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A General Conversion of Phenols to Anilines[1a]

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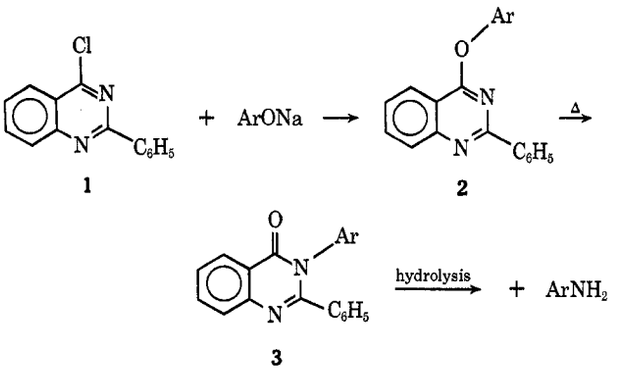
The rearrangement of 4-aryloxy-2-phenylquinazolines (**2**) at 275–325° to 3-aryl-2-phenyl-4(3*H*)-quinazolinones (**3**) has been utilized to convert phenols to anilines. The aniline produced on hydrolysis of **3** has the same substitution pattern as the 4-aryloxy group of **2** and, hence, the phenol from which the latter is made. By this procedure aniline (71%), 2,4-dichloroaniline (64%), 2,3,6-trimethylaniline (70%), and 4-nitroaniline (42%) have been prepared. The thermal rearrangements of 2-methyl-4-phenoxyquinazoline (**14**) and 4-phenoxyquinazoline (**15**) are also described.

While most anilines may be readily transformed to the corresponding phenol by way of a diazonium salt, the reverse path interrelating these two large classes of compounds has remained severely restricted. Two general approaches have been used for the conversion of a phenol into the corresponding aniline: a direct reaction with ammonia[2–5] requiring temperatures of the order of 450°, and an indirect method in which the phenolic ring is dearomatized, treated with ammonia or a derivative, and rearomatized. These methods are limited in scope. Some alkylphenols may be transformed to anilines by way of *o*- or *p*-quinol acetates[6–9] or 4-alkyl-4-fluorocyclohexadienones[10] and their reaction products with 2,4-dinitrophenylhydrazine or benzylamine. Some phenols may be converted to cyclohexenones, and oximes therefrom dehydrated to anilines.[9,11] The well-known Bücherer reaction of phenols with ammonium sulfite is generally limited to naphthols and hydroxy- and aminophenols.[12,13] Electronegatively substituted phenols, such as 2,4-dinitrophenol, and their oxygen derivatives, constitute special cases in which the oxygen function is more readily replaced.[14,15]

We wish to report a procedure we feel to be fairly general for the conversion of aromatic hydroxy compounds to the corresponding amine. It involves the sequence outlined in Chart I. The key step is the

CHART I[a]



[a] Ar: a, C_6H_5; b, 2,4-$Cl_2C_6H_3$; c, 2,3,6-$(CH_3)_3C_6H_2$; d, 4-$NO_2C_6H_4$.

thermal rearrangement of a 4-aryloxy-2-phenylquinazoline (**2**) to a 3-aryl-2-phenyl-4(3*H*)-quinazolinone (**3**). The rearrangement rate depends on the aryl substitution, but, in general, useful rates are obtained in the temperature range of 275–325°. Hydrolysis of the resulting quinazolinone gives the aniline having the same substitution pattern as the starting phenol. An advantage of this sequence over the direct method is that the phenol, the reacting nitrogen function, and the aniline are "protected" in the thermal step from side reactions which might occur with other substituents. By this procedure aniline hydrochloride has been obtained from phenol in 71% overall yield. Other ani-

(1) (a) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, Abstracts, p 33Q. (b) Riker Research Laboratories, 3M Center, St. Paul, Minnesota 55101.

(2) V. Merz and P. Müller, *Chem. Ber.*, **19**, 2901 (1896).

(3) E. Briner, P. Ferrero, and E. de Luserna, *Helv. Chim. Acta*, **7**, 282 (1924).

(4) R. S. Barker, Belgian Patent 635,927 (1964); *Chem. Abstr.*, **61**, 13237*f* (1964).

(5) N. S. Kozlov and L. F. Akhmetshina, *Zh. Obshch. Khim.*, **25**, 485 (1955); *Chem. Abstr.*, **50**, 3336*h* (1956).

(6) E. Hecker and E. Walk, *Chem. Ber.*, **93**, 2928 (1960).

(7) E. Hecker, *ibid.*, **92**, 3198 (1959).

(8) H. Budzikiewicz, F. Wesseley, and O. S. Ibrahim, *Monatsh. Chem.*, **95**, 1396 (1964).

(9) A. M. Gold and E. Schwenk, *J. Amer. Chem. Soc.*, **81**, 2198 (1959).

(10) E. Hecker and M. Hopp, *Justus Liebigs Ann. Chem.*, **692**, 174 (1966).

(11) F. M. Beringer and I. Ugelow, *J. Amer. Chem. Soc.*, **75**, 2635 (1953).

(12) N. L. Drake, *Org. React.*, **1**, 105 (1942).

(13) A. Rieche and H. Seeboth, *Justus Liebigs Ann. Chem.*, **638**, 57 (1960).

(14) E. Y. Spencer and G. F. Wright, *Can. J. Res.*, **24B**, 204 (1946).

