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Heterocyclic Syntheses Based on the Reactions of Dimethyl Acetylenedicarboxylate with the 2-Amino-5-chlorobenzophenone Oximes

Jackson B. Hester, Jr.

The Upjohn Company, Kalamazoo, Michigan 49001

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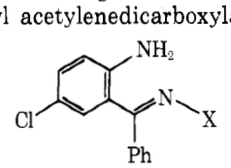
The reaction of dimethyl acetylenedicarboxylate with the 2-amino-5-chlorobenzophenone oximes was studied. It was found that the *Z* oxime gave (2-benzoyl-4-chloroanilino)fumaric acid dimethyl ester (*Z*)-oxime (**4**) and the *E* oxime gave 2-carboxy-6-chloro-1,2-dihydro-4-phenyl-2-quinozolineacetic acid dimethyl ester 3-oxide (**7**). Each of these compounds (**7** and **4**) reacted with triphenylphosphine and carbon tetrachloride to give products resulting from Beckmann rearrangements of the respective oximes.

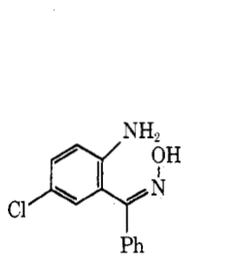
The utility of acetylenedicarboxylic acid esters for the preparation of a variety of five- and six-membered heterocyclic systems has been amply demonstrated during the past decade[1] and at least one example of the formation of a seven-membered ring system has been reported.[2] Our interest in the preparation of benzodiazepines for potential use as medicinal agents[3,4] prompted us to examine the possibility of condensing a bifunctional molecule such as **1** with dimethyl acetylenedicarboxylate (**2**) to produce



1

a new benzodiazepine system. Although this objective was not realized, the chemistry resulting from this study is of sufficient interest to merit reporting at this time.

The facile condensation of **2** with 2-aminobenzophenones to give 4-phenylquinoline-2,3-dicarboxylates has been reported.[5] Since this reaction must proceed *via* a nucleophilic addition of the initially formed enamine system to the benzophenone carbonyl carbon, it occurred to us that the direction of addition might be reversed by altering the electrophilicity of the carbonyl system. We thus investigated the addition of **2** to the aminobenzophenone oximes **3** and **6**. It was found that the reaction was dependent on the geometry of the oxime system. Thus reaction of **2** with the α (*Z*) oxime (**3**)[6] gave the uncyclized adduct (**4**), while the analogous reaction with the β (*E*) oxime (**6**)[6] gave the quinazoline 3-oxide (**7**). Assignment of structure **4** was supported by the vinyl proton signal in the nmr spectrum at δ 5.41 and the NH/OH signals at δ 9.66 and 12.23. The thermodynamically more stable fumarate stereochemistry[7] has generally been assigned to the reaction products of **2** with anilines in alcoholic solvents.[8,9,10,13] In this case the fumarate assignment was supported by the low-frequency ester carbonyl absorption at 1690 cm^{-1} which has been attributed to intramolecular hydrogen bonding of the ester carbonyl with the adjacent NH.[8] Structure **7** is analogous to the six-membered ring



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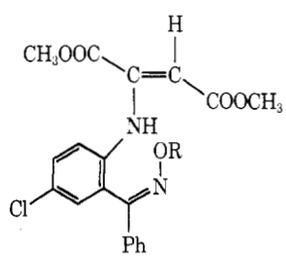
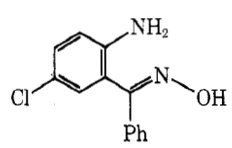


4, R = H
5, R = Ac



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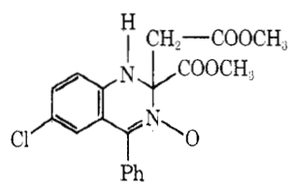
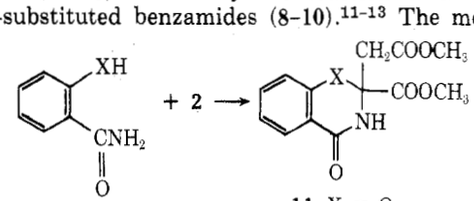


7

adducts (**11**–**13**) formed by the reaction of **2** with the ortho-substituted benzamides (**8**–**10**).[11-13] The methylene

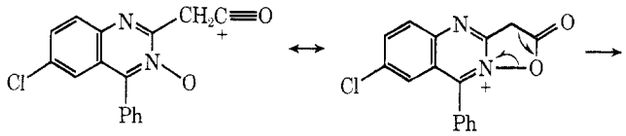


8, X = O
9, X = S
10, X = NH

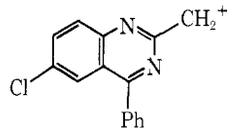
11, X = O
12, X = S
13, X = NH

protons of **7** were represented in the nmr spectrum by an AB quartet centered at δ 3.34 (J = −17 Hz). For compounds **11**, **12**, and **13** the corresponding protons were represented by signals at δ 3.31 (AB quartet, J = −18 Hz),[11] 3.35 (s),[12] and 3.17 (s),[14] respectively. The mass spectrum of **7** was similar to that of **13**;[13] the major peaks resulted from fragmentation of the C-2 substituents with loss of the *N*-oxide. Thus the parent ion (*m/e* 388) suffered successive losses of $COOCH_3$ (*m/e* 329), CH_3OH (*m/e* 297), and CO_2 (*m/e* 253). The *m/e* 329 and 297 fragments are analogous to those derived from the C-2 substituents of

13; the *m/e* 253 ion probably results from fragmentation of the *m/e* 297 ion as shown. Each of these transitions was



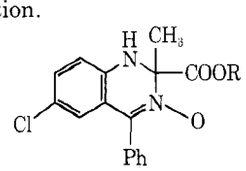
m/e 297



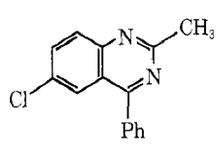
m/e 253

supported by a metastable peak. The electronic spectrum of **7** was similar to that recently reported for 6-chloro-1,2-dihydro-2,2-dimethyl-4-phenylquinazoline 3-oxide, which had λ_{max} 234 nm (ϵ 23,140), 252 (sh, 20,610), 294–304 (7390), 390 (3940).[15]

Saponification of **7** with excess sodium hydroxide and acidification of the resulting salt gave a crystalline product which was insoluble in cold organic solvents. When this material was warmed in methanol it dissolved with vigorous gas evolution to give **14**, which could be converted to the methyl ester **15** with diazomethane. In the nmr the CCH_3 signals for **14** and **15** appeared at δ 1.95 and 1.97, respectively. The mass spectrum of **14** had no molecular ion; the spectrum was essentially identical with that of **16**,[16] which may have been formed by thermolysis of **14** in the inlet port of the instrument. Minor peaks at *m/e* 270 and 269 suggested that 6-chloro-2-methyl-4-phenylquinazoline 3-oxide (**17**),[16,17] resulting from the loss of CO_2 and H_2 from **14**, may also have been formed during this process. Thermolysis of **14** occurred almost explosively at about 160° to give a 49% yield of **16**. None of the quinazoline 3-oxide (**17**) was detected in the reaction mixture; however, we did not exclude the possibility that a small amount of this material might have been formed in the reaction.

