sumably derivable from 3-phenyl-2,3-dihydrobenzofuran, was unsuccessful. Metallation of this heterocycle with either sodium amide, potassium amide, or butyl lithium seemed to occur with ring cleavage.

Acknowledgment. The authors wish to thank Mr. E. F. Shelberg for the microanalyses, Mr. W. H. Washburn for the infrared spectra, and Dr. R. W. Mattoon for interpretation of the proton magnetic resonance data.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Neighboring Group Reactions. II. A Novel Synthesis of Basic Esters of 1-Benzoxacycloalkanecarboxylic Acids

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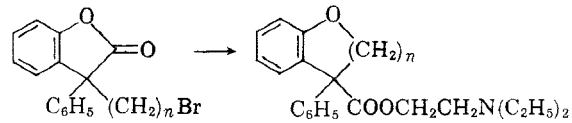
Received May 18, 1961

Sodium derivatives of tertiary aminoalkanols react with the three bromoalkylbenzofuranones (Ia–c) to give the corresponding basic esters II, n = 1–3. With one observed exception, Ia and Ib react in the same way with tertiary aminoalkanols either alone or in the presence of triethylamine; Ic does not. Neither Ia nor Ib reacts with β-diethylaminoethyl mercaptan under amine-catalyzed conditions, but all three bromides, Ia, b, c, are attacked by the sodium derivatives of this mercaptan. Products vary from thiol ester IIIa (containing a minor quantity of IVa) obtained from Ia, to the uncontaminated direct displac ment product IVc secured from Ic. These results, when combined with other supporting evidence, suggest that in the amine-catalyzed reactions of Ia and Ib, the tertiary amine functions as a base to remove a proton from a tetrahedral intermediate.

The accompanying paper[1] of this series describes a route whereby three 1-benzoxycycloalkanecarboxylic acids become easily accessible. That these acids are also analogs of diphenylacetic acid necessitated the preparation of a series of basic esters derived from them.[2] From both the practical and theoretical point of view it seemed desirable to determine whether and under what conditions these esters could be obtained directly from the three ω-bromoalkylbenzofuranones I by treatment with amino alcohols, amino mercaptans, or their sodium derivatives. This is the subject of the present paper.

When the bromomethylbenzofuranone Ia was heated on the steam bath with excess β-diethylaminoethanol or with an equivalent of it in the presence of excess triethylamine (procedure 1), the ester IIa was formed in good yield (60–70%). Likewise, the next homolog Ib gave IIb in fair yield (50–60%). However, when the ω-bromopropyl compound Ic was treated in this manner, 40% of it was covered unchanged and no water insoluble basic material (IIc) was formed. Presumably, that portion of Ic that reacted underwent displacement of bromine by nitrogen to give a quaternary ammonium derivative. When Ic was treated with the sodium derivative of β-diethylaminoethanol (procedure 2), IIc formed smoothly, as expected,[1] in 71% yield. To avoid possible error in the assignment of structure to the basic esters II, each one was independently prepared by treatment of β-diethylaminoethanol with the respective carboxylyl chloride[1] (procedures 3, 3a, or 3b).



Ia. n = 1
Ib. n = 2
Ic. n = 3

IIa. n = 1
IIb. n = 2
IIc. n = 3

Extension of these reactions to the preparation of other basic esters is summarized in Table I. Except for two cases (the reactions of Ia and Ib with 4-hydroxy-1-methylpiperidine) there appears to be little to choose between the use of the amino alcohol or its sodium derivative in the preparation of esters of the first two series (Table IA and IB). However, for preparation of esters of the seven-ring series (Table IC), comparisons in three instances showed that reaction of the sodium alkoxide derivative with Ic (procedure 2) gave significantly better yields of the ester (and in fewer steps) than did the usual esterification method involving the acid chloride (procedure 3a).

The behavior of β-diethylaminoethyl mercaptan and its sodium derivative toward the three bromides I contrasted markedly with that of its oxygen counterpart. In the first place, reaction of the free amino mercaptan with either Ia or Ib (procedure 1) led to none of the corresponding thiol ester, IIIa or IIIb, respectively.[3] Indeed, 85% of Ia was recovered unchanged.

In the second place, reaction of the mercaptide anion (sodium derivative) tended strongly to take

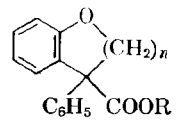
(1) H. E. Zaugg, R. W. De Net, and R. J. Michaels, *J. Org. Chem.*, 26, 4821 (1961).

(2) The significant and diverse physiological activity of basic esters of diphenylacetic acid derivatives is well known. See A. Burger, *Medicinal Chemistry*, Interscience, New York, 1951, p. 419 *et seq.*

(3) Reaction of the amino mercaptan with Ic was not even tried, as it had already been found that β-diethylaminoethanol did not react with Ic to give a basic ester

