The Synthesis of 1,2-Disubstituted 4-Quinazolinones and Related Thiones

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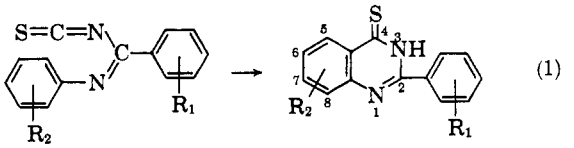
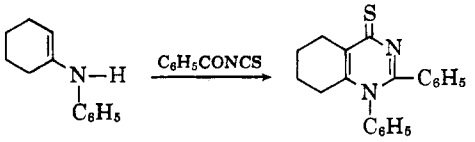
This report is primarily concerned with the application of the Chapman rearrangement (imido esters to substituted amides) to the synthesis of 1,2-disubstituted 4-quinazolinones. Additionally, the structure of the unusual acylation product of 2-methyl-1-phenyl-4-quinazoline (XIV) is elucidated. The spectral characteristics of these compounds are discussed.

In previous studies in our laboratories, the unique thermally induced ring closure of imidoyl isothiocyanates to 4(3H)-quinazolinethiones[1,2] (eq. 1) was found to be an eminently practical means of preparation of this class of heterocyclic compounds. Also, in connection with another project, it was shown that benzoyl



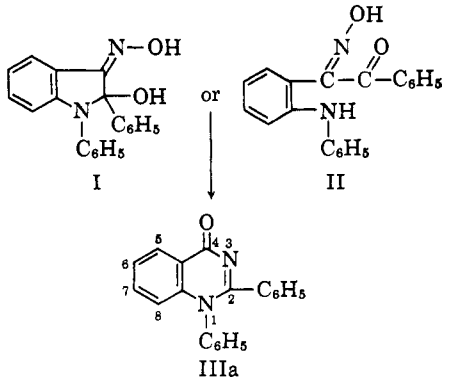
(1)

isothiocyanate readily interacted with N-(1-cyclohexenyl)aniline to afford 1,2-diphenyl-5,6,7,8-tetrahydro-4-quinazolinethione[3] (eq. 2).



(2)

Accordingly, these findings have prompted us to complete the synthetic cycle in this series by preparing 1,2-disubstituted 4-quinazolinethiones and their 4-oxo derivatives with special emphasis on compounds with aryl groups at the 1-position and either aryl or alkyl substituents at C-2. A survey of the literature surprisingly revealed that compounds of this type have received little attention. Huang-Hsinman and Mann[4] reported that 2-hydroxy-3-oximino-1,2-diphenylindoline (I), obtained from 3-amino-1,2-diphenylindole through atmospheric oxidation, was converted by means of ethanolic hydrogen chloride, aqueous sodium hydroxide, or heat alone to a colorless, crystalline substance, m.p. 280–281°, whose molecular formula, $C_{20}H_{14}N_2O$, corresponded to that of the quinazolinone IIIa. These authors acknowledged the tenuity of their structural assignments, and suggested the oxime II as an alternative structure for I. The problem remained at this impasse at the time we began our studies in this series.[5]



Preliminary work[6] indicated that such apparently feasible approaches as dehydrogenation of 1,2-diphenyl-5,6,7,8-tetrahydro-4-quinazolinone[3] and condensation of N-phenylanthranilic acid with benzonitrile[7] or ethyl iminobenzoate[7,8] yielded, respectively, only intractable tars and starting materials. Thus we decided to prepare substituted anthranilamides such as Va by the application of the Chapman rearrangement[9] to imido esters such as IV (Scheme I), which itself could be prepared by the reaction of N-phenylbenzimidoyl chloride with salicylamide in the presence of sodium alkoxide, and then to effect ring closure by heating.[10] This procedure would be similar to that used by Jamison and Turner[11] in their application of the Chapman rearrangement to the synthesis of N-acylated anthranilic acids and esters.

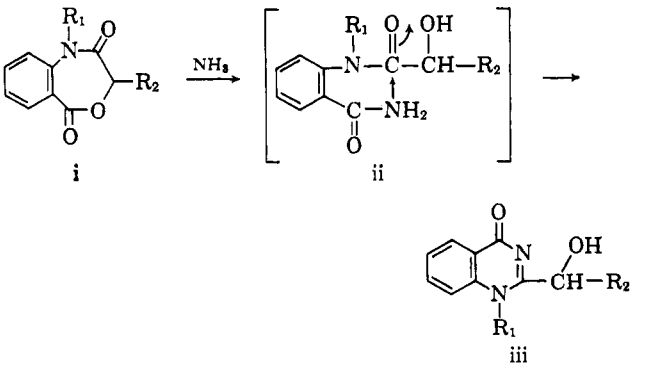
(1) H. M. Blatter and H. Lukaszewski, *Tetrahedron Letters*, 855 (1964).

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

(3) R. W. J. Carney, J. Wojtkunski, and G. deStevens, *J. Org. Chem.*, **29**, 2887 (1964). This substance and related compounds have also been prepared by the reaction of suitable enamines with imidoyl isothiocyanates (unpublished results of H. M. Blatter to be discussed in detail in a forthcoming publication).

(4) Huang-Hsinman and F. G. Mann, *J. Chem. Soc.*, 2903 (1949).

(5) Recently, a new synthesis of 4-quinazolinones applicable to the preparation of 1-aryl derivatives was reported by M. R. Uskoković, J. Jacobelli, and W. Wenner (Abstracts of Papers, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p. 7M). In their case, 4,1-benzoxazepine-2,5(1H,3H)-diones (i) were found to react with ammonia to yield the 4-quinazolinones iii. This reaction undoubtedly



proceeds through the anthranilamide derivative ii with subsequent ring closure, and thus represents an approach to the synthesis of substituted anthranilamides of this type different from those we have successfully employed in this investigation. In addition, their method is apparently limited to the preparation of compounds having an α-hydroxy function on the C-2 substituent.

(6) Unpublished results of Dr. R. W. J. Carney of our laboratories.

(7) W. Ried and W. Stephan, *Chem. Ber.*, **95**, 3042 (1962).

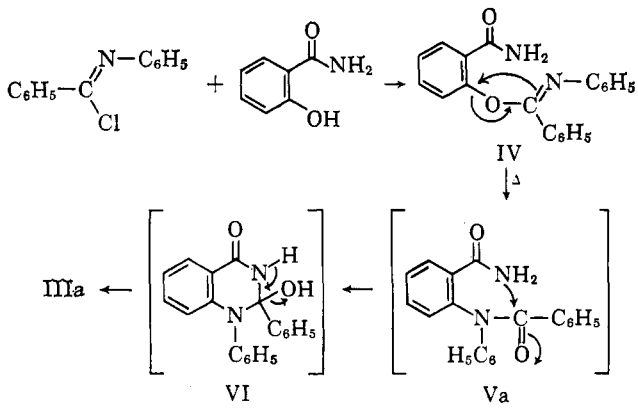
(8) W. Ried and W. Stephan, *ibid.*, **96**, 1218 (1963).

(9) "The Merck Index," P. G. Stecher, Ed., 7th Ed., Merck and Co., Inc., Rahway, N. J., 1960, p. 1413.

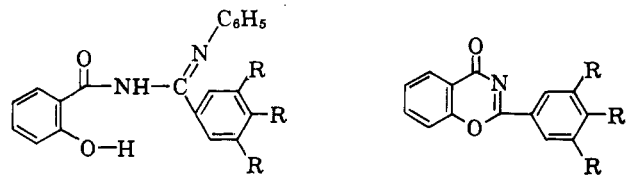
(10) W. L. F. Armarego, *Advan. Heterocyclic Chem.*, **1**, 292 (1963).

(11) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1954 (1937).