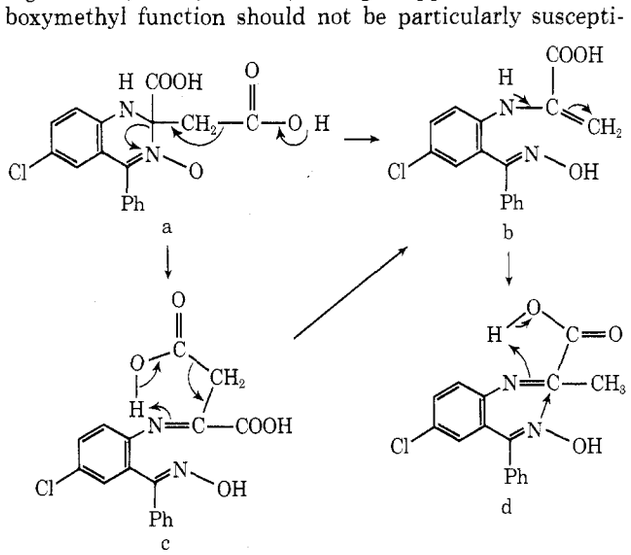


14, R = H
15, R = CH_3



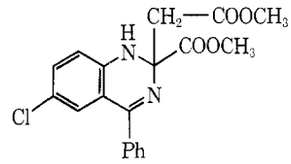
16,
17, 3-oxide

The mechanism for the conversion of **7** to **14** is of passing interest, since, at first, it might appear that the carboxymethyl function should not be particularly susceptible to decarboxylation. We presume that the dibasic acid a is the initial solid isolated from the saponification reaction and suggest that decarboxylation of this material may proceed with ring opening by a 1,4-elimination with cleavage[18] to give b. Alternatively ring opening could precede decarboxylation (*viz.* a → c → b). The intermediate b would be expected to undergo a facile ring closure (*via* d) to give the final product (**14**).



a b c d

Phosphorus trichloride[6,19] effectively cleaved the *N*-oxide bond of **7** to give **18** in about 25% yield. It is interesting that dimethyl 6-chloro-4-phenylquinoline-2,3-dicarboxylate[5] (**19**), obtained in 17% yield, was a major by-



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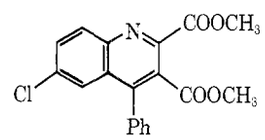
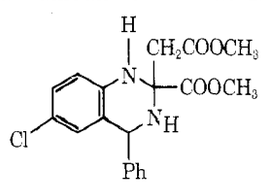


19

product of this reaction. Apparently the reaction of phosphorus trichloride with the *N*-oxide was accompanied by some ring opening (reversal of the original cyclization reaction). Recyclization of the resulting intermediate then occurred at the original carbonyl carbon to give **19**. This cyclization is analogous to the formation of **19** by the reaction of 2-amino-5-chlorobenzophenone with **2**.[5] Catalytic hydrogenation of **18** with platinum oxide in acetic acid gave **20** in 41% yield. This same material (**20**) was obtained as a by-product from the catalytic reduction of **7** under the same conditions. The major product from the latter reaction was **21A**, which was accompanied by a small amount of lactone **22**. Structure **22** was supported



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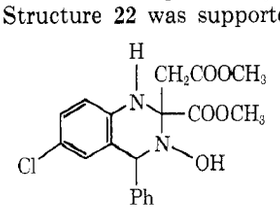

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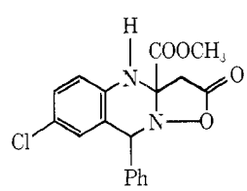

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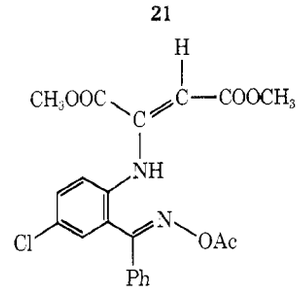


23

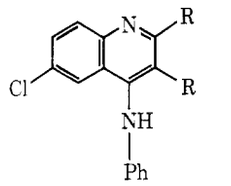
by ester and lactone bands at 1745 and 1780 cm^{-1}, respectively, in the ir and an AB quartet centered at δ 3.15 (J = −16.5 Hz) for the methylene protons in the nmr spectrum. In addition to the molecular ion (*m/e* 358), the mass spectrum of **22** had a minor peak (*m/e* 314) corresponding to loss of CO_2 from the molecular ion and major peaks at *m/e* 299 and 255 corresponding to successive losses of $COOCH_3$ and CO_2 from the molecular ion. In an attempt to convert **21A** to **22** the former compound was subjected to refluxing toluene for several hours. Although a very small amount of **22** was obtained from this reaction, the major product was a second diastereoisomer (**21B**) of **21**. These two compounds (**21A** and **21B**) were readily distinguishable by ir and nmr. For example, **21A** had ir bands at 1740 and 1725 cm^{-1} for the ester carbonyls while **21B** had only one band at 1725 cm^{-1}. In the nmr the methylene protons of **21A** were represented by an AB quartet centered at δ 3.12 (J = −15.5 Hz) while **21B** had

an AB quartet centered at δ 3.16 (J = −16 Hz). The methyl ester protons were represented by three-proton singlets at δ 3.59 and 3.60 for **21A** and at δ 3.72 and 3.75 for **21B**. The benzyl protons were represented by singlets at δ 5.25 and 5.17 for **21A** and **21B**, respectively. Each compound had two peaks corresponding to the exchangeable protons. The mass spectra of **21A** and **21B** were similar but not identical.

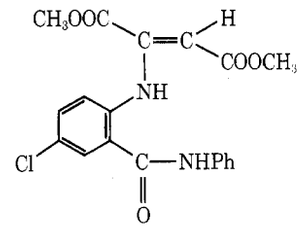
When compound **7** was warmed with acetic anhydride a ring-opened acetoxy oxime (**23**) was obtained. Structure **23** was supported by ester carbonyl bands at 1785, 1735, and 1690 cm^{-1} in the ir and a singlet for the vinyl hydrogen at δ 5.49 in the nmr spectrum. An isomeric material, compound **5**, was obtained from the oxime **4** by its reaction with warm acetic anhydride under similar experimental conditions. From the method of synthesis we must conclude that compounds **23** and **5** are isomeric about the oxime nitrogen. Thus **5** which was obtained by acylation of the Z oxime (**4**) must retain the Z configuration at the oxime nitrogen. On the other hand, simple fragmentation of the quinazoline C-2–N-3 bond would be expected to give oxime derivatives with the E configuration. In this regard it is noteworthy that alkaline hydrolysis of 6-chloro-4-phenylquinazoline 3-oxide is a useful method for preparing the β (E) oxime (**6**) in pure form.[20] It is probable that the enamine system of **23** has the fumarate stereochemistry analogous to that of **4** and, therefore, **5** (*vide supra*). Thus the ir bands and nmr peaks attributable to this system are similar for each of the three compounds. Compare, for example, the ester carbonyl bands in the ir and the methyl ester and vinyl proton signals in the nmr spectra.

