20° and then filtered. The solid (2.41 g.) was mostly *meso*-1,2,3,-4-tetrabenzoylbutane[19b] (XIV) mixed with 1,2-dibenzoylethane and some *dl*-XIV. The solid was treated with warm carbon tetrachloride (20 ml.). The CCl_4-insoluble portion (1.30 g., 30%, melting range 155–193°) was further washed with warm CCl_4 leaving 1.07 g. (24%) of pure *meso*-XIV,[19] m.p. 201–202°. The CCl_4 solution was evaporated and the residue was triturated with ether. The ether-insoluble crystals (0.9 g.) were 1,2-dibenzoylethane, m.p. 142–144°. The ether solution gave more of the latter (100 mg.), yield 24%. The methanol filtrate from above was evaporated. The residue was distilled to remove trimethyl phosphate (6.5 g.). The residue was suspended in hexane, treated with ethanol to dissolve, cooled, and filtered. Some dibenzoylethane (50 mg.) was recovered. The filtrate gave a gummy residue which could contain some diketophosphonate XVII. It was not investigated further.

Reaction of Methanol with the Ylide IV.—A mixture of DBE (II), trimethyl phosphite, and methylene chloride (1:1 mole ratio, 1 *M* solution) was kept 18 hr. at 20°. The infrared spectrum showed strong ylide absorption at 6.6 μ. Methanol (3.5 mole equiv.) was added. The 6.6-μ band still persisted after 19 hr. at 20°; most of it had disappeared after 43 hr. The solution was evaporated after 7 days. The residue was kept under ether and filtered from 1,2-dibenzoylethane, 20% yield, m.p. 146–147°. The ether solution was evaporated and the residue was distilled at 0.1 mm. to collect 40% of $(CH_3O)_3PO$. The residue was taken up in benzene; the solution was passed through neutral Al_2O_3 and evaporated. The residue was mainly the enol phosphonate methyl ether V.

Reaction of Dibenzoylethylene in Methanol Solution with the Alkylidenephosphorane IV.—A mixture of DBE (II) and trimethyl phosphite in methylene chloride (1:1 mole ratio, 1.1 *M* solution) was kept 18 hr. at 20°. The infrared spectrum showed strong 6.6-μ band. A solution of DBE (1 mole equiv.) in methanol was added. A solid separated and was collected after 1 hr.; it was *meso*-1,2,3,4-tetrabenzoylbutane (XIV), m.p. 197–199° (23% yield). The filtrate was evaporated and the residue was kept under methanol at 0° and filtered. The solid (30%) had a wide melting range (116–130°) and from the infrared spectrum is a mixture of *dl*-XIV, dibenzoylethane, and some *meso*-XIV. The filtrate was evaporated and the residue was distilled to collect 55% of trimethyl phosphate. The material balance was a mixture of more *dl*-XIV and enol phosphonate methyl ether V.

Reaction of *trans*-Dibenzoylethylene (II) with Trimethyl Phosphite in Boiling Xylene. Isolation of 2,5-Diphenylfuran[19c] (XI).—A suspension of *trans*-dibenzoylethylene (4.68 g.) and trimethyl phosphite (2.45 g.) in xylene (16 ml.) was kept at reflux temperature (oil bath at 150°). A clear red solution resulted in minutes. After 22 hr. the solution was evaporated to dryness *in vacuo*. The residue was freed from trimethyl phosphate by short-path distillation. The residue was extracted with two 50-ml. portions of hexane. The hexane solution gave 2.53 g. (50%) of 2,5-diphenylfuran,[19c] identified by infrared and proton n.m.r. spectra, m.p. 81–83° (from ethanol–water), lit.[19c] m.p. 88–89°.

The hexane-insoluble material was enol phosphonate methyl ether V and products from 2:1 condensation.

Reaction of *cis*-Dibenzoylethylene[19a] with Trimethyl Phosphite.—The infrared and H^1 and P^{31} n.m.r. spectra of the methylene chloride solutions were examined as indicated in Table I. The reaction followed the same course as in the *trans* isomer, but the alkylidenephosphorane was formed at a considerably faster rate (expt. 11 *vs.* 2).

Studies on the Pyrimidine Derivatives and the Related Compounds. XXXVII.[1] Reactions of Ethyl 3-Ethoxy-2-methoxymethylenepropionate with Thiourea Derivatives

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Ethyl 3-ethoxy-2-methoxymethylenepropionate (I) undergoes condensation with thiourea and N-substituted thioureas in ethanolic acid to 5-ethoxycarbonyl-2-oxo-6H-2,3-dihydro-1,3-thiazine (II). N-Methyl-N′-phenylthiourea gave N-methyldihydro-1,3-thiazine (IV) and aniline. N,N′-Dimethylthiourea condensed with I to give 1,3-dimethyl-5-ethoxycarbonyl-2-thio-1,2,3,4-tetrahydropyrimidine (V) and 5-ethoxycarbonyl-2-methylimino-3-methyl-6H-2,3-dihydro-1,3-thiazine (VI). N,N′-Diphenylthiourea did not condense with I. N-Methylthiourea gave II and 5-ethoxycarbonyl-2-methylamino-6H-1,3-thiazine (VII). Methylation of VII afforded VI and the N,N-dimethyl compound IX. Upon treatment of VII with hydrochloric acid the ester group was saponified, but prolonged refluxing with ethanolic acid yielded II. Rearrangement of VII into 2-thiotetrahydropyrimidine occurs on heating with aqueous formic or acetic acid to give a mixture of 5-ethoxycarbonyl-1-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIa) and the 3-methyl isomer XIIIb. 2-Anilino-5-ethoxycarbonyl-6H-1,3-thiazine also rearranged in this reaction to give 5-ethoxycarbonyl-1-phenyl-2-thio-1,2,3,4-tetrahydropyrimidine (XVI) and the 3-phenyl isomer XVII.

We have previously reported the reaction of 3-ethoxy-2-methoxymethylenepropionitrile with thiourea derivatives to give 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine.[2] Reactions of ethyl 3-ethoxy-2-methoxymethylenepropionate (I) with urea derivatives have also been reported.[3,4] This paper deals with the reaction of I with thiourea and various N-substituted thiourea derivatives.

Reactions of I with thiourea, N-phenylthiourea, and N-α-naphthylthiourea were carried out in ethanol solution in the presence of hydrochloric acid, and the reactions took the same course as with the corresponding nitrile to give 5-ethoxycarbonyl-2-oxo-6H-2,3-dihydro-1,3-thiazine (II) together with ammonium chloride, aniline hydrochloride, and α-naphthylamine hydrochloride, respectively. From the infrared spectrum and proton magnetic resonance (n.m.r.) spectrum[5] this structure was confirmed as discussed extensively in earlier papers.[2-4,6] Acetylation of II with acetic anhydride gave the acetate III. The product II

(1) Part XXXVI: A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* (Tokyo), in press.