TABLE I

BASIC ESTERS



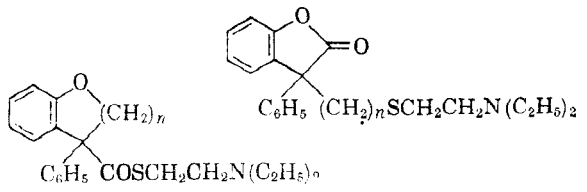
R	Procedure	Yield, %	B.P. (M.P.)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
A. 3-Phenyl-2,3-dihydro-3-benzofurancarboxylic Esters (n = 1)										
—$CH_2CH_2N(C_2H_5)_2$·HCl	1	45	(125–127)	$C_{21}H_{26}ClNO_3$	67.10	67.39	6.97	7.10	3.73	3.77
—$CH_2CH_2N(C_2H_5)_2$·HCl	3	47	(125–127)	$C_{21}H_{26}ClNO_3$	67.10	66.93	6.97	6.84	3.73	3.81
—$CH_2CH_2N(CH_3)_2$·HCl	1[a]	58	(151–152)	$C_{19}H_{22}ClNO_3$	65.60	65.76	6.38	6.47	4.03	4.06
—$CH_2CH_2N[CH(CH_3)_2]_2$	1	32	193 (1 mm.)[b]	$C_{25}H_{29}NO_3$	75.17	75.48	7.95	7.88	3.81	3.65
—$CH_2CH_2NC_4H_8$[c]	1	69	198–201 (1.2 mm.)[d]	$C_{21}H_{23}NO_3$	74.75	74.77	6.87	6.88	4.15	3.90
—$CH_2CH_2NC_5H_{10}$[e]·HCl	1	43	(148–149)	$C_{22}H_{26}ClNO_3$	68.12	68.31	6.75	6.85	3.61	3.84
—$CH_2CH_2N_2C_5H_{11}$[f]·2HCl	1[a]	49	(231–232)	$C_{22}H_{28}Cl_2N_2O_3$	60.14	60.08	6.42	6.53	6.38	6.36
—$CH(CH_3)CH_2N(CH_3)_2$·HCl	2	25[g]	(187–188)	$C_{20}H_{24}ClNO_3$	66.37	66.32	6.68	6.98	3.87	3.85
—$CH(CH_3)CH_2NC_4H_8$[c]	2[h]	48	197–200 (1.1 mm.)[i]	$C_{22}H_{25}NO_3$	75.18	74.95	7.17	7.17	3.99	3.98
—$CH(CH_3)CH_2NC_4H_8$[c]	1	57	190–191 (0.5 mm.)	$C_{22}H_{25}NO_3$	75.18	75.48	7.17	7.41	3.99	3.96
—$CH(CH_3)CH_2NC_5H_{10}$[e]	2	58	195–196 (1 mm.)[j]	$C_{23}H_{27}NO_3$	75.58	75.71	7.45	7.55	3.83	3.91
—$CH(CH_3)CH_2NC_6H_{12}$[k]	2	57	205–208 (1.4 mm.)[l]	$C_{24}H_{29}NO_3$	75.95	76.06	7.70	7.37	3.69	3.66
—CH_2CH_2-2-$C_6H_{12}N$[m]	1	76	215–216 (1.3 mm.)[n]	$C_{23}H_{27}NO_3$	75.58	75.57	7.45	7.19	3.83	3.91
—CH_2-3-$C_6H_{12}N$[o]	1	80	197–198 (1 mm.)[p]	$C_{22}H_{25}NO_3$	75.18	74.94	7.17	7.19	3.99	3.95
—4-$C_6H_{12}N$[q]	2[dd]	48	(90–91)	$C_{21}H_{23}NO_3$	74.75	74.77	6.87	6.97	4.15	4.15
—4-$C_6H_{12}N$[q]	3b	64	(103–104)	$C_{21}H_{23}NO_3$	74.75	74.58	6.87	6.98	4.15	4.19
—3α-$C_8H_{14}N$[r]	2	57	(97–98)[s]	$C_{23}H_{25}NO_3$	76.00	76.18	6.93	6.72	3.85	3.71
—$CH_2C{\equiv}C—CH_2N(CH_3)_2$·$(COOH)_2$	1	59	(88–91)	$C_{23}H_{23}NO_7$	64.94	65.01	5.46	5.64	3.30	3.44
B. 4-Phenyl-4-chromancarboxylic Esters (n = 2)										
—$CH_2CH_2N(C_2H_5)_2$·HCl	1	48	(157–158)	$C_{22}H_{28}ClNO_3$	67.76	67.98	7.24	7.24	3.59	3.40
—$CH_2CH_2N(C_2H_5)_2$·HCl	3	35	(157–158)	$C_{22}H_{28}ClNO_3$	67.76	67.92	7.24	7.18	3.59	3.73
—$CH_2CH_2N(CH_3)_2$·HCl	1[t]	41	(212–213)	$C_{20}H_{24}ClNO_3$	66.37	66.39	6.68	6.64	3.87	3.88
—$CH_2CH_2N[CH(CH_3)_2]_2$·HCl	1	57	(158–159)	$C_{24}H_{32}ClNO_3$	68.96	69.05	7.72	8.02	3.35	3.39
—$CH_2CH_2NC_4H_8$[c]	1	57	206–212 (1.4 mm.)[u]	$C_{22}H_{25}NO_3$	75.18	75.33	7.17	7.04	3.99	3.79
—$CH_2CH_2NC_5H_{10}$[e]·HCl	1	58	(159–160)[v]	$C_{23}H_{28}ClNO_3$	68.73	68.82	7.02	7.26	3.48	3.43
—$CH_2CH_2N_2C_5H_{11}$·2HCl	1[w]	23	(238–239)	$C_{23}H_{30}Cl_2N_2O_3$	60.92	60.60	6.67	6.64	6.18	6.12
—$CH(CH_3)CH_2N(CH_3)_2$	2	64	196–197 (1.6 mm.)[x]	$C_{21}H_{25}NO_3$	74.31	74.53	7.42	7.62	4.13	4.10
—$CH(CH_3)CH_2NC_4H_8$[c]	2	70	200–202 (1.0 mm.)[y]	$C_{24}H_{27}NO_3$	75.58	75.81	7.45	7.40	3.83	3.77
—$CH(CH_3)CH_2NC_5H_{10}$[e]	2	72	205–207 (1.5 mm.)[z]	$C_{24}H_{29}NO_3$	75.95	76.35	7.70	7.58	3.69	3.58
—$CH(CH_3)CH_2NC_6H_{12}$[k]	2	77	215–216 (1.6 mm.)[aa]	$C_{25}H_{31}NO_3$	76.38	76.08	7.94	7.69	3.55	3.55
—CH_2CH_2-2-$C_6H_{12}N$[m]	1	82	221–227 (1.3 mm.)[bb]	$C_{24}H_{29}NO_3$	75.95	75.94	7.70	7.58	3.69	3.66
—CH_2-3-$C_6H_{12}N$[o]	1	84	207–208 (1.0 mm.)[cc]	$C_{23}H_{27}NO_3$	75.58	75.70	7.45	7.40	3.83	3.85
—2-$C_6H_{12}N$[q]	2[dd]	48	180–181 (2.0 mm.)[ee]	$C_{22}H_{25}NO_3$	75.18	75.15	7.17	7.31	3.99	3.89
—3α-$C_8H_{14}N$[r]·HCl	2	65	(175–177)	$C_{24}H_{28}ClNO_3$	69.63	69.48	6.82	6.67	3.38	3.18