We next directed our attention to potential methods for obtaining heterocyctic systems from compound **4**. After initial abortive attempts to cyclize **4** under thermal (pyrolysis at 170–175°) or base-catalyzed (sodium hydride in refluxing benzene) conditions from which only unchanged starting material was recovered, we decided to investigate the possibility of creating an electrophilic center at the oxime nitrogen which might then undergo a cyclization by reacting with the adjacent enamine system. A promising reagent for this purpose appeared to be the triphenylphosphine–carbon tetrachloride combination (**24**), which has become increasingly useful for removing oxygen (OH or H_2O) from various systems with the concomitant formation of triphenylphosphine oxide. Thus **24** has been found to convert alcohols to alkyl halides[21] and carboxylic acids to acid chlorides[22] or, in the presence of amines, to amides.[23] With added base, **24** is useful for converting primary amides[24] and aldoximes[25] to nitriles and formamides to isonitriles.[26]

We found that compound **4** reacted rapidly with 2 equiv of triphenylphosphine in refluxing carbon tetrachloride solution to give, in addition to triphenylphosphine oxide, a mixture of two products which have been identified as **25** and **28**. The structure of **28**, a minor product of the reaction, was established by direct comparison with an authentic sample.[13] The major product of the reaction (**25**) was obtained in 60% yield. Its functional groups were limited to two methyl esters, identified by bands at 1745 and 1680 cm^{-1} in the ir and singlets at δ 3.91 and 4.03 in the nmr, and an NH which was established by the ir absorption at 3270 cm^{-1} and a D_2O-exchangeable peak at δ 9.72 in the nmr. The low-frequency ester carbonyl absorption in the ir is undoubtedly due to the vinylogous relationship of the C-3 ester function with the C-4 nitrogen substituent. Saponification of **25** with sodium hydroxide gave the dibasic acid **26**, which was decarboxylated by heating at 259–268° to give **27**. This compound was identical with an authentic sample which was prepared by the reaction of 4,6-dichloroquinoline[27,28] with aniline.[29]



25, R = $COOCH_3$
26, R = COOH
27, R = H



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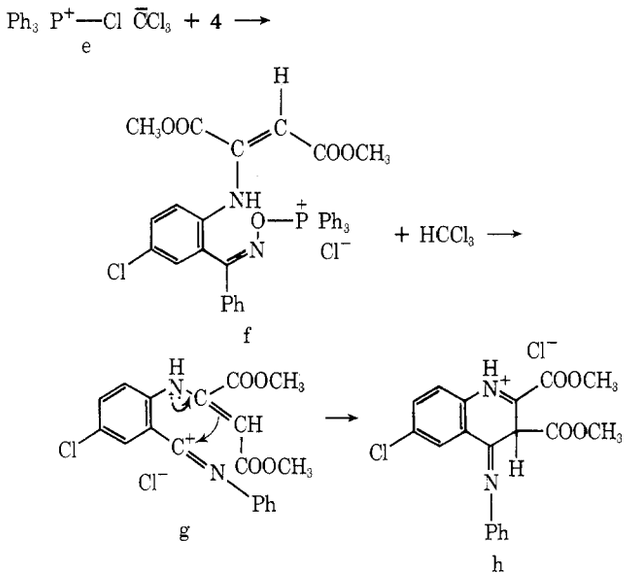
An interpretation of the reaction of **4** with **24** is shown below. The initial reaction of triphenylphosphine with carbon tetrachloride is the result of attack by phosphorus on halogen to give the chlorophosphonium trichloromethylide (e), which is apparently the intermediate responsible for the reactions of **24** with oxygen-containing substrates.[30,31] The reaction of e with the oxime **4** would be expected to give the quasiphosphonium salt f, which could undergo a Beckmann rearrangement with elimination of triphenylphosphine oxide. The resulting intermediate, which may be formulated as the iminocarbonium ion g, could accept a pair of electrons from the enamine system to give h, which is a double-bond tautomer of the observed product (**25**).[32,33] Alternatively the reaction of g with chloride ion would give the imino chloride. Although this derivative could also react with the enamine system to give h, it might survive to be hydrolyzed to the amide **28** during the aqueous work-up.



It was recently reported that 2-*bromo*acetophenone (Z)-oxime reacted with triphenylphosphine to give, after aqueous work-up, acetanilide. This same reaction, however, with 2-*chloro*acetophenone oxime gave (2-phenyl-2-oximinoethyl)triphenylphosphonium chloride.[34] A similar dichotomy was observed in the reactions of 2-bromo- and 2-chloroacetophenone with triphenylphosphine in the presence of a proton donor such as methanol or diethyl malonate.[35] The latter phenomenon was attributed to the propensity of trivalent phosphorus to attack either halogen or carbon of an alkyl halide.[30,35] In an aprotic medium the two mechanisms give the same product, the phosphonium salt; however, in the presence of an acidic proton attack by phosphorus on halogen results in the reduction of the alkyl halide. Thus in the case of 2-bromoacetophenone oxime triphenylphosphine undoubtedly attacks bromine to give initially the enolate bromophosphonium ion pair (i), which proceeds to the quasiphosphonium salt j

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EXPERIMENTAL SECTION

Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, ir spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, high-resolution mass spectra on a Consolidated Electronics Model 21-110 spectrometer, and nmr spectra on a Varian Model A-60A spectrometer. Nmr peaks are recorded in parts per million downfield from tetramethylsilane. In general, only those nmr peaks which are either necessary for the structure proof or are readily assignable to a specific proton or group of protons are reported; the integrated spectra are, however, in all cases in agreement with the assigned structures. Skellysolve B is a commercial hexane, bp 60-70°, made by Skelly Oil Co., Kansas City, Mo. Darco G-60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. Celite is a filter aid manufactured by Johns-Manville, New York, New York. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck AG, Darmstadt, Germany.

(2-Benzoyl-4-chloroanilino)fumaric Acid, Dimethyl Ester (Z)-Oxime (4)-A mixture of 3[8] (2.47 g, 0.01 mol), dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol) and MeOH (20 ml) was stirred at ambient temperature for 1 hr and filtered. The solid was recrystallized from CH_2Cl_2-MeOH to give 2.59 g, mp 162-163° and 0.25 g, mp 164-165.5° (73.2% yield) of 4. The analytical sample had: mp 164.5-165.5°; uv (EtOH) end absorption, λmax 245.5 nm (ε 19,200), 326 (16,200); ir (Nujol) 3250, 3200, 3060 cm^{-1} (NH/OH), 1730, 1690 (C=O); nmr $[(CD_3)_2SO]$ δ 3.68 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 5.41 (s, 1, C=CH), 9.66 (s, 1, NH), 12.23 (s, 1, OH); mass spectrum m/e 355.0616 ($C_{18}H_{14}ClNO_4$), 324, 296, 253, 239.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; Cl, 9.12; N, 7.20. Found: C, 58.67; H, 4.49; Cl, 9.19; N, 7.13.

2-Carboxy-6-chloro-1,2-dihydro-4-phenyl-2-quinazolineacetic Acid, Dimethyl Ester 3-Oxide. (7)-A solution of 6[8] (8.79 g, 0.0357 mol) and dimethyl acetylenedicarboxylate (5.07 g, 0.0357 mol) in MeOH (70 ml) was stirred for 1 hr at ambient temperature and concentrated in vacuo. The residue was crystallized from EtOAc to give 2.80 g, mp 130-134° and 7.16 g, mp 128-132° (72.2% yield) of 7. The analytical sample had: mp 127-128°; uv (EtOH) end absorption, λmax 233 nm (ε 20,550), 250 (18,750), 308 (7050), 384 (3250); ir (Nujol) 3260 cm^{-1} (NH), 1760, 1750, (C=O); nmr $[(CD_3)_2SO]$ δ 3.01, 3.30, 3.38, (3.65) (AB quartet, 2, CH_2), 3.62 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 8.30 (s, 1, NH); mass spectrum m/e (rel intensity) 388 (26), 371 (8), 357 (3), 329 (100), 313 (5), 297 (79), 253 (7) with meta stable peaks at 280.1 (388 → 329), 269 (329 → 297), 216.4 (297 → 253).

