The relative ineffectiveness of the nitro group as a participant in benzhydryl bromide hydrolysis[5] is tentatively ascribed to a geometric situation in the transition state which is unfavorable for electron release by the *ortho* substituent to the vacant p-orbital on the exocyclic carbon atom.[12] Because of the much larger size of the iodine orbital in question this geometric problem apparently does not arise in the *o*-nitroiodobenzene dichloride dissociation reaction.

It is particularly interesting to observe that the *o*- and *p*-cyanoiodobenzene dichlorides are comparable in reactivity. The *o*-CN group, like the *o*-NO_2 and *o*-$COOCH_3$ groups, is potentially nucleophilic in character. The fact that it is nonparticipating can only be explained on geometric grounds. The two atoms of the substituent and the ring carbon to which it is attached are linear. Neither the two π-orbitals of the triple bond nor the p-orbital of the nitrogen atom are properly oriented to release electrons to iodine in the activation process for dichloride dissociation.

Thermodynamic Constants.—Activation energies and entropies for dissociation of the *o*- and *p*-cyano- and *p*-nitroiodobenzene dichlorides (calculated from the results presented in Table II) are listed in Table III. The E_a and ΔS^* values are similar to those reported previously for other dichlorides.

TABLE III
THERMODYNAMIC CONSTANTS FOR DISSOCIATION OF $XC_6H_4ICl_2$ IN ACETIC ACID

X	E_a, kcal./mole	$-\Delta S^*$, e.u.
p-NO_2	21 ± 1	10 ± 3
p-CN	18 ± 2	20 ± 6
o-CN	19 ± 1	16 ± 3

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

(12) For evidence of *o*-NO_2 group participation in certain reactions of benzhydrol, see, however, W. B. Dickinson, *J. Am. Chem. Soc.*, **86**, 3580 (1964).

Mechanism of the Gabriel–Colman Rearrangement

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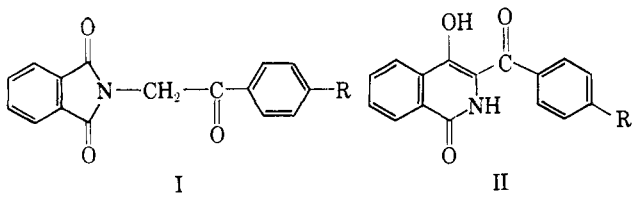
The kinetics of the methoxide-promoted rearrangement of six *p*-substituted N-phenacylphthalimides to the corresponding 3-benzoyl-4-hydroxyisocarbostyrils have been investigated. A mechanism involving opening of the phthalimide ring followed by rearrangement of the resulting imide anion to the carbanion and ring closure is suggested by the identical rates of reaction and products from rearrangement of N-phenacylphthalimide and of methyl N-phenacylphthalamate and by the decreased rate observed when *t*-butoxide was used with the former. The reaction exhibits a linear Hammett plot with $\rho = 1.98$. Cleavage of the 3-benzoyl-4-hydroxyisocarbostyrils by methoxide is a minor side reaction.

Alkoxides effect rearrangement of N-phenacylphthalimides (I) to 3-benzoyl-4-hydroxyisocarbostyrils (II).[1] This, the Gabriel–Colman rearrangement, affords a convenient though little used[2] method for synthesis of isoquinolines. This ring expansion appears to be general when the group attached to nitrogen has an enolizable hydrogen.[3]

