19-Nordihydrotestosterone.[39]—The rotatory dispersion curve was determined in methanol (*c* 0.018) at 25°, "max." $[\alpha]_{305}$ +1101°, "min." $[\alpha]_{265}$ −928°.

Dipole Moments.—The dipole moments of the various ketones were run at 25° in benzene solution, and the data are given in Table V. The dipole moment apparatus has been described previously.[15] The moments were calculated by essentially the method of Halverstadt and Kumler,[41] utilizing an IBM 650 computer programmed as described earlier.[42] Because of the high molecular weights of the compounds, an attempt was made to account approximately for atomic polarization by taking $P_e + P_a = 1.10\ M_D$ where the latter was found from the table of Vogel.[43]

(39) The authors are indebted to Dr. A. Bowers, Syntex, for a sample of this material. The rotatory dispersion curve was measured by L. Tushaus and J. Maul using the previously described[40] instrument.

(40) C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Am. Chem. Soc.*, **77**, 4354 (1955).

(41) I. F. Halverstadt and W. D. Kumler, *ibid.*, **64**, 2988 (1942).

(42) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(43) A. I. Vogel, W. T. Cresswell, G. J. Jeffrey and J. Leicester, *Chemistry & Industry*, 358 (1950).

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES, NORTH CHICAGO, ILL.]

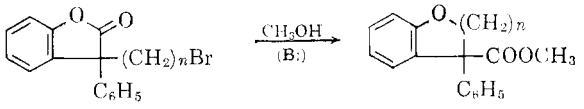
Neighboring Group Reactions. VI. Reactions of 3-(ω-Haloalkyl)-3-phenyl-2-benzofuranones with Secondary Amines. Trapped Tetrahedral Intermediates in a Carbonyl Addition Reaction[1]

BY H. E. ZAUGG, F. E. CHADDE AND R. J. MICHAELS

RECEIVED APRIL 5, 1962

The reactions of a series of ω-bromoalkylbenzofuranones I (n = 0–4) with morpholine are described. The first and last two members of the homologous series (I; n = 0, 3, 4) merely undergo direct displacement to give IV (n = 0, 3, 4). The bromomethyl homolog (n = 1) reacts exclusively with rearrangement to produce the amide III; and the bromoethyl derivative (n = 2) yields mainly (>90%) the trapped tetrahedral intermediate V. A more detailed study of the last reaction is reported. Although solvents of low polarity exert little influence on its course (sp^2 attack), dimethylformamide and dimethyl sulfoxide alter it completely. Then, the sole product IV (n = 2) arises from direct sp^3 displacement of the bromine atom. Other secondary amines, alone or in non-polar media, likewise give corresponding *ortho* amides of type VII; but with increasing basicity of the amine larger quantities of the rearranged amide VI are produced at the expense of VII. Possible mechanisms for these reactions are discussed. The structure VII assigned to these products is documented spectroscopically (infrared, ultraviolet and n.m.r.) and chemically. *Ortho* amides VII are extremely stable bases of widely divergent base strength (spectrophotometrically determined), but each one is less b sic than the amine from which it is derived. Protonation occurs on the phenyl oxygen atom, rather than on nitrogen, to give the cyclic quaternary imidate salt VIII as the more reactive acid form. On the other hand, quaternization with methyl iodide of the pyrrolidine *ortho* amide VII occurs on nitrogen to give XIV.

Previous papers[2] have described the base-catalyzed rearrangement of the three homologous benzofuranones I to the corresponding methyl esters II.



I (n = 1, 2, 3) II (n = 1, 2, 3)

With methoxide ion in methanol, the first two members of this series reacted with extreme rapidity (titration conditions). The third member (n = 3) rearranged more slowly but no less completely (97% yield). In the presence of a weak base (sodium acetate or triethylamine) in refluxing methanol, rearrangement was restricted to the first two members (n = 1,2), and lengthening the chain further (n = 4) exceeded the steric requirements of the reaction so that no rearrangement occurred under any conditions.

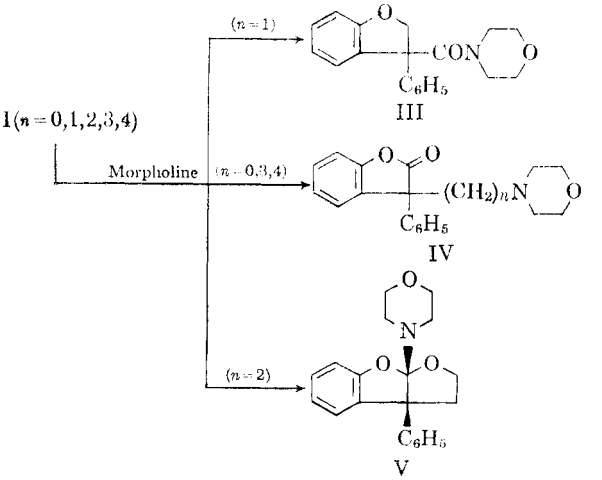
All of these reactions clearly proceed through primary attack of the carbonyl carbon atom by a nucleophilic oxygen atom. Naturally it was of interest to find out what would happen to these bromides in the presence of nitrogen nucleophiles. This paper reports the outcome of such investigations with secondary amines.

(1) Paper V, H. E. Zaugg and R. J. Michaels, *Tetrahedron*, **18**, 893–901 (1962).

(2) (a) H. E. Zaugg, R. W. DeNet and R. J. Michaels, *J. Org. Chem.*, **26**, 4821 (1961); (b) **36**, 4828 (1961).

