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

Neighboring Group Reactions. I. Nucleophilic Attack by Alkoxide and Hydroxide Ion on 3-(ω-Haloalkyl)-3-phenyl-2-benzofuranones. A New Synthesis of 1-Benzoxacycloalkanes

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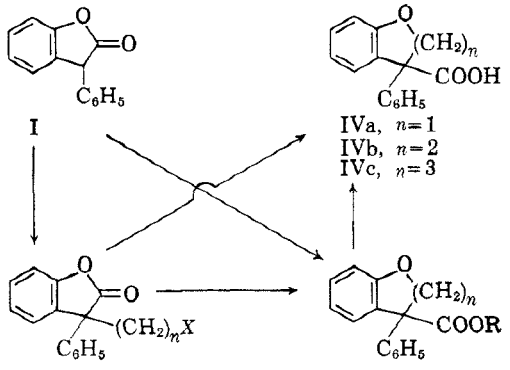
Received May 18, 1961

The reactions of a series of ω-haloalkylbenzofuranones (IIa–f) with sodium hydroxide and alkoxide are described. With alkoxide, all but the last member (IIf) of this series react through a rearrangement process leading to the esters III in high yield. With hydroxide ion the lowest homolog, IIa, gives the corresponding carboxylic acid, IVa, in high yield, but as the chain is lengthened (n = 2,3), yields of IV decrease and formation of by-product (X and IX, respectively) increases. Mechanistic implications of these results are discussed.

Preparation of the necessary halides II is described in some detail. Structural assignments to the previously unreported compounds III and IV are documented both chemically and by means of infrared and proton magnetic resonance spectra. The resistance to ring cleavage by hot hydrobromic acid is shown to decrease with increasing ring size in the series of acids IVa–c.

When a 3-halomethyl, -ethyl, or -propyl substituted 3-phenyl-2-benzofuranone II (n=1,2 or 3) was treated with sodium methoxide or ethoxide in the appropriate alcohol, intramolecular displacement of the halogen occurred exclusively. The only product isolated resulted from initial attack of alkoxide ion on the carbonyl carbon atom. The phenoxide ion which then formed by cleavage of the lactone ring became the nucleophile and displaced the halogen intramolecularly to give the observed product III (n=1,2 or 3).

With n=1 or 2, the over-all reaction rate was



IIa. n = 1, X = Br
IIb. n = 2, X = Cl
IIc. n = 2, X = Br
IId. n = 3, X = Cl
IIe. n = 3, X = Br
IIf. n = 4, X = Br

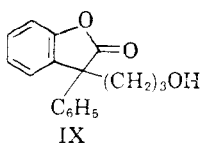
IIIa. n = 1, R = CH_3
IIIb. n = 1, R = C_2H_5
IIIc. n = 2, R = CH_3
IIId. n = 2, R = C_2H_5
IIIe. n = 3, R = CH_3
IIIf. n = 3, R = C_2H_5

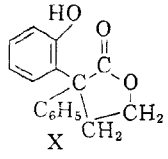
extremely fast. The bulk (85–90%) of the reaction could be carried out under conditions ordinarily employed for the titration of a strong acid with a strong base; and 85–95% yields of the ester III (n=1 or 2) could invariably be isolated. Furthermore, any difference in rate between the chloride IIb and corresponding bromide IIc was not qualitatively apparent, as both were exceedingly fast.

With n=3, reaction was noticeably slower, but, given time (24–48 hr.), the bromide IIe could be converted to the ester IIIe in 97% yield even at room temperature. However, the corresponding chloride IId reacted more sluggishly and much less unidirectionally, deficiencies which were not appreciably overcome by recourse to elevated temperatures.

With n=4, the situation changed. Eighty percent of unchanged bromide IIf was recovered after seven days in contact with sodium methoxide at room temperature; and none of the eight-membered ring ester of type III was formed even at reflux temperature.