Interest in this reaction arose from its similarity to the facile methoxide-promoted rearrangement of N-tosylamidophthalimide to phthalhydrazide[4] and because its mechanism had not been investigated in detail before. Accordingly, the kinetics of the Gabriel–Colman rearrangement of six *p*-substituted N-phenacylphthalimides (Ia–f) to the corresponding 3-benzoyl-4-hydroxyisocarbostyrils (IIa–f) in anhydrous methanol containing sodium methoxide were measured. The rates of formation of IIa–f were determined spectrophotometrically. After removal from ampoules, reaction aliquots were quenched in 10% concentrated hydrochloric acid in methanol and the concentrations of II were estimated at their absorbance maxima in the ultraviolet. A recent report[5] states that comparisons of the spectra of 1,4-naphthoquinone and 1,4-dihydroxynaphthalene with those of Gabriel–Colman rearrangement products indicates that these products exist in the 2,3-dihydro-1,4-dione form in acidic solution and as the enolates of the 4-hydroxy form in basic solution. Consequently in the quenched solutions, which were acidic, the dione form was the only form present during estimation. The reaction products were stable in acidic solution and obeyed Beer's Law with no apparent sensitivity to the acid concentration over a wide range. The kinetic measurements indicate that the reaction is first order in both I and methoxide over about a fourfold ratio of concentrations.[6] The kinetic data are presented in Table I.



I

a, R = OCH_3
b, R = CH_3
c, R = H

II

d, R = C_6H_5
e, R = Br
f, R = NO_2

Two mechanisms of reaction have been suggested previously. In the first,[7] reaction of methoxide with I produces an equilibrium concentration of carbanion

(1) S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900).

(2) A. Ulrich, *ibid.*, **37**, 1689 (1904); H. Kusel, *ibid.*, **37**, 1971 (1904).

(3) Saccharine derivatives are converted into 1,2-benzothiazines [K. Abe, S. Yamamoto, and K. Matsui, *Yakugaku Zasshi*, **86**, 1058 (1956)] or 1,3-benzothiazines [H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **29**, 2068 (1964)], and during the current work it was found that N-phenacylbenzoyleneureas yield benzodiazepindiones.

(4) Unpublished results.

(5) L. R. Caswell and R. D. Campbell, *J. Org. Chem.*, **26**, 4175 (1961).

(6) See Experimental section.

(7) W. J. Gensler, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 378.

TABLE I

KINETIC AND THERMODYNAMIC DATA FOR THE GABRIEL–COLMAN REARRANGEMENT

Compd.	k at 40.2° (l. mole^{-1} sec.$^{-1}$)	k at 24.5° (l. mole^{-1} sec.$^{-1}$)	ΔH^* (kcal./mole)	ΔS^* (e.u.)
Ia	3.61×10^{-4}	5.91×10^{-5}	21.3	−8.3
Ib	8.53×10^{-4}	1.45×10^{-4}	20.9	−8.1
Ic	1.42×10^{-3}	2.36×10^{-4}	21.0	−6.6
Id	1.48×10^{-3}	2.57×10^{-4}	20.6	−7.9
Ie	6.24×10^{-3}	1.17×10^{-3}	19.7	−7.7
If	5.36×10^{-2}	1.03×10^{-2}	19.4	−4.5
III	1.37×10^{-3}	2.38×10^{-4}	20.6	−8.0
Ic[a]	2.46×10^{-4}			
Ic[b]	2.97×10^{-2}	5.38×10^{-3}	20.0	−3.5

[a] Sodium t-butoxide in t-butyl alcohol. [b] Sodium hydroxide in aqueous methanol.

which in turn intramolecularly attacks the phthalimide carbonyl to produce a three-membered ring intermediate. Rapid bond rearrangement of this strained intermediate yields the product. In the second,[8] the initial reaction is an opening of the phthalimide ring by attack of methoxide followed by rapid isomerization of the imide anion to the carbanion which then completes the reaction by displacement of methoxide from the carbomethoxy group formed by the initial ring opening. The last step is analogous to a Dieckmann condensation.