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Anal. Calcd. for $C_{18}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; Cl, 9.12; N, 7.21. Found: C, 58.78; H, 4.74; Cl, 8.72; N, 7.31.

6-Chloro-1,2-dihydro-2-methyl-4-phenyl-2-quinazolinecarboxylic Acid, 3-Oxide (14)-A stirred mixture of 7 (11.7 g, 0.03 mol) THF (100 ml) and water (675 ml) was cooled in an ice bath, treated with 0.945 N NaOH (80 ml) and kept at ambient temperature for 24 hr. It was then filtered, and the filtrate was concentrated in vacuo to remove the THF. The resulting solution was cooled in an ice bath and acidified to pH 2-2.5 with dilute HCl. The mixture was treated with a little $CHCl_3$ and stirred until crystallization was complete. The solid was collected by filtration, washed with water and $CHCl_3$ and dried to give 9.47 g of solid. Dissolution of this material in hot methanol was accompanied by considerable effervescence. Crystallization of the resulting compound from MeOH-EtOAc gave 5.71 g, mp 179-180° dec and 0.698 g, mp 182-183° dec (69.4% yield) of 14. The analytical sample had: mp 172.5° dec; uv (EtOH) λmax 230 nm (ε 31,900), 255 (sh 13,600), 280 (sh 7300), 314 (5450), 380 (1950); ir (Nujol) 3280 cm^{-1} (NH), 2320, 1695 (COOH); nmr $[DCON(CD_3)_2]$ δ 1.95 (s, 3, C-CH_3), mass spectrum m/e (rel intensity) 270 (7.2), 269 (6.8), 254 (100), 253 (69), 235 (4), 219 (86) with a meta stable peak at 189 (254 → 219). The mass spectrum of 6-chloro-2-methyl-4-phenylquinazoline 3-oxide[8] had m/e (rel intensity) 270 (59), 269 (60), 254 (53), 253 (69), 234 (14), 219 (60).

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; Cl, 11.19; N, 8.84. Found: C, 60.71; H, 4.09; Cl, 11.27; N, 8.59.

6-Chloro-1,2-dihydro-2-methyl-4-phenyl-2-quinazolinecarboxylic Acid, Methyl Ester, 3-Oxide (15)-A stirred suspension of 14 (2.83 g) in CH_2Cl_2 (150 ml) was treated during 5 hr with an excess of an ether solution of diazomethane. When most of the solid had dissolved the mixture was filtered, and the filtrate was washed with dilute $NaHCO_3$ and H_2O, dried (Na_2SO_4) and concentrated. The residue was crystallized from EtOAc-Skellysolve B to give 1.26 g, mp 163-165° and 0.316 g; mp 162-163.5° (53.4% yield) of 15. The analytical sample had: mp 163.5-165°, uv (EtOH) end absorption, λmax 233 nm (ε 22,350), 205 (sh 23,050), 251 (19,750), 308 (7700), 383 (3800); ir (Nujol) 3180, 3160 cm^{-1} (NH), 1745 (C=O); nmr ($CDCl_3$) δ 1.97 (s, 3, C-CH_3), 3.75 (s, 3, O-CH_3), 5.65 (s, 1, NH).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; Cl, 10.72; N, 8.47. Found: C, 61.40; H, 4.61; Cl, 10.69; N, 8.50.

6-Chloro-2-methyl-4-phenylquinazoline (16)-A sample of 14 (1.5 g) was warmed under N_2 in an oil bath from 137-160° during 9 min. The material decomposed vigorously with much evolution of gas. The cooled melt was chromatographed on silica gel (75 g) with 20% EtOAc-80% cyclohexane. The product thus obtained was crystallized from EtOAc-Skellysolve B to give: 0.317 g, mp 106-107.5° and 0.276° g,

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mp 105-106° (49.3% yield) of 16. The analytical sample had: mp 106-107.5°. [lit. mp 105-106°[8], 105-107°[43], 107-108°[44]]; mass spectrum m/e (rel intensity) 254 (72) 253 (100) 235 (0.8) 219 (93).

Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; Cl, 13.92; N, 11.00. Found: C, 70.31; H, 4.35; Cl, 14.11; N, 10.83.

This material was identical to an authentic sample of 16 by direct ir, uv, nmr and mass spectral comparison.

Reaction of 7 with Phosphorus Trichloride - A stirred mixture of 7 (1.0 g, 2.57 mmol) and hydrocarbon-stabilized $CHCl_3$ (25 ml) was treated with PCl_3 (1.0 ml), refluxed under N_2 for 30 min and poured onto crushed ice. This mixture was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed (H_2O), dried (K_2CO_3) and concentrated. The residue was dissolved in EtOAc, filtered through a small pad of silica gel and crystallized from EtOAc-Skellysolve B to give 0.152 g (16.5%) of 6-chloro-4-phenyl-2,3-quinolinedicarboxylic acid dimethyl ester (19), mp 164.5-166° [lit[5] mp 162.5-163°]. A mixture melting point of this material with an authentic sample of 19 (mp 166-167.5°) was not depressed. The mother liquor was concentrated and chromatographed on silica gel (150 g) with 15% EtOAc-85% cyclohexane. The product thus obtained was acidified with a solution of HBr in MeOH and crystallized from MeOH-EtOAc to give 0.293 g (25.1%) of 2-carboxy-6-chloro-1,2-dihydro-4-phenyl-2-quinazolineacetic acid, dimethyl ester hydrobromide (18 ·HBr), mp 185-186° dec. The analytical sample had mp 182.5-183° dec.

Anal. Calcd. for $C_{19}H_{18}BrClN_2O_4$: C, 50.29; H, 4.00; Br, 17.61; Cl, 7.82; N, 6.18. Found: C, 50.29; H, 4.39; Br, 17.54; Cl, 7.32; N, 5.75.

A sample of (18 ·HBr) was suspended in dilute $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (K_2CO_3) and concentrated. Crystallization of the residue from EtOAc-Skellysolve B gave 2-carboxy-6-chloro-1,2-dihydro-4-phenyl-2-quinazolineacetic acid dimethyl ester (18), mp 118-121.5°; uv (EtOH) end absorption, λmax 237 nm (ε 31,100), 391 (1950); ir (Nujol) 3360 cm^{-1} (NH), 1750, 1715 (C=O); nmr ($CDCl_3$) δ 2.86, 3.13, 3.32, 3.59 (AB quartet, 2, CH_2), 3.71 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 5.54 (s, 1, NH); mass spectrum m/e (rel intensity) 372 (0.4), 313 (100), 299 (8), 281 (11), 253 (69), 239 (10), 218 (14).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; Cl, 9.51; N, 7.51. Found: C, 60.95; H, 4.60; Cl, 9.55; N, 7.56.