TABLE I (*continued*)

R	Procedure	Yield, %	B.P. (M.P.)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
C. 5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic Esters (n = 3)										
—$CH_2CH_2N(C_2H_5)_2$·HCl	2	71	(193–194)	$C_{23}H_{30}ClNO_3$	68.39	68.18	7.48	7.46	3.46	3.44
—$CH_2CH_2N(C_2H_5)_2$·HCl	3a	66	(194–195)	$C_{23}H_{30}ClNO_3$	68.39	68.11	7.48	7.53	3.46	3.48
—$CH_2CH_2N(CH_3)_2$·HCl·$^1/_2H_2O$	3a	70	(214–215 dec.)	$C_{42}H_{54}Cl_2N_2O_7$[jj]	65.53	65.58	7.07	7.28	3.64	3.79
—$CH_2CH_2[CH(CH_3)_2]_2$·HCl	3a	45	(135–136)	$C_{25}H_{34}ClNO_3$	69.51	69.21	7.93	7.65	3.24	3.30
—$CH_2CH_2NC_4H_8$[c]·HCl·$^1/_2H_2O$	3a	52	(205–206 dec.)	$C_{46}H_{58}Cl_2N_2O_7$	67.22	67.03	7.11	7.28	3.41	3.40
—$CH_2CH_2NC_5H_{10}$[c]·HCl·$^1/_2H_2O$	3a	56	(203–204)	$C_{48}H_{60}Cl_2N_2O_7$[gg]	67.83	67.77	7.35	7.38	3.30	3.16
—$CH_2CH_2N_2C_5H_{11}$[f]·2HCl	3a	48	(242–244 dec.)	$C_{24}H_{32}Cl_2N_2O_3$	61.66	61.80	6.90	6.78	5.99	6.01
—$CH(CH_3)CH_2N(CH_3)_2$·HCl	3a	47	(200–201)	$C_{22}H_{28}ClNO_3$	67.76	67.33	7.24	7.23	3.59	3.59
—$CH(CH_3)CH_2NC_4H_8$[c]·HCl	3a	63	(199–200)	$C_{24}H_{30}ClNO_3$	69.30	69.06	7.27	7.42	3.37	3.36
—$CH(CH_3)CH_2NC_5H_{10}$[c]·HCl	3a	49	(218–220)	$C_{25}H_{32}ClNO_3$	69.82	70.02	7.52	7.67	3.25	3.05
—$CH(CH_3)CH_2NC_6H_{12}$[k]·HCl	3a	38	(223–224[hh])	$C_{26}H_{34}ClNO_3$	70.33	70.29	7.71	7.51	3.15	3.13
—CH_2CH_2-2-$C_6H_{12}N$[m]	3a	80	222–226 (1.0 mm.[ii])	$C_{25}H_{31}NO_3$	76.38	76.03	7.94	8.03	3.55	3.60
—CH_2-3-$C_6H_{12}N$[q]·HCl	3a	31	(233–234)	$C_{24}H_{30}ClNO_3$	69.30	69.63	7.27	7.61	3.37	3.30
—4-$C_6H_{12}N$[q]·HCl	3a	18	(211–212)	$C_{23}H_{28}ClNO_3$	68.73	68.67	7.02	7.25	3.48	3.32
—4-$C_6H_{12}N$[q]·HCl	2	73	(215–217)	$C_{23}H_{28}ClNO_3$	68.73	68.99	7.02	7.22	3.48	3.34
—3α-$C_8H_{14}N$[r]	3a	10	(129–130)	$C_{25}H_{29}NO_3$	76.70	76.46	7.46	7.30	3.57	3.50
—3α-$C_8H_{14}N$[r]	2	20	(131–132)	$C_{25}H_{29}NO_3$	76.70	76.58	7.46	7.72	3.57	3.53

