The Reaction of Imidoyl Isothiocyanates with Enamines. A New Synthesis of 1,2-Disubstituted Pyrimidine Derivatives

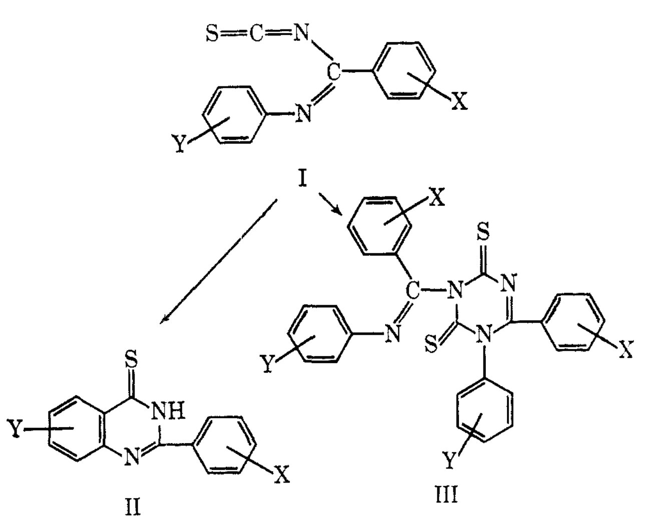
HERBERT M. BLATTER AND HALINA LUKASZEWSKI

Chemical Research Division, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

Received September 15, 1965

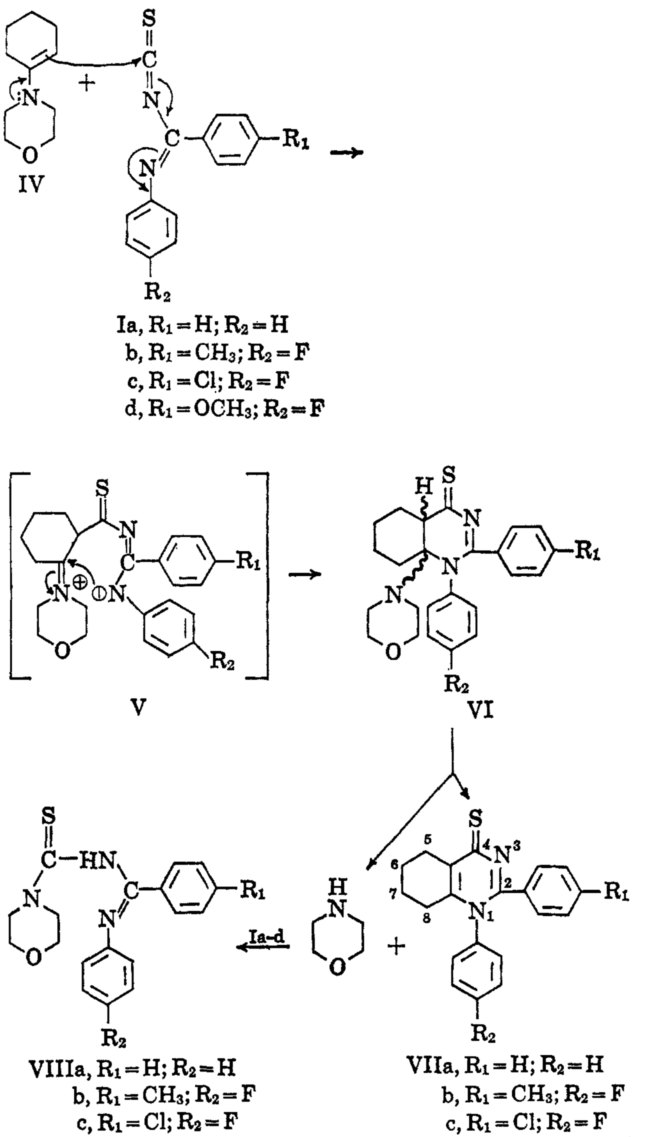
Imidoyl isothiocyanates react with simple enamines to afford readily separable mixtures of 1,2-disubstituted 5,6,7,8-tetrahydro-4-quinazolinethiones (VIIa–d) and substituted thioureas (VIIIa–d). In those cases where morpholine expulsion was not possible, the direct condensation product (Xa, c) was isolated. The spectral properties of these compounds are described.