Catalytic Hydrogenation of 7 with Platinum and Acetic Acid - A mixture of 7 (10 g, 0.0257 mol), HOAc (100 ml) and PtO_2 catalyst (1.0 g) was hydrogenated at ambient temperature for 3 hr at an initial pressure of 2.1 kg/cm^2. The result-

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ing mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was mixed with water, neutralized with Na_2CO_3 and extracted with Et_2O. The extract was washed with brine, dried (K_2CO_3) and concentrated. Crystallization of the residue from EtOAc-Skellysolve B gave 3.56 g (35.4%) of 2-carboxy-6-chloro-1,2,3,4-tetrahydro-3-hydroxy-4-phenyl-2-quinazolineacetic acid, dimethyl ester (21A), mp 154-157°. The analytical sample had: mp 157-157.5°; uv (EtOH) end absorption, λmax 250 nm (ε 11,120), 304 (2545); ir (Nujol) 3420 cm^{-1} (NH/OH), 1740, 1725 (C=O); mass spectrum m/e 390, 373, 331, 317, 313, 252; nmr $[(CD_3)_2SO]$ δ 2.82, 3.08, 3.15, 3.41 (AB quartet, 2, CH_2), 3.59 (s, 3, OCH_3), 3.60 (s, 3, OCH_3), 5.25 (s, 1, CH), 6.33 (s, 1, NH), 8.32 (s, 1, OH).

Anal. Calcd. for $C_{19}H_{19}ClN_2O_5$: C, 58.39; H, 4.90; Cl, 9.07; N, 7.17. Found C, 58.74; H, 4.70; Cl, 8.93; N, 6.76.

The mother liquor was concentrated to give 7.4 g of a mixture which was chromatographed on silica gel (400 g) with 25% EtOAc-75% cyclohexane. The first compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.615 g (6.38%) of 2-carboxy-6-chloro-1,2,3,4-tetrahydro-4-phenyl-2-quinazolineacetic acid, dimethyl ester (20), mp 161.5-163°. The analytical sample had: mp 166-167.5°; uv (EtOH) λmax 207 nm (ε 35,600), 253 (10,800), 307 (2660); ir (Nujol) 3400, 3320 cm^{-1} (NH) 1750, 1700 (C=O), mass spectrum m/e (rel intensity) 374 (3), 343 (2), 315 (100), 301 (9), 281 (8), 255 (4), 216 (17); nmr ($CDCl_3$) δ 2.67, 2.92, 2.98, 3.23 (AB quartet, 2, CH_2), 2.65 (s, 1, NH), 3.70 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 4.99 (s, 1, CH), 5.10 (s, 1, NH).

Anal. Calcd. for $C_{19}H_{19}ClN_2O_4$: C, 60.89; H, 5.11; Cl, 9.46; N, 7.47. Found C, 60.98; H, 5.17; Cl, 9.03; N, 7.43.

The second compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.341 g (3.7%) of 7-chloro-2,3,4,9-tetrahydro-2-oxo-9-phenyl-3aH-isoxazolo[3,2-b]quinazoline-3a-carboxylic acid, methyl ester (22), mp 124.5-127° dec. The analytical sample had: mp 125.5-128° dec; uv (EtOH) end absorption, λmax 247 nm (ε 20,800), 307 (4870); ir (Nujol) 3410 cm^{-1} (NH), 1780, 1745 (C=O); mass spectrum m/e (rel intensity) 358 (10), 314 (4), 299 (100), 255 (64), 214 (33), 179 (30), 152 (25); nmr ($CDCl_3$) δ 2.78 (d, 1, J = -16.5 Hz CH_2), 3.51 (d, 1, J = -16.5 Hz, CH_2), 3.21 (s, 3, OCH_3), 4.77 (s, 1, NH), 5.57 (s, 1, CH).

Anal. Calcd. for $C_{18}H_{15}ClN_2O_4$: C, 60.24; H, 4.21; Cl, 9.88; N, 7.81. Found: C, 59.90; H, 4.30; Cl, 9.86; N, 7.83.

2-Carboxy-6-chloro-1,2,3,4-tetrahydro-4-phenyl-2-quinazolineacetic Acid, Dimethyl Ester (20). - A solution of 18 (0.5 g) in HOAc (20 ml) was treated with PtO_2 catalyst (0.1 g) and hydrogenated for 2.5 hr at ambient temperature and an initial hydrogen pressure of 1.8 kg/cm^2. The resulting mixture was filtered

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through Celite, and the filtrate was concentrated in vacuo. The residue was mixed with dilute aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed (H_2O), dried (K_2CO_3) and concentrated. The residue was crystallized from EtOAc-Skelly B to give 0.204 g (40.5%) of 20, mp 163-164° dec. The analytical sample had mp 164-167° dec. It was the same as the sample obtained from 7 by ir, uv and nmr comparison.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_4$: C, 60.89; H, 5.11; Cl, 9.46; N, 7.47. Found: C, 60.83; H, 5.16; Cl, 9.11; N, 7.47.

Reaction of 21A with Refluxing Toluene - A stirred mixture of 21A (0.783 g, 0.002 mol) and toluene (50 ml) was refluxed under N_2 for 6 hr 35 min. During this time the solvent was slowly distilled from the reaction mixture through a small glass-helex-packed column. The resulting solution was concentrated and the residue was chromatographed on silica gel (50 g) with 20% EtOAc-80% cyclohexane. The first compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.327 g (41.7%) of 2-carboxy-6-chloro-1,2,3,4-tetrahydro-3-hydroxy-4-phenyl-2-quinazolineacetic acid, dimethyl ester (21B), mp 152-154°. The analytical sample had: mp 153.5-155°; uv (EtOH) λmax 207 nm (ε 34,000), 242 (sh 7900), 258 (9930), 307 (2790); ir (Nujol) 3360, 3260 cm^{-1} (NH/OH), 1725 (C=O); nmr ($CDCl_3$) δ 2.75, 3.02, 3.30, 3.57 (AB quartet, 2, CH_2), 3.72 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 5.17 (s, 2, CH and OH/NH), 5.61 (s, 1, NH/OH); mass spectrum m/e (rel intensity) 390 (3), 331 (100), 317 (4), 313 (3), 253 (6), 237 (19). The mixture melting point with 21A was 137.5-148°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O_5$: C, 58.39; H, 4.90; Cl, 9.07; N, 7.17. Found: C, 58.46; H, 4.94; Cl, 9.05; N, 7.05.

The second compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 34 mg of 22, mp 126-128° dec which was identical to the authentic sample by ir comparison.

(2-Benzoyl-4-chloroanilino)fumaric Acid, Dimethyl Ester, (E)-O-Acetyloxime (23) - A mixture of 7 (2.0 g, 5.2 mmol) and Ac_2O (10 ml) was warmed under N_2 on the steam bath for 15 min, cooled and poured into ice water. The resulting mixture was stirred for 45 min, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed (H_2O), dried (Na_2SO_4) and concentrated. The residue was crystallized from Et_2O-Skellysolve B to give 1.42 g (63.8%) of 23, mp 119.5-121°. The analytical sample was crystallized from CH_2Cl_2-Et_2O and had mp 121.5-122.5°; uv (EtOH) end absorption, λmax 355 nm (ε 8500), 235 (sh 14,500), 245 (sh 14,000); ir (Nujol) 3290 cm^{-1} (NH), 1785, 1735, 1690 (C=O); nmr $[(CD_3)_2SO]$ δ 2.21 (s, 3, C-CH_3), 3.65 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 5.49 (s, 1, C=C-H), 9.87 (s, 1, NH).