The behavior of the bromides II toward hydroxide ion was somewhat analogous although the reactions were much slower. The bromomethyl compound IIa formed the carboxylic acid IVa (as sodium salt) in 96% yield when treated with a slight excess (2+ moles) of a 5% aqueous sodium hydroxide solution at 100°. Similarly, the next homolog IIc gave the acid IVb in 71% yield together with a 6.5% yield of the lactone X[1] resulting from replacement of the bromine atom by a hydroxyl group. With n=3, the product of this replacement reaction predominated; treatment of IIe with


IX

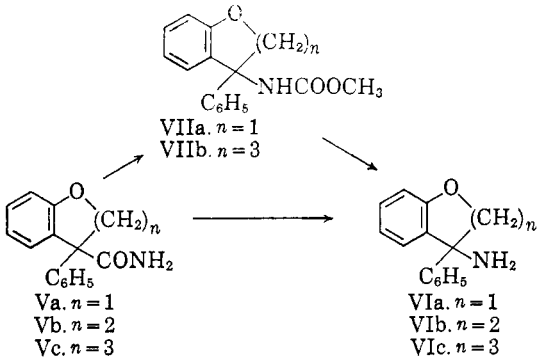

X

aqueous sodium hydroxide for two weeks at room temperature gave only a 35% yield of the acid IVc and a 57% yield of IX[1].

In addition to the microanalytical, infrared, the NMR spectral evidence (see Experimental) to support the assignment of structure to the previously unreported esters III, chemical evidence was secured. The acid IVa was converted through

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

the amide Va to the amine VIa. Dry distillation of the hydrochloride of VIa eliminated ammonium chloride to give 3-phenylbenzofuran (VIII) identical with an authentic[2] specimen. The homologous



acids IVb and c were likewise carried through to the amine stage VI, but as reference compounds corresponding to VIII were not readily available, elimination of ammonium chloride was not attempted.[3]

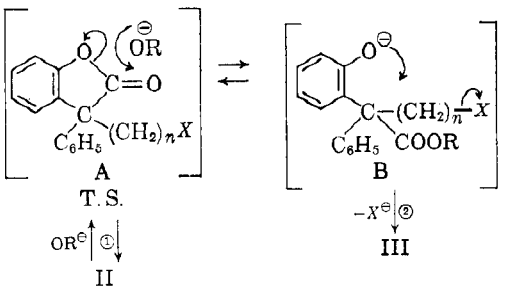
Additional structural evidence was derived from the behavior of the three carboxylic acids IV toward refluxing hydrobromic acid in acetic acid. Treatment of the five-membered ring acid IVa for forty hours under these conditions produced no detectable cleavage of the heterocyclic ring (85% recovery of acid). Under the same conditions the six-membered ring analog IVb gave only a 60% recovery of starting material and a minimal 8% yield of IIc, the product of ring cleavage. (A number of workers[4] have shown that α-mono- and disubstituted o-hydroxyphenylacetic acids cyclize spontaneously to 2-benzofuranones in acid solution.) The seven-membered homolog IVc, however, cleaved quite readily to give a 92% yield of IIe. In addition to furnishing structural evidence for IVb and IVc, these results provide a clear demonstration of the relative stabilities towards acid cleavage of these three heterocyclic systems.

The halides II used in this work were all prepared by alkylation of the sodium derivative of 3-phenyl-2-benzofuranone (I)[5] with the appropriate alkylene dihalides. The choice of solvent and dihalide was sometimes a critical factor in obtaining a good yield. This was especially true for the preparation of the haloethyl derivatives IIb and IIc, where the use of dimethylformamide as solvent led to the desired alkylation product which was unobtainable when benzene was the solvent used.[6] Best yields of the haloethyl and halopropyl derivatives were realized when the appropriate mixed chlorobromoalkanes were employed as the alkylating agents in dimethylformamide solvent. In both cases the products consisted predominantly of the bromoalkyl derivatives IIc and IIe mixed with smaller amounts of the corresponding chloroalkyl derivatives IIb and IId, respectively. However, these mixtures could be converted almost entirely to the pure bromoalkyl derivatives by further heating with sodium bromide in dimethylformamide. With the probable exception of dibromomethane, alkylation with these dihalides undoubtedly led to some bisalkylation. However, only from the reaction with 1,4-dibromobutane in dimethylformamide (preparation of IIf) was any product actually isolated which involved displacement of both bromine atoms.

Obviously, alcohols could not be used as solvents for the preparation of the halomethyl and haloethyl derivatives. As expected, alkylation in alcohol of the sodium derivative of I with dibromomethane or with 1,2-dihaloethane, in one step, gave the corresponding esters III ($n=1$ or 2), but in uniformly poor over-all yield (30–40%).

DISCUSSION

It seems clear that the general mechanism of these halide reactions can be represented by the following sequence:



The extraordinarily rapid reaction with alkoxide of even the neopentyl-type halogen atom present, IIa ($n=1$), is consistent with the intramolecular nature of the displacement.[7] However, this very rapidity when n = 1 or 2 renders difficult the designation of the slow step in this scheme for these two

(2) W. Davies and S. Middleton, *J. Chem. Soc.*, 822 (1958).