Both mechanisms are in accord with the kinetic data presented in Table I if steady-state approximations are made and if the rate-determining steps are assumed to be formation of the three-membered ring in the first mechanism or ring opening or closing in the second. It is not possible to choose between these two mechanisms on the basis of the rate data alone. Moreover, the thermodynamic results are also inconclusive since both mechanisms involve pre-equilibria before the rate-determining step and thus the moderately negative values of ΔS^* obtained are essentially a composite of those of the pre-equilibria and the ring closure.[9] The latter would be expected to have an appreciable steric requirement, particularly in the case of the first mechanism. Direct evidence in support of the second mechanism comes from the fact that methyl N-phenacylphthalamate (III) undergoes cyclization to IIc in excellent yield and at the same rate as Ic when treated with methoxide in anhydrous methanol. This suggests that ring opening precedes the rate-determining step and it is attack of the carbanion on the carbomethoxy group that completes the reaction and is rate determining. It could be argued that the phthalimide ring is rapidly re-established by attack of the imide anion and thus the first mechanism is operative. However, when ring expansion of Ic to IIc is carried out in anhydrous t-butyl alcohol containing sodium t-butoxide, the observed rate of reaction is substantially slower than with methoxide in methanol. The greater steric hindrance at a carbo-t-butoxide group compared with that at a carbomethoxy group has been demonstrated in ester hydrolyses[10] and is presumably the reason for the slower rate observed here. The carbomethoxy group must therefore be formed before the rate-determining step. Furthermore, if the first mechanism were operative, an increased rate due to the greater base strength of t-butoxide would be expected and just the opposite is observed. The formation of N-phenacylphthalamic acid from reaction of hydroxide with Ic is about 20 times faster than the rearrangement with methoxide. This is further confirmation that ring opening occurs more rapidly than ring closure, since the nucleophilicities of hydroxide and methoxide are nearly equal.[11] A Hammett plot of the logarithms of the rate constants in Table I against σ shows good linearity with $\rho = 1.98$. This indicates that the Gabriel–Colman rearrangement is facilitated by electron withdrawal by the p-substituent on the phenacyl group which reinforces the effect of the phenacyl carbonyl in stabilizing the adjacent carbanion with respect to the imide anion. This sensitivity to the substituent would not be expected if the attack of methoxide on the ring carbonyl were rate controlling.

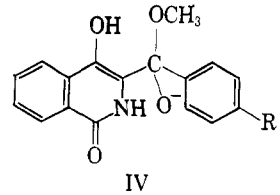
Difficulty was experienced initially in obtaining reproducible kinetics. Rigorous exclusion of moisture and carbon dioxide were found to be necessary. Failure to do so resulted in reactions that slowed and then appeared to reverse themselves. At first this was thought to be due to attack of methoxide on II but investigation of the reverse Claisen reaction under strictly anhydrous conditions showed that this reaction was quite slow and interfered with the kinetics appreciably only in the latter part of the reaction. The rate constants for this reaction were determined spectrophotometrically and are presented in Table II. This

TABLE II

KINETIC DATA FOR THE REVERSE CLAISEN REACTION OF METHOXIDE WITH p-SUBSTITUTED 3-BENZOYL-4-HYDROXYISOCARBOSTYRILS AT 40.2°

Compd.	$k \times 10^5$ (min.$^{-1}$)	Compd.	$k \times 10^5$ (min.$^{-1}$)
IIa	8.37	IId	5.32
IIb	6.32	IIe	4.69
IIc	4.04	IIf	3.62

reaction is first order in II when methoxide is present in large excess. A mechanism similar to the well-known cleavage of β-diketones by alkoxides is probably operative.[12] An indication of this is isolation of methyl benzoate, though not in good yield, from the reaction of IIc with methoxide on a preparative scale. This reaction does not show a linear Hammett correlation but nontheless is facilitated by electron donation. Electron donating groups decrease enolization of the benzoyl carbonyl and allow more efficient attack by methoxide and hence increase the concentration of the tetrahedral intermediate IV.[13]



IV

(8) C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).
(9) Thanks is due to a referee for pointing out this important fact.
(10) H. Olsson, *Z. physik. Chem.* (Leipzig), **118**, 107 (1925).
(11) M. I. Bender, *Chem. Rev.*, **60**, 62 (1960).
(12) R. G. Pearson and A. C. Sandy, *J. Am. Chem. Soc.*, **73**, 931 (1951).
(13) Interestingly, N-desylphthalimide, when treated with methoxide, produces only 3-phenyl-4-hydroxyisocarbostyril which suggests rapid cleavage of the benzoyl group when enolization is not possible.