Imidoyl isothiocyanates (I) have previously[1] been found to undergo ring closure readily to 4(3H)-quinazolinethiones (II) without catalytic assistance. They may also dimerize[2] to *s*-triazine derivatives (III) either spontaneously or under the apparent influence of light or heat.[3]



Recently Carney, *et al.*,[4] have reported the formation of novel pyrimidine derivatives from the reaction of acyl isothiocyanates with suitable enamines. We have found that these same types of compounds may be more easily prepared through the reaction of imidoyl isothiocyanates with enamines. Since the method of Carney, *et al.*, seems to be limited[4,5] to the preparation of those compounds related to VIIa–d (see Scheme I) which only have a phenyl group at ring position 2, it is evident that this new method is considerably more versatile.

SCHEME I



N-(1-Cyclohexenyl)morpholine (IV) reacted rapidly with imidoyl isothiocyanates (Ia–d) (see Scheme I) in a variety of solvents to give a mixture of two readily separable products, a 1,2-diaryl-5,6,7,8-tetrahydro-4-quinazolinethione (VIIa–d) and a thiourea derivative (VIIIa–d), in fair yield. 1,2-Diphenyl-5,6,7,8-tetrahydro-4-quinazolinethione (VIIa) was compared directly with an authentic sample.[4] The thiourea derivative (VIIId) was identical with the adduct formed from the reaction of morpholine with N-(*p*-fluorophenyl)-*p*-anisimidoyl isothiocyanate (Id).

The postulated nucleophilic attack by N-(1-cyclohexenyl)morpholine (IV) on the isothiocyanate function, as depicted in Scheme I, would certainly be in accord with the published findings on the reactions of enamines with both aroyl[4,6] and aryl[7] isothiocyanates.

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[1] H. M. Blatter and H. Lukaszewski, *Tetrahedron Letters*, 855 (1964).

[2] H. M. Blatter and H. Lukaszewski, *ibid.*, 1087 (1964).

[3] Dimerization of imidoyl isothiocyanate oils sometimes occurred spontaneously at room temperature in the presence of sunlight. Crystalline imidoyl isothiocyanates were quite stable under comparable conditions. In most cases, the conversion of imidoyl chlorides to isothiocyanates with lead thiocyanate in refluxing benzene was accompanied by the formation of relatively small amounts of dimerization product. Ring closure of imidoyl isothiocyanates in boiling toluene or xylene to 4(3H)-quinazolinethiones was often accompanied by a minor degree of dimerization.

[4] R. W. J. Carney, J. Wojtkunski, and G. deStevens, *J. Org. Chem.*, **29**, 2887 (1964), and references therein.

[5] Personal communication from Dr. R. W. J. Carney and Dr. deStevens.

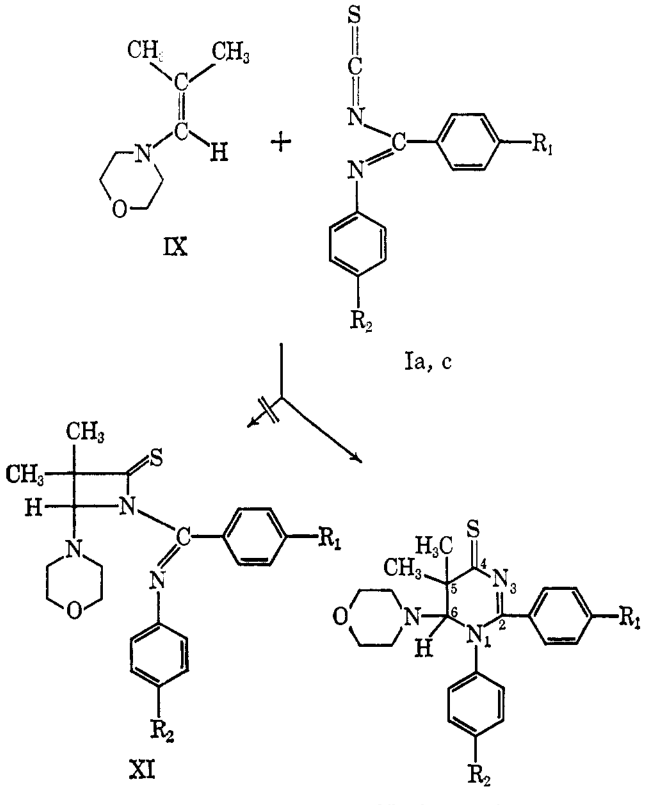
[6] S. Hünig and K. Hübner, *Chem. Ber.*, **95**, 937 (1962).