(15) V. A. Lavrischchev, V. L. Plakidin, and A. E. Kretov, *Zh. Obshch. Khim.*, **30**, 3064 (1960); *Chem. Abstr.*, **55**, 18646*h* (1961).

lines prepared are 2,4-dichloroaniline (64%) and 2,3,6-trimethylaniline (70%) as hydrochlorides and *p*-nitroaniline (42%). Since our initial report[1a] Morrow and coworkers[16] have described the use of this method for the conversions of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one and estrone to the 1-amino and 3-amino derivatives in 67 and 58% yields. Conrow and Bernstein[17] obtained the 3-amino analog of estrone in 67% yield compared with a 10% yield by a dearomatization sequence. Several variations of this procedure using other quinazolines will be described.

Discussion

As outlined in Chart I, this aniline synthesis consists of three steps: (1) preparation of a 4-aryloxy-2-phenylquinazoline; (2) thermal rearrangement to a 3-aryl-2-phenyl-4(3*H*)-quinazolinone; and (3) hydrolysis of the quinazolinone to give the aniline. These steps will be discussed in order.

Preparation of Aryloxyquinazolines.—The aryloxyquinazolines may be obtained in high yield by condensation of a sodium phenoxide with 4-chloro-2-phenylquinazoline in an inert solvent such as dimethylacetamide or diethylene glycol dimethyl ether (diglyme). The salt is conveniently prepared with sodium hydride. Conrow and Bernstein[17] used potassium carbonate in acetone to prepare the ether of estrone in 95% yield. The crude aryl ethers (**2**) may be used directly in the next step. The aryloxyquinazolines prepared in this study are listed in Table I.

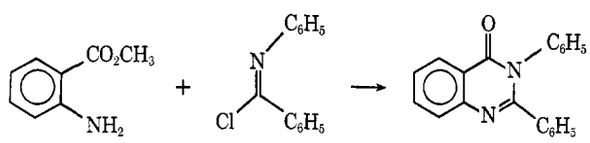
TABLE I
4-ARYLOXY-2-PHENYLQUINAZOLINES

Compd	Mp, °C	Yield, %	Formula[c]
2a	119–120[a]	70	$C_{20}H_{14}N_2O$
2b	177–178[a]	82	$C_{20}H_{12}Cl_2N_2O$
2c	146–147[a]	84	$C_{23}H_{20}N_2O$
2d	218.5–219.5[b]	69	$C_{20}H_{13}N_3O_3$

[a] Recrystallized from *n*-heptane. [b] Recrystallized from benzene. [c] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

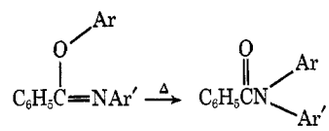
Aryloxyquinazoline Rearrangement.—The second step in this sequence is a thermally induced 1,3-O to N aryl migration around the quinazoline ring. This type of rearrangement was first observed by Chichibabin and Jeletzky.[18] By passing 2-phenoxyquinoline and 2-phenoxypyridine through a tube heated at a *dull red heat* (*i.e.*, above 700°) they were able to isolate *N*-phenylcarbostyril and *N*-phenyl-α-pyridone, respectively, in unspecified yields. This rearrangement has not attracted attention but it appears to be quite general. We have applied it to a number of heterocyclic systems, including 2-aryloxyquinolines,[19,20] 2-aryloxylepidines,[20] and 2-aryloxy-4(3*H*)-quinazolinones.[21] A double rearrangement takes place with 2,4-diaryloxyquinazolines[19,21,22] (**19**) and 3,6-diaryloxypyridazines.[23] Hey and Moynehan[24] have reported the rearrangement of 9-aryloxyphenanthridines to 10-aryl-9-phenanthridones at 350–360°.

The rearrangement product from 4-phenoxy-2-phenylquinazoline was proven to be **3a** by comparison with an authentic sample prepared according to Levy and Stephen[25] from methyl anthranilate and *N*-phenylbenzimidoyl chloride.

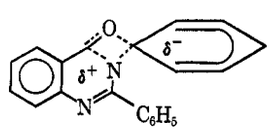


3a

The Chichibabin rearrangement bears a formal resemblance to the Chapman rearrangement of aryl *N*-arylbenzimidates to *N*,*N*-diarylbenzamides.[26] The factors which influence the latter rearrangement have been studied by Chapman[27a] and by Wiberg and Rowland,[27b]



and recently reviewed by Schulenberg and Archer.[27c] They seem to apply as well to the Chichibabin rearrangement.[28] They include the findings that electron-withdrawing groups and ortho substitution on the migrating aryl ring aid the rearrangement. Both reactions follow first-order kinetics. These data imply an intramolecular nucleophilic displacement of the incipient amide oxygen by the imine nitrogen in a four-membered transition state **4**.



4

The 4-aryloxy-2-phenylquinazoline (**2**) may be rearranged neat, but the reaction is generally cleaner when run in an inert solvent such as heavy mineral oil.[29] The course of the rearrangement is conveniently followed by infrared or ultraviolet spectroscopy.

The first-order course of the reaction is illustrated by the rate data in the Experimental Section. By a rough estimate, the rate doubles for a 10° rise in temperature in the 300° range. This is about the same as found for the Chapman rearrangement.[27b] The large decrease

(16) (a) D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964); (b) D. F. Morrow and R. M. Hofer, *J. Med. Chem.*, **9**, 249 (1966).