SCHEME I



The possible formulation of IV as the isomeric phenol VIIa was ruled out because of the reported[12] lower melting range (by 30°) and bright yellow color of compound VIIa. In addition, the product IV lacks the phenolic OH stretching band in the infrared spectrum (Nujol) which is so prominently displayed by VIIb at 3483 cm.$^{-1}$ as a sharp band of medium intensity (*vide infra*).



VIIa, R = H
b, R = OCH_3

VIIIa, R = H
b, R = OCH_3

Heating the imido ester IV alone at oil-bath temperatures of 270–275° to effect its rearrangement to Va as depicted in Scheme I invariably resulted in the formation of a mixture of difficultly separable products. Benzanilide could be readily identified as one of these. It undoubtedly arises from the reaction of IV with either atmospheric water or water generated along the lines shown in Scheme I. Refluxing a solution of the imido ester IV in diphenyl ether for 2, 12, or 24 hr. gave, respectively, a 10, 9, and 9% yield of a white, crystalline solid whose molecular formula, $C_{20}H_{14}N_2O$, corresponded to that of 1,2-diphenyl-4-quinazolinone (IIIa) and not to the expected rearrangement product Va. The presence of a characteristic[13] intense carbonyl absorption in the infrared (Nujol) at 1644 cm.$^{-1}$ coupled with the absence of absorption in the OH and NH stretching region was consistent with IIIa. Additionally, the proton n.m.r. spectrum[14] of its analog, 1-(*p*-methoxyphenyl)-2-phenyl-4-quinazolinone (IIIb), was also consistent with the 4-quinazolinone designation. A proton ratio of 1:12:3 was obtained in ascending field strength. The doublet signal (12 c.p.s. approximate width) at lowest field centered at about 495 c.p.s. with each signal split into an unsymmetrical quartet was assigned to the C-5 proton, *peri* to the carbonyl group, based on the chemical shifts and splitting patterns of similarly situated protons in other 4-quinazolinones.[15] The twelve remaining aromatic proton signals were seen as a broad multiplet (73 c.p.s. approximate width) centered at about 441 c.p.s., while the $-OCH_3$ singlet signal was at 227 c.p.s. Confirmatory chemical evidence for the structural assignment was obtained through the synthesis of 1,2-diphenyl-4-quinazolinone (IIIa) by two different routes (*vide infra*).[16] Since the anthranilamide derivative Va and its analogs have indeed been found to ring close readily to 4-quinazolinones, the direct isolation of 1,2-diphenyl-4-quinazolinone (IIIa) under these conditions was not surprising. While an improvement in the yield to 22% could be obtained by the utilization of anhydrous sodium sulfate to absorb the liberated water (see Scheme I), the generality of this synthetic route was soon found to be wanting because of the preponderant formation of by-products. For an example, the reaction of salicylamide with N-phenyl-3,4,5-trimethoxybenzimidoyl chloride in an alkaline medium yielded predominantly the phenolic isomer VIIb, previously alluded to, as well as a small amount of 2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazin-4-one (VIIIb). Both of these structural designations are in accord with the spectral data and elemental analyses. Unfortunately, none of the desired imido ester analogous to IV was isolated. Ring closures of compounds such as VIIb to compounds such as VIIIb have previously been observed.[12] The likelihood of a mobile equilibrium involving, among others, compounds such as IV, VIIa, aniline, and VIIIa would seem to limit severely the utility of Scheme I. In order to avoid these pitfalls, methyl salicylate was substituted for salicylamide in Scheme I (see Scheme II), and the requisite N-acylated anthranilic acids (XIa–d) were prepared by the method of Jamison and Turner.[11]

The acid chlorides prepared by the action of phosphorus oxychloride on the anthranilic acid derivatives (XIa–d) readily reacted with ammonia in methylene chloride or benzene solution with cooling to give a mixture in good yield of the anthranilamide derivatives (Va–d) and the 4-quinazolinones (IIIa–d). It was possible to convert completely these mixtures to the 4-quinazolinones in good yield by simply heating them at about 300° for a few minutes. In certain instances the mixtures could be readily resolved into their components. The infrared and ultraviolet spectra of just such an isolated anthranilamide derivative (Vc) were, as expected, essentially identical with those of Va prepared by the benzoylation of *o*-anilinobenzamide (see later Discussion). 1,2-Diphenyl-4-quinazolinone (IIIa) prepared by Scheme II was identical with the compound isolated *via* Scheme I which was previously identified as such. The procedures depicted in Scheme II thus represent an excellent pathway to 4-quinazolinones. Each step is high yielding, and the formation of by-products is held to a minimum. 4-Quinazolinones substituted at C-5, -6, -7, or -8 can also be prepared by this method. These

(12) A. W. Titherley, *J. Chem. Soc.*, **97**, 200 (1910).

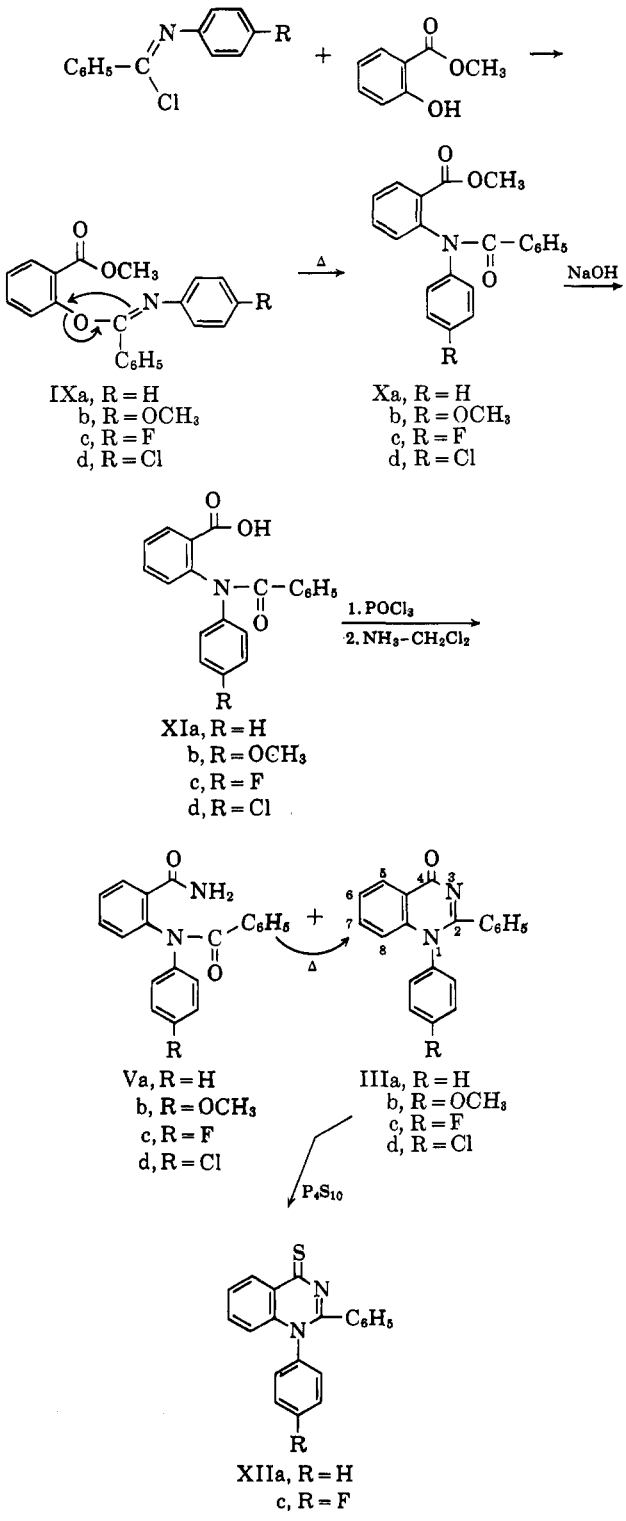
(13) G. deStevens, B. Smolinsky, and L. Dorfman, *J. Org. Chem.*, **29**, 1115 (1964).