Results

In order to examine the effect of chain length on the reaction course, each of the five homologous bromides I (n = 0–4) was dissolved in excess morpholine and allowed to stand at room temperature for several days. Results are summarized as



Reactions of all but the bromoethyl derivative (n = 2) can be disposed of briefly. With the bromo methyl derivative (n = 1) rearrangement occurred exclusively and the amide III was the only product

TABLE I

REACTION[a] OF 3-(β-BROMOETHYL)-3-PHENYL-2-BENZOFURANONE WITH SECONDARY AMINES

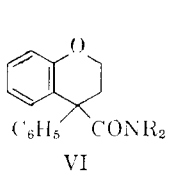
I (n = 2) + R_2NH ⟶ VII + VI

R_2NH	Yield of VII,[b] %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield of VI, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$, C=O, μ
Morpholine	92	113–114	$C_{20}H_{21}NO_3$[c]	74.28	74.47	6.55	6.61	4.33	4.47	4[d]	127–128[e]	6.15
Piperidine	51	137–138	$C_{21}H_{23}NO_2$	78.47	78.46	7.21	7.26	4.36	4.30	27	106–107[f]	6.15
Pyrrolidine	30	123–124[g]	$C_{20}H_{21}NO_2$	78.14	78.29	6.89	6.85	4.56	4.55	58	104–105[h]	6.12[n]
Diethylamine	55	71–72	$C_{20}H_{23}NO_2$	77.63	77.80	7.50	7.69	4.53	4.40	..[i]		
Piperazine[j]	59	150–153	$C_{20}H_{22}N_2O_2$	74.46	74.07	6.89	7.03	8.69	8.35	..[k]		
1-Methylpiperazine	23	104–107	$C_{21}H_{24}N_2O_2$[l]	74.97	74.89	7.19	7.32	8.33	8.29	..[m]		

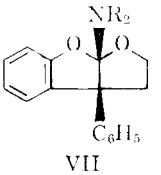
[a] According to procedure 2. [b] These compounds are completely transparent to infrared radiation in the range 3.6 to 6.25 μ. [c] Calcd.: O, 14.84. Found: O, 14.86. [d] Estimated from the intensity of amide absorption in the infrared spectrum of the neutral fraction. [e] *Anal.* Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.16; H, 6.33; N, 4.29. [f] *Anal.* Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.19; H, 7.24; N, 4.36. [g] The 60 megacycle n.m.r. spectrum in carbon tetrachloride solution is (chemical shifts in c.p.s. from tetramethylsilane with relative integrated areas, assuming 9 aromatic protons, in parentheses): [85.7 (4.04)], [142.3, 171.4, 154.0 (5.95)], [215.0, 239.4 (1.95)], [408.7, 429.8 (9.00)]. [h] *Anal.* Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.14; H, 6.89; N, 4.44. [i] No amide could be isolated from neutral fraction; instead, a 22% yield of the lactone IX[4] was obtained. [j] Reaction was conducted in benzene solution for 2 weeks at room temperature. [k] A 14% yield of the lactone IX was obtained. [l] Calcd.: O, 9.51. Found: O, 9.43. [m] The neutral fraction was not examined for product. [n] In carbon tetrachloride.

isolated (81% yield).[3] In contrast, the three extreme members of the series (n = 0,3,4) underwent simple halogen displacement to give the corresponding benzofuranone derivatives IV in yields ranging from 76% (n = 0) to 85% (n = 3,4). No products of rearrangement could be detected. Structural assignments for both III and IV were facilitated by characteristic carbonyl absorption in the infrared (5.54μ for the lactone carbonyl of IV) and, in two instances (III and IV, n = 3), by the easy availability of independently synthesized samples.

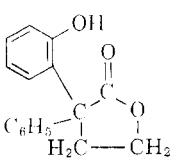
The main product obtained (92% yield) from the bromoethyl homolog I (n = 2) was a weakly basic substance showing no carbonyl absorption in the infrared and possessing the unusual *ortho* amide structure V. Infrared examination of neutral residues indicated the presence of only small amounts of the rearranged amide VI (NR_2 = morpholino) and of the lactone IX,[4] probably derived from hydrolysis of the *ortho* amide V during its isolation.



VI



VII



IX

This reaction of the bromoethyl derivative I (n = 2) was extended to other secondary amines with variable results. These are summarized in Table I. In excess piperidine or pyrrolidine increased amounts of rearranged amide VI were formed at the expense of the *ortho* amide VII. In diethylamine, piperazine and 1-methylpiperazine, no formation of rearranged amide VI was detectable, but lower yields of the *ortho* amides VII were obtained, presumably because of their lower hydrolytic stability: their neutral residues consisted mainly of the lactone IX.

The bromoethyl homolog I (n = 2) could not be induced to react with the more weakly basic secondary amines, imidazole (pK_a 6.92) and cytisine (pK_a 6.11), nor would it react with the strongly basic tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO).

The capricious nature of the reactions of the bromoethyl derivative I (n = 2) with secondary amines was further revealed by a study of solvent effects. These are summarized by the data listed in Table II.

TABLE II

EFFECT OF SOLVENT ON THE REACTION[a] OF 3-(β-BROMOETHYL)-3-PHENYL-2-BENZOFURANONE WITH SECONDARY AMINES

I (n = 2) + R_2NH → VII + VI

Amine[b]	Solvent[c]	Reaction time (days)	Yield of VII, %	Yield[d] of VI, %
Morpholine	Morpholine	1	92	4
Morpholine[e]	Triethylamine	8	55	0[f]
Morpholine	Benzene	7	70	..
Morpholine	1,2-Dimethoxyethane	6	43	0[g]
Morpholine	Dimethylformamide	3	0	0[h]
Morpholine	Dimethyl sulfoxide	3	0	0[i]
Piperidine	Piperidine	1	51	27
Piperidine	Benzene[j]	3	78	12
Pyrrolidine	Pyrrolidine	3	30	58
Pyrrolidine	Benzene	3	23	55
Diethylamine	Diethylamine	13	55	0
Diethylamine	Benzene	10	7	0[k]

[a] Except for modifications indicated in the table, all reactions were conducted at room temperature according to procedure 2. [b] Except when otherwise indicated, two molecular equivalents of the amine were used. [c] Volumes of solvent used ranged between 10 and 20 ml. per 0.01 mole of I. [d] A zero yield indicates that none could be detected by infrared analysis of the neutral fraction. [e] One molecular equivalent of the amine was used. [f] 40% of I (n = 2) was recovered. [g] 54% of I was recovered. [h] A 91% yield of IV (n = 2) was obtained. [i] A quantitative yield of IV (n = 2) was formed. [j] Under the same conditions, but for 16 days at room temperature, the chloro analog of I (n = 2) gave a 75% yield of VII and a 17% yield of VI. [k] 68% of I (n = 2) was recovered.