[7] S. Hünig, K. Hübner, and E. Benzing, *ibid.*, **95**, 926 (1962).

Subsequent ring closure of V would yield VI (undetermined stereochemistry) which could probably readily lose the elements of morpholine under the impetus of "aromatization" as a prime driving force. It is significant that the product ratio in each case (VIIa–d: VIIIa–d) was essentially unity and was virtually independent of solvent (ether, pentane, and dioxane), temperature, reactant molar ratios, and the rate and order of reactant addition. This is certainly a reflection of the extreme lability of VI (of probable *trans* ring fusion) concomitant with the higher order of reactivity of the expelled morpholine, in comparison to N-(1-cyclohexenyl)morpholine (IV), toward imidoyl isothiocyanates.

Stable analogs of intermediate VI, *i.e.*, those incapable of morpholine expulsion, could indeed be readily prepared by the reaction of suitably substituted enamines, *e.g.*, N-(2-methylpropenyl)morpholine (IX), with imidoyl isothiocyanates (Scheme II). The alternative four-membered ring structure XI[8] was excluded from consideration because of its incompatibility with the ultraviolet long-wave absorptions; *e.g.*, Xa shows $\lambda_{\max}^{CH_3OH}$ 365 mμ (ε 15,140). Both of the structural designations Xa and Xc are in accord with the spectral data and elemental analyses. The proton nmr spectrum[9] of 5,6-dihydro-5,5-dimethyl-6-morpholino-1,2-diphenyl-4-pyrimidinethione (Xa) clearly revealed the C-6 proton as a singlet signal at δ 4.53. The singlet signals (three protons each) at δ 1.53 and 1.63 were attributed to the protons of the two environmentally distinct methyl groups at C-5. Interestingly, the singlet signal (four protons) at δ 1.43 due to cyclohexane directly confirmed the analytical results, which indicated the presence of $^1/_3$ mole of solvent of recrystallization (cyclohexane). The cyclohexane signal increased at the expense of the other signals on the further addition of cyclohexane to the solution.

SCHEME II



Xa, $R_1 = H$; $R_2 = H$
c, $R_1 = Cl$; $R_2 = F$

Significant quantities of the thiourea derivatives, VIIIa and VIIIc, could be isolated during the preparation of Xa and Xc, respectively, in dioxane. This can in all likelihood be attributed to the presence of trace amounts of water in the solvent. Partial hydrolysis of the enamine (IX) would release morpholine, which could then react with the imidoyl isothiocyanates.

The imidoyl isothiocyanates utilized in this investigation were prepared by the reaction of lead thiocyanate with imidoyl chlorides in refluxing benzene.[1] Compounds Ib, c, and d were stable, crystalline materials. They showed the typically broad, strong isothiocyanate absorption, punctuated by several shoulders and bands, in the infrared spectrum (Nujol)[10,11] centered at 1960–2060 cm^{-1}. This absorption pattern was also characteristic of the acyl isothiocyanates.[12]

It would be anticipated that enamines derived from acyclic ketones would react similarly with imidoyl isothiocyanates (see IX, Scheme II).

The long-wave absorption in the ultraviolet of the 1,2-diaryl-5,6,7,8-tetrahydro-4-quinazolinethiones (VIIa–d) was virtually identical, both as to position and intensity, with that of the 1-alkyl-5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethiones[4,13] and the 1,2-disubstituted (either alkyl or aryl)-4-thiopyrimidines.[4] This apparent independence from substituent effects at C-1 and C-2 (alkyl or aryl) of the long-wave absorptions in these basically identical chromophores was previously found to be a characteristic of the 1,2-disubstituted 4-quinazolinethiones.[14]

Experimental Section[15]

N-(1-Cyclohexenyl)morpholine (IV) was prepared by the procedure of Hünig, *et al.*[16]

Benzanilides were prepared in the usual manner from the appropriate anilines and benzoyl chlorides in pyridine solution.

4'-Fluoro-*p*-toluanilide was obtained as white crystals, mp 186–188°.

Anal. Calcd for $C_{14}H_{12}FNO$: C, 73.34; H, 5.27; N, 6.11. Found: C, 73.37; H, 5.28; N, 6.03.

