weighed. The residue then was dissolved in commercial absolute alcohol and the calculated amount of C.P. concentrated hydrochloric acid required to form the monohydrochloride was added. The salt which crystallized was recrystallized from a mixture of water and alcohol. The yield was 2.75 g. (60%). The substance did not melt below 250°. *Anal.* Calcd. for $C_{14}H_{21}Cl_1N_2O_2S$: S, 10.12. Found: S, 10.31.

ω-(4-Tetrahydrothiapyranylamino)-2,6-dimethylacetanilide (X).—In a flask fitted with a reflux condenser were mixed 7 g. (0.073 mole) of ω-chloro-2,6-dimethylacetanilide,[10] 8.5 g. (0.035 mole) of 4-aminotetrahydrothiapyran (II) and 80 ml. of dry benzene. The mixture was refluxed for six hours. After cooling, the mixture was saturated with dry hydrogen chloride gas. The hydrochlorides which precipitated were removed by filtration and washed with ether to remove the benzene. The crystals then were dissolved in boiling water and the resulting solution cooled to effect crystallization of ω-(4-tetrahydrothiapyranylamino)-2,6-dimethylacetanilide hydrochloride. A second crop of crystals were obtained when the solution was concentrated to half its volume. 4-Aminotetrahydrothiapyran hydrochloride was recovered by evaporating the solution to dryness. Unreacted ω-chloro-2,6-dimethylacetanilide was recovered by evaporating the original benzene solution to dryness. The compound was purified further by recrystallization from water. The yield was 8.1 g. (52%), based on the amine. The substance did not melt below 250°. *Anal.* Calcd. for $C_{15}H_{23}ClN_2OS$: S, 10.18. Found: S, 10.42.

The free base was prepared by dissolving the hydrochloride in water and adding a solution of potassium hydroxide. The base which precipitated was filtered and recrystallized from a water–ethanol mixture. A sample purified in this way had a melting point of 109.2°. *Anal.* Calcd. for $C_{15}H_{22}N_2OS$: S, 11.51. Found: S, 11.42.

N-(*p*-Nitrobenzoyl)-N-(2-hydroxyethyl)-4-aminotetrahydrothiapyran-1-dioxide (VIII).—To a solution of 5 g. (0.026 mole) of 4-(2-hydroxyethyl)-aminotetrahydrothiapyran-1-dioxide (V) in 25 ml. of chloroform was added, in portions and with shaking, a solution of 4.85 g. (0.026 mole) of *p*-nitrobenzoyl chloride in 25 ml. of chloroform. The mixture was shaken for one-half hour, diluted with 100 ml. of ether and allowed to stand for one hour. The precipitate was filtered with suction and washed with ether. The crude product was purified by crystallization from a mixture of ethanol and ether. The yield was 5.5 g. (61%). The purified product did not melt below 250°. *Anal.* Calcd. for $C_{14}H_{18}N_2O_6S$: S, 9.28. Found: S, 9.34.

N-*p*-Aminobenzoyl-N-(2-hydroxyethyl)-4-aminotetrahydrothiapyran-1-dioxide Hydrochloride (IX).—One gram (0.0044 mole) of stannous chloride dihydrate was dissolved in 2 ml. of C.P. hydrochloric acid and the solution cooled to 0°. To this solution was added 0.65 g. (0.0027 mole) of N-(*p*-nitrobenzoyl)-N-(2-hydroxyethyl)-4-aminotetrahydrothiapyran-1-dioxide, the mixture shaken for five minutes and cooled at room temperature. The mixture was poured into an excess of ice-cold, concentrated potassium hydroxide solution with continuous cooling in an ice-bath,

(10) N. Lofgren, *Arkiv Kemi, Mineral. Geol.*, **22a**, No. 18 (1946).

and the resulting mixture extracted well with chloroform. After drying over anhydrous sodium sulfate and filtering from the drying agent, the chloroform extract was saturated with gaseous hydrogen chloride. The hydrochloride was collected on a suction filter and recrystallized from a mixture of water and ethanol. The yield was 0.27 g. (40%). The salt did not melt below 250°. *Anal.* Calcd. for $C_{14}H_{21}ClN_2O_4S$: S, 9.20. Found: S, 9.36.

LEXINGTON, KENTUCKY

[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, STATE COLLEGE OF WASHINGTON]

Schiff Bases and Related Substances. II. Reactions of Thiols with N-Benzylideneaniline and N-Benzylideneanthranilic Acid[1]

BY GARDNER W. STACY, RICHARD I. DAY AND RICHARD J. MORATH[2]

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No substituent effect has been observed in the addition of thiols to *m*- and *p*-benzylideneaminobenzoic acids or *m*- and *p*-benzylideneaminoacetophenones. Under appropriate conditions, N-benzylideneaniline (III) has been found to form addition products with thiols as readily as N-benzylideneanthranilic acid (I). Schiff base-thiol adducts are decomposed readily by dilute sodium hydroxide solution to yield constituent thiols and Schiff bases. Reduction of the *p*-toluenethiol adduct of N-benzylideneaniline (VI) occurs as readily as direct reduction of N-benzylideneaniline (III) with *p*-toluenethiol. Cleavage of Schiff bases by thiols in the presence of small amounts of water has been observed to yield corresponding amines and mercaptals.