(3) It is interesting to note that, although Va and Vb readily underwent the Hoffmann rearrangement with aqueous hypobromite to give the amines VIa and VIb directly, the hydrobenzoxepin analog Vc did not. Employment of a methanolic solution and the consequent intermediacy of the carbamate VIIb were necessary for the successful preparation of VIc.

(4) (a) T. Kariyone and S. Imai, *J. Pharm. Soc. Japan*, **55**, 679 (1935); (b) J. A. Barltrop, *J. Chem. Soc.*, 958 (1946); (c) E. C. Horning and R. U. Schock, *J. Am. Chem. Soc.*, **70**, 2941 (1948).

(5) A. Bistrzycki *et al.*, *Ber.*, **28**, 989 (1895); *Ber.*, **31**, 2812 (1898).

(6) Compare H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961).

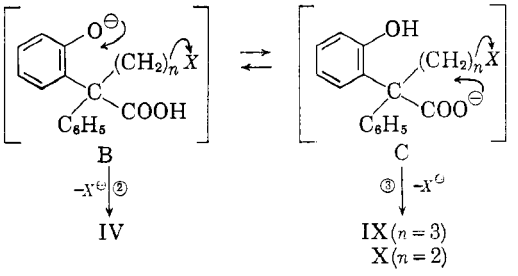
(7) The facile reactivity of neopentyl-(or neophyl-)type halides toward *intramolecular* displacement has been noted in several instances.[8,9]

(8) G. S. Hammond in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., Wiley, New York, 1956, p. 464.

(9) (a) J. L. Greene, Jr., and H. J. Hagemeyer, Jr., *J. Am. Chem. Soc.*, **77**, 3016 (1955); (b) H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 2998 (1950).

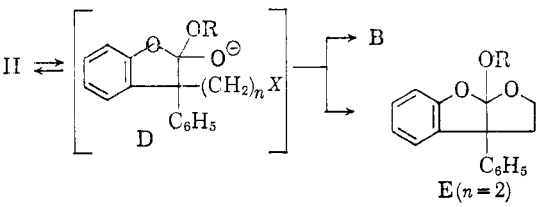
cases, especially as the chloride IIb is noticeably less reactive than the corresponding bromide IIc. However, the distinctly lower reactivity of the chloride IId ($n = 3$) compared to the corresponding bromide IIe, coupled with the observed lower over-all rate of reaction of IIe compared to IIc, clearly indicates that when $n = 3$, the slow step is indeed the one involving halide displacement (step 2). This trend extends to the higher homolog IIf ($n = 4$) where the over-all rate becomes vanishingly small. As there is no reason to assume any marked decrease in the rate of alkoxide ion attack (step 1) merely as a consequence of the lengthened side-chain, it seems clear that IIf fails to react because even minimal steric requirements of step 2 are no longer satisfied.

With hydroxide ion as the attacking nucleophile the above scheme ($OR^- = OH^-$) becomes complicated by a fast proton-transfer equilibrium leading to the possibility of intramolecular halide displacement by carboxylate ion:



Although the relative pK's of the two acidic groups favor higher equilibrium concentrations of C at the expense of B, formation of IV still can be competitive, as phenoxide ion is a much better nucleophile toward displacement at saturated carbon than is carboxylate ion.[10] Consequently reaction 2 can be much faster than reaction 3 provided that steric factors are favorable. This is the situation when $n = 1$; intramolecular displacement by carboxylate ion requires intermediate β-lactone formation. Consequently, reaction 2 is much faster than reaction 3 and IVa is the exclusive product (96% yield) despite the unfavorable equilibrium between B and C. With $n = 2$, reaction 2 still preponderates (71% of IVb and 6.5% of X). But when the side-chain is lengthened still further ($n = 3$), the steric disadvantage associated with the formation of a seven-membered ring tips the balance in favor of reaction 3, and IX becomes the main product (57% *vs.* 35% of IVc).[11]

The process leading to the intermediate B is pictured as a concerted one involving the transition state A. Although firm evidence[13] has proved the existence of tetrahedral intermediates in many nucleophilic reactions of carboxylic acid derivatives, their stabilities appear to be highly[12-14] variable. In the present case, expulsion of the phenoxide ion is represented as occurring in concert with the approach of alkoxide ion.[15] Alternatively, the *ortho* ester anion D may intervene between II and B; but if it does, when $n = 2$, expulsion of phenoxide



ion to give B must be even faster than intramolecular displacement of halide ion to give the ortho-ester E. Compound E should be stable and isolable under the reaction conditions, but numerous attempts to demonstrate its presence have failed.[16]