4-Chloro-4'-fluorobenzanilide was obtained as white crystals, mp 179–181°.

Anal. Calcd for $C_{13}H_9ClFNO$: C, 62.54; H, 3.64; N, 5.85. Found: C, 62.64; H, 3.92; N, 5.92.

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[8] G. Opitz and J. Koch [*Angew. Chem.*, **75**, 167 (1963)] have reported the formation of similar four-membered ring compounds from the reaction of isocyanates with N-(2-methylpropenyl)pyrrolidine.

[9] The nmr spectrum was determined on a Varian A-60 spectrometer at 60 Mc/sec in deuteriochloroform using tetramethylsilane as internal reference. Chemical shifts are quoted in field-independent δ units (parts per million).

[10] E. Lieber, C. N. R. Rao, and J. Ramachandran, *Spectrochim. Acta*, **13**, 296 (1959).

[11] G. L. Caldow and H. W. Thompson, *ibid.*, **13**, 212 (1958).

[12] P. A. S. Smith and D. W. Emerson, *J. Am. Chem. Soc.*, **82**, 3076 (1960).

[13] For 1-benzyl-5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethione, $\lambda_{\max}^{C_2H_5OH}$ 343 mμ (ε 25,350), and for 1-decyl-5,6,7,8-tetrahydro-2-phenyl-4-quinazolinethione, $\lambda_{\max}^{C_2H_5OH}$ 341–345 (ε 24,820).

[14] H. M. Blatter, H. Lukaszewski, and G. deStevens, *J. Org. Chem.*, **30**, 1020 (1965).

[15] The melting points are uncorrected. The ultraviolet spectra were determined in methanol unless otherwise indicated. The abbreviations w, m, s, sh, and plat refer respectively to weak, medium, and strong relative absorptions, and to shoulder and plateau.

[16] S. Hünig, E. Lücke, and W. Brenninger, *Org. Syn.* **41**, 65 (1961).

4′-Fluoro-*p*-anisanilide was obtained as white crystals, mp 197–199°.

Anal. Calcd for $C_{14}H_{12}FNO_2$: C, 68.56; H, 4.94; N, 5.71. Found: C, 68.69; H, 4.87; N, 5.74.

Benzimidoyl chlorides were prepared by refluxing the preceding benzanilides with excess thionyl chloride.

N-Phenylbenzimidoyl chloride was prepared by the procedure of von Braun and Pinkernelle.[17]

N-(*p*-Fluorophenyl)-*p*-toluimidoyl chloride was obtained as white needles, mp 89–91°.

Anal. Calcd for $C_{14}H_{11}ClFN$: C, 67.88; H, 4.48; N, 5.66. Found: C, 67.53; H, 4.68; N, 5.42.

***p*-Chloro-N-(*p*-fluorophenyl)benzimidoyl chloride** was obtained as white crystals, mp 78–80°.

Anal. Calcd for $C_{13}H_8Cl_2FN$: C, 58.24; H, 3.01; N, 5.23. Found: C, 58.36; H, 3.05; N, 5.18.

N-(*p*-Fluorophenyl)-*p*-anisimidoyl chloride was obtained as white crystals, mp 78–80°.

Anal. Calcd for $C_{14}H_{11}ClFNO$: C, 63.76; H, 4.21; N, 5.32. Found: C, 63.98; H, 4.30; N, 5.21.

Benzimidoyl Isothiocyanates (Ia–d).—The preparation of Ib will serve to illustrate the general method.

N-(*p*-Fluorophenyl)-*p*-toluimidoyl Isothiocyanate (Ib).—To a solution of 5.7 g (0.023 mole) of N-(*p*-fluorophenyl)-*p*-toluimidoyl chloride in 50 ml of benzene, there was added 7.45 g (0.023 mole) of lead thiocyanate. The mixture was refluxed for 2 hr and filtered, and the filtrate was evaporated to dryness *in vacuo*. On the addition of *n*-pentane to the residual oil, a small amount of crude orange solid formed. Filtration, followed by concentration and refrigerator cooling, gave 4.10 g (66% yield) of yellow product, mp 74–78°. Further recrystallization from *n*-pentane gave Ib as yellow crystals: mp 77–79°; infrared (Nujol), broad absorption centered at 2015 cm^{-1} (s) (–N═C═S); ultraviolet (cyclohexane), λ_{max} 222 mμ (ε 21,440), 270 (21,440), 342 (4170); λ_{min} 217 mμ (ε 21,140), 246 (12,550), 321 (3660); proton nmr,[9] methyl singlet at δ 2.43.