TABLE III

3-BENZOYL-4-HYDROXYISOCARBOSTYRILS

Compd.	M.p., °C.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	λ (mμ)[a]	ε[a]
IIa	219–220	$C_{17}H_{13}NO_4$	69.10	69.38	4.41	4.36	4.74	4.31	381	14,400
IIb	227–228	$C_{17}H_{14}NO_3$	73.02	73.27	4.66	4.88	5.01	4.90	378	12,350
IIc	208–210[b]								382	11,960
IId	273–275	$C_{22}H_{15}NO_3$	77.40	77.06	4.39	4.26	4.11	4.41	384	16,050
IIe	273–274	$C_{16}H_{10}BrNO_3$	55.70	55.45	2.91	2.70	4.06	4.31	380	11,780
IIf	278–280[c]	$C_{16}H_{10}N_2O_5$	61.60	61.98	3.22	3.44	9.02	9.34	390	10,500

[a] Determined in methanolic HCl. [b] S. Gabriel and J. Colman [*Ber.*, **33**, 2633 (1900)] reported m.p. 196–198°. [c] Recrystallized from dimethylformamide.

Experimental[14]

Materials.—Dry methanol and sodium methoxide in anhydrous methanol were prepared and stored in the absence of moisture and carbon dioxide. The concentration of sodium methoxide was determined by hydrolysis of aliquots and titration of the base with standard acid. The solutions were dispensed under nitrogen from siphons.

Phenacylphthalimides (Ia–e).—These were prepared by the method of Sheehan and Bolhoffer[15] from potassium phthalimide and the *p*-substituted phenacyl bromides in dimethylformamide. They were recrystallized from ethanol or 2-propanol: N-*p*-methoxyphenacylphthalimide (Ia), m.p. 172–173°, lit.[16] m.p. 175–176°; N-*p*-methylphenacylphthalimide (Ib), m.p. 164–165°, lit.[17] m.p. 164–165°; N-phenacylphthalimide (Ic), m.p. 165–166°, lit.[15] m.p. 166–167°; N-*p*-phenylphenacylphthalimide (Id), m.p. 207–208°; and N-*p*-bromophenacylphthalimide (Ie), m.p. 228–230°.

Anal. Calcd. for $C_{22}H_{15}NO_3$ (Id): C, 77.40; H, 4.39; N, 4.11. Found: C, 77.27; H, 4.44; N, 3.80.

Anal. Calcd. for $C_{16}H_{10}BrNO_3$ (Ie): C, 55.78; H, 2.91; N, 4.06. Found: C, 55.66; H, 3.10; N, 4.10.

N-*p*-nitrophenacylphthalimide (If).—A mixture of *p*-nitrophenacyl bromide (18.2 g., 0.07 mole) and potassium phthallmide (9.3 g., 0.05 mole) in dry acetone (150 ml.) was refluxed for 3 days. The brown mixture was poured into water (1 l.) and filtered. The solid was triturated with several portions of ether to remove unreacted *p*-nitrophenacyl bromide and the tan residue was crystallized from dimethylformamide to yield 8.7 g. (56%), m.p. 243–244°.

Anal. Calcd. for $C_{16}H_{10}N_2O_5$: C, 61.60; H, 3.22; N, 9.02. Found: C, 61.27; H, 3.30; N, 9.33.

3-Benzoyl-4-hydroxyisocarbostyrils (IIa–f).—The following general procedure was used to prepare pure samples of these compounds. A solution of I (typically 0.004 mole) was added to a flask containing a solution of sodium methoxide in anhydrous methanol (typically 50 ml., 2 *N*). The mixture was refluxed in the absence of moisture and carbon dioxide until homogeneous and then for a further 2 hr., cooled, and neutralized with dilute hydrochloric acid. The solid was filtered, washed with water, and crystallized several times from glacial acetic acid. Table III presents physical constants and analytical data for these compounds.