(17) R. B. Conrow and S. Berstein, *Steroids*, **11**, 151 (1968).

(18) A. E. Chichibabin and N. P. Jeletsky, *Chem. Ber.*, **57**, 1158 (1924). We propose that this 1,3 O to N aryl rearrangement to a heterocyclic nitrogen be called the Chichibabin rearrangement.

(19) R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, Ninth Annual Medicinal Chemistry Symposium, Minneapolis, Minn., June 1964, p 11i.

(20) R. A. Scherrer, U. S. Patent 3,238,201 (1966); *Chem. Abstr.*, **64**, 17614b (1966).

(21) R. A. Scherrer, German Patent 1,190,951 (1965); *Chem. Abstr.*, **63**, 4209d (1965).

(22) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968).

(23) Unpublished work by the authors.

(24) D. H. Hey and T. M. Moynehan, *J. Chem. Soc.*, 1563 (1959).

(25) P. R. Levy and H. Stephen, *ibid.*, 985 (1956).

(26) A. W. Chapman, *ibid.*, **127**, 1992 (1925).

(27) (a) A. W. Chapman, *ibid.*, 1743 (1927); (b) K. B. Wiberg and B. I. Rowland, *J. Amer. Chem. Soc.*, **77**, 2205 (1955); (c) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965).

(28) These conclusions come from this work and rearrangements in other systems as well.[19-21,23]

(29) An attempt to rearrange 4-(*p*-nitrophenoxy)-2-phenylquinazoline in heavy mineral oil at 275° led to decomposition products including the formation of water. There was also some decomposition when the reaction was run neat, probably owing to free-radical reactions involving the nitro group.[30]

(30) E. G. Janzen, *J. Amer. Chem. Soc.*, **87**, 3531 (1965).

in ultraviolet absorption at about 260 mμ in going from **2** to **3** (Δε of about 25,000) is useful in quantitatively following the rearrangement. It is apparently due to hindrance to coplanarity of the 2-phenyl group in **3** resulting from introduction of the 3 substituent. A distinct difference in the infrared absorption spectra of the Chichibabin rearrangement products (C=O) compared with the starting ethers makes this a simple qualitative tool to use in following the rearrangement. (This is not true of the carbonyl region for the Chapman rearrangement.)

The half-times for the rearrangement of **2a–d** to **3a–d** are listed in Table II as an aid in estimating the required conditions for other aryl derivatives. The rates were determined by uv for reactions run neat, but did not seem out of line with the gross observations on larger scale rearrangements run in mineral oil. In estimating half-times for other aryl substitution it should be kept in mind that ortho substitution on the migrating aryl ring is favorable, presumably because it reduces the entropy of activation for the rearrangement by restricting rotation of the *O*-aryl group in the ground state.[27] All these data in comparison with the Chapman reaction are consistent with the fact that the aniline produced has the same substitution as the starting phenol.

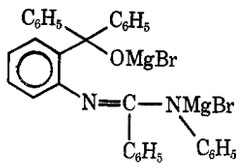
TABLE II

3-ARYL-2-PHENYL-4(3*H*)-QUINAZOLINONES

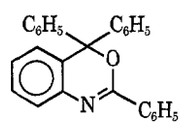
Compd	Estd rearr half-time,[a] min (°C)	Mp, °C[b]	Formula[d]
3a	60 (325) 175 (308)	158–158.5[c]	$C_{20}H_{14}N_2O$
3b	35 (315)	128–129	$C_{20}H_{12}Cl_2N_2O$
3c	35 (315)	124–125	$C_{23}H_{20}N_2O$
3d	15 (295)	226–228	$C_{20}H_{13}N_3O_3$

[a] Neat. [b] Recrystallized from aqueous ethanol. [c] Lit.[25] mp 158°. [d] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

Hydrolysis Step.—The hydrolysis is carried out by either of two procedures (Chart II). The mildest consists of an alkaline hydrolysis to the presumed amidine intermediate **5** (and tautomer) which is considerably more resistant to further base hydrolysis. Acidification in most cases readily liberates the aniline with the formation of 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**). The formation of **6** indicates a participation by the carboxyl group in the hydrolysis of **5**, since acidification of sodium *o*-benzamidobenzoate merely gives the free acid. This closely parallels the finding[31] that the reaction product of **3a** and excess phenylmagnesium bromide, **9**, gives the oxazine **10** and aniline on acidification.



9



10

When Ar is 2,3,6-trimethylphenyl, **5** recyclizes to **3c** on acidification. Recyclization also occurred, but to a lesser extent, in the preparation of 1-amino-4-methylestra-1,3,5(10)-trien-17-one.[16a]

An alternative procedure for hydrolysis is to heat **3** with potassium hydroxide in ethylene glycol until completion. The mineral oil mixture from the rearrangement step may conveniently be treated directly in such a manner. The first three anilines in Table III were obtained in the overall yields indicated using this procedure.