(2) A. Takamizawa, K. Hirai, Y. Sato, and K. Tori, *J. Org. Chem.*, **29**, 1740 (1964).

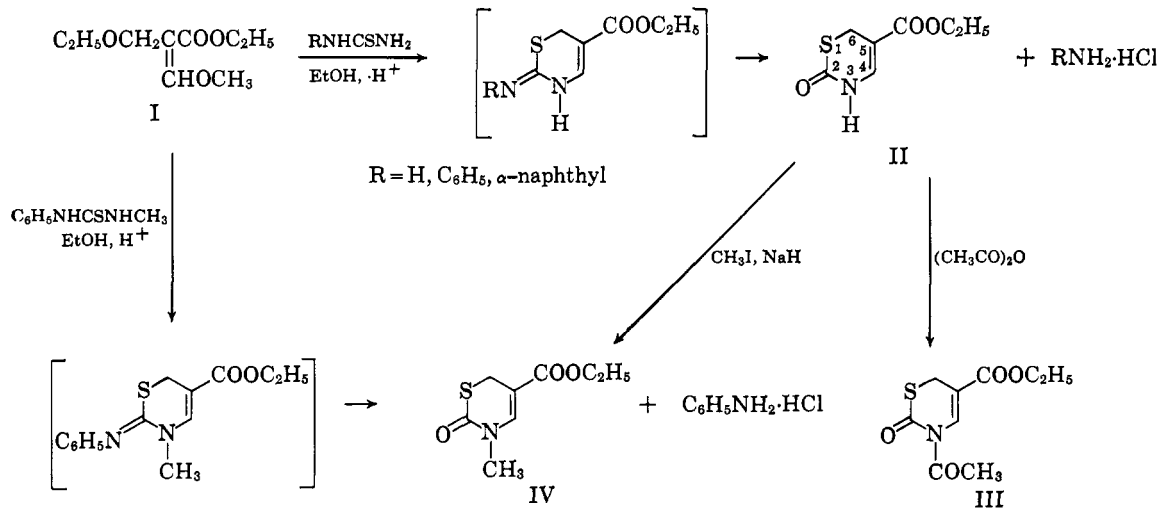
(3) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* (Tokyo), **12**, 804 (1964).

(4) A. Takamizawa and K. Hirai, *ibid.*, **12**, 1418 (1964).

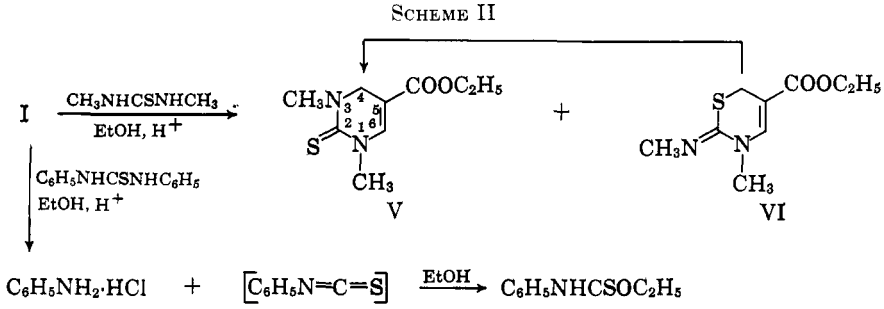
(5) All of the n.m.r. spectra were taken with a Varian A-60 spectrometer on about a 10% solution in deuteriochloroform containing about 1% tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in τ values and coupling constants are in cycles per second

(6) K. Tori, K. Aono, K. Hirai, and A. Takamizawa, *Shionogi Kenkyusho Nempo*, **14**, 198 (1964).

SCHEME I



SCHEME II



would result from hydrolysis of the probable 2-imino intermediate.

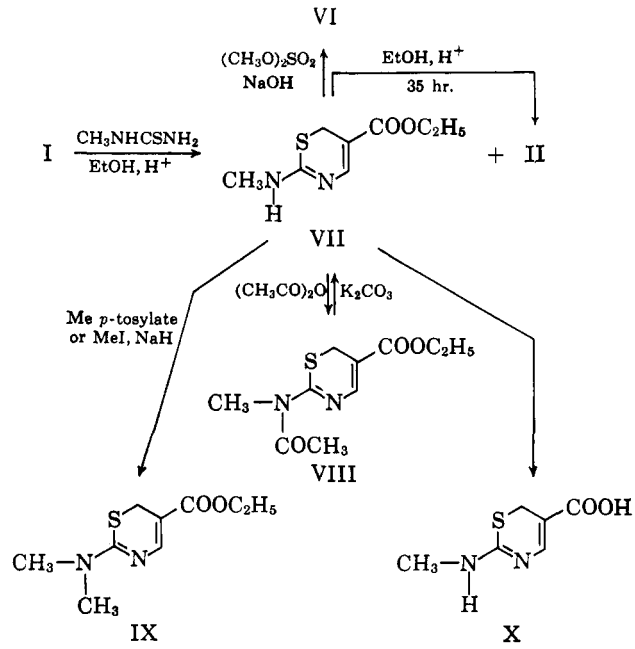
Similarly, the reaction of I with N-methyl-N′-phenylthiourea gave aniline hydrochloride and the N-methylthiazine IV, which was also obtained by methylation of II with methyl iodide and sodium hydride (see Scheme I).

When N,N′-dimethylurea and I were heated in ethanol solution in the presence of hydrochloric acid, the nonbasic product V, $C_9H_{14}N_2O_2S$, and the basic product VI, $C_9H_{14}N_2O_2S$, were obtained. From n.m.r. data (see Experimental), the structures of V and VI are assigned as 1,3-dimethyl-5-ethoxycarbonyl-2-thio-1,2,3,4-tetrahydropyrimidine and 5-ethoxycarbonyl-2-methylimino-3-methyl-6H-2,3-dihydro-1,3-thiazine, respectively. However, similar reaction of N,N′-diphenylthiourea with I afforded aniline hydrochloride and ethyl N-phenylthionocarbamate and no condensation product was obtained. This may be due to decomposition of N,N′-diphenylthiourea into aniline and isothiocyanate by hydrochloric acid[7] and subsequent addition of ethanol to isothiocyanate (Scheme II).

When I reacted with N-methylthiourea, II and the basic product VII (pK_a = 5.41), $C_8H_{12}N_2O_2S$, were isolated (Scheme III). We assign the structure of VII as 5-ethoxycarbonyl-2-methylamino-6H-1,3-thiazine, since ultraviolet spectra of VI and VII are not similar, and the absorption at long wave length in the spectrum of VII suggests more extensive conjugation in VII.