Anal. Calcd for $C_{15}H_{11}FN_2S$: C, 66.64; H, 4.10; N, 10.37. Found: C, 66.41; H, 4.33; N, 10.10.

***p*-Chloro-N-(*p*-fluorophenyl)benzimidoyl isothiocyanate (Ic)**, yellow crystals, mp 85–87° (from *n*-pentane), was isolated in 80% yield: infrared (Nujol), broad absorption centered at 2063 cm^{-1} (s) (–N═C═S); ultraviolet (cyclohexane), λ_{max} 222 mμ (ε 21,230), 270 (24,080), 276 (sh) (22,260), 346 (4120); λ_{min} 221 mμ (ε 21,140), 240 (14,390), 322 (3400).

Anal. Calcd for $C_{14}H_8ClFN_2S$: C, 57.84; H, 2.77; N, 9.64. Found: C, 58.17; H, 2.99; N, 9.33.

N-(*p*-Fluorophenyl)-*p*-anisimidoyl isothiocyanate (Id), yellow needles, mp 80–82° (from *n*-pentane), was isolated in 61% yield: infrared (Nujol), broad absorption centered at 1964 cm^{-1} (s) (–N═C═S); ultraviolet (cyclohexane), λ_{max} 226 mμ (ε 23,120), 290 (20,650), 336 (5490); λ_{min} 218 mμ (ε 20,710), 254 (6820), 330 (5440).

Anal. Calcd for $C_{15}H_{11}FN_2OS$: C, 62.92; H, 3.87; N, 9.79. Found: C, 62.92; H, 3.90; N, 9.60.

N-Phenylbenzimidoyl isothiocyanate (Ia) was prepared as described below and utilized *in situ*.

N-(Morpholinothiocarbonyl)-N′-phenylbenzamidine (VIIIa).—To a solution of 2.15 g (0.01 mole) of N-phenylbenzimidoyl chloride in 30 ml of benzene, there was added 3.23 g (0.01 mole) of lead thiocyanate. The mixture was refluxed for 2 hr and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residual red oil was dissolved in hexane and the small amount of insoluble material was removed by filtration. The hexane solution was evaporated to dryness, and the red viscous oil that remained showed isothiocyanate absorption in the infrared spectrum (neat) as a broad band centered at 2030 cm^{-1} (s).

The addition of excess morpholine to an ice bath cooled solution of the red oil in hexane solution resulted in the rapid formation of VIIIa as a yellow solid. Recrystallization from methanol gave the yellow, crystalline product (VIIIa), mp 85°, which retained 1 mole of methanol: infrared (Nujol), 3281 cm^{-1} (m) (–NH and –OH stretching frequencies); ultraviolet, $\lambda_{max}^{C_2H_5OH}$ 200 mμ (ε 37,040), 238 (19,570), 286 (15,460); $\lambda_{min}^{C_2H_5OH}$ 226 mμ (ε 18,540), 268 (14,460).

Anal. Calcd for $C_{18}H_{19}N_3OS \cdot CH_3OH$: C, 63.85; H, 6.48; N, 11.76. Found: C, 63.58; H, 6.41; N, 11.59.

N′-(*p*-Fluorophenyl)-*p*-methoxy-N-(morpholinothiocarbonyl)-benzamide (VIIId).—To an ice bath cooled solution of 0.285 g (0.001 mole) of N-(*p*-fluorophenyl)-*p*-anisimidoyl isothiocyanate (Id) in 50 ml of anhydrous ether there was added 0.12 g (0.0014 mole) of morpholine in 5 ml of anhydrous ether. There was no obvious reaction, so the solution was allowed to warm to room temperature. After a few minutes, crystals began to form. Filtration, after 18 hr at room temperature, gave 0.325 g (87% yield) of VIIId as pale yellow crystals, mp 198–201°. Two recrystallizations from acetone gave VIIId as pale yellow crystals: mp 204–206°; infrared (Nujol), 3221 cm^{-1} (m) (–NH stretching frequency); ultraviolet, λ_{max} 275 mμ (ε 26,060), λ_{min} 238 mμ (ε 15,680).