TABLE III

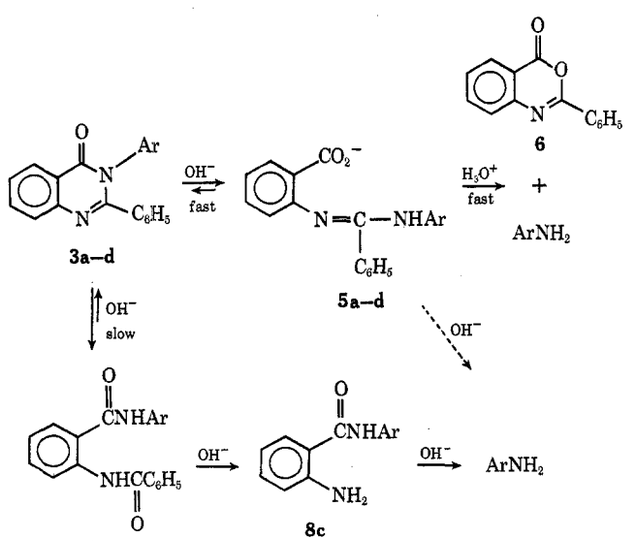
$ArNH_2$ FROM ArOH

Ar	Derivative	Mp, °C	Yield from ArOH, %	Formula[g]
C_6H_5	Hydrochloride	193.5–196.5[a,b]	71.6	C_6H_8NCl
$2,4\text{-}Cl_2C_6H_3$	Hydrochloride	235–242[a,c]	64	$C_6H_6Cl_3N$
	p-Toluenesulfonamide	126–127[d]		$C_{13}H_{11}Cl_2NO_2S$
$2,3,6\text{-}(CH_3)_3\text{-}C_6H_2$	Hydrochloride	245–249[a]	70.4	$C_9H_{14}NCl$
	Acetamide	190–191[e]		$C_{11}H_{15}NO$
	p-Toluenesulfonamide	126.5–128.5		$C_{16}H_{19}NO_2S$
$4\text{-}NO_2C_6H_4$		144–145.5[f]	42	$C_6H_6N_2O_2$

[a] Determined in an evacuated capillary. [b] Lit.[41] mp 198°. [c] A simultaneous melting point on authentic hydrochloride gave mp 230–240° (evacuated capillary). [d] Lit.[39] mp 126°. [e] A. Huender, *Recl. Trav. Chim. Pays-Bas*, **34**, 1 (1915), gives mp 187°. [f] Lit.[41] mp 148°. [g] Satisfactory analytical values (±0.3% for C, H, N) for all compounds were reported: Ed.

It is possible that alkaline hydrolysis to anilines proceeds entirely *via* **7**. The interconversion of **5a** and **3a** and the formation of **7a** under alkaline conditions is described in the Experimental Section. The alkaline hydrolysis of 2-aminobenzoxazin-4-one (**11**) to 2-ureidobenzoic acid has been shown to proceed exclusively by attack of hydroxide and water on the carbonyl of **11**, even though species **12** and **13** exist under the hydrolysis conditions.[32] Other cyclizations involving carboxylate anions are described by Hegarty.[32c] In

CHART II[a]

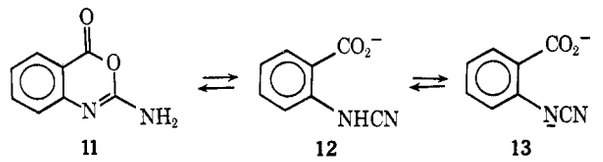


[a] a to d same as Chart I.

(31) A. Mustafa, *et al.*, *J. Amer. Chem. Soc.*, **77**, 1612 (1955).

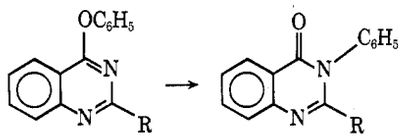
(32) (a) A. F. Hegarty and T. C. Bruice, *ibid.*, **92**, 6561 (1970); (b) *ibid.*, **92**, 6568 (1970); (c) *ibid.*, **92**, 6575 (1970).

the hydrolysis of **3c**, **8c** was isolated as an intermediate. No satisfactory acid hydrolysis conditions for **3** were found.



11 **12** **13**

Other Quinazolines.—The Chichibabin rearrangement was also carried out using 2-methyl-4-phenoxyquinazoline (**14**) and 4-phenoxyquinazoline (**15**) to



14, R = CH_3 **16**, R = CH_3
15, R = H **17**, R = H

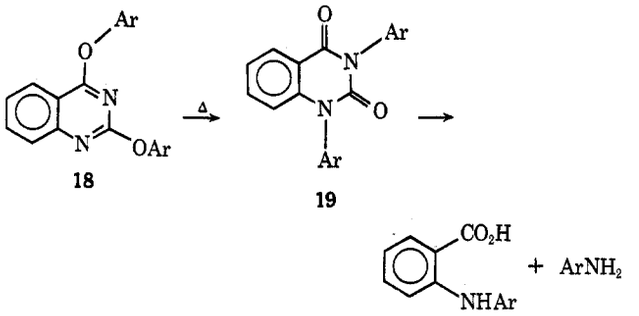
determine if either of these offered advantages over the 2-phenyl series. It was considered possible that the rearrangement could be faster in one of these series, depending on the importance of steric and electronic factors in the transition state. The relative rates of rearrangement of the three 2-substituted 4-phenoxyquinazolines (2-phenyl:2-methyl:2-hydrogen) were found to be 1:1.7:0.5 at 308° (neat, in evacuated ampoules). The steric effect of a substituent in the 2 position of the quinazoline is probably minimized by the geometry of the transition state (**4**), which requires the migrating ring to be perpendicular to the plane of the quinazoline.