[a] An equivalent amount of triethylamine was used with 1,2-dimethoxyethane as solvent in place of the excess triethylamine specified in the procedure. [b] n_D^{25} 1.5402; λ_{max}^{liq} 5.78 μ (>C=O). [c] —NC_4H_8 = 1-pyrrolidyl. [d] n_D^{26} 1.5642; hydrochloride salt, m.p. 135–136°. *Anal.* Calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75. Found: C, 67.51; H, 6.45; N, 3.78. [e] —NC_5H_{10} = 1-piperidyl. [f] —$N_2C_5H_{11}$ = 4-methyl-1-piperazinyl. [g] Yield of one diastereoisomer. An additional 50% yield of a mixture of the two optical isomers was obtained. [h] Triethylamine was used as solvent in place of the 1,2-dimethoxyethane specified in the procedure. [i] n_D^{25} 1.5564; λ_{max}^{liq} 5.79 μ (>C=O). [j] n_D^{25} 1.5553; λ_{max}^{liq} 5.79 μ (>C=O). [k] —NC_6H_{12} = 1-hexamethyleneimino. [l] n_D^{27} 1.5527. [m] 2-$C_6H_{12}N$ = 1-methyl-2-piperidyl. [n] n_D^{26} 1.5594; λ_{max}^{liq} 5.79 μ (>C=O); acid oxalate salt, m.p. 141–142° (from ethanol). *Anal.* Calcd. for $C_{25}H_{31}NO_7$: C, 65.92; H, 6.42; N, 3.08. Found: C, 65.85; H, 6.41; N, 3.17. [o] 3-$C_6H_{12}N$ = 1-methyl-3-piperidyl. [p] n_D^{25} 1.5593. λ_{max}^{liq} 5.79 μ (>C=O). [q] 4-$C_6H_{12}N$ = 1-methyl-4-piperidyl. [r] —3α-$C_8H_{14}N$ = 3α-tropanyl. [s] B.p. 222° (1 mm.); n_D^{25} 1.5742; λ_{max}^{liq} 5.80 μ (>C=O). [t] An equivalent amount of triethylamine was used with dimethylformamide as solvent in place of the excess triethylamine specified in the procedure. [u] n_D^{26} 1.5708; acid oxalate salt, m.p. 126–127° (from ethanol-ether). *Anal.* Calcd. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.17; N, 3.17. Found: C, 65.12; H, 6.32; N, 3.28. [v] Free base, b.p. 215–218° (1.1 mm.); n_D^{25} 1.5672. *Anal.* Calcd. for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.38; H, 7.60; N, 3.70. [w] An equivalent amount of triethylamine was used with benzene as solvent in place of the excess triethylamine specified in the procedure. [x] n_D^{25} 1.5506; λ_{max}^{liq} 5.81 μ (>C=O). [y] n_D^{25} 1.5572; λ_{max}^{liq} 5.80 μ (>C=O). [z] n_D^{25} 1.5560; λ_{max}^{liq} 5.80 μ (>C=O). [aa] n_D^{25} 1.5554. [bb] n_D^{26} 1.5632; λ_{max}^{liq} 5.89 μ (>C=O). [cc] n_D^{25} 1.5659; λ_{max}^{liq} 5.80 μ (>C=O). [dd] Procedure 1 led only to a predominent recovery of starting bromide. [ee] n_D^{25} 1.5638. [ff] *Anal.* Calcd.: Cl, 9.22; O, 14.52. Found: Cl, 9.22; O, 14.64. [gg] *Anal.* Calcd.: H_2O, 2.1. Found: 1.8. [hh] Also isolated was a lower melting diastereomer, m.p. 182–184°. *Anal.* Found: C, 70.28; H, 7.70; N, 3.35. [jj] n_D^{25} 1.5632.

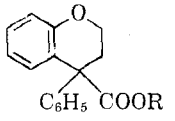
a course different from that of the corresponding alkoxide anion. Reaction of Ia did indeed lead to the thiol ester IIIa, but it was contaminated by an appreciable quantity (10–15%) of IVa, the product



IIIa. $n = 1$ IVa. $n = 1$
IIIb. $n = 2$ IVb. $n = 2$
IIIc. $n = 3$ IVc. $n = 3$

of direct halogen displacement. The homolog Ib, under the same conditions (procedure 2), gave a product consisting of approximately equal amounts of IIIb and IVb; and from Ic the direct displacement product IVc was the only detectable outcome. As a check on the infrared method of product analysis, pure samples of the thiol esters IIIa and IIIc, were prepared from the corresponding carboxylyl chlorides.

To help delineate certain details of the mechanism of the reaction of the bromides Ia and Ib with amino alcohols (procedure 1), several other reactions were performed. When the bromoethyl

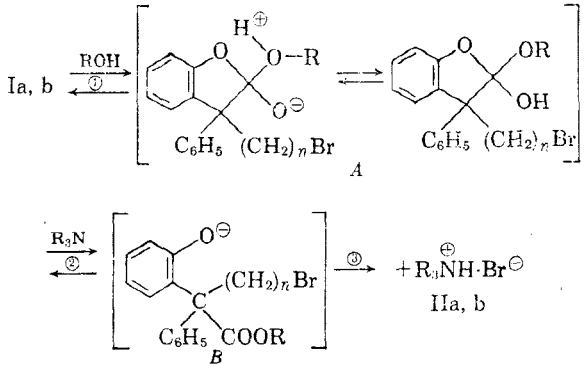


V. R = CH_3
VI. R = H
VII. R = $COCH_3$

derivative Ib was refluxed for twenty-four hours with sodium acetate in dry methanol, a nearly quantitative yield of the methyl ester V was secured. In neutral refluxing methanol, however, the bromide Ib was unaffected; under acid catalyzed conditions the reaction took a completely different course.[4] When the mixed anhydride VII (prepared by the action of ketene on the acid VI) was refluxed with dry methanol in the presence of sodium acetate, 85% of the acid VI was recovered. Therefore, the possible intermediacy of VII in the acetate-catalyzed methanolysis of Ib to V must be ruled out.