Anal. Calcd for $C_{19}H_{20}FN_3O_2S$: C, 61.11; H, 5.40; N, 11.26. Found: C, 61.12; H, 5.42; N, 10.90.

Reaction of N-(*p*-Fluorophenyl)-*p*-anisimidoyl Isothiocyanate (Id) with N-(1-Cyclohexenyl)morpholine (IV).—To an ice bath cooled solution of 3.34 g (0.02 mole) of IV in 20 ml of *p*-dioxane (Spectrograde) there was added slowly a solution of 5.72 g (0.02 mole) of Id in 30 ml of *p*-dioxane (Spectrograde). The resulting solution was allowed to warm to room temperature and then was allowed to stand overnight. A yellow solid precipitated during this period. Filtration afforded 2.3 g (63% yield based on the utilization of one-half of Id) of 1-(*p*-fluorophenyl)-5,6,7,8-tetrahydro-2-(*p*-methoxyphenyl)-4-quinazolinethione (VIId) as a yellow solid, mp >300°. Two recrystallizations from dimethylformamide gave VIId as yellow crystals: mp 302–304° dec; infrared (Nujol), absence of –NH or –OH stretching frequencies; ultraviolet, λ_{max} 230 mμ (ε 12,400), 274 (sh) (8170), 288 (sh) (10,160), 297 (sh) (11,420), 342 (26,830); λ_{min} 224 mμ (ε 11,300), 251 (6500).

Anal. Calcd for $C_{21}H_{19}FN_2OS$: C, 68.64; H, 5.23; N, 7.64. Found: C, 68.93; H, 5.39; N, 7.64.

To the *p*-dioxane mother liquors there was added an excess of ether until the precipitation of a pink solid was completed. One recrystallization from dioxane with Norit decolorization followed by recrystallization from acetone gave 2.5 g (62% yield based on the utilization of one-half of Id) of VIIId as pale yellow crystals, mp 204–206°. A mixture melting point with VIIId prepared by the method described previously was not depressed.

Reaction of N-(*p*-Fluorophenyl)-*p*-toluimidoyl Isothiocyanate (Ib) with N-(1-Cyclohexenyl)morpholine (IV).—To an ice bath cooled solution of 1.67 g (0.01 mole) of IV in 10 ml of *p*-dioxane (Spectrograde) there was added slowly a solution of 2.7 g (0.01 mole) of Ib in 15 ml of *p*-dioxane. The resulting solution was allowed to warm to room temperature and was then seeded with an authentic sample of VIIb obtained from an initial run. After standing overnight a total of 1.4 g (80% yield based on the utilization of one-half of Ib) of 1-(*p*-fluorophenyl)-5,6,7,8-tetrahydro-2-(*p*-tolyl)-4-quinazolinethione (VIIb) was obtained as a yellow precipitate, mp 289–294° dec. Two recrystallizations from acetone gave VIIb as yellow crystals: mp 291–293° dec; infrared (Nujol), absence of –NH or –OH stretching frequencies; ultraviolet, λ_{max} 258 mμ (ε 8370), 276 mμ (sh) (7740), 342 (26,260); λ_{min} 252 mμ (ε 8280), 298 (6560).

Anal. Calcd for $C_{21}H_{19}FN_2S$: C, 71.97; H, 5.47; N, 7.99. Found: C, 72.10; H, 5.29; N, 7.73.

Reaction of *p*-Chloro-N-(*p*-fluorophenyl)benzimidoyl Isothiocyanate (Ic) with N-(1-Cyclohexenyl)morpholine (IV).—From 2.3 g (0.014 mole) of IV and 4.0 g (0.014 mole) of Ic in a total of 30 ml of dioxane there was obtained, after one recrystallization from acetone, 1.9 g (74% yield based on the utilization of one-half of Ic) of 2-(*p*-chlorophenyl)-1-(*p*-fluorophenyl)-5,6,7,8-tetrahydro-4-quinazolinethione (VIIc) as yellow crystals, mp >300° dec. One additional recrystallization from acetone gave VIIc as yellow crystals: mp >300° dec; infrared (Nujol), absence of –NH or –OH stretching frequencies; ultraviolet, λ_{max} 202 mμ (sh) (ε 32,740), 252 (sh) (10,540), 343 (26,600); λ_{min} 296 mμ (ε 5860).