(3) When the reaction was conducted in dimethyl sulfoxide as solvent a 99% yield of III was secured. N-Methylpiperazine also gave the amide corresponding to III in comparable yield.

(4) H. E. Zaugg, R. W. DeNet, R. J. Michaels, W. H. Washburn and F. E. Chadde, *J. Org. Chem.*, **26**, 4753 (1961).

TABLE III

CYCLIC IMIDATE CHLORIDES VIII

Amine of the =NR₂ function	M.p., °C.	$\lambda_{max}^{CHCl_3}$ μ C=N,	pK_a[a] (±0.2)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Morpholine	137–138	6.02[b]	4.6	$C_{20}H_{22}ClNO_3$	66.75	64.70[c]	6.16	6.08	3.89	3.86
Piperidine	173–174	5.98	7.4	$C_{21}H_{24}ClNO_2$	70.47	70.39	6.77	6.66	3.92	3.83
Pyrrolidine	182–183	5.97	10.6[d]	$C_{20}H_{22}ClNO_2$	69.85	69.89	6.45	6.46	4.07	4.18
Diethylamine	183–184	6.00	8.4	$C_{20}H_{24}ClNO_2$	69.45	68.99	6.99	7.00	4.05	3.96

[a] In aqueous alcoholic solution (28.5% ethanol, v./v.) at 26 ± 1°. [b] In Nujol suspension. [c] Repeated analyses on many different samples invariably and unaccountably, gave low values for carbon. [d] Potentiometric titration with 0.1 *N* methanolic potassium hydroxide in various pyridine–water mixtures followed by extrapolation to 100% water gave $pK_a^{H_2O}$ 10.75.

Dilution of the amines by non-polar solvents retarded the over-all reaction rate (Table II; compare reaction in morpholine alone with that in triethylamine and in 1,2-dimethoxyethane) but exerted little effect on the relative amounts of rearranged amide VI and *ortho* amide VII that were produced. In marked contrast, however, was the effect of the polar solvents dimethylformamide and dimethyl sulfoxide. In these media neither rearranged amide VI nor *ortho* amide V were formed in the reaction with morpholine. Instead, the morpholinoethylbenzofuranone IV (n = 2), formed by direct halogen displacement, was the sole product (>90% yields).[5]

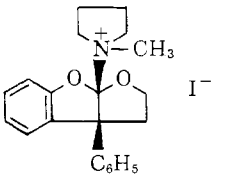
The effect of changing the halogen atom on the course of these reactions was insignificant. Thus, treatment of 3-(β-chloroethyl)-3-phenyl-2-benzofuranone with excess morpholine or pyrrolidine or with piperidine in benzene led to essentially the same yields of rearranged amide VI and *ortho* amide VII as were obtained from its bromo analog I (n = 2) under the same conditions.

In an experiment designed to gauge the competitive efficiency of the morpholine reaction, the bromoethyl derivative I (n = 2) was allowed to react with a mixture of equimolar quantities of morpholine and methanol. The *ortho* amide V was produced in only 17% yield. The main product was the methyl ester II (n = 2; 81% yield) formed as a consequence of preferential nucleophilic attack by methanol.[2b]

Properties of the *Ortho* Amides VII.—In their basic form, these compounds are all characterized by complete transparency in the carbonyl region of their infrared spectra. Added to this fact, their mode of preparation, the agreement of their elemental analyses, the compatibility of the n.m.r. spectrum of the pyrrolidine derivative (Table I, footnote g) and their basic properties, all support the assigned structure VII. Because only one form is ever isolated under reaction conditions that can only be classed as energetically mild, they are written with the five-membered rings in the *cis*-fused configuration.[6]

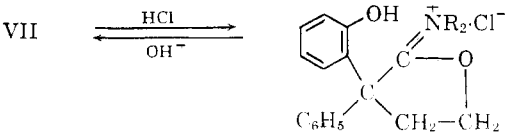
These *ortho* amides are surprisingly inert. They exist as crystalline solids that melt sharply without decomposition. They can be heated for long periods in neutral hydroxylic solvents without solvolyzing; and they do not undergo exchange reactions with secondary amines.[8]

Although quaternization of the morpholine and piperidine derivatives of the *ortho* amide VII with methyl iodide could not be effected, the less hindered pyrrolidine analog gave a poor yield (29%) of the desired salt XIV.



XIV

Protonation, however, occurs predominantly on oxygen rather than nitrogen to give the phenolic cyclic quaternary imidate chlorides VIII. Four of these salts have been isolated in fairly pure



VIII

form by treating the corresponding bases VII with ethereal hydrogen chloride. Data pertaining to them are listed in Table III.

Properties of the Cyclic Quaternary Imidate Chlorides (VIII).—Best evidence for the structure assigned to these compounds derives from their infrared and ultraviolet spectra. Without exception they absorb strongly in the 6.0μ region. This is entirely consistent with the presence of a carbon–nitrogen double bond of an imino-ether.[9] Although both the *ortho* amide bases VII and their salts VIII absorb in the ultraviolet at a peak of 278 mμ the absorbance of the latter is significantly lower. Of the three likely basic centers in the *ortho* amide VII, the phenolic oxygen is the only one which, on protonation, should greatly influence the ultraviolet absorption of one of the aromatic rings.