EXPERIMENTAL[17]

3-Bromomethyl-3-phenyl-2-benzofuranone (IIa). To a stirred suspension of 14.4 g. (0.3 mole) of sodium hydride (50% dispersion in mineral oil) in 50 ml. of dry 1,2-dimethoxyethane (monoglyme) was added dropwise over a period of 1 hr., a solution of 63 g. (0.3 mole) of 3-phenyl-2-benzofuranone (I)[6] in 175 ml. of 1,2-dimethoxyethane. The temperature rose spontaneously to 65° during the addition. After stirring the mixture at room temperature for 2 hr., 52.2 g. (0.3 mole) of dibromomethane was added in one portion. The solution was then stirred and refluxed for 21 hr. after which it had become neutral (after 6 hr. of reflux it was still strongly alkaline). Removal of the precipitate from the cooled reaction mixture by filtration gave 34 g. of sodium bromide (theoretical yield for displacement of one bromine atom-31 g.). The filtrate was concentrated to dryness under reduced pressure using a rotating evaporator. The crude red-orange crystalline product, m.p. 119–123° (100% yield), was recrystallized from 600 ml. of 95% ethanol to give 72 g. (79%) of colorless IIa, m.p. 128–129°. Another recrystallization for analysis raised the m.p. to 129–130°, $\lambda_{max}^{CHCl_3}$ 5.55 μ (>C=O).

Anal. Calcd. for $C_{15}H_{11}BrO_2$: C, 59.42; H, 3.66; Br, 26.36; O, 10.56. Found: C, 59.52; H, 3.86; Br, 26.18; O, 10.69.

(10) J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954).

(11) The structures of IX and X and the intramolecular translactonization reactions relating them to each other are considered in an accompanying Note.[1] The possibility remains that X and, especially, IX could arise, at least in part, from direct S_N2 displacement by hydroxide ion of the bromine atoms of IIc and IIe, respectively. However, Swain and Scott[12] have shown that hydroxide ion is relatively more reactive toward the carbonyl carbon atom and less reactive toward alkyl carbon than are many uncharged nucleophiles. This, coupled with the relative immunity to methoxide ion attack observed for the higher homolog IIf ($n = 4$), suggests that the side reactions leading to IX and X are *intramolecular* nucleophilic displacements.

(12) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

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

(14) E. Gaetjens and H. Morawetz, *J. Am. Chem. Soc.*, **82**, 5328 (1960).

(15) This is in line with what is known of the relative stability of alkoxide *vs.* phenoxide ion as a leaving group. Compare, U. K. Pandit and T. C. Bruice, *J. Am. Chem. Soc.*, **82**, 3386 (1960), and ref. 13, pp. 61-64.

(16) Unpublished work in these laboratories has revealed that with certain amine nucleophiles, related orthoacid derivatives of this type do indeed form readily in high yield, and possess remarkable stability.

(17) Melting points and boiling points are uncorrected.

When the preparation of IIa was carried out using dimethylformamide as solvent, the reaction was complete in 3 hr. at 90–100°. Yet, only a 30% yield of desired product was obtained.

3-(β-Chloroethyl)-3-phenyl-2-benzofuranone (IIb). The sodium derivative from 21.0 g. (0.1 mole) of 3-phenyl-2-benzofuranone was prepared as above using 0.11 mole of sodium hydride and 75 ml. of dry dimethylformamide instead of 1,2-dimethoxyethane as solvent. The temperature was kept below 45° during this operation. To the stirred solution of the sodium derivative was added in one portion at room temperature, 11.0 g. (0.11 mole) of 1,2-dichloroethane. After being stirred for 2 hr. at room temperature, the mixture was heated on the steam bath for 16 hr. Isolation in the above manner gave a crude oil (24 g.) which was distilled to give 13.3 g., b.p. 170–195° (0.7 mm.), n_D^{25} 1.595. After standing for several months, the crystalline material (4.4 g., m.p. 66–68°) which had formed slowly was separated by filtration and was washed with cold 95% ethanol. Recrystallization from 95% ethanol gave 3.3 g. of IIb, m.p. 72.4°, $\lambda_{max}^{CHCl_3}$ 5.55 μ (>C=O).