In a recent publication[1] from this Laboratory, it was demonstrated that N-benzylideneanthranilic acid (I) would form crystalline adducts (II) with a variety of thiols. Earlier, Gilman and Dickey[3] had investigated the possibility of conjugate,

$$\underset{\text{I}}{C_6H_5CH{=}NC_6H_4COOH\text{-}o} + RSH \longrightarrow \underset{\text{II}}{C_6H_5CH(SR)NHC_6H_4COOH\text{-}o}$$

nuclear addition of *p*-toluenethiol to N-benzylideneaniline (III). They observed no addition products, however, but instead found that III was reduced to N-benzylaniline (IV). More recently, some examples of reduction of conjugated azomethine systems have been reported.[4]

$$\underset{\text{III}}{C_6H_5CH{=}NC_6H_5} \xrightarrow{p\text{-}CH_3C_6H_4SH} \underset{\text{VI}}{p\text{-}CH_3C_6H_4SCH(C_6H_5)NHC_6H_5}$$

$$\text{III} + 2\ p\text{-}CH_3C_6H_4SH \longrightarrow \underset{\text{IV}}{C_6H_5CH_2NHC_6H_5} + \underset{\text{V}}{(p\text{-}CH_3C_6H_4S\text{-})_2} \longleftarrow \text{VI} + p\text{-}CH_3C_6H_4SH$$

Because the Schiff bases I and III had been observed to react differently with thiols, it was of obvious interest to study the different factors involved in the two cases. Initially, we wished to investigate the possibility of a substituent effect as a basis for adduct formation. An electron-attracting substituent (as in the case of the carboxyl group in I) *ortho* or *para* to the Schiff base nitrogen might be expected to enhance the polarization of the carbon–nitrogen double bond, and hence adduct formation might be expected to occur readily. The same electron displacement, of course, would not obtain in the case of *meta* isomers, and therefore it might be thought that these would form adducts less readily or not at all, as also would be the case with the unsubstituted Schiff base (III).[5]

Such considerations were studied relative to the *m*- and *p*-benzylideneaminobenzoic acids (VII) and the *m*- and *p*-benzylideneaminoacetophenones (VIII). However, as indicated by the yields (Table I), there was no indication that *meta* isomers underwent adduct formation any less readily than *para* isomers. And certainly there were no striking differences in reactivity, as had been observed with the isomeric nitrostyrenes.[5]

$$C_6H_5CH{=}N\langle\text{C}_6\text{H}_4\rangle R^1 + R^2SH \longrightarrow C_6H_5CH(SR^2)NH\langle\text{C}_6\text{H}_4\rangle R^1$$

VII, R^1 = COOH
VIII, R^1 = $COCH_3$

IX

The above results suggested that the difference in the reactions that had been observed when I and III were treated with thiols must be due to differences in conditions under which the reactions had been carried out. Gilman and Dickey[3] had run their reduction (III → IV) in refluxing *p*-xylene with a threefold excess of thiol, whereas our additions (I → II and VII, VIII → IX) were carried out equally well at room temperature or in refluxing benzene with one to two equivalents of thiol. Therefore, the formation of adducts of N-benzylideneaniline (III) was attempted employing the conditions that had led to addition in our previous experience. And, indeed, it was found that adducts of III were obtained in excellent yield (Table I). On the other hand, when the conditions that Gilman and Dickey[3] had reported were em-

(1) Presented in part before the Division of Organic Chemistry at the 125th Meeting of the American Chemical Society, Kansas City, Mo., March 24, 1954, and in part before the Montana Section of the American Chemical Society, Missoula, Mont., May, 1953. Paper I, G. W. Stacy and R. J. Morath, THIS JOURNAL, **74**, 3885 (1952).

(2) Abstracted from theses submitted by Richard I. Day and Richard J. Morath in partial fulfillment of the requirements for degrees of Master of Science and Doctor of Philosophy, respectively, State College of Washington, February, 1955, 1954.

(3) H. Gilman and J. B. Dickey, THIS JOURNAL, **52**, 4573 (1930).

(4) H. Gilman, J. L. Towle and R. K. Ingham, *ibid.*, **76**, 2920 (1954).

(5) Systems of comparative interest involve substituted styrenes. Recently, it has been reported that *o*- or *p*-nitrostyrenes will add active methylene compounds in the presence of sodium alkoxide, whereas *m*-nitrostyrene and styrene itself will not; W. J. Dale and C. W. Strobel, *ibid.*, **76**, 6172 (1954).