The 2-phenyl series, of the three, is the preferred one for the conversion of phenols to anilines. In addition to a rate advantage in the Chichibabin rearrangement of the 2-phenyl series over the 2-unsubstituted series, the former appears to be cleaner, as judged by lack of darkening. In the 2-methyl series a red-orange by-product was obtained in the rearrangement step. A side reaction is also indicated by the rate studies. The apparent rate of rearrangement of the 2-methyl series appeared to fall off with time as determined from the ratio of starting material to product by gas chromatography. In duplicate experiments this apparent rate ranged from an initial half-time of 105 min to a half-time of 360 min after 200 min of reaction time. This seems best explained by a loss of quinazolinone to a nonvolatile by-product rather than by postulating a higher order rearrangement. It should be pointed out that special care must be taken in the preparation of the 4-chloro-2-methylquinazoline to avoid chlorination of the methyl group.[33,34] A by-product having a persistent nauseating odor is also formed in this chlorination.

In spite of the drawbacks, the 2-methyl series would be useful for the preparation from phenols of 3-aryl analogs of the sedative methaqualone,[35] 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone, when the required arylamine is not available. Use of an inert solvent in the rearrangement step could lessen the extent of by-product formation.

The double Chichibabin rearrangements[21,22] of 2,4-diaryloxyquinazolines **18** to 2,4-quinazolinediones **19** (Chart III) were run primarily to obtain the *N*-aryl-

CHART III[a]



18 **19**

[a] Ar: **e**, 2,3-xylyl; **f**, 2,6-dichloro-3-tolyl.

anthranilic acids resulting on hydrolysis, but also provided in each case the aniline corresponding to the starting phenol. Juby[22] obtained 2,6-dichloro-*m*-toluidine in 77% yield from **19f** and the latter in 75% yield from **18f**. The rearrangement in this series is slower than for the corresponding 4-aryloxy-3-phenylquinazoline such that we estimate[1a,23] that a 25° higher temperature is required to obtain a comparable reaction rate.

The aniline synthesis described here should lend itself to the preparation of ^{15}N anilines since the required quinazoline-3-^{15}N derivative should be readily obtainable (by way of reaction of isatoic anhydride or 2-phenyl-4*H*-3,1-benzoxazin-4-one with $^{15}NH_4OH$).

Experimental Section[36]

4-Chloro-2-phenylquinazoline (**1**).—This material was obtained by the sequence benzoylanthranilamide to 2-phenyl-4-(3*H*)-quinazolinone[37] to **1**.[38] It is now available from the Aldrich Chemical Co. under the name "AM-ex-OL."

4-Phenoxy-2-phenylquinazoline (**2a**).—Phenol (10.0 g, 0.106 mol) was added in portions to a cooled suspension of 5.1 g (0.112 mol) of 53% sodium hydride (dispersed in mineral oil) in 35 ml of dry diglyme. When hydrogen evolution subsided, 24.0 g (0.10 mol) of 4-chloro-2-phenylquinazoline was added. The temperature of the mixture rose to 75°. The mixture was heated to 110° for 10 min, then cooled and poured onto ice and water. The dense granular product, 29.8 g, had mp 112–116°. Recrystallizations from aqueous ethanol and *n*-heptane gave 20.9 g (70%) of 4-phenoxy-2-phenylquinazoline as white needles: mp 119–120°; λ_{max} 287 and 257 mμ (ε 16,700 and 34,500); $\nu_{max}^{CCl_4}$ 1625, 1395, 1380, 1205, and 935 cm^{-1}, not in the spectrum of the isomeric quinazolinone.

Other 4-Aryloxy-2-phenylquinazolines (Table I).—The method described for the 4-phenoxy derivative was used. The condensations were run on a 0.05-mol scale under the following conditions: **2b**, 45 min at 130–150°; **2c**, 1.5 hr at 165°; **2d**, 7 hr at 165°. Two grams of each aryloxyquinazoline was recrystallized for analysis and yield.

(33) H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton, *J. Org. Chem.*, **27**, 957 (1962).

(34) R. F. Smith and R. A. Kent, *ibid.*, **30**, 1312 (1965).

(35) K. H. Boltze, H. D. Dell, H. Lehwald, D. Lorenz, and M. Rüberg-Schweer, *Arzneim.-Forsch.*, **13**, 688 (1963).

(36) Melting points are corrected; reaction temperatures are uncorrected. Ultraviolet spectra were determined in methanol on a Cary Model 11 spectrophotometer, infrared spectra were obtained on a Beckman IR-7 or IR-9 spectrophotometer, and nmr spectra were obtained in deuteriochloroform on a Varian A-60 spectrometer. Gas–liquid phase chromatography was run on a Model 810 F & M chromatograph.

(37) (a) R. Anschütz, O. Schmidt, and A. Greiffenberg, *Chem. Ber.*, **35**, 3480 (1902); (b) H. Stephen and G. Wadge, *J. Chem. Soc.*, 4420 (1956).

(38) M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherrill, *J. Amer. Chem. Soc.*, **68**, 1299 (1946).