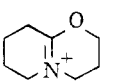
(5) The possible intermediacy of V in this process was ruled out by the observation that, *at room temperature*, V is quite inert to the action of morpholine plus morpholine hydrobromide in dimethyl sulfoxide solution.

(6) Although systems containing two five-membered rings fused *trans* to each other are known in the carbocyclic series, they are energetically decidedly unstable relative to their *cis*-fused isomers.[7]

(7) (a) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934); (b) A. H. Cook and R. P. Linstead, *ibid.*, 946 (1934); (c) R. Granger, P. Nau and J. Nau, *Bull. soc. chim. France*, [5] **27**, 1350 (1960).

(8) Refluxing either the morpholine derivative in piperidine or the piperidine derivative in morpholine for 24 hours led, in each case, to complete recovery of the original adduct.

(9) Compare, A. I. Meyers, *J. Org. Chem.*, **26**, 218 (1961) and D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960). The nearest analog, reported by N. J. Leonard and W. K. Musker, *ibid.*, p. 5148, appears to be the salt i, λ_{max}^{Nujol} 5.98 μ.

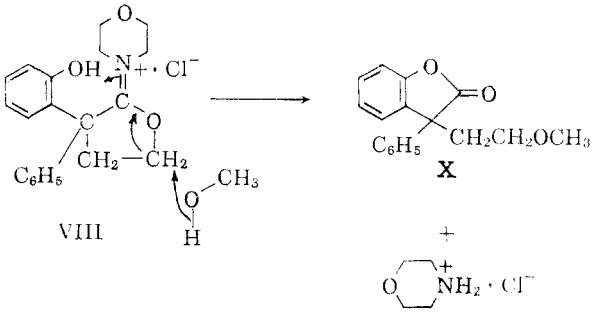


i

Indeed, the reversible change in the 278 mμ absorbance between VII and VIII is sufficiently large to enable measurement[10] of the equilibrium constant with moderate precision (see pK_a values in Table III).[11,12] It is interesting to note that, although the pK_a's of the imidate salts VIII are all smaller than those of the amines from which they are derived, they are not uniformly diminished. The range of the former (4.6 to 10.6) is twice that of the latter (8.4 to 11.3).

Compared to the *ortho* amide bases VII, the imidate salts VIII are quite reactive. Although, at the necessary low *p*H, the morpholine derivative of VIII dissolves in water to form a clear solution, stable for several hours at room temperature, it eventually deposits the neutral hydrolysis product IX. As expected, this process is greatly accelerated at elevated temperatures. (In contrast, the less acidic pyrrolidine derivative of VIII forms a water solution which is stable indefinitely at room temperature.) Heating the morpholine *ortho* amide V (or its corresponding salt) in concentrated hydrobromic or hydrochloric acid in acetic acid leads to excellent yields of the bromoethylbenzofuranone I (n = 2) or, respectively, its chloro analog.

Further evidence consistent with the assignment of structure VIII derives from two reactions involving nucleophilic attack at the ether–methylene carbon atom of the imidate salts. Methanolysis of the morpholine imidate salt VIII led to the methyl ether X in 33% yield; and refluxing the piperidine *ortho* amide VII in morpholine *in the presence of morpholine hydrobromide* gave the morpholinoethylbenzofuranone IV (n = 2), in a 78% yield. (From the morpholine *ortho* amide V, an 87% yield was secured.)



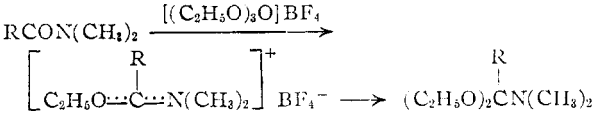
VIII X

Discussion

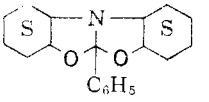
The homologous series of bromobenzofuranones I (n = 0–4) provides, in effect, a complete spectrum of halogen reactivity. Activated by at least one phenyl as well as by the lactonic carbonyl group, the bromine atom of the lowest homolog (I, n = 0) is directly displaced by amines with extreme ease.[14] By contrast, the bromine atom of the next homolog I (n = 1) undergoes no *direct* displacement. As a consequence of its neopentyl configuration its reactions with amines are restricted to *indirect* intramolecular displacements (*i.e.*, I → III). In the case of the bromoethylbenzofuranone I (n = 2) a similar steric hindrance factor may operate, but in diminished degree. Such a borderline steric effect can account for the observed ability of this compound to react in three different ways, only one of which involves direct halogen displacement. As the halogen side chain is lengthened still more (I; n = 3, 4), neighboring group effects disappear and the bromine atom once again, as with the lowest homolog (n = 0), undergoes, exclusively, direct displacement with amines, but this time, undoubtedly, through an SN2 process.

The *Ortho* Amides VII.—Although substances possessing a nitrogen and two oxygen atoms attached to a single tetrahedral carbon atom often have been postulated as unstable reaction intermediates, few examples of their isolation are known. Tetrahedral intermediates of this type have been proposed for the reaction of Grignard reagents with N-substituted 2-oxazolidones,[15] for the reaction of ketene acetals and orthoesters with amines,[16] for the aminolysis of esters and solvolysis of amides,[17] and even for the active site of a hydrolytic enzyme.[18]

Their actual isolation has only recently been described. Meerwein and co-workers[19] prepared mixed orthoester amides by successive treatment of N,N-disubstituted amides with triethyloxonium fluoborate and sodium ethoxide



Although thermally stable, they readily underwent a wide variety of reactions with nucleophilic substances, including facile exchange with secondary amines. More recently, Taguchi and Kawazoe,[20] incidental to other work, were able to prepare two geometric isomers of the tetracyclic compound XI. Compared to Meerwein's acyclic



XI

(10) Compare H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(11) Protonation of the aliphatic oxygen atom would lead to a cyclic imidate salt, isomeric with VIII. Unpublished work in this Laboratory has shown that the carbon–nitrogen double bond in this isomeric system absorbs in the 5.8 μ region. The observed absorption in the 6.0 μ region for VIII therefore provides additional evidence against protonation of the aliphatic oxygen.