Anal. Calcd for $C_{20}H_{16}ClFN_2S$: C, 64.76; H, 4.35; N, 7.55. Found: C, 64.63; H, 4.31; N, 7.33.

From the *p*-dioxane mother liquors there was obtained 2.0 g of crude solid which yielded 1.55 g of *p*-chloro-N′-(*p*-fluorophenyl)-N-(morpholinothiocarbonyl)benzamidine (VIIIc) (60% yield based on the utilization of one-half of Ic) as a yellow solid, mp 200–205°, after one recrystallization from acetone. Further recrystallizations from acetone gave VIIIc as pale yellow crystals: mp 203–205°; infrared (Nujol), 3316 cm^{-1} (m) (–NH stretching frequency); ultraviolet, λ_{max} 246 mμ (ε 24,580), 284 (sh) (17,630); λ_{min} 226 mμ (ε 20,720).

Anal. Calcd for $C_{18}H_{17}ClFN_3OS$: C, 57.21; H, 4.53; N, 11.12. Found: C, 57.48; H, 4.63; N, 10.85.

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[17] J. von Braun and W. Pinkernelle, *Ber.*, **67**, 1218 (1934).

Reaction of N-Phenylbenzimidoyl Isothiocyanate (Ia) with N-(1-Cyclohexenyl)morpholine (IV).—To a solution of 6.45 g (0.03 mole) of N-phenylbenzimidoyl chloride in 90 ml of benzene (dried over sodium wire) there was added 9.7 g (0.03 mole) of lead thiocyanate. The mixture was refluxed for 2 hr and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residual red oil was dissolved in 150 ml of *n*-pentane (dried over sodium wire). Approximately 1.0 g of insoluble material [mostly compound II (X = Y = H) with a small amount of compound III (X = Y = H)][1,2] was removed by filtration. The *n*-pentane filtrate was then assumed to contain 0.026 mole of N-phenylbenzimidoyl isothiocyanate, based on 100% conversion of the imidoyl chloride to Ia, II, and III. The infrared spectrum of Ia has been described previously (see preparation of VIIIa). The solution was divided into three equal portions.

A.—The first portion (0.0089 mole of Ia) was evaporated to dryness and the residue was dissolved in 15 ml of *p*-dioxane (Spectrograde). To this solution, cooled in an ice bath, there was added 1.57 g (0.0094 mole) of IV, dropwise and with stirring. The resulting solution was allowed to warm to room temperature and then was allowed to stand overnight. A yellow solid, 0.85 g, mp 260–274°, precipitated during this period (60% yield based on the utilization of one-half of Ia). Two recrystallizations from acetone gave 1,2-diphenyl-5,6,7,8-tetrahydro-4-quinazolinethione (VIIa) as yellow crystals, mp 270–272°, $\lambda_{\max}^{C_2H_5OH}$ 342–345 mμ (ε 27,100). A mixture melting point with authentic material was not depressed.

B.—To an ice bath cooled solution of the second portion (*n*-pentane solution, 0.0089 mole of Ia), there was added 1.57 g (0.0094 mole) of IV, dropwise and with stirring. A yellow, fluffy solid started to precipitate immediately. The mixture was allowed to warm to room temperature and then was allowed to stand overnight. A total of 2.1 g of solid, mp 70–210°, was obtained. This material was shown to be essentially an equal mixture of VIIa and VIIIa by thin layer chromatography.

C. The third equal portion was evaporated to dryness and the residue was dissolved in 15 ml of anhydrous ether. To this solution, cooled in an ice bath, there was added 1.57 g (0.0094 mole) of IV, dropwise and with stirring. The resulting solution was allowed to warm to room temperature and then was allowed to stand overnight. Filtration gave 1.02 g (72% yield based on the utilization of one-half of Ia) of VIIa, mp 255–270°.

D.—To an ice bath cooled solution of 0.0089 mole of Ia (prepared as described previously) in 15 ml of dioxane, there was added 4.71 g (0.028 mole) of IV all at once. After standing at room temperature overnight, 1.1 g (78% yield based on the utilization of one-half of Ia) of VIIa, mp 265–274°, was obtained.