(14) The n.m.r. spectrum was determined on a Varian A-60 spectrometer in dimethyl-d_6 sulfoxide. Values are given in cycles per second relative to tetramethylsilane as internal standard.

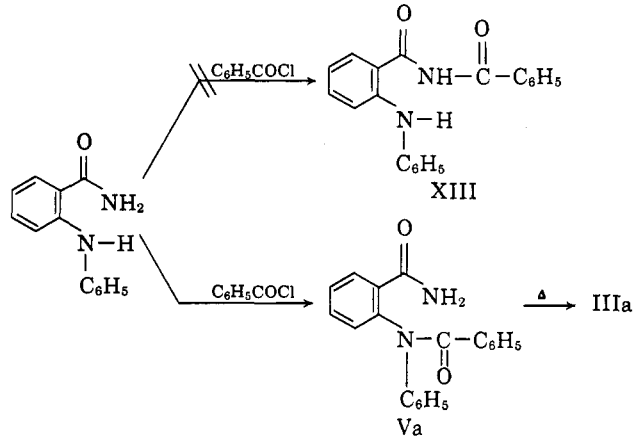
(15) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

(16) The close correspondence between the melting ranges of 1,2-diphenyl-4-quinazolinone (IIIa) and its methiodide as prepared by us and the melting ranges reported by Huang-Hsinman and Mann[4] leave little doubt as to the authenticity of their preferred tentative structural assignments (at least for IIIa).

SCHEME II



SCHEME III



compounds (IIIa-d) have been converted to the 4-quinazolinethiones (XIIa and c) by the standard method, *i.e.*, the action of phosphorus pentasulfide (P_4S_{10}) in xylene.

Another approach to the synthesis of 1,2-disubstituted 4-quinazolinones that was investigated involved direct acylation of *o*-anilinobenzamide. *o*-Anilinobenzamide reacted with benzoyl chloride in pyridine solution to give Va[17] (Scheme III), but in poor yield.[18]

As mentioned previously, the infrared and ultraviolet spectra of Va were essentially identical with those of N-(*o*-carbamoylphenyl)-N-(*p*-fluorophenyl)-benzamide (Vc) which was prepared *via* Scheme II. While the chemical and spectral evidence does not conclusively preclude the possibility that Va may actually be the isomeric imide XIII or the ring tautomer[19] VI (Scheme I) or even a mixture in solution, this does not seem too likely based on the structural assignments of previous investigators[18] and the synthetic pathways employed. Additionally, the appearance and position of the broad absorption in the NH stretching region in the infrared (Nujol), punctuated by peaks of weak to medium intensity at 3350, 3425, and 3480 cm.$^{-1}$, would appear to be more indicative of a mixture of free and hydrogen-bonded absorptions of a primary amide. Ring closure of Va at about 300° proceeded readily and in good yield to 1,2-diphenyl-4-quinazolinone (IIIa).

o-Anilinobenzamide reacted with acetic anhydride under reflux to give a mixture of products of which two could be readily isolated and characterized (Scheme IV). When a 1:1 molar ratio of reactants was used, the main product that was isolated was 2-methyl-1-phenyl-4-quinazolinone (XIV), albeit in poor yield. However, when the quantity of acetic anhydride was doubled, the primary product that was isolated, again in poor yield, was 2-acetonylidine-1-phenyl-4(3H)-quinazolinone (XV), which apparently arises from further acylation of XIV. 2-Acetonylidine-1-phenyl-4(3H)-quinazolinone (XV) could indeed be isolated in fair yield from the reaction of XIV with 1 mole of acetic anhydride. Both structural designations are in accord with the elemental analyses and the spectral data (*vide infra*). (See Scheme IV.)

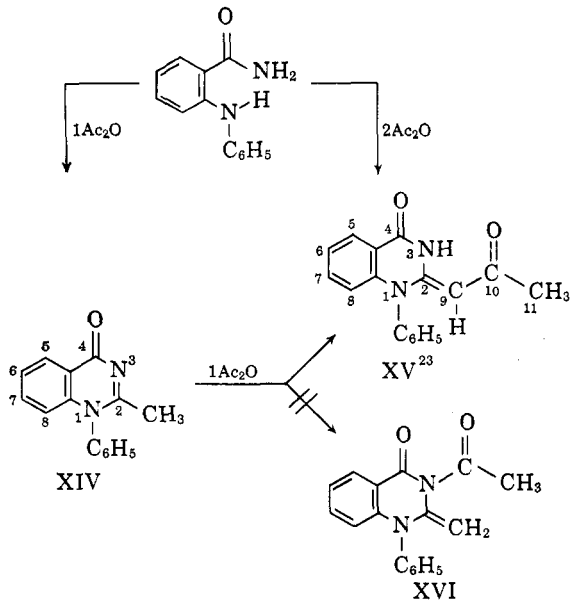
The presence of a strong carbonyl absorption at 1649 cm.$^{-1}$ in the infrared spectrum (Nujol) of XIV coupled with the absence of absorption in the NH and OH stretching region was in accord with that found for the 1,2-diaryl-4-quinazolinones (IIIa–d). Indeed, even its ultraviolet long-wave absorption, both as to position and intensity, was virtually identical with that of the

(17) The fact that the melting point of Va is very sensitive to both the rate of heating and the initial bath temperature negates a comparison between it and the recorded value for compound I (see ref. 4 and text). However, on the basis of their chemical properties and especially their ready conversion to IIIa on melting, we believe them to be identical.

(18) G. B. Jackman, V. Petrow, and O. Stephenson [*J. Pharm. Pharmacol.*, **12**, 529 (1960)] have reported that anthranilamide under similar reaction conditions undergoes dehydration as well as aroylation to the *o*-aminobenzonitrile derivative.

(19) P. R. Jones *Chem. Rev.*, **63**, 461 (1963).

SCHEME IV



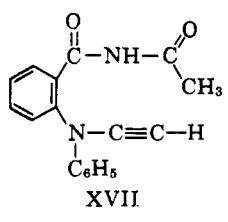
1,2-diaryl-4-quinazolinones and even to that of 1-methyl-2-phenyl-4-quinazolinone[1] and 1-methyl-4-quinazolinone.[20] Since 1,2-diphenyl-5,6,7,8-tetrahydro-4-quinazolinone absorbs at considerably shorter wave lengths,[3] and since the nature of the substituent at C-1 and C-2 (alkyl or aryl) does not apparently influence the long-wave absorption of 1,2-disubstituted 4-quinazolinones, it would seem that this absorption in such compounds is principally a consequence of ring resonance alone as symbolized by the arrows in the formula in Table I. A similar comparison of the ultraviolet long-wave absorptions of 1,2-diphenyl-4-quinazolinethione (XIIa), 1-methyl-2-phenyl-4-quinazolinethione,[1] 1-methyl-4-quinazolinethione,[21] and 1,2-diphenyl-5,6-7,8-tetrahydro-4-quinazolinethione[3] leads one to an identical conclusion for the 1,2-disubstituted 4-quinazolinethiones. The ultraviolet long-wave absorptions are listed in Table I.