Acetylation of VII with acetic anhydride gave the monoacetate VIII from which VII was regenerated

SCHEME III



by hydrolysis with aqueous potassium carbonate solution. Therefore, it was considered that no change had occurred in the skeleton through these reactions. The signal of the N-methyl of VIII in the n.m.r. spectrum shifted to lower field and this suggests that an acetyl group in VIII should be present at N of the exocyclic methylamino group.[3,4,6]

Treatment of VII with diazomethane or methyl iodide in ether solution or with hydrogen peroxide in acetic acid solution gave only starting material.

(7) A. Rahman, M. A. Modrano, and B. E. Jeanneret, *J. Org. Chem.*, **27**, 3315 (1962).

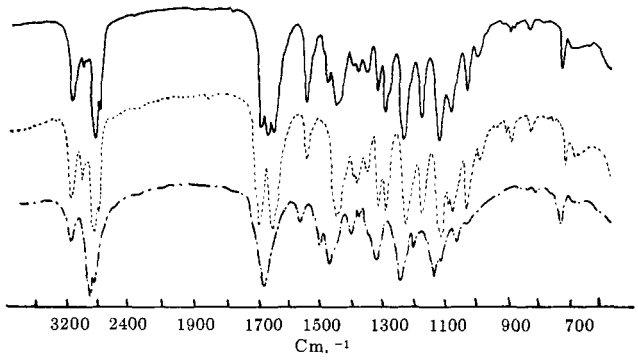


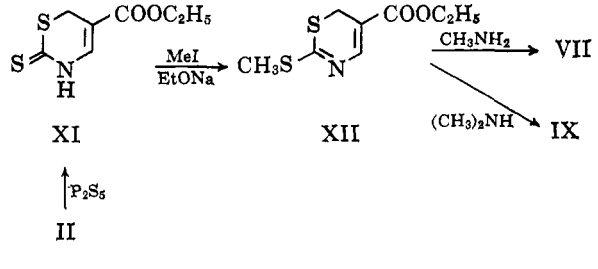
Figure 1.—Infrared spectra in Nujol of the product of m.p. 138–140° (———), 5-ethoxycarbonyl-1-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIa) (-----), and 5-ethoxycarbonyl-3-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIb) (- - -).

Reaction of VII with dimethyl sulfate in aqueous alkaline solution afforded the N,N′-dimethyl compound VI. However, when VII was treated with methyl *p*-tosylate or methyl iodide and sodium hydride in absolute dioxane solution, a different dimethyl compound (IX) was isolated as the picrate. This product IX showed two equivalent N-methyl signals in its n.m.r. spectrum and was therefore 2-(N,N-dimethyl)-amino-5-ethoxycarbonyl-6H-1,3-thiazine.

When VII was refluxed in 15% hydrochloric acid or heated with concentrated hydrochloric acid in a bomb, saponification of the ester group occurred to yield the amino acid X. However, when VII was refluxed in ethanol in the presence of hydrochloric acid for 35 hr., the methylamino group was hydrolyzed to yield II. These facts account for the formation of II and VII in the condensation reaction.

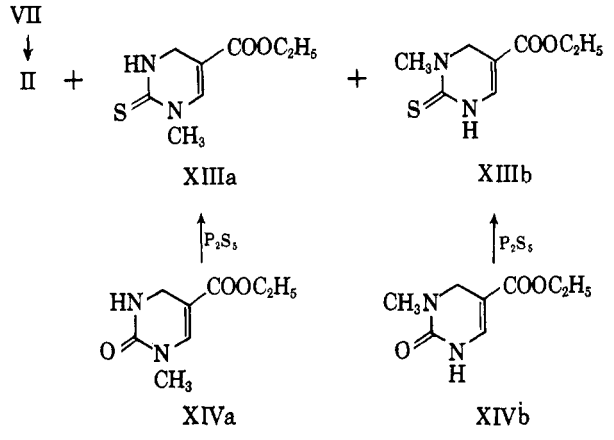
The structure of VII was confirmed by an alternative synthesis (Scheme IV). Thiation of II gave the 2-thio derivative XI, which was methylated with methyl iodide in sodium ethoxide solution to give the 2-methylmercapto derivative XII. Subsequent amination with methylamine afforded the 2-methylamino derivative. The identity with VII was confirmed by mixture melting point and comparison of the spectra of both products. Furthermore, amination of XII with dimethylamine afforded the N,N-dimethyl compound, which was identical with IX.

SCHEME IV



An attempt to formylate VII by heating with formic acid failed. However, addition of triethylamine and heating of VII at 160° for 6 hr. afforded a mixture of isomers (XIIIa and XIIIb) as a nonbasic product of m.p. 138–140°, isomeric with VII (see Scheme V). Essentially the same product was also isolated from the reaction of VII with the mixture of formic acid and formalin instead of the expected methylated compound.