(12) The observed lack of any normal hydroxyl absorption in either the near (1.45 μ) or middle (2.7–2.9 μ) infrared spectra of the imidate salts VIII was initially disturbing. However, the n.m.r. spectrum (60 Mc., 10% in $CDCl_3$) of the pyrrolidine derivative of VIII shows a single proton peak at 666.5 c.p.s. (relative to tetramethylsilane) (δ = 11.1 p.p.m.; τ = −1.1) consistent with a strongly bonded phenolic hydroxyl group.[13] Furthermore, this peak disappeared instantly when 2–3% of D_2O was added to the $CDCl_3$ solution.

(13) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 71.

(14) G. Cramer, *Ber.*, **31**, 2813 (1898), has shown that this compound (I, n = 0) solvolyzes completely in only 30 minutes in refluxing ethanol. Undoubtedly, the bromine atom undergoes displacement primarily through an SNi process.

(15) G. Fodor, *Experientia*, **11**, 129 (1955).

(16) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **67**, 202 (1945).

(17) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

(18) S. A. Bernhard, in "Rates and Mechanisms of Reactions," Part I, Editors: S. L. Friess, E. S. Lewis and A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1961, p. 625.

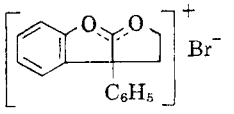
(19) H. Meerwein, W. Florian, H. Schön and G. Stopp, *Ann.*, **641**, 1 (1961).

(20) T. Taguchi and Y. Kawazoe, *J. Org. Chem.*, **26**, 2699 (1961).

analogs, these derivatives were relatively inert. However, quaternization on the nitrogen could be accomplished with methyl iodide, and mineral acid treatment resulted in protonation on oxygen (as with VII).

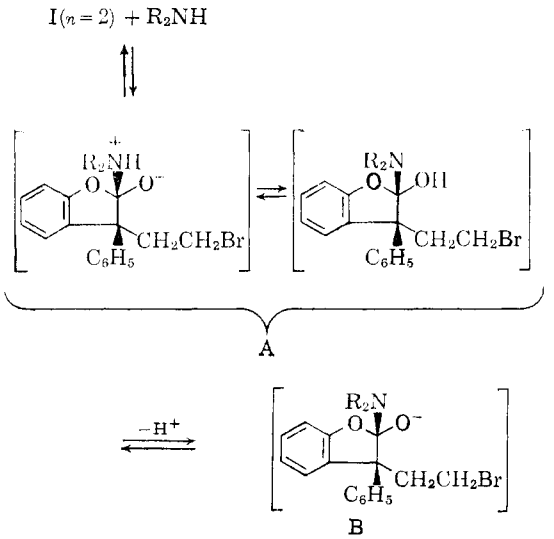
The observed inability of the *ortho* amides VII to undergo exchange with secondary amines (by contrast to Meerwein's acyclic analogs) and their reluctance to form quaternary ammonium salts (in contrast to XI) can be ascribed to their particular geometry. Assuming that inversion must accompany exchange, such a process involving VII would necessarily lead to the high energy isomer containing *trans*-fused five-membered rings.[6] As regards quaternization, examination of a space-filling model of VII reveals that, in the required *cis* configuration of the two fusion atom substituents, the lone pair orbital on nitrogen is necessarily pointed toward the phenyl ring, rendering it relatively inaccessible (compared to the situation in XI) to attack by an electrophilic agent.

Although insufficient data are available to allow the assignment of a single mechanistic scheme to the formation of the *ortho* amides VII, the number of possibilities can be somewhat restricted by what is known. Despite the existence of good precedent[21] for the intermediacy of the carboxonium ion XII in the formation of the *ortho* amides, it can safely be ruled out for theoretical and experimental reasons already enumerated.[1]

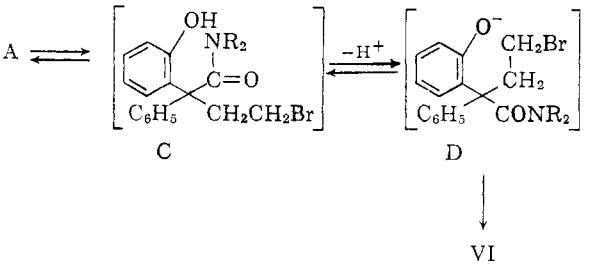


XII

A more credible mechanism involves reversible attack of the carbonyl carbon atom by amine to give A and/or B. The negatively charged oxygen atom of A or B then (or concertedly) displaces

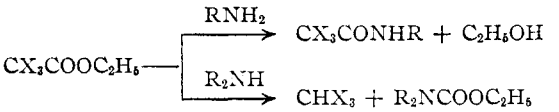


bromide ion intramolecularly and irreversibly to give the *ortho* amide VII.[22] The processes and the timing of proton transfers involving these tetrahedral intermediates cannot be specified. However, it is reasonable to assume that, in the formation of the *ortho* amide VII, the tetrahedral structure of A or B must remain intact during the bromide displacement step. Any process leading to the expulsion of the phenolic oxygen atom before bromide ion is displaced (*i.e.*, A→C ⇄ D or B→D) would favor the competitive production of rearranged amide VI. In view of the complex equi-



libria involved in this system, it is not surprising that observed product formation (*i.e.*, VI, VII or IV) is so sensitive to changes in reagent and reaction conditions (solvent and temperature).

In this connection there seems to be a parallel between these reactions and some interesting observations of Joullié and Day.[26] They found that aminolysis of ethyl trichloro- and trifluoroacetates with primary amines led to the expected amides, but with secondary amines haloform cleavage and N,N-disubstituted urethans resulted. They explained these findings in terms of a generally



greater acidity of the N–H bond of the tetrahedral intermediates derived from primary amines as compared to that in the tetrahedral intermediates derived from secondary amines. The consequent difference in ease and direction of proton transfers was held to account for the marked divergence in reaction course.