DISCUSSION

Mechanisms. The observed course of most of these reactions carried out in the presence of tertiary amines can be explained in terms of either one or both of two mechanisms involving basic catalysis.[5] The amine may serve to abstract a proton (step 2) from the tetrahedral intermediate *A* to give *B*[6] which cyclizes irreversibly to product; or the amine may first (or synchronously) remove a proton from the carbinol hydroxyl group to produce alkoxide ion which next (or concertedly) attacks the carbonyl carbon atom of I by the mechanism already outlined.[1] In both schemes, the pre-equilibria leading to the common penultimate stage *B* favor reactants I—in one case, because the attacking reagent (ROH) is a poor nucleophile, and, in the



other because the reagent ($RO^{\ominus}$), although strongly nucleophilic toward carbonyl carbon, is necessarily present in low concentration.[8]

Either route serves to explain why Ia and Ib react with alcohols in the presence of tertiary amines (procedure 1) to give the corresponding esters (II. n = 1,2) while Ic does not. According to previous evidence,[1] step 3 leading from B to products is fast when n = 1 or 2 (Ia,b) and slow when n = 3 (Ic). Thus, when n = 3, the limiting step 3 combines with the low steady-state concentration of *B* to produce an over-all rate so small that competing reactions—(*i.e.*, amine quaternizations)—can predominate. In contrast, the particular geometry of Ia and Ib which favors ring closure and a rapid step 3, combined with a decreased tendency for direct halogen displacement (especially in Ia), accounts for their conversion in good yield to the corresponding esters (II. n = 1,2), even though the kinetic characteristics of their equilibrium steps should not differ greatly from those of Ic.

However, the reason for the inability of even Ia and Ib to react with 4-hydroxyl-1-methylpiperidine according to procedure 1 is less than obvious. If the reasonable assumption is made that the hydroxyl group of this aminoalkanol is no less ionized than is that of any other under the same

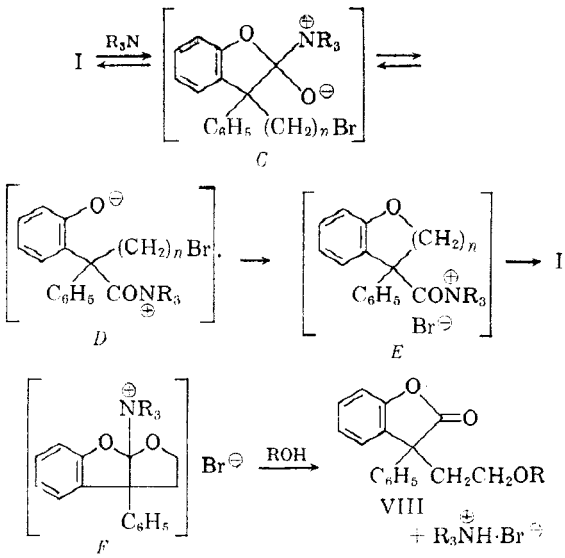
(4) This will be the subject of another paper.
(5) M. L. Bender, *Chem. Revs.*, 60, 53 (1960).
(6) Because the leaving group involved in the collapse of the tetrahedral intermediate *A* is a relatively stable phenoxide ion, the possible requirement[7] of general acid catalyzed assistance for this process has been disregarded. Compare, W. P. Jencks and J. Carriulo, *J. Am. Chem. Soc.*, 82, 675 (1960).
(7) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 82, 665 (1960).
(8) The fraction of an alcohol of acidity equal to ethanol (pK_a ~18) existing as alkoxide ion in the presence of an equivalent of a tertiary amine (pK_a ~10) would be roughly of the order of 10^{-4}.

conditions, then, in view of the normal reactivity shown by its sodium derivative (procedure 2), one must conclude that in the amine-catalyzed reactions the unionized carbinol is the principal nucleophile, and the lack of reactivity stems from some steric factor possibly related to conformational interactions of the hydroxyl group in the piperidine ring.

The failure of Ia and Ib to undergo amine-catalyzed reaction with β-diethylaminoethyl mercaptan is no less puzzling. The extent of ionization of the mercaptan should be greater than that of any of its oxygen analogs. Yet, if kinetically significant concentrations of mercaptide anion were present, one should observe at least some products from Ia and Ib corresponding to those obtained with sodium mercaptide (procedure 2). In their absence one can only conclude that a kinetically significant concentration of mercaptide anion is not present, and, further, that RSH is so much less nucleophilic than is ROH toward the carbonyl carbon atom that a significant concentration of the intermediate A (ROH = RSH) does not form when Ia or Ib is treated with the mercaptan.[9] However, in the absence of more positive evidence derivable from quantitative kinetic data, these conclusions must be regarded as tentative.

Basic vs. nucleophilic catalysis. That the conversion of Ib to V does not take place in neutral methanol, but does in the presence of sodium acetate, clearly shows that the reaction must be base catalyzed in order to proceed at a practical rate. That sodium acetate functions in this reaction as a base and not as a nucleophilic catalyst is also clearly demonstrated by the proof that the mixed anhydride VII, a necessary stage in the nucleophilic mechanism, cannot be an intermediate in the reaction leading to V. But in general, amines are known[10] to be better nucleophiles toward the carbonyl carbon atom than is acetate ion. Hence, it does not necessarily follow that tertiary amines, like acetate ion, must function as bases rather than as nucleophilic catalysts. Nevertheless, several reasons argue strongly against the likelihood that tertiary amines act as nucleophiles in these reactions.