SCHEME V

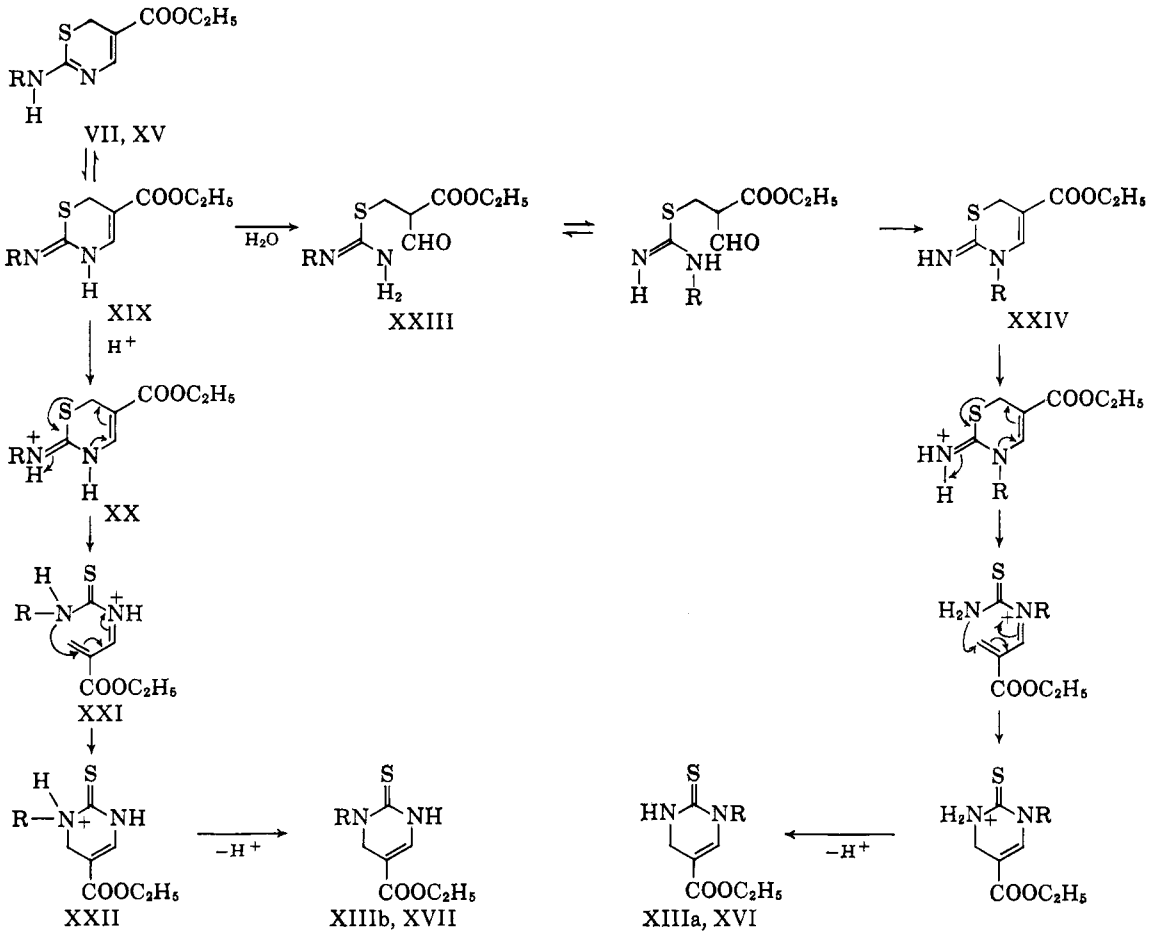


The ultraviolet spectrum of this product (m.p. 138–140°) was very similar to that of V, which suggests a change of the skeleton of VII in these reactions. From the elemental analysis, the structure of this product was postulated to be 5-ethoxycarbonyl-1-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIa) or the 3-methyl isomer XIIIb. XIIIa and XIIIb were prepared from 5-ethoxycarbonyl-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIVa) and the 3-methyl isomer (XIVb),[3] respectively, by treatment with phosphorus pentasulfide in pyridine. The infrared spectra of XIIIa and XIIIb were not identical with that of the product of m.p. 138–140°; however, when the spectra of XIIIa and XIIIb were superposed, a spectrum identical with that of the product of m.p. 138–140° was obtained (Figure 1). Therefore, it became clear that the product of m.p. 138–140° was the mixture of XIIIa and XIIIb. The n.m.r. spectrum of XIIIa showed a N-1 methyl signal at τ 6.50 and that of XIIIb showed a N-3 methyl signal at τ 6.63, and a doublet of triplets due to the C-6 methylidyne proton was converted into a triplet by proton exchange of NH. Therefore, the spin coupling between the N-1 proton and the C-6 methylidyne proton was present with a coupling constant of about 6 c.p.s. characteristic of the thioureido derivatives. Superposition of the n.m.r. spectra of XIIIa and XIIIb coincided with that of the product of m.p. 138–140°. The integrated ratio of the signals of N-methyl protons in the n.m.r. spectrum of the product of m.p. 138–140° showed about 3:2; thus, the product of m.p. 138–140° was revealed to be a mixture of XIIIa and XIIIb in a ratio of approximately 3:2.

It was then found that rearrangement of the dihydro-1,3-thiazine derivative into 2-thiotetrahydropyrimidine derivative occurs simply by heating with aqueous formic acid. Heating VII with 50% formic acid or 50% acetic acid also afforded the rearranged products. The ratio of the mixture of the rearranged products was different to some extent in each case, and, when heated with 50% formic acid, the ratio of XIIIa to XIIIb was about 5:1.

This rearrangement was applied to VI by heating with formic acid and triethylamine and the rearranged product V was readily obtained. In this case; V was also obtained by prolonged refluxing of VI in ethanol–hydrochloric acid solution. Treatment of VII with hot 10% potassium carbonate gave only recovered starting material. No interconversion between XIIIa

SCHEME VI

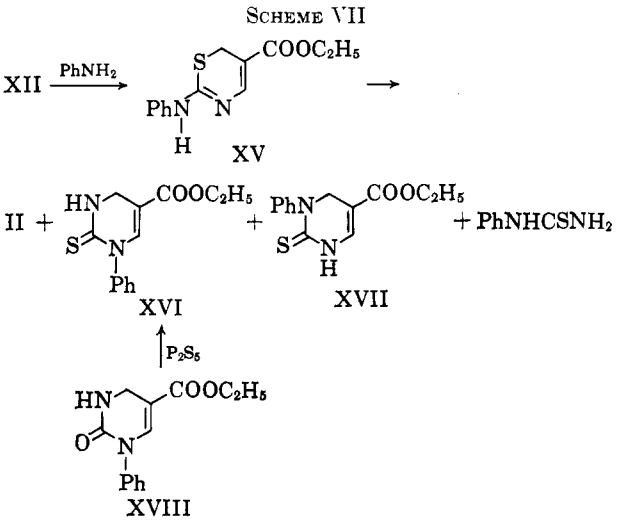


and XIIIb was observed under the conditions of the reaction.

Recently the reaction of α,β-unsaturated ketones with thioureas has been found to give 2-iminodihydro-1,3-thiazines and 2-thiotetrahydropyrimidines.[8,9] Zimmerman[9] has described the reaction of thiourea in aqueous hydrochloric acid in both its normal and mesomeric forms. Cavallito, *et al.*,[10] have reported a rearrangement of 2-imino-2H-1,3-thiazine to 2-mercaptopyrimidine by treatment with mild alkali; however, no absolute proof of the 1,3-thiazine structure was offered.[11] The interconversion between 2-thio-4-oxo-hexahydropyrimidine and 2-imino-6-oxo-1,3-thiazane has recently been reported.[12,13]

A postulated mechanism for the rearrangement of VII into the mixture of XIIIa and XIIIb is shown in Scheme VI. XX formed by acid would suffer Michael retrogression to afford XXI. The intramolecular Michael addition of acrylic ester XXI and subsequent deprotonation would give XIIIb. On the other hand, hydrolysis of XIX to aminoaldehyde XXIII and ring closure by dehydration would lead to XXIV,[14] and thence by the same process to XIIIa.