E.—To an ice bath cooled solution of 4.71 g (0.028 mole) of IV in 10 ml of dioxane, there was added 0.0089 mole of Ia (prepared as described previously) in 5 ml of dioxane, dropwise and with stirring. After standing at room temperature overnight, 1.0 g (71% yield based on the utilization of one-half of Ia) of VIIa, mp 265–274°, was obtained.

F.—To an ice bath cooled solution of 4.71 g (0.028 mole) of IV in 10 ml of *n*-pentane (dried over sodium wire), there was added 0.0089 mole of Ia in 25 ml of *n*-pentane, dropwise and with stirring. After standing at room temperature overnight, 1.95 g of solid, mp 170–220°, was obtained. This material was shown to be essentially an equal mixture of VIIa and VIIIa by thin layer chromatography.

N-(2-Methylpropenyl)morpholine (IX) was prepared by the procedure of Benzing.[18]

Reaction of N-Phenylbenzimidoyl Isothiocyanate (Ia) with N-(2-Methylpropenyl)morpholine (IX).—To an ice bath cooled solution of 2.64 g (0.028 mole) of IX in 20 ml of *p*-dioxane (Spectrograde), there was added 0.018 mole of Ia (prepared as described previously) in 10 ml of dioxane. After standing at room temperature for 2 days, the solution was evaporated to dryness *in vacuo*. The red residue was extracted with boiling cyclohexane. On cooling, the extract yielded 2.8 g, mp ~80° (bubbling), of 5,6-dihydro-5,5-dimethyl-6-morpholino-1,2-diphenyl-4-pyrimidinethione (Xa) as an orange-red solid containing $^1/_3$ mole of cyclohexane of crystallization (38% yield based on Ia and minus solvent of crystallization). One recrystallization from cyclohexane gave Xa as orange-red crystals: mp ~80° (bubbling); infrared (Nujol), absence of –NH or –OH stretching frequencies; ultraviolet, $\lambda_{\max}$ 223 mμ (sh) (ε 15,160), 276 (sh) (6420), 365 (15,140); $\lambda_{\min}$ 258 mμ (ε 5310); proton nmr spectrum, see text.

Anal. Calcd for $C_{22}H_{25}N_3OS \cdot {}^1/_3C_6H_{12}$: C, 70.73; H, 7.15; N, 10.35; S, 7.87. Found: C, 70.30; H, 6.95; N, 10.29; S, 7.85.

The cyclohexane-insoluble material was undoubtedly VIIIa, based on the analogous reaction described below, although this was not verified in this case. There was no indication of a reaction, even after 2 days, when *p*-dioxane was replaced by *n*-pentane.

Reaction of *p*-Chloro-N-(*p*-fluorophenyl)benzimidoyl Isothiocyanate (Ic) with N-(2-Methylpropenyl)morpholine (IX).—To an ice bath cooled solution of 2.94 g (0.021 mole) of IX in 20 ml of *p*-dioxane, there was added 6.1 g (0.021 mole) of Ic in 20 ml of dioxane. After standing at room temperature for 2 days, the solution was evaporated to dryness *in vacuo*. The residue was extracted with boiling anhydrous ether. Recrystallization of the ether-insoluble material from acetone gave 1.45 g of the thiourea derivative VIIIc, mp 203–206°, which was previously characterized. The ether extract yielded, on cooling, 4.1 g, mp 160–163°, of 2-(*p*-chlorophenyl)-1-(*p*-fluorophenyl)-5,6-dihydro-5,5-dimethyl-6-morpholino-4-pyrimidinethione (Xc) as an orange-red crystalline solid (45% yield based on 100% conversion of Ic). One recrystallization from anhydrous ether gave Xc as orange-red crystals: mp 161–163°; infrared (Nujol), absence of –NH or –OH stretching frequencies; ultraviolet, $\lambda_{\max}$ 222 mμ (sh) (ε 13,180), 281 (sh) (7290), 365 (16,580); $\lambda_{\min}$ 257 mμ (ε 4780).

Anal. Calcd $C_{22}H_{23}ClFN_3OS$: C, 61.17; H, 5.37; N, 9.73. Found: C, 61.36; H, 5.40; N, 9.48.

Pure samples of Xc very slowly turned tan on continued exposure to light.

Acknowledgment.—We are grateful to Mr. L. Dorfman and his staff for the microanalyses and for helpful discussions concerning the spectral data.

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