The behavior of the bromoalkylbenzofuranones I toward primary amines is presently under study.

Experimental[27]

4-(2,3-Dihydro-3-phenylbenzofuran-3-carboxy)-morpholine (III). Procedure 1.—3-Bromomethyl-3-phenyl-2-benzofuranone[23a] (2.4 g., 0.008 mole) was dissolved in morpholine (20 ml.) at room temperature. The solution warmed slightly and morpholine hydrobromide shortly (10–15 min.) began to precipitate. After standing for 3 days, the mor-

(21) (a) S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948); (b) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert and K. Wunderlich, *Ann.*, **632**, 38 (1960); (c) G. Baddeley, E. K. Baylis, B. G. Heaton and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961).

(22) Similar indirect nucleophilic displacements of halogen properly located with respect to a carbonyl group are well-known. Thus, many α-haloketones with alkoxide and cyanide ion give epoxyethers[23] and α,β-oxidonitriles,[24] respectively, while certain γ-bromoketones yield the corresponding hydrofuran derivatives.[25]

(23) C. L. Stevens and A. J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958), and earlier papers.

(24) C. F. Koelsch, *ibid.*, **66**, 306 (1944).

(25) (a) L. I. Smith and J. R. Holum, *ibid.*, **78**, 3417 (1956); (b) H. Normant, *Compt. rend.*, **232**, 1942 (1951).

(26) M. M. Joullié and A. R. Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954).

(27) Melting points and boiling points are uncorrected.

pholine hydrobromide (1.3 g., m.p. 210–213°) was removed by filtration and washed with ether. The filtrate and washings were combined and concentrated to dryness under water-pump vacuum using a rotating evaporator in conjunction with a water-bath held at 45–50°. Trituration of the residual oil with dry ethanol followed by one recrystallization of the resulting solid (2.0 g., 81%, m.p. 142–145°) from dry ethanol gave pure III, m.p. 147–148°, $\lambda_{max}^{CHCl_3}$ 6.11 μ.

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.52; H, 6.35; N, 4.39.

When the foregoing reaction was conducted in dimethyl sulfoxide (50 ml.) solution for 7 days, a 99% yield of III, m.p. 142–146°, was obtained.

The structure of III was also confirmed by independently synthesizing it from 2,3-dihydro-3-phenylbenzofurancarbonyl chloride[2a] and morpholine. The amide obtained in this way was identical (m.p., mixed m.p. and infrared spectrum) with the product of procedure 1.

1-Methyl-4-(2,3-dihydro-3-phenylbenzofuran-3-carboxy)-piperazine, m.p. 155–156°, was prepared by substituting 1-methylpiperazine for morpholine in procedure 1.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.77; H, 7.18; N, 8.84.

3-Morpholino-3-phenyl-2-benzofuranone (IV; n = 0).—Treatment of 3-bromo-3-phenyl-2-benzofuranone[28] (I, n = 0; 5 g., 0.0173 mole) with morpholine (20 ml.) according to procedure 1 gave IV (n = 0; 3.85 g., 76% yield), m.p. 133–134° from isopropyl alcohol, $\lambda_{max}^{CHCl_3}$ 5.51 μ.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.81; N, 4.75. Found: C, 73.12; H, 5.83; N, 4.65.

When 3-(γ-bromopropyl)-3-phenyl-2-benzofuranone[2a] (I, n = 3) was treated with morpholine according to procedure 1, there was obtained an 85% yield of **3-(γ-morpholinopropyl)-3-phenyl-2-benzofuranone (IV, n = 3)**, isolated as the **hydrochloride**, m.p. 239–240°, $\lambda_{max}^{CHCl_3}$ 5.55 μ, which, by mixed m.p., was shown to be identical with an authentic sample.[29]

Likewise, from 3-(δ-bromobutyl)-3-phenyl-2-benzofuranone (I, n = 4),[2a] there was obtained,[30] in 85% yield, **3-(δ-morpholinobutyl)-3-phenyl-2-benzofuranone (IV, n = 4)**, m.p. 60–61°, $\lambda_{max}^{CHCl_3}$ 5.54 μ.

Anal. Calcd. for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.35; H, 7.01; N, 4.03.

6a-Morpholino-3a-phenyl-2,3,3a,6a-tetrahydro-4,5-benzofuro[2,3-b]furan (V). Procedure 2.—3-(β-Bromoethyl)-3-phenyl-2-benzofuranone (I, n = 2)[28] (12.7 g., 0.04 mole) was treated (24 hours) with morpholine (50 ml.) according to procedure 1. After the morpholine was removed by evaporation from the filtered reaction mixture, the residue was taken up in ether (200 ml.) and extracted with two 50-ml. portions of ice-cold 6 N hydrochloric acid. The chilled combined extracts were rendered alkaline by the slow addition of cold 50% sodium hydroxide solution and the precipitated base was taken up in a benzene–ether mixture, separated and concentrated to dryness under reduced pressure to give crude V (12.0 g., 92%, m.p. 105–110°). Two recrystallizations from ethanol gave pure V (9.7 g., 75%), m.p. 113–114° (for microanalytical results, see Table I).

Infrared examination of the neutral fraction (1.0 g.) obtained after removal of the ether by distillation indicated the presence of the amide VI (NR_2 = morpholino), $\lambda_{max}^{CHCl_3}$ 6.15 μ, representing about a 4% yield, together with 2-(o-hydroxyphenyl)-2-phenyl-4-hydroxybutyric acid γ-lactone (IX),[4] $\lambda_{max}^{CHCl_3}$ 5.74 μ, in an amount corresponding to a 3% yield.