SCHEME VII



2-Anilino-5-ethoxycarbonyl-6H-1,3-thiazine (XV) prepared by action of aniline on XII was also heated in 50% formic acid and four products were isolated as follows: a compound of m.p. 192° (XVI), a compound of m.p. 178° (XVII), II, and N-phenylthiourea. 5-Ethoxycarbonyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (XVIII)[2] was converted into the 2-thio derivative by treatment with phosphorus pentasulfide in pyridine solution and identity with the

(8) J. Williams and A. Vardenberghe, *Ind. chim. belge*, 467 (1958); *Chem. Abstr.*, **54**, 22657 (1960).

(9) R. Zimmerman, *Angew. Chem.*, **75**, 1124 (1963).

(10) C. J. Cavallito, C. M. Martini, and F. C. Nachol, *J. Am. Chem. Soc.*, **73**, 2544 (1951).

(11) R. C. Elderfield and E. E. Harris, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 603.

(12) M. Deržaj-Bizjak, S. Oblak, and M. Tišler, *J. Org. Chem.*, **27**, 1343 (1962).

(13) A. Prosen, S. Stanovnik, and M. Tišler, *ibid.*, **29**, 1623 (1964).

(14) Recently, it has been reported that exocyclic alkylaminopyrimidine rearranged to a ring-alkylated isomer: T. Ueda and J. J. Fox, *ibid.*, **29**, 1762, 1770 (1964).

compound XVI was confirmed by comparison of their infrared spectra. Compound XVII was found to be an isomer of XVI and their ultraviolet spectra were very similar. Accordingly, XVII should be the 3-phenyl isomer (see Scheme VII).

Experimental

5-Ethoxycarbonyl-2-oxo-2,3-dihydro-6H-1,3-thiazine (II). **A.**—A solution of 7.6 g. of thiourea, 19 g. of I, and 20 ml. of concentrated hydrochloric acid in 800 ml. of ethanol was refluxed for 16 hr. The reaction mixture was concentrated *in vacuo* and chloroform was added to the residue. Separated ammonium chloride was removed, the chloroform solution was washed with water and dried over anhydrous magnesium sulfate, and the solvent was evaporated. Petroleum ether (b.p. 35–80°) was added to the residue and the resulting solid was collected and recrystallized from the mixture of benzene and petroleum ether to give 10.8 g. (58%) of pale yellow crystals, m.p. 69°. This may be distilled under reduced pressure to give an oil, b.p. 175–178° (3 mm.), which solidified after cooling to give pale yellow prisms, m.p. 78–79°. The infrared spectrum showed a broad C=O band at about 1650 cm.$^{-1}$; ultraviolet spectrum, λ_{max}^{EtOH} 240, 292 mμ (log ε 3.77, 3.96). The n.m.r. spectrum showed resonance peaks at τ: 1.08 (NH, broad doublet), 6.13 (C-6 H, doublet, J = 1 c.p.s.), 2.77 (C-4 H, doublet of triplets, J = 6, 1 c.p.s.). Proton exchange of NH by addition of deuterium oxide to the solution examined changed the spectrum, and the doublet of triplets due to the C-4 methylidyne proton was converted into a triplet (J = 1 c.p.s.).

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 45.06; H, 4.94; N, 7.82; S, 16.78.

B.—From 1.5 g. of N-phenylthiourea and 1.9 g. of I under the same conditions, 0.8 g. of aniline hydrochloride and 1.1 g. (59%) of II were obtained.

C.—From 1.0 g. of 1-(1-naphthyl)-2-thiourea and 0.94 g. of I under the same conditions, 0.5 g. of 1-naphthylamine hydrochloride and 0.6 g. (64%) of II were obtained.

3-Acetyl-5-ethoxycarbonyl-2-oxo-2,3-dihydro-6H-1,3-thiazine (III).—A mixture of 0.5 g. of II and 5.0 ml. of acetic anhydride was refluxed for 6 hr. After removing excess reagent, the residue was distilled under reduced pressure to give 0.4 g. of an oil, b.p. 147–148° (2 mm.). The n.m.r. spectrum had τ 7.38 (N-3 $COCH_3$, singlet), 6.23 (C-6 H, singlet), 2.07 (C-4 H, singlet).

Anal. Calcd. for $C_9H_{11}NO_4S$: C, 47.15; H, 4.83; N, 6.11; S, 13.98. Found: C, 47.30; H, 4.83; N, 5.94; S, 13.67.

5-Ethoxycarbonyl-3-methyl-2-oxo-2,3-dihydro-6H-1,3-thiazine (IV). **A.**—A solution of 1.66 g. of N-methyl-N′-phenylthiourea, 1.9 g. of I, and 2.0 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo* and chloroform was added to the residue. The separated solid was collected to give 0.3 g. of aniline hydrochloride and the filtrate was concentrated *in vacuo*. The residue was chromatographed on Al_2O_3 with AcOEt and 1.5 g. of the oil was obtained.

This was distilled in reduced pressure to give 0.75 g. (40%) of the oil of b.p. 132–142° (1.4 mm.), which solidified to give colorless prisms: m.p. 34–35°; λ_{max}^{EtOH} 241, 298 mμ (log ε 3.74, 3.86); n.m.r., τ 6.77 (N-3 CH_3, singlet), 6.17 (C-6 H, singlet), 2.72 (C-4 H, singlet).

Anal. Calcd. for $C_8H_{11}NO_3S$: C, 47.76; H, 5.51; N, 6.96; S, 15.93. Found: C, 48.24; H, 5.64; N, 6.83; S, 15.64.

From the following fractions, 0.3 g. of N-methyl-N′-phenylthiourea was recovered.

B.—To the solution of 0.6 g. of I in 8.0 ml. of absolute dioxane, 0.16 g. of sodium hydride (50% oil suspension) and 1.0 ml. of methyl iodide were added and the mixture was refluxed for 1 hr. The reaction mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was distilled under reduced pressure to give 0.5 g. of IV.

Reaction of N,N′-Diphenylthiourea with I.—A solution of 2.3 g. of N,N′-diphenylthiourea, 1.9 g. of I, and 2.0 ml. of concentrated hydrochloric acid in 150 ml. of ethanol was refluxed for 8 hr. The reaction mixture was concentrated *in vacuo* and chloroform was added to the residue. Separated aniline hydrochloride (1.0 g.) was filtered off and the filtrate was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residual oil was distilled under reduced pressure to give 0.74 g. of ethyl N-phenylthionocarbamate, b.p. 122–123° (1.3 mm.), m.p. 66–68°.