If the unlikely possibility of ready formation of the zwitterionic intermediate *D* is granted, one is faced with the problem of explaining why Ia and Ib do not react with either 4-hydroxy-1-methylpiperidine or β-diethylaminoethylmercaptan in the presence of triethylamine, when the acid chloride of 3 - phenyl - 2,3 - dihydro - 3 - benzofurancarboxylic acid does (procedure 3b). Surely, the acyl-



ammonium intermediate *E* should be at least as reactive as the corresponding acid chloride in triethylamine.[5]

Furthermore, judging from the observed cause of the reaction of Ib ($n = 2$) with primary and secondary amines,[11] at least some of the tetrahedral intermediate *C* should form the salt *F*, which by analogy[11] would react with alcohols to give the alkoxyethylbenzofuranone VIII. In neither of the two basic esters of 4-phenylchromancarboxylic acid, which were prepared by procedure 1 and isolated as liquid bases (Table IB, footnotes bb and cc), could any of the isomeric substance corresponding to VIII (λ_{max} > C=O, 5.55 μ) be detected by spectral means.

Relative nucleophilicity of alkoxide and mercaptide anions. Sodium alkoxides react with the three bromides I (n = 1,2,3) to give the corresponding esters of type II as the only isolable products. In contrast, the sodium derivative of β-diethylaminoethyl mercaptan reacts with the same bromides to give increasing amounts of direct displacement product IV (at the expense of thiol ester III) as the side chain lengthens.[12] This provides a plain demonstration that, compared to mercaptide anion, alkoxide ion is relatively more nucleophilic to carbonyl carbon than to saturated carbon. Clearly, part if not most, of this difference stems from the much more nucleophilicity toward saturated carbon of alkoxide as compared to mercaptide ion.[13] How much, if any, is due to relative reactivity toward carbonyl carbon remains problematical.[10]

(9) In support of this view, J. P. Danehy and C. J. Noel [*J. Am. Chem. Soc.*, **82**, 2511 (1960)] found that in the reaction of nonaromatic mercaptans with ethylene oxide, the mercaptide anion is the only kinetically significant nucleophilic species.

(10) W. P. Jencks and J. Carriulo, *J. Am. Chem. Soc.*, 82, 1778 (1960).

(11) Unpublished work in these laboratories.

(12) It may seem surprising that Ia, possessing a neopentyl-type halogen gives any direct displacement product IVa at all. However, F. G. Bordwell, B. M. Pitt, and M. Knell [*J. Am. Chem. Soc.*, **73**, 5004 (1951)] found that neopentyl tosylate reacts with mercaptide anion to give unrearranged displacement product in good yield.

(13) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 581 (1956).

EXPERIMENTAL[14]

β-Diethylaminoethyl 3-phenyl-2,3-dihydro-3-benzofurancarboxylate (IIa) *from the bromide* Ia. *Procedure 1.* A mixture of 12.1 g. (0.04 mole) of Ia[1], 4.7 g. (0.04 mole) of β-diethylaminoethanol, and 25 ml. of triethylamine was heated on the steam bath for 18 hr. The cooled reaction mixture was filtered to remove triethylamine hydrobromide and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in ether, washed to neutrality with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by evaporation gave 11.2 g. (84%) of crude ester IIa which was redissolved in dry ether and treated with a slight excess of ethereal hydrogen chloride. The precipitated salt (9.6 g., 64%,) m.p. 118–120°, was recrystallized three times to give 6.7 g. (45%) of pure IIa hydrochloride, m.p. 125–127° (from 2-butanone–ether). (See Table IA for elemental analyses.) When other basic esters unlike IIa, would not form crystalline hydrochlorides, they were isolated either by vacuum distillation or by crystallization as the free base.

β-Diethylaminoethyl 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepincarboxylate (IIc) *from the bromide* Ic. *Procedure 2.* To 3.0 g. (0.026 mole) of β-diethylaminoethanol in 15 ml. of 1,2-dimethoxyethane was added in portions 1.25 g. (0.026 mole) of a 50% mineral oil suspension of sodium hydride. After gas evolution ceased (warming if necessary to complete the reaction), the mixture was cooled to room temperature and 8.3 g. (0.025 mole) of the bromide Ic[1] was added in portions with thorough mixing. After standing at room temperature overnight, the semisolid reaction mixture was treated with 100 ml. of cold water and worked up as in procedure 1. There was obtained 7.2 g. (71%) of IIc hydrochloride, m.p. 193–194° (Table IC).

An attempt to prepare IIc by procedure 1 gave no water-insoluble basic material and 40% of the starting material was recovered. Similarly, using procedure 1 to try to make the analogous β-diisopropylaminoethyl ester gave none of the desired product and only a 20% recovery of a water-insoluble neutral oil which was not identified.

Likewise, when either Ia or Ib and the secondary carbinol, 4-hydroxy-1-methylpiperidine, were submitted to the conditions of procedure 1, mainly starting material was recovered (74% of Ia and 82% of Ib) along with small amounts of crude hygroscopic product which could not be purified, but which behaved much like quaternary ammonium salts. In contrast, procedure 2 gave 48% yields of the desired 1-methyl-4-piperidyl esters (Table IA and IB). Nevertheless, procedure 1 served satisfactorily in the reaction of the secondary alcohol, 1-pyrrolidino-2-propanol, with the bromomethyl derivative, Ia (Table IA). Hence, the failure of 4-hydroxy-1-methylpiperidine to react under the conditions of procedure 1 cannot be due to the fact that it is a secondary carbinol.