Methyl N-Phenacylphthalamate (III).—Methyl hydrogen phthalate (4.5 g., 0.025 mole) was refluxed with redistilled thionyl chloride (5.0 ml.) for 1 hr. The solution was treated with dry benzene (5 ml.) and the mixture was evaporated *in vacuo* at room temperature. The last procedure was repeated three times. The pale yellow solid was dissolved in dry benzene (10 ml.) and this solution was added dropwise to a solution of phenacylamine hydrochloride (3.40 g., 0.02 mole) in dry pyridine (25 ml.), which was cooled in an ice bath. The resulting red solution was left overnight at room temperature and was then poured into a stirred mixture of water (100 ml.) and ether (100 ml.) and the organic layer was separated. This layer was washed with cold 2 *N* hydrochloric acid (six portions of 20 ml.), then with saturated sodium bicarbonate, and was dried with sodium sulfate. Removal of the solvent left a yellow oil which was triturated with dry methanol to produce a cream-colored powder. Crystallization from methanol yielded granular crystals, 2.6 g. (18%), m.p. 102°.

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.58; H, 5.07; N, 4.40.

Kinetic Procedures.—Initial work was carried out using the stoppered divided flask previously described.[18] It was found difficult to obtain reproducible results with this flask owing to introduction of moisture and carbon dioxide during removal of aliquots. A conventional sealed-ampoule technique was used and found to be satisfactory. Solutions of Ia–f, IIa–f,[19] or III in methanol and of sodium methoxide in methanol were mixed under nitrogen and approximately 5-ml. aliquots were pipetted into glass ampoules which were flushed with nitrogen and sealed. Time of immersion in the thermostat was chosen as zero time. At noted time intervals ampoules were withdrawn, cooled rapidly, and opened; 2.0-ml. aliquots were pipeted into volumetric flasks containing methanolic hydrochloric acid (100 ml. of concentrated HCl made up to 1 l. with methanol at room temperature.) After adjustment to the required volume with methanolic hydrochloric acid, concentrations were determined from absorbances at the appropriate wave lengths given in Table III. Ia–f and III have no measurable absorption at the maxima of IIa–f. Reactions were followed to at least 65% completion. At least three runs were carried out for each compound: concentrations of Ia–d and of methoxide were varied independently between 1×10^{-2} and 2×10^{-3} *M* for each of these; concentrations of Ie and If were varied between 2×10^{-4} and 4×10^{-4} *M* and, because of their low solubilities, the reactions were carried out under pseudo-first-order conditions with methoxide in 100-fold excess. The rate constants were calculated graphically from the plots of $1/(b - \bar{a}) \log [a(b - x)/b(a - x)]$ or $\log (a - x)$ against time where appropriate and were reproducible to within ±2%. The infinity values were calculated from the absorbance data for pure samples of IIa–f because of the drift of experimental infinity values due to the reaction of methoxide with IIa–f. Values of ΔH^* and ΔS^* were determined as described by Bunnett.[20]

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(14) Melting points were determined on a Fisher-Johns block and are uncorrected. Ultraviolet determinations were made with a Beckman DB spectrophotometer.

(15) J. C. Sheehan and W. A. Bolhoffer, *J. Am. Chem. Soc.*, **72**, 7286 (1950).

(16) F. Tutin, *J. Chem. Soc.*, **97**, 2508 (1910).

(17) H. Ryan, *Ber.*, **31**, 2131 (1898).

(18) J. H. M. Hill and J. G. Krause, *J. Org. Chem.*, **29**, 1641 (1964).

(19) Suspensions of IIa–f in a known volume of methanol were adjusted to the required volume with methoxide solution. This produced homogeneous solutions rapidly.

(20) J. F. Bunnett, "Techniques of Organic Chemistry," Vol. VIII, S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 199.