2,3-Diphenyl-4(3*H*)-quinazolinone (3a). A. From 2a.—Five grams of 4-phenoxy-2-phenylquinazoline was heated under nitrogen in a 50-ml round-bottom flask equipped with a magnetic stirrer and thermometer. The flask was heated with a mantle. After 50 min at 325° the rearrangement was estimated by infrared to be about 50% complete. Heating was continued for a total of 130 min at 325°. Two recrystallizations from aqueous ethanol gave 3.0 g (60%) of 2,3-diphenyl-4(3*H*)-quinazolinone as white needles: mp 158–158.5°; λ_{max} 278 and 229 mμ (ε 12,050 and 31,800); λ_{min} 257 mμ (ε 8900); $\nu_{max}^{CCl_4}$ 1694 (s) and 1270 cm^{-1} (m). This product was identical with that prepared under B by the infrared and ultraviolet spectra and mixture melting point.

B. By the Method of Levy and Stephen.[25]—A solution of 32.0 g (0.212 mol) of methyl anthranilate and 21.5 g (0.10 mol) of *N*-phenylbenzimidoyl chloride in 45 ml of dry dimethylformamide was prepared. After an initial exothermic reaction the solution was allowed to stand overnight at room temperature, then was heated for 10 min at about 100°. The latter heating period was required to complete cyclization of the intermediate. Dilution with ethanol and water precipitated the product, which was recrystallized from aqueous ethanol to give 20.7 g (69.5%) of **3a**, mp 158.5–159° (lit.[25] mp 158°).

Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.37; H, 4.56; N, 9.33.

Other 3-Aryl-2-phenyl-4(3*H*)-quinazolinones (Table II).—A 2.00-g sample of the aryloxy derivative was heated neat to determine an effective rearrangement temperature. This sample was purified for analysis by chromatography and recrystallization.

Preparation of Anilines (Table III). A. Single-Stage Alkaline Hydrolysis Procedure. Aniline.—4-Phenoxy-2-phenylquinazoline from 5.00 g of phenol (16.3 g, mp 114–117.5°) was heated in 30 ml of heavy mineral oil under nitrogen for 4 hr at 320–325°. The mixture was transferred to a larger flask with the aid of 160 ml of hot ethylene glycol. After addition of 32 g of 85% potassium hydroxide it was heated under nitrogen at 125–138° for 9.5 hr. Dilution with water, extraction with ether, and treatment of the washed and dried ether solution with hydrogen chloride gas gave 5.23 g (76%) of aniline hydrochloride as tan needles, mp 191–194° (evacuated capillary). Sublimation of 270.1 mg of this material at 130–140° (22–27 mm) gave 254.6 mg of aniline hydrochloride, mp 193.5–196.5° (evacuated capillary); identity was verified by mixture melting point and infrared comparison with authentic aniline hydrochloride, Eastman White Label, mp 197–198°. This corresponds to a yield of 71.6% from phenol.

2,4-Dichloroaniline.—This compound was prepared in the same manner as aniline. The infrared spectrum of the hydrochloride was identical with that of an authentic sample prepared from Eastman White Label base. Vapor phase chromatography of the crude dichloroaniline indicated a single volatile component identical in retention time with authentic 2,4-dichloroaniline (6-ft ethylene glycol succinate column, 175°). In addition the *p*-toluenesulfonanilide, mp 126–127°, was in agreement with the literature value,[39] 126°.

2,3,6-Trimethylaniline.—The crude ether **2c** obtained from 10.0 g of 2,3,6-trimethylphenol (Aldrich Chemical Co.) was heated in two volumes of mineral oil at 320° for 3.5 hr. Hydrolysis in 250 ml of ethylene glycol with 50 g of potassium hydroxide for 20 hr at 140° gave mostly 2-amino-2′,3′,6′-trimethylbenzanilide (**8c**), which crystallized from the mixture on cooling. This anilide had mp 136.5–137° (benzene–hexane); λ_{max} 330 and 250 mμ (ε 4780 and 10,600); $\nu_{max}^{CCl_4}$ 3510 (w), 3460 (w), 3365 (w), 1670 (s), 1560 (w), and 1250 cm^{-1} (m).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.13; N, 11.02. Found: C, 75.96; H, 7.26; N, 10.90.

The crude product mixture of anilide plus some aniline was further hydrolyzed by heating in 70 ml of ethylene glycol containing 14 g of sodium hydroxide and 14 g of potassium hydroxide for 48 hr at 145°. (These conditions approach the limits of durability of a magnetically stirred Pyrex flask.) The washed and dried ether extract of the mixture was treated with hydrogen chloride gas to give 7.48 g of 2,3,6-trimethylaniline hydrochloride as a white solid, mp 241–248° (evacuated capillary), and a second crop, 1.93 g, mp 236–244° (evacuated capillary). Sublimation of 124.8 mg at 110–140° (20 mm) gave 117.4 mg of sublimate, mp 245–249° (evacuated capillary), for a 70.4% yield from 2,3,6-trimethylphenol. The infrared spectrum of the free base compares well with the published spectrum.[40] Other derivatives are listed in Table III.

B. Two-Stage Alkaline and Acid Hydrolysis Procedure.—These results suggest the presence of intermediate **5** and document the formation of **6**.