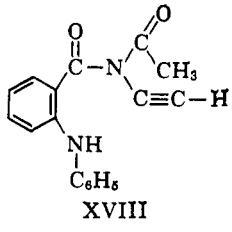
Compound XV, $C_{17}H_{14}N_2O_2$, an acylation product of XIV, was determined to be monomeric by osmometry. The N-acylation product (XVI) could be immediately ruled out due to the presence of only one vinyl proton in the proton n.m.r. spectrum, *vide infra*.[22] Compound XV showed a broad, weak absorption ranging from about 2250–2850 cm.$^{-1}$ in the infrared (Nujol and CH_2Cl_2) at which point it merged with the CH stretching bands. There was virtually no change in band position and relative intensity throughout the entire spectrum in going in turn from Nujol to methylene chloride solution to dilute methylene chloride solution. These findings are very suggestive of that type of strong intramolecular hydrogen bonding (O–H or N–H) which has been attributed to such resonance effects as "conjugate chelation."[23–25] The proton n.m.r. spectrum[26] was also in accord with structure XV. A proton ratio of 1:1:7:1:1:3 (ascending field strength) was observed. The broad absorption (20 c.p.s. approximate width) at about 850 c.p.s. (1 proton) was due to the "chelated" proton.[27] Its signal rapidly disappeared on the addition of deuterium oxide. The C-5 and C-8 protons were centered at about 493 (15 c.p.s. approximate width) and 383 c.p.s. (15 c.p.s. approximate width), respectively. Their splitting patterns were quite similar to those of their counterparts in compound XIV (*vide infra*). The overlapping signals for the seven remaining aromatic hydrogens were a multiplet centered at approximately 449 c.p.s. (53 c.p.s. approximate width), while the two singlet signals at 260 (1 proton) and 117 c.p.s. (3 protons) were due, respectively, to the "vinyl" proton[28] at C-9 and the three equivalent protons on C-11.[29]

(20) J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 3318 (1951).

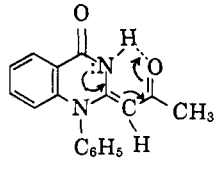
(21) D. J. Fry, J. D. Kendall, and A. J. Morgan, *ibid.*, 5062 (1960).

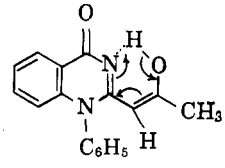
(22) The ring-opened isomers of XVI, *i.e.*, XVII and XVIII, have been excluded on the basis of the physical evidence and on such chemical evidence as the stability of XV to acid at room temperature.


XVII


XVIII

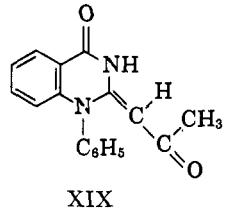
(23) Since "resonating hydrogen bonds" in chelate structures such as XV have previously been considered to be improbable, then XV might be best represented by XVa or XVb alone or as a tautomeric equilibrium of the two. Strong intramolecular hydrogen bonding would be present in both XVa and XVb.

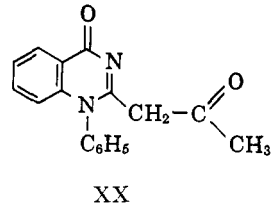

XVa


XVb

(24) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 142–145, 254–255.

(25) If XIX were the structure of the acylation product, it might be expected to show only weak intermolecular hydrogen bonding at considerably higher wave lengths than the strong intramolecular hydrogen bonding which was actually found. If the intermolecular hydrogen bonding was sufficiently strong to remain largely intact in dilute solution, then this would be inconsistent with the monomeric molecular weight exhibited by the acylation product (XV) in dilute solution. The ring-opened isomers of XIX or XV (*via* ring–chain tautomerism) as well as the tautomer XX can be excluded on both physical and chemical grounds.


XIX


XX

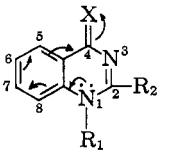
(26) The n.m.r. spectrum was determined on a Varian A-60 spectrometer in deuteriochloroform. Values are given in cycles per second relative to tetramethylsilane as internal standard.

(27) W. von Philipsborn, H. Stierlin, and W. Traber [*Helv. Chim. Acta*, **46**, 2592 (1963)] have reported absorptions at low-field strength for "chelated" protons in somewhat similar environments.

(28) Certain simple enamines such as N-(1-cyclohexenyl)morpholine show atypical "vinyl" proton absorption at 281 c.p.s. [C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.*, **28**, 3134 (1963)].

(29) The significance of the absence of coupling between the C-9 "vinyl" proton and the C-11 protons is difficult to assess owing to a lack of knowledge about their intimate chemical environments. At best only a small J value would be anticipated for the H—C=C—CH_3 system.

TABLE I



Compd.	X	R_1	R_2	$\lambda_{max}^{C_2H_5OH}$, mμ	ε
IIIa	O	C_6H_5	C_6H_5	306	10,810
				316 sh	9,690
IIIb	O	p-CH_3O-C_6H_4	C_6H_5	306	11,120
				317 sh	10,070
IIIc	O	p-F-C_6H_4	C_6H_5	305	10,550
				311–315 plateau	9,420
IIId	O	p-Cl-C_6H_4	C_6H_5	305[a]	10,970
				314 sh	9,820
XIV	O	C_6H_5	CH_3	303	10,040
				314	8,380
b	O	CH_3	C_6H_5	306	9,820
				312–316 plateau	8,770
c	O	CH_3	H	306.5	6,920
				317	6,170
5,6,7,8-Tetrahydro[d] IIIa	O	C_6H_5	C_6H_5	250	17,570[e]
XIIa	S	C_6H_5	C_6H_5	387	21,430
XIIc	S	p-F-C_6H_4	C_6H_5	388	21,900
b	S	CH_3	C_6H_5	388	17,720
f	S	CH_3	H	380	16,980
5,6,7,8-Tetrahydro[d] XIIa	S	C_6H_5	C_6H_5	342–345	27,100[e]

[a] Methanol solution. [b] Ref. 1. [c] Ref. 20. [d] Ref. 3. [e] Kindly supplied by Dr. R. W. J. Carney of our laboratories. [f] Ref. 21.

Experimental[30]

o-(**N-Phenylbenzimidoyloxy**)**benzamide** (**IV**).—To an ice-bath cooled solution of 1.35 g. (0.025 mole) of sodium methoxide in 25 ml. of absolute ethanol, there was added in rapid succession a solution of 4.1 g. (0.030 mole) of salicylamide in 25 ml. of absolute ethanol followed by a solution of 4.3 g. (0.020 mole) of N-phenylbenzimidoyl chloride[31] in 25 ml. of anhydrous ether. After standing at room temperature for 1.5 hr., the cloudy mixture was evaporated *in vacuo*, and water was then added to the residue. The yellow, oily residue was separated, wetted with a small amount of absolute ethanol, and cooled with scratching until it solidified. The crude solid in ether solution was dried over anhydrous sodium sulfate. It crystallized from ether–*n*-pentane to give 2.0 g. (32% yield based on N-phenylbenzimidoyl chloride) of product as a white solid, m.p. 133–137°. Recrystallization from acetone–hexane gave IV: m.p. 136–138°; infrared (Nujol) 3133 w, 3338 w, 3431 w, 3463 w (free and bonded $-NH_2$ of primary amide), and 1681 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 233 mμ sh (ε 24,100), 276 mμ sh (ε 5720).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.00; H, 5.09; N, 8.89.

Chapman Rearrangement of *o*-(**N-Phenylbenzimidoyloxy**)**benzamide** (**IV**). **A.**—*o*-(N-Phenylbenzimidoyloxy)benzamide (IV), 0.5 g. in an open flask, was placed in an oil bath that was preheated to 270–275°. It instantly formed a melt which progressively darkened during the 15-min. heating period. On cooling to room temperature, the melt was extracted with boiling cyclohexane in which it was mostly soluble. The solution was partially decolorized with Norit, and was then concentrated to dryness *in vacuo*. The yellow, oily residue lacked the characteristic long-wave ultraviolet absorption patterns, *vide infra*, of 1,2-diphenyl-4-quinazolinone (IIIa), and could not be readily purified.

When the heating period was shortened to 1 min., there was obtained from the cooled cyclohexane extract a few milligrams of a white solid, m.p. 160–170°, whose mixture melting point with benzanilide was not depressed.