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Anal. Calcd. for $C_{21}H_{19}ClN_2O_6$: C, 58.54; H, 4.44; Cl, 8.23; N, 6.50. Found: C, 55.73; H, 4.64; Cl, 8.25; N, 6.78.

(2-Benzoyl-4-chloroanilino)fumaric Acid Dimethyl Ester (Z)-O-Acetyloxime (5) - A stirred mixture of 4 (3.89 g, 0.01 mol) and Ac_2O (20 ml) was warmed under N_2 on the steam bath for 20 min. The resulting yellow solution was cooled and poured into ice water. This mixture was stirred until the excess Ac_2O had hydrolyzed and the resulting yellow solid was collected by filtration, washed (H_2O) and dried. It was recrystallized from EtOAc to give 2.21 g, mp 157-159°, 0.881 g, mp 158-159° and 0.583 g, mp 157.5-159° (85.2% yield) of 5. The analytical sample had: mp 157.5-160°; uv (EtOH) end absorption, λmax 247 nm (ε 19,950), 326 (14,850); ir (Nujol) 3240 cm^{-1} (NH), 1765, 1740, 1665 (C=O); nmr ($CDCl_3$) δ 2.23 (s, 3, C-CH_3), 3.67 (s, 3, OCH_3), 3.69 (s, 3, OCH_3), 5.53 (s, 1, C=C-H), 9.53 (s, 1, NH).

Anal. Calcd. for $C_{21}H_{19}ClN_2O_6$: C, 58.54; H, 4.44; Cl, 8.23; N, 6.50. Found: C, 58.84; H, 4.46; Cl, 8.28; N, 6.55.

Reaction of 4 with Triphenylphosphine and CCl_4 - A stirred mixture of 4 (3.89 g, 0.01 mole) triphenylphosphine (5.24 g, 0.02 mol) and dry CCl_4 (10 ml) was refluxed under N_2 for 2 hr 15 min. Additional CCl_4 (10 ml) was added and the mixture was refluxed for an additional 25 min, cooled and poured into water. This mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (200 g) with 20% EtOAc-80% cyclohexane. The first compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.324 g (8.34%) of [4-chloro-2-(phenylcarbamoyl)anilino]fumaric acid dimethyl ester (28), mp 145-147°. The analytical sample had: mp 141-141.5°; [lit.[13] mp 143-145°]; uv (EtOH) end absorption, λmax 224 nm (ε 29,600), 255 (sh 11,450), 343 (8350); ir (Nujol) 3370, 3140 cm^{-1} (NH), 1745, 1710, 1680, 1665, 1650 (C=O); nmr ($CDCl_3$) δ 3.71 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 5.65 (s, 1, =CH), 8.57 (s, 1, NH), 10.58 (s, 1, NH); mass spectrum m/e 388, 328, 297, 269. This material was identical to an authentic sample of 28[13] by ir, uv and nmr comparison. The mixture melting point was undepressed.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_5$: C, 58.69; H, 4.41; Cl, 9.12; N, 7.20. Found: C, 58.31; H, 4.61; Cl, 9.16; N, 7.46.

The second compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 2.16 g, mp 148.5-154° and 0.073 g, mp 147.5-148.5° (60.1% yield) of 4-anilino-6-chloro-2,3-quinolinedicarboxylic acid, dimethyl ester (25). The analytical sample had: mp 148-153°; uv (EtOH) end absorption, λmax 236 nm (ε 43,400), 270 (sh 15,600), 359 (10,250); ir (Nujol) 3270 cm^{-1} (NH), 1745, 1680 (C=O); nmr ($CDCl_3$) δ 3.91 (s, 3, OCH_3), 4.03 (s, 3, OCH_3), 9.72 (s, 1, NH); mass

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spectrum m/e 370, 338, 309, 292, 280.

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; Cl, 9.56; N, 7.55. Found: C, 61.35; H, 3.98; Cl, 9.47; N, 7.44.

Further elution of the column with EtOAc gave triphenylphosphine oxide which was crystallized from EtOAc-Skellysolve B to yield 2.63 g, mp 157-158°. A mixture melting point of this material with an authentic sample was undepressed.

4-Anilino-6-chloro-2,3-quinolinedicarboxylic Acid (26) - A stirred mixture of 25 (3.71 g, 0.01 mol), water (225 ml), THF (75 ml) and 0.945 N NaOH (26.5 ml) was kept under N_2 for 22 hr and concentrated in vacuo at 30° to remove the THF. The resulting aqueous solution was filtered and the filtrate was cooled in an ice bath and acidified to pH 4 with dilute HCl. The solid was collected by filtration, washed (H_2O) and dried to give 3.64 g of 26, mp 255.5-257° dec. This material was very insoluble in most organic solvents. The analytical sample, obtained by recrystallizing some of this material from MeOH, had: mp 257.5° dec; uv (EtOH) end absorption, λmax 237 nm (ε 38,900), 268 (sh, 16,000), 325 (sh 5940), 357 (9700); ir (Nujol) 2900 cm^{-1} (NH/OH), 1695, 1640 (C=O); mass spectrum m/e (rel intensity) 324 (4), 298 (49), 280 (100), 252 (10), 245 (76), 217 (36), 216 (63).

Anal. Calcd. for $C_{17}H_{11}ClN_2O_4$: C, 59.58; H, 3.24; Cl, 10.34; N, 8.17. Found: C, 60.01; H, 3.18; Cl, 10.53; N, 7.84.

4-Anilino-6-chloroquinoline (27) - A sample of 26 (1.5 g) was warmed under N_2 in an oil bath at 259-268° for 4 min. The cooled melt was dissolved in EtOAc, decolorized with Darco G60, filtered through a small pad of silica gel and crystallized to give 0.635 g (57%) of 27, mp 192-195°. The analytical sample had: mp 193-194.5°, uv (EtOH) end absorption, λmax 219 nm (ε 45,400), 249.5 (25,100), 343 (14,200).

Anal. Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; Cl, 13.92; N, 11.00. Found: C, 70.81; H, 4.12; Cl, 14.12; N, 11.05.

4-Anilino-6-chloroquinoline (27) - A stirred solution of 4,6-dichloroquinoline[27,28] (0.59 g, 3 mmol), aniline (0.28 g, 3 mmol) and 3.71 N HCl in EtOH (0.8 ml) was kept at ambient temperature for 5 hr and at reflux for 1 hr. It was then concentrated in vacuo, and the residue was mixed with water, neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The extract was washed (H_2O), dried and concentrated. The residue was crystallized from EtOAc to give 0.32 g, mp 192-193.5° and 0.12 g, mp 191-193° (57.5% yield) of 27. This material was identical to that obtained from 26 by ir, uv and nmr comparison. The mixture melting point was undepressed.