Treatment of the bromide I (n = 2) with several other secondary amines under the conditions of procedure 2 gave results which are summarized in Table I. Neither imidazole nor cytisine gave any evidence of reacting with I (n = 2) in benzene solution (2 weeks at room temperature). In each case more than 90% of the starting material was recovered. Also, the tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO) failed to react.

Substitution of the chloro analog of I (n = 2), 3-(β-chloroethyl)-3-phenyl-2-benzofuranone,[2a] into procedure 2 did not affect the course of the reaction appreciably. Thus, yields of compounds VII and VI were, respectively, from morpholine 89% and 5% and from pyrrolidine, 26% and 60%.

However, both the over-all rate and ratio of products were influenced by changing the solvent. This is illustrated by the data summarized in Table II.

Quaternization of VII (NR_2 = Pyrrolidino). Preparation of XIV.—A solution of VII (NR_2 = pyrrolidino; 1.0 g., 0.0032 mole) and methyl iodide (1.4 g., 0.01 mole) in chloroform (20 ml.) was refluxed for 48 hours. Removal of solvent by distillation gave a viscous oil which was taken up in 2-butanone and crystallized by the addition of dry ether. Recrystallization from the same solvent pair gave analytically pure XIV (0.40 g., 29% yield), m.p. 138–139°, insoluble in carbon tetrachloride, soluble in chloroform and water; the infrared spectrum exhibited no absorption between 3.4 and 6.3 μ, and the n.m.r. spectrum (10% in $CDCl_3$) contained an unsplit three-proton peak at τ = 6.89 showing the presence of a methyl attached to a quaternary nitrogen atom.[31]

Anal. Calcd. for $C_{21}H_{24}INO_2$: C, 56.01; H, 5.39; N, 3.12. Found: C, 56.31; H, 5.26; N, 3.13.

Similar treatment of the morpholine and piperidine analogs of VII led to predominant recovery (80–95%) of unchanged starting material.

Cyclic imidate chlorides VIII were prepared by treating dry ethereal or alcoholic solutions of the tetrahedral intermediates VII with a slight excess of ethereal hydrogen chloride and recrystallizing the precipitated salts from ethanol–ether mixtures. Data for the four salts prepared are listed in Table III. By treatment of these salts with aqueous alkali the corresponding bases VII were easily recovered in good yield.

Spectrophotometric pK_a Determinations.—These were carried out by the method of Brown and Mihm[10] using the change in absorbance with pH of the 278 mμ maximum in water containing 28.5% (v./v.) ethanol. Absorbances were measured with a Beckman DU spectrophotometer and the reversibility of the acid–base equilibrium was checked with a Cary recording spectrophotometer. pH's of the buffer solutions were determined with a Beckman model G pH meter. The following molar extinction coefficients (at 278 mμ) were observed, first in acid solution (0.1 N HCl), then in alkaline solution (0.1 N NaOH) and finally in the buffer of given pH: for the morpholine derivative of VII ⇌ VIII, 2250, 2820, 2670 (pH 5.02); for the piperidine derivative, 2310, 3100, 2580 (pH 7.12); for the pyrrolidine derivative, 2360, 2700, 2600 (pH 10.87); and for the diethylamine derivative, 2400, 3040, 2530 (pH 8.36). The pK_a observed for the pyrrolidine derivative was checked potentiometrically (see Table III, footnote *d*).

Reaction of 3-(β-Bromoethyl)-3-phenyl-2-benzofuranone (I, n = 2) with Morpholine at 100°.—A mixture of I (n = 2; 6.3 g., 0.02 mole) and morpholine (40 ml.) was heated on the steam-bath for 8 hours and then worked up according to procedure 2. A quantitative yield (m.p. 77–84°) of basic material was obtained. This was heated in 10% hydrochloric acid (50 ml.) for 3 hours on the steam-bath. The hydrochloride salt thus obtained was taken up in chloroform and the chloroform was removed by distillation. The solid residue was triturated with dry ether and collected at the filter. Recrystallization from an ethanol–ether mixture gave 4.8 g. (66%) of 3-(β-morpholinoethyl)-3-phenyl-2-benzofuranone (IV, n = 2) hydrochloride, m.p. 214–215°, identical (mixed m.p. and infrared spectrum) with an authentic sample.[29]

Reaction of 3-(β-Bromoethyl)-3-phenyl-2-benzofuranone (I, n = 2) with an Equimolar Mixture of Morpholine and Methanol.—A solution of I (n = 2; 5.0 g., 0.0158 mole) in 43.5 g. (0.5 mole) of morpholine and 16.0 g. (0.5 mole) of dry methanol was allowed to stand at room temperature for 3 days. The reaction was then worked up according to procedure 2. The basic fraction gave 0.9 g. (17%) of crude V, m.p. 90–97°, identified by its infrared spectrum, and the neutral fraction (liquid) gave 3.4 g. (81%) of methyl 4-phenyl-4-chromancarboxylate (II, n = 2) identified by its infrared spectrum[2a] and by hydrolysis to the corresponding carboxylic acid, m.p. 151–152°.[2a]

Reactions of the Imidate Salts VIII. A. Hydrolysis.—Compound V (1.62 g., 0.005 mole) was suspended in 0.100 N hydrochloric acid (50 ml., 0.005 mole) and heated to reflux.

(28) A. Bistrzycki and J. Flatau, *Ber.*, **30**, 124 (1897).

(29) A. W. Weston and W. B. Brownell, *J. Am. Chem. Soc.*, **74**, 653 (1952).

(30) The three reactions involving direct displacement of the bromine atom to give IV (n = 0, 3, 4) were carried out by R. W. DeNet.

(31) Reference 13, p. 56.

A clear solution formed within a few minutes, but on further heating a solid began to precipitate. After refluxing for 2 hours the mixture was cooled and the solid was collected at the filter and washed with water. Drying gave 1.2 g. (92%) of 2-(*o*-hydroxyphenyl)-2-phenyl-4-hydroxybutyric acid γ-lactone (IX),[4] m.p. 159–161°, identified by mixed melting point and infrared spectrum.