B.—A solution of 1 g. (0.0032 mole) of compound IV in 10 ml. of diphenyl ether was refluxed for 2 hr. The solution was concentrated to dryness *in vacuo*, and then an excess of diethyl ether was added to the residue. A 10% yield of 1,2-diphenyl-4-quinazolinone (IIIa), *vide infra*, m.p. 265–273°, 0.090 g., was obtained. When the reflux period was increased to 12 and 24 hr., the yield remained at the same level, *i.e.*, 9%.

C.—A solution of 2 g. (0.0064 mole) of compound IV in 200 ml. of diphenyl ether was refluxed for 2 hr. The condensate was continuously passed through anhydrous sodium sulfate contained in the thimble of a Soxhlet extractor. Due to the high boiling point of diphenyl ether, the efficiency of this operation, in terms of rate of solvent passing through the thimble, was minimal. The solution was concentrated to dryness *in vacuo*, and then an excess of diethyl ether was added to the residue. The product, 1,2-diphenyl-4-quinazolinone (IIIa), m.p. 265–273°, 0.410 g., was obtained in 22% yield.

D.—A mixture of 0.50 g. (0.0016 mole) of compound IV and 0.328 g. (0.0016 mole) of dicyclohexylcarbodiimine was added all at once to boiling diphenyl ether. The solution was refluxed for 35 min., and was then allowed to stand at room temperature overnight. A 15% yield of IIIa was obtained.

Reaction of Salicylamide with N-Phenyl-3,4,5-trimethoxybenzimidoyl Chloride.—To an ice-bath cooled solution of 0.67 g. (0.012 mole) of sodium methoxide in 10 ml. of absolute ethanol, there was added in rapid succession a solution of 2.05 g. (0.015 mole) of salicylamide in 15 ml. of absolute ethanol followed by a solution of 3.05 g. (0.010 mole) of N-phenyl-3,4,5-trimethoxybenzimidoyl chloride[32] in 50 ml. of anhydrous ether. After standing at room temperature for 1.5 hr., the mixture was evaporated *in vacuo*, and water was then added to the residue. On the addition of ethanol, the residue solidified. The crude solid was recrystallized from acetone–hexane to give 0.30 g. of 2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazin-4-one (VIIIb) (10% yield based on the complete conversion of N-phenyl-3,4,5-trimethoxybenzimidoyl chloride to VIIIb) as a white solid, m.p. 190–194°. Recrystallization from acetone alone gave VIIIb as white crystals: m.p. 191–193°; infrared (Nujol) 1681 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 220 mμ sh (ε 33,030), 298 (16,910), 317 (16,910), λ_{min} 263 mμ (ε 5210), 305 (16,490).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.46; H, 4.91; N, 4.31.

On standing at room temperature for several hours, the mother liquors yielded about 1 g. of N-(*o*-hydroxybenzoyl)-N′-phenyl-3,4,5-trimethoxybenzamidine (VIIb) (25% yield based on the complete conversion of N-phenyl-3,4,5-trimethoxybenzimidoyl chloride to VIIb) as a white solid, m.p. 115–120°. Recrystalliza-

(30) The melting points are uncorrected. The ultraviolet spectra were determined in ethanol 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.

(31) J. von Braun and W. Pinkernelle, *Ber.*, **67**, 1218 (1934).

(32) A. Sonn and E. Müller, *ibid.*, **52**, 1927 (1919).

tion from ether gave VIIb: m.p. 116–118°; infrared (Nujol) 3144 m, 3277 w, 3348 w (bonded –NH stretching modes), 3483 m (phenolic –OH stretching mode), 1671 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 220 mμ sh (ε 43,700), 274 (12,510), λ_{min} 249 mμ (ε 8610).

A duplicate experiment run on twice the scale gave about the same yield of VIIIb; however, a considerably larger amount (46% yield) of VIIb was obtained.

General Method[11] for the Preparation of Salicylic Acid Esters (IXa–d).—**Methyl *o*-(N-phenylbenzimidoyloxy)benzoate (IXa)** was isolated as white crystals from ethanol, m.p. 109–112° (previously reported[11] m.p. 110–111°).

Methyl *o*-(N-*p*-methoxyphenylbenzimidoyloxy)benzoate (IXb) was prepared from methyl salicylate and N-(*p*-methoxyphenyl)-benzimidoyl chloride[33] in 65% yield (based on imidoyl chloride) by the method of Jamison and Turner.[11] Crystallization from ethanol gave IXb as yellow crystals: m.p. 115–117°; infrared (Nujol) 1710 s (ester carbonyl), 1666 cm.$^{-1}$ s (>C=N—); ultraviolet λ_{max} 230 mμ (ε 27,710), 288 (6420), 328 sh (3720), λ_{min} 220 mμ (ε 26,320), 266 (5290).

Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.88. Found: C, 73.01; H, 5.36; N, 3.96.

Methyl *o*-(N-*p*-fluorophenylbenzimidoyloxy)benzoate (IXc) was prepared from methyl salicylate and N-(*p*-fluorophenyl)-benzimidoyl chloride[34] in 81% yield (based on imidoyl chloride) by the method of Jamison and Turner.[11] Crystallization from ethanol gave IXc as white crystals; m.p. 130–132°; infrared (Nujol) 1710 s (ester carbonyl), 1665 cm.$^{-1}$ s (>C=N—); ultraviolet λ_{max} 230 mμ sh (ε 24,410), 278 (5550), λ_{min} 264 mμ (4930).

Anal. Calcd. for $C_{21}H_{16}FNO_3$: C, 72.20; H, 4.62; N, 4.01. Found: C, 72.26; H, 4.65; N, 4.17.

Methyl *o*-(N-*p*-chlorophenylbenzimidoyloxy)benzoate (IXd) was isolated as white crystals from ethanol, m.p. 130–132° (lit.[11] m.p. 130–131°).

General Method[11] for the Preparation of Anthranilic Esters (Xa–d) and Acids (XIa–d).—**N-(*o*-Methoxycarbonylphenyl)-N-phenylbenzamide (Xa)** was isolated as white crystals from ethanol, m.p. 127–131° (previously reported[11] m.p. 132–133°).

N-(*o*-Methoxycarbonylphenyl)-N-(*p*-methoxyphenyl)benzamide (Xb) was prepared by heating 22 g. of compound IXb at 270–275° in an oil bath for 10 min. The crude product was recrystallized from acetone–hexane with Norit decolorization to give 16.5 g. (73% yield) of Xb as a white solid, m.p. 148–152°. Further recrystallization of Xb from acetone–hexane gave pure material: m.p. 151–153°; infrared (Nujol) 1722 s (ester carbonyl), 1659 cm.$^{-1}$ s (amide carbonyl); ultraviolet λ_{max} 230 mμ sh (ε 21,310), 250 sh (13,520), 276–285 plat. (7460).

Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.88. Found: C, 72.94; H, 5.47; N, 3.79.

N-(*p*-Fluorophenyl)-N-(*o*-methoxycarbonylphenyl)benzamide (Xc) was prepared by heating 90 g. of compound IXc at 275° in an oil bath for 10 min. The crude melt solidified in ether. It was recrystallized once from methanol and then once from ether to give 70 g. (78% yield) of Xc as a white solid, m.p. 113–117°. One additional recrystallization from ether yielded Xc: m.p. 114–116°; infrared (Nujol) 1724 s (ester carbonyl), 1659 cm.$^{-1}$ s (amide carbonyl); ultraviolet λ_{max} 230 mμ sh area (ε 19,740), 278 sh area (6830).

Anal. Calcd. for $C_{21}H_{16}FNO_3$: C, 72.20; H, 4.62; N, 4.01. Found: C, 72.08; H, 4.76; N, 4.17.

N-(*p*-Chlorophenyl)-N-(*o*-methoxycarbonylphenyl)benzamide (Xd) was isolated as white crystals from ether, m.p. 139–141° (lit.[11] m.p. 139–140°).