Reaction of 7 with Triphenylphosphine and Carbon Tetrachloride - A stirred mixture of 7 (11.7 g, 0.03 mol); hydrocarbon stabilized $CHCl_3$ (100 ml) and CCl_4 (30 ml) was treated with triphenylphosphine (9.48 g), kept at ambient temperature for 40 min and at reflux for 2 hr. It was then kept at ambient temperature for

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12 hr, poured into ice water and neutralized with $NaHCO_3$. The layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic solution was washed with brine, dried (Na_2SO_4) and concentrated. The residue was carefully chromatographed on silica gel (1 kg) with 15% EtOAc - 85% cyclohexane. The first compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.501 g (4.5%) of (5-chloro-3-phenyl-1-indazolyl) fumaric acid, dimethyl ester (29), mp 112.5-115°. The analytical sample had: mp 113-114.5°; uv (EtOH) λmax 203 nm (ε 37,000), 236 (21,200), 242 (sh 20,650), 277 (14,560), 337 (27,000); ir (Nujol) 1730, 1715, sh 1695 (C=O); nmr ($CDCl_3$) δ 3.82 (s, 3, OCH_3), 4.07 (s, 3, OCH_3), 6.51 (s, 1, =CH); mass spectrum m/e (rel intensity) 370 (100), 339 (9), 311 (9), 281 (4), 252 (4), 251 (4), 228 (6).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; Cl, 9.56; N, 7.55. Found: C, 61.38; H, 4.19; Cl, 9.72; N, 7.76.

The second compound eluted from the column was an oil which was obtained in low yield and could not be obtained pure.

The third compound eluted from the column was crystallized from EtOAc-Skelly B to give 2.25 g (20.2%) of (5-chloro-2-phenyl-1-benzimidazolyl)maleic acid, dimethyl ester (30), mp 130-135°. The analytical sample had: mp 131.5-134.5°; uv (EtOH) λmax 204 nm (ε 29,100), 252 (sh 19,000), 268 (24,000), 315 (sh 10,000), 350 (sh 5680); ir (Nujol) 1735, 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.28 (s, 3, OCH_3), 3.98 (s, 3, OCH_3), 6.69 (s, 1, =CH); mass spectrum m/e (rel intensity) 370 (100), 339 (4), 311 (95), 310 (56), 279 (23), 267 (30), 252 (28), 251 (33).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; Cl, 9.56; N, 7.55. Found: C, 61.40; H, 4.06; Cl, 9.65; N, 7.67.

The fourth compound eluted from the column was crystallized from EtOAc-Skelly B to give 0.841 g, mp 145.5-147°; 0.538 g, mp 145.5-146.5°; 0.377 g, mp 145.5-147° (15.8% yield) of (5-chloro-2-phenyl-1-benzimidazolyl) fumaric acid, dimethyl ester (31). The analytical sample had: mp 145.5-147°; uv (EtOH) λmax 206 nm (ε 55,500), 220 (sh 31,900), 261 (12,300), 294 (15,300); ir (Nujol) 1730 cm^{-1} (C=O), 1645 (C=C); nmr ($CDCl_3$) δ 3.56 (s, 3, OCH_3), 3.64 (s, 3, OCH_3), 6.94 to 7.86 (m, 9, =CH and ArH); mass spectrum m/e (rel intensity) 370 (100), 339 (4), 311 (62), 310 (47), 279 (19), 267 (20), 252 (23), 251 (28).

Anal. Calcd. for $C_{19}H_{15}ClN_2O_4$: C, 61.55; H, 4.08; Cl, 9.56; N, 7.55. Found: C, 61.84; H, 4.09; Cl, 9.68; N, 7.67.

The fifth compound was eluted from the column with the trailing portion of compound 31. After 31 had been removed by crystallization, the mother liquor was acidified with a MeOH solution of HBr. The resulting salt was crystallized from MeOH-EtOAc to give 1.07 g (7.86%) of 18 ·HBr, mp 184-185° dec. This material was the same as the authentic sample by ir, uv and nmr comparison.

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5-Chloro-3-phenylindazole - A stirred mixture of 2-amino-5-chlorobenzophenone (23.2 g, 0.1 mol), water (200 ml) and conc HCl (41.7 ml) was cooled in a salt-ice bath and treated dropwise with a solution of $NaNO_2$ (8.3 g) in water (30 ml). The mixture was stirred at -5 to 0° for 20 min and then treated during 45 min with a solution of $SnCl_2 \cdot 2H_2O$ (54.0 g, 0.24 mol) in conc HCl (85 ml). The resulting mixture was kept in the ice bath for 1 hr and allowed to warm slowly to ambient temperature during 3 hr. The solid was collected by filtration, washed with water and dissolved in $CHCl_3$. This solution was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (1 kg) with 15% EtOAc-85% cyclohexane. The product thus obtained was crystallized from EtOAc-Skellysolve B to give 3.73 g, mp 137-137.5° and 4.51 g, mp 137-139° of 5-chloro-3-phenylindazole. [lit mp 135-136°[45], 125-127°[46]].

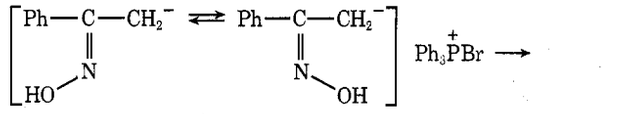
Anal. Calcd. for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; Cl, 15.51; N, 12.25. Found: C, 68.33; H, 4.03; Cl, 15.45; N, 12.77.

(5-Chloro-3-phenyl-1-indazolyl)fumaric Acid, Dimethyl Ester (29) - A stirred solution of 5-chloro-3-phenylindazole (1.14 g, 0.005 mol) in dry benzene (40 ml) was treated with dimethyl acetylenedicarboxylate (0.782 g, 0.0055 mol) and refluxed under N_2 for 9 hr. The solution was concentrated in vacuo and the residue was chromatographed on silica gel (100 g) with 15% EtOAc-85% cyclohexane. The first product eluted from the column was crystallized from EtOAc-Skellysolve B to give 89 mg (4.8%) of 29, mp 117.5-119.5°. This material was the same as that obtained from 7 by ir, uv, nmr and mass spectral comparison. The mixture melting point was not depressed.

The major product was eluted from the column next. It was an oil which had: uv (EtOH) λmax 206 nm (ε 28,400), 217 (29,000), 240 (sh 13,700), 247 (sh 12,650), 270 (sh 7700), 296 (sh 7550), 308 (sh 9500), 319 (10,400), 334 (10,100), 349 (8250); ir (film) 1740 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 370 (68), 339 (7), 311 (33), 279 (22), 251 (19), 252 (30); nmr ($CDCl_3$) δ 3.63 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 6.43 (s, 1, =CH). This material was not pure and was not further characterized.

(5-Chloro-2-phenyl-1-benzimidazolyl)fumaric Acid, Dimethyl Ester (31) - A stirred mixture of 5-chloro-2-phenylbenzimidazole[47] (1.6 g, 0.007 mol), dimethyl acetylenedicarboxylate (1.1 g, 0.0077 mole) and benzene (60 ml) was refluxed under N_2 for 9 hr and concentrated in vacuo. The residue was carefully chromatographed on silica gel (150 g) with 0.5% MeOH-99.5% $CHCl_3$. Little separation of the mixture was obtained, but several of the first fractions eluted from the column crystallized from EtOAc-Skellysolve B to give 0.244 g, mp 145-146°, 0.085 g, mp 145-146° and 0.158 g, mp 141-142.5° (18.7% yield) of 31. This material was identical to that obtained from 7 by ir, uv and nmr comparison. The mixture melting point with the authentic sample was not depressed.

and thence to the Beckmann products. This sequence is analogous to that proposed above for the reaction of 4



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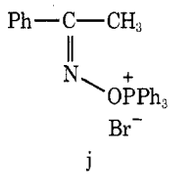
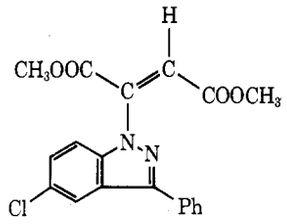


j

with 24. The reaction of triphenylphosphine dibromide and triethylamine with acetophenone (*E*)-oxime to give Beckmann products[34] is an additional example of this reaction.