Reaction of N,N′-Dimethylthiourea with I. **A.**—A solution of 1.0 g. of N,N′-dimethylthiourea, 1.9 g. of I, and 2.0 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 6 hr. The reaction mixture was concentrated *in vacuo*, and aqueous sodium bicarbonate solution was added to the residue which was then extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated. To the residue, 15% hydrochloric acid was added and the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and evaporated. The residue was treated with petroleum ether to give 0.75 g. (37%) of 1,3-dimethyl-5-ethoxycarbonyl-2-thio-1,2,3,4-tetrahydropyrimidine (V). This may be recrystallized from ethyl acetate to give colorless prisms: m.p. 95–99°; λ_{max}^{EtOH} 291, 328 mμ (log ε 4.05, 4.04); n.m.r., τ 6.58 (N-3 CH_3, singlet), 6.45 (N-1 CH_3, singlet), 5.77 (C-4 H, doublet, J = 1 c.p.s.), 2.80 (C-6 H, triplet, J = 1 c.p.s.).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.46; H, 6.59; N, 13.08; S, 14.98. Found: C, 50.55; H, 6.79; N, 13.01; S, 14.87.

The hydrochloric acid layer was neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and evaporated to give 0.7 g. (34%) of 5-ethoxycarbonyl-3-methyl-2-methylimino-6H-2,3-dihydro-1,3-thiazine (VI), which was recrystallized from petroleum ether to give colorless prisms: m.p. 51–53°; λ_{max}^{EtOH} 247, 309 mμ (log ε 3.53, 4.23); n.m.r., τ 6.83 (N-3 CH_3, singlet), 6.32 (C-6 H, singlet), 2.58 (C-4 H, singlet), 6.70 (N-2 CH_3, singlet).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.46; H, 6.59; N, 13.08; S, 14.98. Found: C, 50.72; H, 6.77; N, 12.96; S, 15.18.

The picrate was prepared; yellow scales, m.p. 167–168°.

Anal. Calcd. for $C_9H_{14}N_2O_2S \cdot C_6H_3N_3O_7$: C, 40.63; H, 3.86; N, 15.79; S, 7.23. Found: C, 40.91; H, 3.93; N, 15.71; S, 7.61.

B.—On refluxing for 25 hr. and treatment as above, V and VI were obtained in 61 and 13% yields, respectively.

Reaction of N-Methylthiourea with I.—A solution of 3.6 g. of N-methylthiourea, 7.6 g. of I, and 8.0 ml. of concentrated hydrochloric acid in 400 ml. of ethanol was refluxed for 7 hr. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized with sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate extract was shaken with 15% hydrochloric acid and the hydrochloric acid layer was made alkaline with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and evaporated. The residue was treated with ether to give 2.5 g. (31%) of 5-ethoxycarbonyl-2-methylamino-6H-1,3-thiazine (VII), m.p. 105–107°. Recrystallization from benzene gave colorless scales: m.p. 108–109°; pK_a = 5.41; ν^{CCl_4} 3450 (NH), 1696 (C=O), 1540 (conjugated C=N) cm.$^{-1}$; λ_{max}^{EtOH} 240, 266, 330 mμ (log ε 3.66, 3.77, 4.14); $\lambda_{max}^{EtOH\text{-}HCl}$ 261, 297 mμ (log ε 4.03, 3.81); n.m.r., τ 6.97 (N-CH_3, singlet), 3.8 (NH, broad), 6.35 (C-6 H, doublet, J = 1 c.p.s.), 2.18 (C-4 H, triplet, J = 1 c.p.s.).

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 48.01; H, 6.38; N, 13.55; S, 16.03.

The hydrochloride was prepared and recrystallized from methanol–ethyl acetate as colorless prisms, m.p. 178–179°.

Anal. Calcd. for $C_8H_{12}N_2O_2S \cdot HCl$: C, 40.59; H, 5.53; Cl, 14.48; N, 11.83. Found: C, 41.13; H, 5.62; Cl, 15.64; N, 11.88.

The picrate was prepared; yellow needles, m.p. 195° (from ethanol).

Anal. Calcd. for $C_8H_{12}N_2O_2S \cdot C_6H_3N_3O_7$: C, 39.15; H, 3.52; N, 16.31. Found: C, 39.25; H, 3.66; N, 16.33.

The first ethyl acetate layer from above was washed with water, dried over anhydrous magnesium sulfate, and evaporated to give 2.0 g. (27%) of II.

2-(N-Acetyl)methylamino-5-ethoxycarbonyl-6H-1,3-thiazine (VIII).—A mixture of 0.5 g. of VII and 5.0 ml. of acetic anhydride was refluxed for 3 hr. The reaction mixture was concentrated *in vacuo* and the residue (0.53 g.) was distilled at 160–180° (0.07 mm.): λ_{max}^{EtOH} 207, 277, 330 mμ (log ε 3.90, 3.87, 3.87); n.m.r., τ 6.57 (N-CH_3, singlet), 7.67 (N-$COCH_3$, singlet), 6.52 (C-6 H, doublet, J = 1 c.p.s.), 2.22 (C-4 H, triplet, J = 1 c.p.s.).

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.57; S, 13.24. Found: C, 48.86; H, 5.79; N, 10.97; S, 13.13.

This acetate was refluxed for 3 min. in dilute ethanol–potassium carbonate solution to give VII in almost quantitative yield.

2-Methylamino-5-carboxy-6H-1,3-thiazine (X). A.—A solution of 0.2 g. of VII in 3.0 ml. of 15% hydrochloric acid was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from ethanol–ethyl acetate to give 0.15 g. of colorless prisms, m.p. 153–155° dec.

Anal. Calcd. for $C_6H_8N_2O_2S \cdot HCl$: C, 34.53; H, 4.35; Cl, 16.99; N, 13.42. Found: C, 34.52; H, 4.96; Cl, 17.17; N, 13.12.

These were neutralized with sodium bicarbonate to give colorless prisms, m.p. 165° dec.

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.86; H, 4.68; N, 16.28. Found: C, 41.44; H, 4.95; N, 15.77.

B.—A solution of 0.2 g. of VII in 10 ml. of concentrated hydrochloric acid was heated at 100° for 2 hr. in a bomb. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from ethanol–ethyl acetate to give 0.19 g. of X hydrochloride.

5-Ethoxycarbonyl-3-methyl-2-methylimino-2,3-dihydro-6H-1,3-thiazine (VI).—To a suspension of 1.0 g. of VII in 5.0 ml. of 15% NaOH, 1.5 g. of dimethyl sulfate was added and the mixture was heated on the steam bath for 10 min. After cooling and extraction with ether, the ether extract was dried over anhydrous magnesium sulfate and evaporated to give 0.74 g. (69%) of an oil, which was identified with VI obtained in the reaction of N,N'-dimethylthiourea with I by comparison of the infrared spectra of their picrates.