N-(*o*-Carboxyphenyl)-N-phenylbenzamide (XIa) was prepared as previously reported by Jamison and Turner.[11]

N-(*o*-Carboxyphenyl)-N-(*p*-methoxyphenyl)benzamide (XIb) was obtained in 73% yield from the hydrolysis of compound Xb. The analytical sample was obtained as white crystals after several recrystallizations from acetone–hexane, m.p. 184–187°.

Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 73.03; H, 5.23; N, 3.70.

N-(*o*-Carboxylphenyl)-N-(*p*-fluorophenyl)benzamide (XIc).—To a mixture of 28 g. (0.080 mole) of Xc, 160 ml. of ethanol, and 88.5 ml. of water, there was added 88.5 ml. of a stock solution which consisted of 5.4 g. of sodium methoxide, 100 ml. of ethanol, and 20 ml. of water. The mixture was refluxed for 1 hr. It was then concentrated *in vacuo*, and the residue was acidified with concentrated hydrochloric acid. The crude precipitate was extracted with methylene chloride, and the methylene chloride extract was dried over anhydrous sodium sulfate. The crude solid from the methylene chloride solution was treated with aqueous sodium bicarbonate at the boil, and the basic extract, on cooling, was acidified with concentrated hydrochloric acid. The precipitated solid was recrystallized once from methylene chloride–hexane to give 16 g. (60% yield) of XIc as a white solid, m.p. 175–179°. Further recrystallization from ether gave XIc as white crystals: m.p. 176–178°; ultraviolet λ_{max} 227 mμ sh area (ε 18,880), 278 sh area (6720).

Anal. Calcd. for $C_{20}H_{14}FNO_3$: C, 71.64; H, 4.21; N, 4.18. Found: C, 71.95; H, 4.42; N, 4.13.

N-(*o*-Carboxyphenyl)-N-(*p*-chlorophenyl)benzamide (XId) was isolated as white crystals from acetone–hexane, m.p. 189–192° (lit.[11] m.p. 191–192°).

General Method for the Ring Closure of Anthranilic Acids (XIa–d) to 1,2-Disubstituted 4-Quinazolinones (IIIa–d). 1,2-Diphenyl-4-quinazolinone (IIIa).—N-(*o*-Carboxyphenyl)-N-phenylbenzamide (XIa), 13 g. (0.041 mole), was dissolved in about 100 ml. of hot phosphorus oxychloride.[35] The solution was refluxed for approximately 19 hr., and the excess phosphorus oxychloride ($POCl_3$) was then removed by distillation *in vacuo*. Ammonia gas was slowly bubbled through a methylene chloride solution of the oily residue over a period of about 15 min. The mixture of precipitated solid plus solution was allowed to stand at room temperature for 1 hr. After being washed with water, the methylene chloride solution was dried over anhydrous sodium sulfate and was decolorized with Norit. The addition of hexane to the concentrated methylene chloride solution resulted in the precipitation of a mixture of IIIa and Va, m.p. 220–275°. The mixture was heated at about 300° in an oil bath for a few minutes, and the crude product was crystallized from ethanol with Norit decolorization to give a total of 7.3 g. (60% yield) of IIIa as a white solid, m.p. 273–276°. Further recrystallization from ethanol gave IIIa as white crystals: m.p. 273–275°; infrared, see text; ultraviolet λ_{max} 236 mμ (ε 25,340) (see Table I), λ_{min} 224 mμ (ε 23,130), 287 (6860).

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.86; H, 4.88; N, 9.39.

The methiodide derivative of IIIa was prepared by refluxing a mixture of 200 mg. of IIIa and 10 ml. of methyl iodide for 0.5 hr. On cooling, the cloudy solution deposited a pale yellow solid. Recrystallization from methanol afforded the crystalline, yellow methiodide, m.p. 258–266°, which retained 1 mole of methanol[16]; infrared (Nujol) 3429 w (O–H stretching frequency), 1726 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 220 mμ (ε 50,710), 285 sh (8790), 294–298 (9080), 306 sh (7530), 348 sh area (480), λ_{min} 208 mμ (ε 40,320), 264 (6270).

Anal. Calcd. for $C_{21}H_{17}IN_2O \cdot CH_3OH$: C, 55.94; H, 4.70; N, 5.93. Found: C, 55.73; H, 4.47; N, 5.72.

The methiodide derivative was designated as 3-methyl-4-oxo-1,2-diphenylquinazolinium iodide in accordance with the physical data and the literature.[21]

1-(*p*-Methoxyphenyl)-2-phenyl-4-quinazolinone (IIIb).—N-(*o*-Carboxyphenyl)-N-(*p*-methoxyphenyl)benzamide (XIb), 3.0 g. (0.0086 mole), was treated with 50 ml. of phosphorus oxychloride and then with ammonia as previously described for XIa. A mixture of IIIb and Vb, 1.8 g., m.p. 200–240°, was obtained by an identical work-up. The mixture was heated at about 300° in an oil bath for a few minutes, and the crude product was crystallized from ethanol with Norit decolorization to give 1.25 g. (44% yield) of IIIb as an off-white solid, m.p. 235–239°. Further recrystallization from ethanol gave IIIb as white crystals: m.p. 241–243°; infrared (Nujol) 1647 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 236 mμ (ε 34,060), 278–290 plat. (8410) (see Table I), λ_{min} 222 mμ (ε 25,300), 273 (8270).

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.64; H, 5.09; N, 8.55.

1-(*p*-Fluorophenyl)-2-phenyl-4-quinazolinone (IIIc).—N-(*o*-Carboxyphenyl)-N-(*p*-fluorophenyl)benzamide (XIc), 20 g. (0.060 mole), was treated with 100 ml. of phosphorus oxychloride and then with ammonia in essentially the manner previously described. The only variation was the increased time, to 1 hr., allotted for the bubbling of ammonia through the methylene

(33) I. Ugi, F. Beck, and U. Fetzer, *Ber.*, **95**, 126 (1962).

(34) F. Benington, E. V. Shoop, and R. H. Poirier, *J. Org. Chem.*, **18**, 1506 (1953).

(35) The quantity of phosphorus oxychloride used, within a wide range, did not significantly affect the outcome of the procedure.

chloride solution. In contrast to the previous examples, a total of 13.1 g. (69% yield) of IIIc, m.p. 287–290°, was obtained directly without recourse to further heating. Recrystallization from acetone–hexane for analysis gave IIIc as white crystals: m.p. 289–290°; infrared (Nujol) 1649 cm.$^{-1}$ s (carbonyl); ultraviolet λ_{max} 234 mμ (ε 24,620), 265 sh area (8770) (see Table I), λ_{min} 223 mμ (ε 22,650), 286 (6870).

Anal. Calcd. for $C_{20}H_{13}FN_2O$: C, 75.93; H, 4.14; N, 8.86. Found: C, 75.99; H, 4.14; N, 8.80.

When the reaction was carried out in the same manner, except for the substitution of benzene for methylene chloride, there was obtained from 8.5 g. of XIc a total of 2 g. of IIIc, m.p. 288–290°, and 2.1 g. of N-(*o*-carbamoylphenyl)-N-(*p*-fluorophenyl)benzamide (Vc), m.p. ~210° (very sensitive to both the rate of heating and the initial bath temperature). The fact that Vc was very much more soluble in acetone than IIIc led to their ready separation. Recrystallization of Vc from acetone–hexane gave white crystals: m.p. ~210°; infrared (Nujol) 3352 w, 3424 m, 3484 w (free and bonded $-NH_2$ of primary amide), 1679 s (amide carbonyl), 1646 s, 1636 cm.$^{-1}$ s (either value could be an amide carbonyl or an $-NH_2$ deformation absorption of a primary amide); ultraviolet λ_{max} 276 mμ sh (ε 6900).