***p*-Nitroaniline.**—The rearranged product from 10.00 g of crude 4-(*p*-nitrophenoxy)-2-phenylquinazoline was heated for 30 min in 100 ml of ethanol containing 20 g of 50% sodium hydroxide. A *sample* of the solution remained clear on dilution with water, suggesting **5d**, but gave a precipitate on acidification. This precipitate consisted of 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**, CCl_4 soluble) and *p*-nitroaniline (CCl_4 less soluble), identified by their infrared spectra. To facilitate work-up, the main hydrolysis mixture was acidified with 12 *N* hydrochloric acid, kept at 40–50° for 10 min to hydrolyze the benzoxazinone, and then made alkaline again and concentrated to near dryness. Dilution with 200 ml of water gave a granular solid which was extracted several times with ether and with hot water to obtain 3.55 g of crude *p*-nitroaniline. Recrystallization from water afforded 1.81 g of yellow needles, mp 144–145.5° (lit.[41] mp 148°), 42% yield from *p*-nitrophenol. The structure of the aniline was further substantiated by its ultraviolet and infrared spectra.

Aniline.—A solution of 7.0 g of 2,3-diphenyl-4(3*H*)-quinazolinone in 100 ml of 80% ethanol containing 18 g of sodium hydroxide was heated at reflux for 10 hr, after which only a 13% yield of aniline could be extracted from the water-diluted alkaline reaction mixture. The alkaline solution was then acidified and extracted with ether to obtain 3.6 g of white needles, mp 108–113°, consisting of about 10% benzoylanthranilic acid and 90% 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**). The benzoxazine was purified by extraction of an ether solution with sodium bicarbonate and recrystallization from cyclohexane, mp 117.5–119.5°, undepressed by admixture with an authentic sample (lit.[42] mp 123°). The infrared spectrum of **6** has strong characteristic absorption at 1773 cm^{-1} in CCl_4.

The acidic aqueous solution from which **6** was extracted was made alkaline and extracted twice with ether to obtain an additional 23% of aniline as the hydrochloride.

Recyclization of Amidine 5a to 3a.—Potassium hydroxide (2.0 g, 85% pellets) was added to a solution of 1.00 g of **3a** in 10 ml of ethylene glycol at 120°. The solution was heated for 30 min at 110°, then poured into 200 ml of water. There was obtained by filtration 0.38 g of 2-benzamidobenzanilide (**7a**), mp 244–267° (lit.[37a] mp 279°), confirmed by comparison of the infrared spectrum with that of an authentic sample.[37] When the alkaline filtrate, presumed to contain **5a**, was heated on a steam bath for 15 min there was obtained a flocculent precipitate, 0.46 g of **3a**, mp 156–157°, verified by its infrared spectrum. If the alkaline filtrate is acidified without heating one obtains 2-phenyl-4*H*-3,1-benzoxazin-4-one (**6**) and aniline.

2-Methyl-4-phenoxyquinazoline (14).—4-Chloro-2-methylquinazoline[33] (15.0 g, 0.084 mol) was treated with 1 equiv of sodium phenoxide in the general manner outlined for the 2-phenyl series. Recrystallizations from *n*-hexane and aqueous ethanol afforded 13.6 g (69%) of **14**: mp 69.5–70.5° (lit.[43] mp 71–71.5°); λ_{max} 313, 303, 279, and 220 mμ (ε 4040, 4220, 6590, and 51,100); $\delta_{TMS}^{CDCl_3}$ 2.63 ppm (2-CH_3). The strong absorption at $\nu_{max}^{CHCl_3}$ 1625, 1375–1385, and 1205 cm^{-1} is lost on rearrangement.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.43; H, 5.18; N, 11.88.

2-Methyl-3-phenyl-4(3*H*)-quinazolinone (16).—A solution of 1.0 g of 2-methyl-4-phenoxyquinazoline in 2 ml of heavy mineral oil was heated under nitrogen in a Wood's metal bath at 308–311° for 3 hr. Chromatography (Florisil) gave 0.22 g of recovered starting material (C_6H_{12}:C_6H_6, 1:1) and 0.37 g of **16** (C_6H_6 and C_6H_6–Et_2O, 10:1). A red-orange by-product followed closely and partly overlapped with **16**. Recrystallization gave 0.22 g of **16** as light orange crystals, mp 145–146° (lit.[37a] mp 147°), undepressed on mixture with authentic material with which it compared in other physical and spectral properties. Compound **16** has λ_{max} 316, 305, 264, and 225 mμ (ε 2930, 3680, 9250, and 1490); $\nu_{max}^{CHCl_3}$ 1680 (s) and 1280 cm^{-1} (m); $\delta_{TMS}^{CDCl_3}$ 2.22 ppm (2-CH_3). In glpc on a 6-ft SE-30 column at 250°, **16** had

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(42) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).

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a retention time of 7 min compared with 4.2 min for 2-methyl-4-phenoxyquinazoline.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.42; H, 5.24; N, 11.73.

4-Phenoxyquinazoline (15).—This compound was prepared in the same manner as **2a** from 8.00 g of 4-chloroquinazoline.[38] Recrystallizations from cyclohexane–*n*-hexane and aqueous ethanol gave 7.74 g (71%) of 4-phenoxyquinazoline: mp 72.5–74° (lit.[44] mp 78–79°); λ_{max} 310, 299, 263, and 219 mμ (ε 4160, 4000, 5850, and 48,700); $\nu_{max}^{CCl_4}$ 1625 (s), 1385 (s), and 1220 cm^{-1} (broad, m) not found in **17**. The nmr signal at $\delta_{TMS}^{CDCl_3}$ 8.82 (2 H) was absent in the spectrum of the rearranged product.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 76.65; H, 4.53; N, 12.61. Found: C, 75.82; H, 4.62; N, 12.73.