Hydrolysis of VII into II.—A solution of 0.5 g. of VII in 1.0 ml. of concentrated hydrochloric acid in 30 ml. of ethanol was refluxed for 35 hr. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated to give 0.33 g. of II.

5-Ethoxycarbonyl-2-thio-2,3-dihydro-6H-1,3-thiazine (XI).—To the solution of 1.9 g. of II in 20 ml. of absolute pyridine, 3.3 g. of phosphorus pentasulfide was added and the mixture was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, and water was added to the residue which was then extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated. The residual oil was chromatographed on alumina with ethyl acetate, and 1.15 g. (56%) of a solid was obtained. Recrystallization from benzene–petroleum ether gave pale yellow prisms: m.p. 72–75°; λ_{max}^{EtOH} 340 mμ (log ε 4.27); n.m.r., τ 0.25 (NH, broad doublet, J = 6 c.p.s.), 6.27 (C-6 H, doublet, J = 1 c.p.s.), 2.67 (C-4 H, doublet of triplets, J = 6, 1 c.p.s.). Addition of a small amount of deuterium oxide to the solution examined altered the spectrum; the signal of NH disappeared, and the doublet of triplets due to the C-4 methylidyne proton was converted into a triplet (J = 1 c.p.s.).

Anal. Calcd. for $C_7H_9NO_2S_2$: C, 41.35; H, 4.46; N, 6.89; S, 31.55. Found: C, 41.98; H, 4.72; N, 6.91; S, 31.30.

5-Ethoxycarbonyl-2-methylthio-6H-1,3-thiazine (XII).—Sodium (0.144 g.) was allowed to react with 6.3 ml. of absolute ethanol. To this were added 1.25 g. of XI and 1.13 g. of methyl iodide and the mixture was refluxed for 30 min. The reaction mixture was concentrated *in vacuo*, and water was added to the residue which was then extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by alumina chromatography with benzene and the oil (0.75 g., 56%) obtained was distilled under reduced pressure to give 0.6 g. of an oil: b.p. 126–128° (1.2 mm.); λ_{max}^{EtOH} 240, 330 mμ (log ε 4.11, 4.06); n.m.r., τ 7.45 (SCH_3, singlet), 6.42 (C-6 H, doublet, J = 1 c.p.s.), 2.20 (C-4 H, doublet, J = 1 c.p.s.).

Anal. Calcd. for $C_8H_{11}NO_2S_2$: C, 44.22; H, 5.10; N, 6.45; S, 29.51. Found: C, 44.20; H, 5.30; N, 6.46; N, 29.25.

5-Ethoxycarbonyl-2-methylamino-6H-1,3-thiazine (VII).—A solution of 0.25 g. of XII and 1.5 g. of methylamine in 15 ml. of methanol was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in dilute hydrochloric acid, and the acid solution was washed with ethyl acetate. The hydrochloric acid layer was neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried over magnesium sulfate and evaporated. The residue was treated with petroleum ether to give 0.09 g. (39%) of VII, which was identical with the sample obtained in the reaction of N-methylthiourea with I.

2-Dimethylamino-5-ethoxycarbonyl-6H-1,3-thiazine (IX). A.—A solution of 0.217 g. of XII and 1.8 g. of dimethylamine in 10 ml. of methanol was refluxed for 1 hr. The reaction mixture was treated as above and the oil obtained was converted into the picrate, yielding 0.245 g. (55%). Recrystallization from ethanol gave 0.227 g. of yellow prisms: m.p. 126°; n.m.r., τ 6.45 ($N-CH_3$, 6H, singlet), 6.05 (C-6 H, doublet, J = 1 c.p.s.), 2.42 (C-4 H, triplet, J = 1 c.p.s.).

Anal. Calcd. for $C_{15}H_{17}N_5O_9S$: C, 40.63; H, 3.86; N, 15.79; S, 7.23. Found: C, 40.92; H, 4.13; N, 15.72; S, 7.49.

B.—To the solution of 0.21 g. of VII in 2.0 ml. of absolute dimethylformamide, 0.08 g. of sodium hydride (50% oil suspension) was added and stirred for 1 hr. at room temperature. To this was added 0.2 g. of methyl *p*-tosylate and the mixture was warmed at 50° for 1 hr. with stirring. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in ethanol and converted into picrate, yielding 0.06 g., which was identical with the sample obtained from A.

C.—To the solution of 1.0 g. of VII in 20 ml. of absolute dioxane, 0.24 g. of sodium hydride (50% oil suspension) was added and the mixture was stirred for 3 hr. at room temperature. After the addition of 0.85 g. of methyl iodide the mixture was refluxed for 12 hr. and filtered. The filtrate was concentrated *in vacuo*, the residue was chromatographed on alumina with chloroform, and the two oils obtained were converted into picrates to give 0.11 g. of VI picrate and 0.04 g. of IX picrate.

5-Ethoxycarbonyl-1-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIa).—To the solution of 0.21 g. of 5-ethoxycarbonyl-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIVa)[3] in 2.0 ml. of absolute pyridine, 0.2 g. of phosphorus pentasulfide was added and refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, and water was added to the residue which was then extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to give 0.2 g. (88%) of pale yellow crystals, which was recrystallized from benzene–petroleum ether to give yellow needles: m.p. 139–141°; λ_{max}^{EtOH} 315 mμ (log ε 4.14); n.m.r., τ 6.50 (N-1 CH_3, singlet), 2.45 (N-3 H, broad), 5.85 (C-4 H, doublet, J = 1 c.p.s.), 2.85 (C-6 H, triplet, J = 1 c.p.s.).

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.04; N, 13.99; S, 16.01. Found: C, 47.80; H, 6.17; N, 13.76; S, 16.23.

5-Ethoxycarbonyl-3-methyl-2-thio-1,2,3,4-tetrahydropyrimidine (XIIIb).—To the solution of 0.3 g. of 5-ethoxycarbonyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIVb)[3] in 3.0 ml. of absolute pyridine, 0.3 g. of phosphorus pentasulfide was added and refluxed for 4.5 hr. The reaction mixture was treated as above and 0.19 g. (58%) of pale yellow needles, m.p. 135–137° (from benzene), was obtained: λ_{max}^{EtOH} 312 mμ (log ε 4.12); n.m.r., τ 6.63 (N-3 CH_3, singlet), 1.42 (N-1 H, broad), 5.85 (C-4 H, doublet, J = 1 c.p.s.), 2.92 (C-6 H, doublet of triplets, J = 6, 1 c.p.s.). Addition of a small amount of deuterium oxide to the solution examined altered the spectrum; the signal of NH disappeared, and the doublet of triplets due to the C-6 methylidyne proton was converted into a triplet (J = 1 c.p.s.).