Anal. Calcd. for $C_{20}H_{15}FN_2O_2$: C, 71.85; H, 4.52; N, 8.38. Found: C, 72.35; H, 4.79; N, 8.15.

On heating 1.95 g. (0.0058 mole) of Vc at 315° for a few minutes, a total of 1.4 g. (76% yield) of IIIc was obtained after recrystallization from acetone with Norit decolorization, m.p. 288–290°.

1-(*p*-Chlorophenyl)-2-phenyl-4-quinazolinone (IIId).—N-(*o*-Carboxyphenyl)-N-(*p*-chlorophenyl)benzamide (XId), 8.0 g. (0.023 mole), was treated with phosphorus oxychloride and then with ammonia as previously described for XIa and XIb. A mixture of IIId and Vd, 5.5 g., m.p. 200–230°, was obtained by an identical work-up. The mixture was heated at about 300° in an oil bath for a few minutes, and the crude product was crystallized from methanol to give 4.0 g. (53% yield) of IIId as a white solid, m.p. 243–245°. One additional recrystallization from methanol gave IIId as white crystals: m.p. 243–245°; infrared (Nujol) 1649 cm.$^{-1}$ s (carbonyl); ultraviolet $\lambda_{max}^{CH_3OH}$ 233 mμ (ε 29,010), 281 (7520) (see Table I), $\lambda_{min}^{CH_3OH}$ 221 mμ (ε 27,090), 276 (7350), 287 (7130).

Anal. Calcd. for $C_{20}H_{13}ClN_2O$: C, 72.18; H, 3.94; N, 8.42. Found: C, 71.89; H, 3.99; N, 8.23.

General Method for the Preparation of 1,2-Disubstituted 4-Quinazolinethiones (XIIa and c). 1,2-Diphenyl-4-quinazolinethione (XIIa).—A mixture of 3.5 g. (0.012 mole) of IIIa, 3.13 g. of phosphorus pentasulfide, and 35 ml. of xylene was refluxed for 2 hr. with stirring. An excess of 10% aqueous sodium hydroxide solution was then added dropwise with stirring and ice-bath cooling. The mixture was stirred for an additional 15 min. and was then filtered. The collected solid, 2.5 g., was washed with boiling ethanol and was then recrystallized from hot dimethylformamide (DMF) to give 2.1 g. of XIIa (57% yield) as an orange solid, m.p. >300°. One additional recrystallization from DMF gave XIIa as orange crystals: m.p. 305–307°; infrared (Nujol) no absorption in the N–H, O–H stretching region and between 1610–1700 cm.$^{-1}$; ultraviolet λ_{max} 216–222 mμ plat. (ε 36,870), 241 sh (17,710), 266 sh (12,910) (see Table I), λ_{min} 327 mμ (ε 2800).

Anal. Calcd. for $C_{20}H_{14}N_2S$: C, 76.40; H, 4.49; N, 8.91. Found: C, 76.22; H, 4.53; N, 8.98.

1-(*p*-Fluorophenyl)-2-phenyl-4-quinazolinethione (XIIc).—1-(*p*-Fluorophenyl)-2-phenyl-4-quinazolinone, 10.5 g. (0.033 mole), was treated with 8.9 g. of phosphorus pentasulfide in 150 ml. of xylene as previously described. The crude solid obtained by a work-up identical with that for XIIa (60 ml. of a 10% aqueous sodium hydroxide solution had been added) was washed with a minimum amount of boiling ethanol. It was then recrystallized from acetone with Norit decolorization to afford 5.7 g. (52% yield) of XIIc as an orange solid, m.p. 293–296°. One additional recrystallization from acetone gave XIIc as orange crystals: m.p. 294–296°; infrared (Nujol) no absorption in the N–H, O–H stretching region and between 1610–1700 cm.$^{-1}$; ultraviolet λ_{max} 214–221 mμ plat. (ε 35,740), 257–267 plat. (12,660) (see Table I), λ_{min} 325–328 mμ (ε 2850).

Anal. Calcd. for $C_{20}H_{13}FN_2S$: C, 72.27; H, 3.95; N, 8.43. Found: C, 71.98; H, 4.00; N, 8.15.

Both XIIa and XIIc slowly turned tan on standing at room temperature. Since they appear to be stable when wrapped in aluminum foil or kept in a brown bottle, this would seem to be a light effect.

***o*-Anilinobenzamide.**—To a suspension of 17.4 g. (0.082 mole) of N-phenylanthranilic acid in 250 ml. of dry pentane, there was added 16.8 g. (0.081 mole) of phosphorus pentachloride in small portions. A great deal of hydrogen chloride was evolved, and most of the starting solids were observed to dissolve. After the addition was completed, the mixture was allowed to stand at room temperature for about 1 hr. It was then filtered, and the filtrate was decolorized with Norit. The solid that precipitated from the concentrated solution at Dry Ice–acetone temperatures, *o*-anilinobenzoyl chloride,[36] was quickly collected and added to about 250 ml. of ice-cold concentrated ammonium hydroxide (28–30% ammonia by weight). After about 3 hr. at room temperature, the crude product was dried on filter paper and was then recrystallized once from ether. A total of 10.5 g. (61% yield) of *o*-anilinobenzamide was obtained as a pale yellow solid, m.p. 128–131°. Recrystallization from ether gave pale yellow crystals: m.p. 129–131° (lit.[37] m.p. 127.5–129°); ultraviolet λ_{max} 220 mμ sh (ε 20,520), 288 (15,890), 345 (6450), λ_{min} 255 mμ (ε 3220), 317 (3960).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.83; H, 5.72; N, 13.07.

N-(*o*-Carbamoylphenyl)-N-phenylbenzamide (Va).—To a solution of 212 mg. (0.001 mole) of *o*-anilinobenzamide in 2 ml. of pyridine, there was added 140 mg. (0.001 mole) of benzoyl chloride. After standing at room temperature for 15 min., the yellow solution was poured into water. The mixture was extracted with methylene chloride, and the methylene chloride extract was dried over anhydrous sodium sulfate. On the addition of excess ether to the concentrated methylene chloride solution, a small quantity, approximately 50 mg., of a white solid precipitated. Two recrystallizations from ethanol gave Va as white crystals: m.p. 235–237° (the capillary was placed in the oil bath at 230°; the melting point is very sensitive to both the rate of heating and the initial bath temperature); infrared (Nujol), see text, 1681 s (amide carbonyl), 1648 s, 1642 cm.$^{-1}$ s (either value could be an amide carbonyl or an $-NH_2$ deformation absorption of a primary amide); ultraviolet λ_{max} 244 mμ sh area (ε 12,100), 276 sh area (7260).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.84; H, 5.29; N, 8.83.

On heating to about 300°, Va rapidly ring closed to 1,2-diphenyl-4-quinazolinone (IIIa) in good yield.

Reaction of *o*-Anilinobenzamide with Acetic Anhydride. A.—A mixture of 10.6 g. (0.05 mole) of *o*-anilinobenzamide and 5.1 g. (0.05 mole) of acetic anhydride was refluxed for about 17 hr. After the acetic anhydride was removed *in vacuo*, the residue was dissolved in a small volume of acetone. On seeding with an authentic sample of XIV obtained from an initial run, a total of 2.8 g. (24% yield) of 2-methyl-1-phenyl-4-quinazolinone (XIV) was obtained as pale yellow crystals, m.p. 225–230°. Several recrystallizations from acetone gave XIV as pale yellow crystals: m.p. 231–233°; infrared, see text; ultraviolet λ_{max} 229 mμ (ε, 21,500), 234 sh (19,580), 265 (5290), 274 (5560) (see Table I); λ_{min} 219 mμ (ε 18,910), 256 (4450), 268 (5120), 281 (4310), 310 (8310).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.46; H, 5.17; N, 12.14.

The pale yellow coloration of XIV is probably due to traces of an impurity, since the color is present in solution.