Preparation of basic esters II *from the corresponding carboxylic acids. Procedure 3. Preparation of ester* IIa. A solution of 4.1 g. (0.017 mole) of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid[1] and 3.6 g. (0.03 mole) of thionyl chloride in 25 ml. of dry benzene was refluxed for 2 hr. The excess of thionyl chloride and benzene was removed by distillation under reduced pressure, the residual oil was taken up in 25 ml. of dry 1,2-dimethoxyethane and was added in a steady stream from a dropping funnel to a stirred solution of 2.6 g. (0.022 mole) of β-diethylaminoethanol and 3.0 g. (0.03 mole) of triethylamine in 75 ml. of dry 1,2-dimethoxyethane. The temperature rose spontaneously to 33° and an insoluble salt began forming immediately. After the exothermic reaction stopped, the mixture was stirred and warmed at 50–55° for 3 hr. and then was stirred overnight at room temperature. Insoluble salt (2.1 g., 91% yield based on triethylamine hydrochloride) was removed by filtration and the filtrate was concentrated to dryness under reduced pressure using a rotating evaporator. The residue was treated with 100 ml. of cold water and worked up as described in procedure 1. There was obtained 3.0 g. (47%) of IIa hydrochloride, m.p. 125–127°, which did not depress the melting point of a sample prepared by procedure 1.

In the same manner, a 35% yield of β-diethylaminoethyl 4-phenyl-4-chromancarboxylate (IIb), m.p. 157–158°, was obtained, which proved, by mixed melting point, to be identical with the ester IIb prepared by procedure 1. When benzene was substituted for the 1,2-dimethoxyethane as solvent in this reaction (see procedure 3a below), none of the ester IIb could be isolated, and 95% of the β-diethylaminoethanol was recovered unchanged.

Procedure 3a. *Preparation of ester* IIc. A solution of 9.2 g. (0.032 mole) of 4-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylyl chloride,[1] 3.74 g. (0.032 mole) of β-diethylaminoethanol, and 3.3 g. (0.0325 mole) of triethylamine in 150 ml. of dry benzene was refluxed for 16 hr. The reaction was worked up in the usual way (procedure 1) to give 8.5 g. (66%) of IIc, m.p. 194–195°, identified by mixed melting point with the IIc prepared by procedure 2.

Procedure 3b. *Preparation of 1-methyl-4-piperidyl 3-phenyl-2,3-dihydro-3-benzofurancarboxylate.* The acid chloride, prepared from 9.6 g. (0.04 mole) of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid according to the method outlined in procedure 3, was dissolved in 30 ml. of cold triethylamine. To this ice-cold solution was added in one portion, with stirring, 4.6 g. (0.04 mole) of 4-hydroxy-1-methylpiperidine. The mixture was stirred for 3 hr. at room temperature and then allowed to stand overnight. After heating for 1 hr. on the steam bath, the cooled reaction mixture was treated with 50 ml. of cold water and worked up in the usual way. From the basic fraction was obtained 8.7 g. (64%) of the title compound, m.p. 103–104°, $\lambda_{max}^{CHCl_3}$ 5.80 μ. A mixture with a sample of the same ester, m.p. 90–91° (Table IA), prepared by procedure 2, melted at 103–104°. The infrared spectra of the two samples (7% in chloroform) were superimposable. Hence, they represent dimorphic forms of the same material.

All of the basic esters prepared by the above methods are listed in Table I, which is divided into three parts according to the size of the oxygen heterocycle involved. The amino alcohols used were obtained from commercial sources. As those possessing asymmetric centers were *dl*-mixtures, preparation from them of esters II of the three *dl*-carboxylic acids must necessarily have involved in each case the formation of two diastereomeric esters. Esters isolated by distillation of the free base undoubtedly comprise mixtures of the two respective *dl*-compounds. Those isolated as salts were recrystallized to constant melting point and hence probably consist essentially of one *dl*-compound. Yields reported in Table I refer to yields of analytically pure material of melting point or boiling point indicated in the fourth column.

β-Diethylaminoethyl 3-phenyl-2,3-dihydro-3-benzofurancarbothiolate (IIIa). *By procedure* 3b. The acid chloride prepared from 9.6 g. (0.04 mole) of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid in the usual way was treated with 6.6 g. (0.042 mole) of β-diethylaminoethanethiol according to the method of procedure 3b. There was obtained 10.2 g. (72%) of the thiol ester IIIa as a thick light yellow oil, b.p. 188–189° (1.0 mm.), n_D^{25} 1.5758, $\lambda_{max}^{CHCl_3}$ 5.97 μ.

Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 71.13; H, 7.07; N, 4.12.

Impure thiol ester IIIa *by procedure* 2. Using β-diethylaminoethanethiol in place of the β-diethylaminoethanol, and the bromide Ia in place of Ic in procedure 2, and heating on the steam bath for 18 hr., led to a 50% yield of product, b.p. 208–211° (1.5 mm.), n_D^{25} 1.5657 $\lambda_{max}^{CHCl_3}$ 5.97 μ (s), 5.55 μ (w).

Anal. Calcd. for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94 Found: C, 70.62; H, 7.15; N, 4.10.

The relative intensities of the two carbonyl absorptions indicated that this product was mainly IIIa contaminated by approximately 10–15% of IVa. Essentially the same mixture was obtained when the reaction was carried out at room temperature for 70 hr. An attempt to prepare IIIa by proce-

(14) Melting points and boiling points are uncorrected.

dure 1 failed. The bulk (85%) of the starting bromide Ia was recovered.

Mixture of IIIb *and* IVb. Substituting β-diethylaminoethanethiol and the bromide Ib in procedure 2 gave a 52% yield of a viscous liquid base, b.p. 221–223° (1.6 mm.), n_D^{25} 1.5756 $\lambda_{max}^{CHCl_3}$ 5.98 μ (m), 5.56 μ (m).

Anal. Calcd. for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.37; N, 3.79. Found: C, 71.32; H, 7.50; N, 3.86.