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.04; N, 13.99; S, 16.01. Found: C, 48.43; H, 5.94; N, 14.27; S, 15.64.

Rearrangement of VII. A.—A solution of 0.4 g. of VII in 2.0 ml. of absolute formic acid was refluxed for 6 hr. The reaction mixture was concentrated *in vacuo*, to the residue was added dilute sodium hydroxide, and the separated crystals were collected to give 0.35 g. of starting material.

B.—A solution of 0.5 g. of VII in 2.0 ml. of formic acid and 1.5 ml. of triethylamine (not anhydrous) was heated in an oil bath at 160° for 6 hr. The reaction mixture was concentrated *in vacuo*, and water was added to the residue which was then extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to give 0.17 g. of pale yellow crystals, which were recrystallized from benzene–petroleum ether to give pale yellow needles, m.p. 138–140°. These crystals were found to be the mixture of XIIIa and XIIIb in a ratio of about 3:2.

C.—A solution of 1.0 g. of VII in 2.0 ml. of 50% formic acid was heated on the steam bath for 6 hr. After cooling, the separated needles, m.p. 134–139°, were collected, yielding 0.45 g., which was found to be a mixture of XIIIa and XIIIb in a ratio of 5:1 (50% acetic acid also gave this mixture; however, the yield was lower).

D.—A solution of 2.0 g. of VII in 2.0 ml. of formic acid and 0.6 ml. of 38% formalin was heated on the steam bath for

7 hr. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated. The residual oil was chromatographed on alumina with ethyl acetate and 0.2 g. of II and 0.1 g. of the mixture of XIIIa and XIIIb in a ratio of about 3:1, m.p. 138–140° (from benzene–petroleum ether), were obtained.

Rearrangement of VI. A.—A solution of 0.5 g. of VI and 1.5 ml. of triethylamine in 2.0 ml. of formic acid was heated at 160° for 6 hr. The reaction mixture was concentrated *in vacuo*, water was added to the residue, and the separated crystals were extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated to give 0.4 g. of yellow crystals, which were found to be identical with V by comparison of their infrared spectra.

B.—A solution of 0.5 g. of VI and 0.6 ml. of concentrated hydrochloric acid in 30 ml. of ethanol was refluxed for 37 hr. The reaction mixture was concentrated *in vacuo*, and the residue was neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and evaporated to give 0.4 g. of residual crystals, which were found to be identical with V.

2-Anilino-5-ethoxycarbonyl-6H-1,3-thiazine (XV).—To a solution of 0.58 g. of XII in 10 ml. of methanol, 0.4 g. of aniline was added and refluxed for 1.5 hr. The reaction mixture was concentrated *in vacuo* and the residue was extracted with ether. Evaporation of ether left a crystalline residue, which was recrystallized from benzene–petroleum ether to give 0.43 g. (61%) of pale brown needles: m.p. 121–123°; λ_{max}^{EtOH} 311 mμ (log ε 4.34); n.m.r., τ 6.38 (C-6 H, singlet), 0.97 (NH, broad).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.45; H, 5.51; N, 10.66; S, 12.46.

5-Ethoxycarbonyl-1-phenyl-2-thio-1,2,3,4-tetrahydropyrimidine (XVI).—To the solution of 0.2 g. of 5-ethoxycarbonyl-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine[3] in 3.0 ml. of absolute pyridine, 0.2 g. of phosphorus pentasulfide was added and refluxed for 3.5 hr. The reaction mixture was concentrated *in vacuo*, and water was added to the residue which was then extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by chromatography on alumina and 0.05 g. of pale yellow needles, m.p. 192°, was obtained: λ_{max}^{EtOH} 315 mμ (log ε 4.13).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.53; H, 5.38; N, 10.68; S, 12.20. Found: C, 59.45; H, 5.55; N, 10.74; S, 12.20.

Rearrangement of XV.—A solution of 0.6 g. of XV in 1.2 ml. of 50% formic acid was heated on the steam bath for 8 hr. Water was added to the reaction mixture which was then extracted with ethyl acetate.

The ethyl acetate extract was dried over anhydrous magnesium sulfate and evaporated. The residual oil was chromatographed on alumina with ethyl acetate and the following products were obtained: 0.03 g. of N-phenylthiourea; 0.051 g. of pale yellow needles, m.p. 192°, which was found to be identical with XVI obtained above; 0.07 g. of II; and 0.017 g. of pale yellow needles (XVII) of m.p. 175–178°, λ_{max} 316 mμ (log ε 4.17).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.53; H, 5.38; N, 10.68; S, 12.20. Found: C, 58.99; H, 5.26; N, 10.13; S, 12.21.

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p-Alkoxy- and *p*-Carbalkoxybenzoates of Diphenols. A New Series of Liquid Crystalline Compounds[1]

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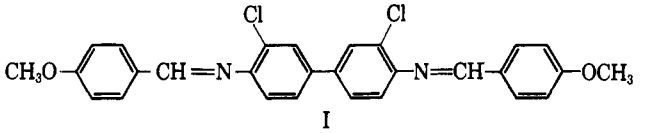
Nineteen liquid crystalline *p*-phenylene and *p,p'*-biphenylene esters of *p*-alkoxy- and *p*-carbalkoxybenzoic acids have been synthesized. Ten of them exhibit very broad mesomorphic ranges and high (mesophase → liquid) transition temperatures. The effects of structural changes on phase transitions in this series are discussed. Four new *n*-alkyl terephthalates were also prepared in the course of this work.

Since we plan a general survey of the use of liquid crystals[2] as solvents, we have been concerned with the choice of suitable materials for this work. Any unusual solvent properties of such compounds should be greater, the greater the anisotropic ordering of the molecules in them. This in turn should be greater, the stronger the anisotropic forces between the molecules and the lower the temperature. Now strong anisotropic forces should be reflected in a high transition temperature from nematic[2] to normal liquid; clearly what we need is a compound with a high transition temperature and a long mesomorphic range. The molecular orientation in such a compound should be particularly strong at the lower end of its mesomorphic range, near the melting point.

We had a further interest in compounds of this type in view of their possible use as stationary phases in gas chromatography. Our preliminary work[3] was carried out with compounds that had short mesomorphic ranges and low transition temperatures to normal liquid; the range of materials that could be separated on such columns is clearly limited.

One series of compounds has been described that appeared to meet our specifications, the 4,4'-bis(*p*-methoxybenzylideneamino)biphenyls; the 3,3'-dichloro derivative (I) in particular is stated[4] to be nematic



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from 149 to above 340°. However, when we examined this substance, we found it to be thermally unstable,

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