Having thus demonstrated that 24 was able to achieve a Beckmann rearrangement, it was of interest to find a second example of this reaction. Since the quinazoline 3-oxide (7) was known to behave as an oxime under some circumstances (*viz.* 7 → 23), we next investigated the reaction of this compound with 24. When this reaction was carried out a mixture of four compounds was obtained. The mixture was separated by chromatography and the compounds were identified as 29, 31, 30, and 18.



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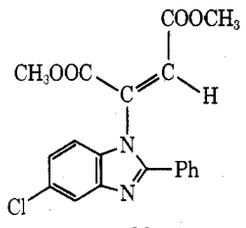

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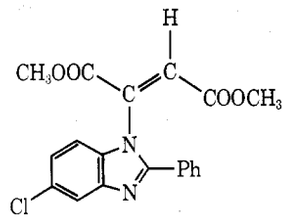


31

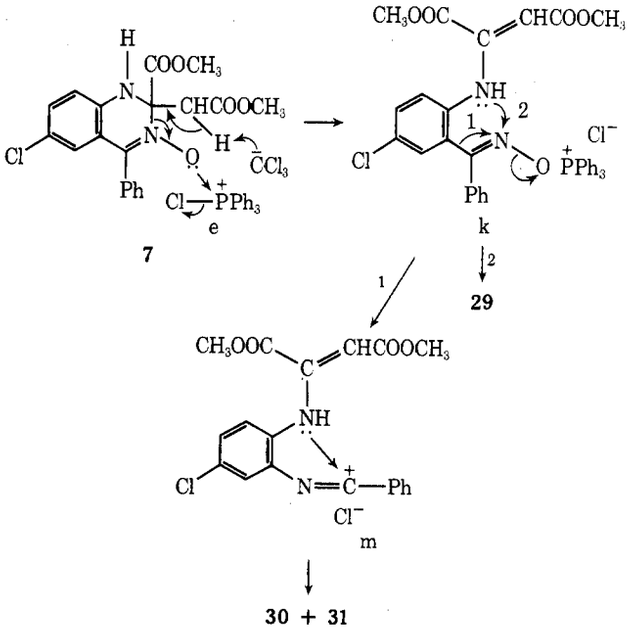
Compound 18 was identical with the imine obtained by the reaction of 7 with phosphorus trichloride.[36]

Structure 31 was suggested by the spectral data. The ir had bands at 1730 and 1645 cm^{-1} for the esters and carbon–carbon double bond, respectively, and the nmr had singlets at δ 3.56 and 3.64 for the methyl ester protons. The vinyl proton signal for this molecule fell within the aromatic multiplet at δ 6.94–7.86. An independent synthesis of 31 was achieved by the reaction of 5-chloro-2-phenylbenzimidazole[37] with 2 in refluxing benzene. Although the yield of 31 from this reaction was low (19%), it was the only crystalline product that could be isolated. Since 2 can react with 5-chloro-2-phenylbenzimidazole at either N-1 or N-3, this synthesis of 31 is ambiguous with regard to the exact nature of attachment of the vinyl side chain to the benzimidazole nucleus. We will infer, however, that the side chain is attached at N-1 based on our mechanistic interpretation of the reaction of 7 with 24 which is discussed below. Compound 30 had ester carbonyl bands at 1735 and 1715 cm^{-1} in the ir and peaks at δ 3.28, 3.98, and 6.69 in the nmr for the methyl ester and vinyl protons, respectively. The mass spectrum of 30 was essentially identical with that of 31, which suggests that the two compounds are closely related. Since double-bond isomers often behave in this manner, we propose that compounds 30 and 31 are in fact isomeric about the side-chain double bond.

Acheson and coworkers have studied the reaction of 2 with a variety of heterocyclic systems. In general the Michael adducts obtained from these reactions have been assigned the fumarate stereochemistry.[38] Of particular interest for this discussion, the reaction of 2-benzylimidazol with 2 gave a normal Michael adduct which was also assumed to be a fumaric acid derivative.[39] It has been found that the vinyl proton of fumarate ester derivatives experiences a greater deshielding by the diamagnetic anisotropy of the adjacent ester carbonyls than does the vinyl proton of the corresponding maleate ester derivative.[40] This effect is useful for assigning stereochemistry when both isomers of a particular system are available.[41] In the case at hand the vinyl proton absorption for compound 31 was at least 0.57 ppm downfield from that of compound 30. This is consistent with the stereochemical assignment for these compounds and supports Acheson's conclusions with regard to the stereochemistry of the Michael adducts (see above).

Compound 29 was isolated in low yield (4.5%). It was an isomer of compounds 30 and 31 which had ester carbonyl bands at 1730 and 1715 cm^{-1} in the ir and singlets at δ 3.82, 4.07, and 6.51 in the nmr for the methyl ester and vinyl protons, respectively. The mass spectrum was similar to but not identical with that of 30 and 31. The structure of 29 was established by an independent synthesis. Thus the reaction of 5-chloro-3-phenylindazole with 2 in refluxing benzene gave the Michael adduct 29 in 5% yield. Assignment of the fumarate stereochemistry to the side chain was based on analogy with similar reactions in the literature.[42]

The reaction of 7 with 24 must proceed in a manner somewhat analogous to that already discussed for the reaction of 4 with 24. The chlorophosphonium salt e apparently reacts with 7 to give the quasiphosphonium salt of the *E* oxime (k). In this intermediate the electron-deficient center which is being created on the oxime nitrogen by the departure of triphenylphosphine oxide may be satisfied in either of two ways. On the one hand, aryl migration leads to the Beckmann intermediate m, which can react with the anilino nitrogen to give 30 and 31. On the other hand, the anilino nitrogen apparently can react with the oxime nitrogen of k prior to aryl migration, with the result being the formation of 29.



These results would suggest that the triphenylphosphine–carbon tetrachloride combination may have some potential for carrying out Beckmann rearrangements under mild and essentially neutral conditions. This speculation must, however, await the results of future research in this area.

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Registry No.—**3,** 5013-10-5; **4,** 51519-93-8; **5,** 51519-94-9; **6,** 15185-66-7; **7,** 51519-95-0; **14,** 51519-96-1; **15,** 51519-97-2; **16,** 4765-61-1; **18,** 51519-98-3; **18 HBr,** 51519-99-4; **20,** 51520-00-4; **21A,** 51520-01-5; **21B,** 51520-02-6; **22,** 51520-03-7; **23,** 51520-04-8; **25,** 51520-05-9; **26,** 51520-06-0; **27,** 51520-07-1; **28,** 51703-31-2; **29,** 51520-08-2; **30,** 51520-09-3; **31,** 51520-10-6; dimethyl acetylenedicarboxylate, 762-42-5; phosphorus trichloride, 7719-12-2; triphenylphosphine, 603-35-0; carbon tetrachloride, 56-23-5; 4,6-dichloroquinoline, 4203-18-3; aniline, 62-53-3; 5-chloro-3-phenylindazole, 13097-03-5; 2-amino-5-chlorobenzophenone, 719-59-5; 5-chloro-2-phenylbenzimidazole, 4887-82-5.

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