3-Phenyl-4(3*H*)-quinazolinone (17).—A solution of 2.00 g of 4-phenoxyquinazoline in 4 ml of heavy mineral oil was heated under nitrogen at 321 ± 3° for 5 hr. A combination of recrystallizations and chromatography (Florisil) yielded 1.18 g (59%) of **17** as white needles, mp 137–137.5° (lit.[45] mp 136–136.5°), undepressed on mixture with, and comparable in spectral and physical properties to, purchased quinazolinone (Aldrich Chemical Co.), and 0.21 g of recovered starting material. The ultraviolet spectrum of **17** has λ_{max} 303, 277, 267, and 225 mμ (ε 3740, 7820, 8500, and 35,200); the infrared spectrum has $\nu_{max}^{CCl_4}$ 1698 (s), 1615 (s) and 1300 cm^{-1} (m) not found in 4-phenoxyquinazoline. In glpc on a 6-ft SE-30 column at 250°, **17** had a retention time of 6 min compared with 4.1 min for 4-phenoxyquinazoline.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.53; N, 12.61. Found: C, 75.76; H, 4.52; N, 12.74.

Relative Rearrangement Rates of 2a, 14, and 15.—In order to avoid differences in reaction temperature owing to the volatility of **14** and **15**, the rearrangements were run in sealed evacuated ampoules. Three 100-mg portions of each aryl ether were sealed in 6-mm tubing at 10–15-mm nitrogen pressure. The tubes were bundled in groups of three and immersed in a silicone oil bath maintained at 308 ± 3°.

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A. Compound 2a and 3a.—At 257 mμ, **2a** has an E_1^1 of 1155 and **3a** an E_1^1 of 298. The following calculated values (E_1^1 minus 298) at 257 mμ for various times were obtained: 0 time, 857; 55 min, 699; 130 min, 508; and 255 min, 324. From these values the half-time at 308° was determined to be 175 min. A duplicate determination at 309 ± 2° gave a half-time of 185 min.

B. Compound 14 to 16.—A rate study at 308 ± 3° gave the following values for the percentage of **14** as determined by glpc: 55 min, 68.5%; 130 min, 50.4%; and 255 min, 36%. In a duplicate determination at 309 ± 2° the following values were obtained: 5 min, 94%; 50 min, 71%; 110 min, 56%; 175 min, 44%; and 225 min, 40%. If a first-order reaction is assumed, the values for the first 50 min correspond to a half-time of 105 min, and the values at 175 min and 225 min to a half-time of 360 min. The apparent deviation from first-order kinetics may be due to loss of **16** to a nonvolatile by-product.

C. Compound 15 to 17.—Gas–liquid phase chromatography gave the following values for the percentage of **15**: 55 min, 88%; 130 min, 77%; 255 min, 58%. These values correspond to a reaction with a half-time of 325 min or about 0.5 times the rate for the conversion of **2a** to **3a**.

Registry No.—**2a,** 18600-27-6; **2b,** 34281-52-2; **2c,** 34281-53-3; **2d,** 18600-28-7; **3b,** 34280-97-2; **3c,** 34280-98-3; **3d,** 34280-99-4; **6,** 1022-46-4; **8c,** 34297-91-1; **14,** 34297-92-2; **15,** 16347-97-0; **16,** 2385-23-1; **17,** 16347-60-7; 2,4-dichloroaniline HCl, 29084-76-2; 2,3,6-trimethylaniline HCl, 34297-93-3; 2,3,6-trimethylaniline *p*-toluenesulfonamide, 34297-94-4.

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α-Azocarbinols. The Synthesis and Some Reactions of 3-Hydroxypyrazolines[1]

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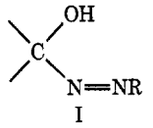
3-Hydroxy-1-pyrazolines, cyclic examples of α-azocarbinols, have been synthesized by hydrolysis or hydrogenolysis of 3-acetoxy-1-pyrazolines. These carbinols undergo both acid- and base-catalyzed ring opening to give ketones. The acid reactions produce both saturated and unsaturated ketones while the base reactions yield only saturated ketones but principally those of rearranged carbon skeleton. The carbinols may be esterified and etherified under closely controlled conditions.

The geminal juxtaposition of an azo linkage and a hydroxyl group (I) produces a chemical structure whose



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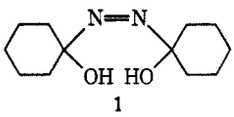
properties will depend upon the interplay of competing factors. Thus α-azocarbinols might resemble cyanohydrins in that they are adducts of carbonyl compounds and diazenes. From this point of view they would be expected to be unstable in basic solution and to avoid carbonium ion intermediate reactions. On the other hand, they might be viewed as diaza allylic alcohols and thus to show unusual reactivity toward electrophilic reagents.

Little is known about these compounds because it is only recently that some have been reported. The first example, 1,1′-dihydroxyazocyclohexane (**1**), was reported in 1963.[2] This compound was relatively un-



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stable, reverting to cyclohexanone with loss of diimide.

Recently, Hünig has generated α-azocarbinols by two methods: the action of base on alkoxydiazenium

(1) This research was supported by grants from the Petroleum Research Fund and the National Science Foundation.

(2) E. Schmitz, R. Ohme, and E. Schramm, *Justus Liebigs Ann. Chem.*, **702**, 131 (1967).