The relative intensities of the two carbonyl absorptions indicated that this product was a mixture of approximately equal quantities of IIIb and IVb. Attempts to prepare IIIb by procedure 1 gave 40–50% yields of triethylamine hydrobromide, but the basic fraction consisted mainly of unchanged aminomercaptan. Not a trace of thiol ester was formed (no absorption at 5.95–6.0 μ).

β-Diethylaminoethyl 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carbothiolate IIIc. Substituting β-diethylaminoethanethiol for the β-diethylaminoethanol in procedure 3a gave a 75% yield of IIIc, isolated as the hydrochloride salt, m.p. 165–166°, $\lambda_{max}^{CHCl_3}$ 5.94 μ.

Anal. Calcd. for $C_{23}H_{30}ClNO_2S$: C, 65.77; H, 7.20; N, 3.33. Found: C, 65.85; H, 7.09; N, 3.33.

3-(β-Diethylaminoethylmercaptopropyl)-3-phenyl-2-benzofuranone IVc. The reaction of 6.6 g. (0.02 mole) of Ic, 3.3 g. (0.025 mole) of β-diethylaminoethanethiol, and 1.2 g. (0.025 mole) of a 50% mineral oil dispersion of sodium hydride was carried out in 30 ml. of 1,2-dimethoxyethane according to procedure 2. The crude basic product (5.9 g.) obtained as a thick green oil showed in its infrared spectrum only a single carbonyl peak at 5.55 μ indicating that IVc was the sole product containing no detectable amounts of thiolester IIIc. Treatment with ethereal hydrogen chloride gave 5.7 g. of IVc hydrochloride, m.p. 110–112°. Several recrystallizations from dry ethanol-ether raised the m.p. to 117–118°.

Anal. Calcd. for $C_{23}H_{30}ClNO_2S$: C, 65.77; H, 7.20; N, 3.33. Found: C, 65.55; H, 7.59; N, 3.39.

Treatment of 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (Ib) *with sodium acetate in methanol.* A solution of 5.0 g. (0.0158 mole) of Ib and 1.3 g. (0.0158 mole) of freshly fused sodium acetate in 50 ml. of dry methanol was refluxed for 24 hr. The methanol was removed under reduced pressure using a rotating evaporator, and 50 ml. of water was added to the semisolid residue. Insoluble oil was taken up in ether, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave 4.2 g. (100%) of pale yellow oil having an infrared spectrum qualitatively identical to that of methyl 4-phenyl-4-chromancarboxylate (V).[1] When Ib was refluxed in neutral methanol, no reaction occurred. When mineral acid was present, the methanolysis took an entirely different course.[4]

Methanolysis of the mixed anhydride VII. A solution of 4.0 g. of 4-phenyl-4-chromancarboxylic acid (VI)[1] in 60 ml. of dry benzene was gassed for 0.5 hr. with ketene (excess).[15] After standing for 1 hr. at room temperature, the benzene and excess ketene were removed under reduced pressure using a rotating evaporator. The infrared spectrum of the residual light yellow oil indicated (λ_{max}^{liq} 5.52 μ, 5.75 μ) complete conversion to the mixed anhydride VII. There was no evidence for the presence of any starting material VI ($\lambda_{max}^{CHCl_3}$ 5.85 μ and 7.35 μ both absent). This oil was taken up in 50 ml. of dry methanol, 1.3 g. of fused sodium acetate was added and the mixture was refluxed for 24 hr. Removal of the methanol in the usual way followed by appropriate work-up gave 0.3 g. of a neutral oil (not further investigated) and 3.4 g. (85%) of starting acid VI, m.p. 150–151°, identified by mixed melting point.

Acknowledgment. Portions of the experimental work were carried out by N. F. Ryan. E. F. Shelberg was responsible for the microanalyses and W. H. Washburn for the infrared spectra.

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(15) W. E. Hanford and J. C. Sauer, *Org. Reactions*, 132 (1946).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, NORTHWESTERN UNIVERSITY]

A New Type of Assistance at a Distance

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Received May 26, 1961

Mercuric chloride in refluxing chloroform replaces one of the two iodine atoms of *meso-* or of racemic-1,4-diiodo-2,3-butanediol, (I) or (III), rapidly to yield the corresponding 1-chloro-4-iodo-2,3-butanediols (II or IX), but the second iodine atom is relatively inert even to an excess of mercuric chloride. A cyclic intermediate (XIII) is proposed to explain the activating influence of one iodine atom on another at a distance of four carbon atoms. Similar enhanced activity of the first iodine over the second is shown by 1,4-diiodo-2,3-diethoxybutane (VII) and *cis*-2,3-bis(iodomethyl)-*p*-dioxane (VIII) in contrast to *trans*-2,3-bis(iodomethyl)-*p*-dioxane (XI) and *cis*-2,6-bis(iodomethyl)-*p*-dioxane (XII) in which both iodine atoms are unreactive. Preliminary experiments indicate that 1,4-diiodobutane reacts to form the chloroiodo derivative more rapidly than does 1,5-diiodopentane, and much more rapidly than does 1,3-diiodopropane. Butyl iodide is also relatively inert. The supposed diiodobutanediol in the literature has been shown to be *erythro* II.

There are a large number of displacement reactions in which a properly placed nucleophile within the molecule aids in the removal of the leaving group, a phenomenon known as neighboring group participation. Halogens are among the nucleophiles commonly listed as neighboring group participants, and of the halogens, iodine is particularly effective. Whereas many of these neighboring groups are at varying distances from the reaction site, the examples employing halogen that we have found in the literature are those in which the halogen atom is on the carbon adjacent to that of the leaving group. In the present work are several examples in which an iodine atom assists in the replacement of a second iodine atom four carbons removed.

(1) This research was supported by N.S.F. Grant 7335.