Similar results were obtained using aqueous sulfuric acid instead of hydrochloric acid, and by substituting the diethyl amino analog (VII, R = C_2H_5) for the morpholino derivative in the above procedure.

B. Reaction with Halogen Acids in Acetic Acid.—Compound V (3.24 g., 0.01 mole) was refluxed for 6 hours with a mixture of glacial acetic acid (15 ml.) and 48% aqueous hydrobromic acid (15 ml.). The mixture was then concentrated to a small volume (~5 ml.), treated with water (50 ml.) and extracted with two portions (50 ml.) of ether, which were combined, washed with water and dried over anhydrous magnesium sulfate. The original aqueous layer was combined with the water washings and concentrated to dryness. Trituration of the residue with ethanol, cooling, collecting the solid product at the filter and washing with dry ether gave 1.61 g. (96%) of morpholine hydrobromide, m.p. 210–211°, identified by mixed melting point with an authentic sample. Filtration of the dry ethereal extract followed by removal of the ether by distillation gave an oil (2.92 g., 92%) that solidified slowly (m.p. 64–69°). One recrystallization from ethanol gave pure 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I, n = 2; 2.30 g., 73%, m.p. 75–76°).[2a]

Substitution of concentrated hydrochloric acid for the hydrobromic acid in the foregoing procedure led to equally good yields of the chloro analog of I (n = 2), 3-(β-chloroethyl)-3-phenyl-2-benzofuranone.[32]

C. Methanolysis. Preparation of 3-(β-Methoxyethyl)-3-phenyl-2-benzofuranone (X).—When the morpholino derivative V, as the base, was refluxed in dry methanol for 54 hours, 94% of it was recovered unchanged. However, when 6.9 g. (0.019 mole) of the corresponding imidate salt VIII (NR_2 = morpholino) was refluxed in methanol (100 ml.) for 18 hours, the methanol removed by distillation, the semi-solid residue triturated with dry ether and collected at the filter, a 78% yield of morpholine hydrochloride, m.p. 174–175°, was secured. From the neutral solution, upon evaporation of the ether, was obtained an oil (4.3 g.) which, after trituration with hexane, gave 3.5 g. of a solid, m.p. 55–95°. Tedious fractional crystallization using pentane, hexane, cyclohexane and benzene, alone and in various combinations, separated this mixture into two products, the lactone IX (0.2 g., 4%), m.p. 158–159°, identified by infrared spectrum,[4] and 3-(β-methoxyethyl)-3-phenyl-2-benzofuranone (X) (1.7 g., 33%), m.p. 56–58°, $\lambda_{max}^{CHCl_3}$ 5.55 μ (C=O), identical (mixed m.p. and infrared spectrum) with the authentic material.[1]

D. Reaction with Morpholine.—When the morpholino derivative V was refluxed in morpholine for 16 hours, 92% of it was recovered unchanged. Refluxing in piperidine for 24 hours gave the same result. However, when a salt of the amine was added to the refluxing mixture, reaction occurred: a mixture of compound V (1.62 g., 0.005 mole), morpholine hydrobromide (0.84 g., 0.005 mole) and morpholine (10 ml.) was refluxed for 7 hours. The mixture was concentrated to dryness, the residue was partitioned between ether (75 ml.) and water (50 ml.) and separated. The ethereal solution was extracted with two portions (30 ml.) of 10% hydrochloric acid which were combined and rendered alkaline with cold 40% sodium hydroxide solution. The liberated oil was taken up in ether and recovered in the usual way to give 1.6 g. of crude solid, m.p. 93–96°. Recrystallization from ethanol gave 1.4 g. (87%) of pure 3-(β-morpholinoethyl)-3-phenyl-2-benzofuranone (IV, n = 2), m.p. 95–97°, identified by elemental analysis, infrared spectrum and mixed m.p. with a known sample.[29]

When the piperidine analog VII (NR_2 = piperidino) was substituted for V in the foregoing procedure the same product IV (n = 2) was obtained in 78% yield, at first in a metastable dimorphic form, m.p. 78–81°, but on mixing with the stable dimorph it, too, melted at 95–97°. Its structure was also checked by elemental analysis and infrared spectrum.

When the above procedure was carried out at room temperature with the addition of enough dimethyl sulfoxide to solubilize the morpholine hydrobromide, 94% of V was recovered unchanged after 3 days. Thus, it appears that raised temperatures are necessary for appreciably reaction to occur. This also shows that in the reaction of the bromide I (n = 2) with morpholine at room temperature to give IV (n = 2) (in dimethyl sulfoxide or dimethylformamide) compound V cannot be an intermediate.

Acknowledgments.—We wish to thank Mr. D. C. Wimer for the potentiometric titrations, Mr. W. H. Washburn for the infrared spectra, Mr. E. F. Shelberg and associates for the microanalyses, Mr. G. M. Bradford for the large-scale preparation of intermediates, Dr. R. W. Mattoon and Mr. T. F. Page, Jr., Battelle Memorial Institute, for the determination and interpretation of the n.m.r. spectra, and Mr. N. F. Ryan for technical assistance.

(32) This procedure has been successfully carried out on a much larger scale (>300 g.). It therefore provides a convenient means of obtaining large quantities of pure chloro or bromoethyl derivatives of type I (n = 2). It was found previously[2a] that alkylation of the sodio-derivative of 3-phenyl-2-benzofuranone proceeded in good yield only when the mixed halide 1-bromo-2-chloroethane was used as the alkylating agent in dimethylformamide as solvent. Unfortunately, this led to an intractable mixture of the two halides in the product. Resolution of this mixture is now best carried out by converting it to the morpholine adduct V (procedure 2) followed by heating with the appropriate halogen acid in acetic acid.