The proton n.m.r. spectrum[14] revealed a proton ratio of 1:7:1:3 in ascending field strength. The doublet signal (15 c.p.s. approximate width) at lowest field centered at about 489 c.p.s. with each signal split into an unsymmetrical quartet was assigned to the C-5 proton, *peri* to the carbonyl group, based on the chemical shifts and splitting patterns found for similarly situated protons both in this investigation and elsewhere.[15] A very similarly patterned doublet signal (1 proton) centered at 395 c.p.s. (15 c.p.s. approximate width) was assigned to the C-8 proton. The overlapping signals for the remaining aromatic protons were a multiplet centered at about 453 c.p.s. (46 c.p.s. approximate width), while the 2-methyl singlet signal was at 129 c.p.s. Small quantities of *o*-anilinobenzamide were obtained from the mother liquors.

(36) A. M. Grigorovskii, *Chem. Abstr.*, **44**, 2953*d* (1950).

(37) Prepared by M. Goodman, N. Arbiter, and G. Powell [*J. Am. Chem. Soc.*, **55**, 4294 (1933)] in poor yield by treating ethyl *o*-anilinobenzoate with ammonia in a sealed tube.

B.—A mixture of 6.36 g. (0.030 mole) of *o*-anilinobenzamide and 6.12 g. (0.060 mole) of acetic anhydride was refluxed for about 20 hr. After the acetic anhydride was removed *in vacuo*, excess ether was added to the residue. The crude solid, m.p. 180–220°, that was obtained was recrystallized from a small amount of hot methanol to give 0.75 g. (9% yield) of **2-acetonylidine-1-phenyl-4(3H)-quinazolinone (XV)** as a white solid, m.p. 240–243°. One additional recrystallization from ether gave XV as white crystals; m.p. 241–243°; infrared (CH_2Cl_2) 1699 s (amide carbonyl), 1615 s, and 1568 $cm.^{-1}$ s (either could be the "NH" deformation band or the "ketone" carbonyl absorption of the conjugated system); ultraviolet $\lambda_{max}^{CH_3OH}$ 220 mμ sh (ε 18,600), 268 (5120), 318 (35,090); $\lambda_{min}^{CH_3OH}$ 258 mμ (ε 4620), 282–283 (4420); λ_{max} (0.1 *N* KOH–CH_3OH) 280 mμ sh (ε 5780), 317 (33,150); λ_{min} (0.1 *N* KOH–CH_3OH) 260–264 mμ (ε 5060); λ_{max} (0.1 *N* HCl–CH_3OH) 220 mμ sh area (ε 17,590), 268 sh area (6370), 276 (6810), 318 (29,160); λ_{min} (0.1 *N* HCl–CH_3OH) 257 mμ (ε 5170), 282–285 (6540); $\lambda_{max}^{cyclohexane}$ 216 mμ (ε 20,360), 223 sh (19,640), 278 (7790), 312 (31,270); $\lambda_{min}^{cyclohexane}$ 211 mμ (ε 19,970), 254 (4210), 282 (7440).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07; mol. wt., 278.30. Found: C, 73.09; H, 4.94; N, 10.05; mol. wt., 264.5. (by osmometry[38] in chloroform solution).

Small quantities of compound XIV were obtained from the mother liquors.

2-Acetonylidine-1-phenyl-4(3H)-quinazolinone (XV).—A mixture of 0.495 g. (0.0021 mole) of 2-methyl-1-phenyl-4-quinazolinone (XIV) and 0.224 g. (0.0022 mole) of acetic anhydride was refluxed for about 19 hr. A methanol solution of the residue was partially decolorized with Norit and was then cooled in a Dry Ice–acetone bath. A total of 0.24 g. (41% yield) of XV, m.p. 230–240°, was obtained. One recrystallization from a small volume of methanol with Norit treatment gave 0.14 g. of XV as an off-white solid, m.p. 240–243°.

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(38) Vapor pressure osmometer, Model 301A, from Mechrolab, Inc., Mountain View, Calif.

A One-Step Synthesis of 1,1-Difluoro Olefins from Aldehydes

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1,1-Difluoro olefins can be prepared in good yield by heating a solution of an aldehyde, triphenylphosphine, and sodium chlorodifluoroacetate. The synthesis appears quite generally applicable to aromatic, aliphatic, and heteroaromatic aldehydes. The yield of the 1,1-difluoro olefin VI from *p*-nitrobenzaldehyde, however, is poor, the major product being *p*-nitro-β,β,β-trifluoroethylbenzene (VII).

1,1-Difluoro olefins can be prepared in good yield by heating a solution of an aldehyde, triphenylphosphine, and sodium chlorodifluoroacetate.[2]

Presumably the reaction proceeds with the *in situ* formation from sodium chlorodifluoroacetate of a carbene (difluoromethylene) which is trapped by triphenylphosphine to form an ylid which undergoes a Wittig reaction with an aldehyde to form the 1,1-difluoro olefin.[3] Formation of difluorocarbene by decomposition of sodium chlorodifluoroacetate in solution has been reported.[4,5] Seyferth demonstrated that chlorocarbene, generated from methylene chloride and butyllithium, reacted with triphenylphosphine to form the ylid.[6] Similar trapping with triphenylphosphine of dichlorocarbene,[7,8] of chlorocarbene,[9] and of methylene,[10,11] and the use, in a Wittig reaction, of the ylids formed have been reported. Speziale[8] was unsuccessful in attempts to trap difluorocarbene, generated from chlorodifluoromethane, with triphenylphosphine, nor could he substantiate Franzen's[11] claims that difluorocarbene generated from dibromodifluoromethane could be trapped with triphenylphosphine.

$$ClCF_2COONa \longrightarrow CF_2 + NaCl + CO_2 \xrightarrow{(C_6H_5)_3P}$$

$$(C_6H_5)_3P{=}CF_2 \xrightarrow{RCHO} RCH{=}CF_2 + (C_6H_5)_3PO$$

I, R = C_6H_5
II, R = *p*-F-C_6H_4
III, R = *p*-MeO-C_6H_4
IV, R = *n*-C_6H_{13}
V, R = 2-furyl
VI, R = *p*-NO_2-C_6H_4

The synthesis appears quite generally applicable to aromatic, aliphatic, and heteroaromatic aldehydes. Good yields (yields of isolated product in parentheses) were obtained from benzaldehyde (74%), *p*-fluorobenzaldehyde (65%), anisaldehyde (60%), heptaldehyde (52%), and furfural (69%).

No other simple, general route to 1,1-difluoro olefins has been reported. The recorded preparation[12] of β,β-difluorostyrene, for example, consists of seven steps from sodium difluoroacetate, the last step involving pyrolysis at 600°; the over-all yield was 5%.

(1) Deceased.

(2) Preliminary communication: S. A. Fuqua, W. G. Duncan, and R. M. Silverstein, *Tetrahedron Letters*, **No. 23**, 1461 (1964). Note that V was erroneously reported as the tetrahydrofuryl compound (p. 1462, last line).

(3) Two other plausible mechanisms were suggested by a referee (a and b).

$$ClCF_2COONa + (C_6H_5)_3P \longrightarrow (C_6H_5)_3\overset{+}{P}-CF_2-\overset{O}{\overset{\|}{C}}-O^- \; Na^+ \; Cl^- \longrightarrow$$

$$(C_6H_5)_3P{=}CF_2 + CO_2 + NaCl \quad (a)$$

$$ClCF_2COONa + (C_6H_5)_3P \longrightarrow \left[CF_2{=}C<^{O^-}_{ONa} \quad \overset{+}{P}(C_6H_5)_3Cl\right] \longrightarrow \text{products} \quad (b)$$

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(11) V. Franzen, *ibid.*, **72**, 566 (1960).

(12) M. Prober, *J. Am. Chem. Soc.*, **75**, 968 (1953).