Anal. Calcd. for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.31; H, 5.06.

An attempt to carry out the preparation of IIb in a benzene-dimethyl formamide mixture (1:1) was unsuccessful.

3-(β-Bromoethyl)-3-phenyl-2-benzofuranone (IIc). Substitution of 20.8 g. (0.11 mole) of 1,2-dibromoethane for the 1,2-dichloroethane in the above procedure gave 9.9 g. of distilled oil, b.p. 182–197° (0.7 mm.), n_D^{25} 1.600 which solidified slowly, and from which 7.0 g. of solid, m.p. 65–68°, could be obtained by trituration with 95% ethanol. Repeated recrystallization from ethanol gave 1.2 g. of pure IIc, m.p. 75–76°, $\lambda_{max}^{CHCl_3}$ 5.56 μ (>C=O).

Anal. Calcd. for $C_{16}H_{13}BrO_2$: C, 60.58; H, 4.13. Found: C, 60.61; H, 4.23.

Preparation of a mixture of IIb *and* IIc. Substitution of 1-bromo-2-chloroethane for the 1,2-dichloroethane in the above procedure (IIb) and increasing the equivalent quantities of reagents by a factor of five, gave 91.2 g. of a distilled oil, b.p. 170–183° (0.7 mm.), n_D^{25} 1.5975, which eventually solidified almost completely, m.p. 60–70°. Halogen analysis showed that this material consisted of approximately 67% bromo derivative IIc and 33% chloro-derivative IIb. In addition to the better yield of alkylation product obtained using the 1-bromo-2-chloroethane in place of either the corresponding dichloride or dibromide, the greater reactivity of the mixed halide was evident from the fact that the reaction became neutral after only 2.5 hr. of heating on the steam bath. The importance of dimethylformamide as solvent in this reaction was strikingly demonstrated by the fact that an attempted alkylation in benzene led only to recovered starting material even after refluxing for 42 hr.[6]

Halogen exchange. Preparation of IIc *from* IIb. A mixture of 4 g. (0.0147 mole) of 3-(β-chloroethyl)-3-phenyl-2-benzofuranone (IIb), 2 g. (0.0195 mole) of powdered sodium bromide and 30 ml. of dimethylformamide was stirred and heated on the steam bath for 24 hr. Filtration of insoluble salt (0.8 g.), removal of solvent under reduced pressure, and recrystallization of the solid residue twice from 95% ethanol gave 3.2 g., m.p. 64–65°.

Anal. Calcd. for $C_{16}H_{13}BrO_2$: Br, 25.20. Found: Br, 21.79; Cl, 1.82. Hence, halogen exchange predominated but was not complete.

3-(γ-Chloropropyl)-3-phenyl-2-benzofuranone (IId) was prepared in 48% yield by alkylation of the sodium derivative with 1-bromo-3-chloropropane in refluxing benzene according to the method of Weston and Brownell.[18] Apparently the bromine atom is displaced exclusively, and little, if any, halogen exchange occurs under these conditions.

3-(γ-Bromopropyl)-3-phenyl-2-benzofuranone (IIe). A solution of the sodium derivative of 3-phenyl-2-benzofuranone (52.5 g., 0.25 mole) in 200 ml. of dimethylformamide prepared as described above (see preparation of IIa) was cooled in an ice bath and treated with 55 g. (0.27 mole) of 1,3-dibromopropane in one portion. The mixture was stirred at 0–5° for 40 hr. after which it had attained neutrality. Working up in the usual way gave 73 g. of a crude oil only half (42 g.) of which could be distilled, b.p. 170–205° (0.8 mm.). (The undistillable residue probably represents product resulting from displacement of both bromine atoms.) The distillate solidified to give, after trituration with hexane (petroleum ether, b.p. 60–68°), 38.6 g. (46.5%) of IIe, m.p. 92–93°. Recrystallization of a sample from ethanol raised the m.p. to 94–95°, $\lambda_{max}^{CHCl_3}$ 5.55 μ (>C=O).

Anal. Calcd. for $C_{17}H_{15}BrO_2$: C, 61.64; H, 4.56; Br, 24.15; O, 9.65. Found: C, 61.44; H, 4.48; Br, 23.92; O, 9.86.

When this reaction was conducted at room temperature (16 hr.) the undistillable fraction of the product increased and the yield of IIe was only 38%. When carried out in refluxing benzene (16 hr.) the yield decreased to 22%. In 1,2-dimethoxyethane the yield was unaffected by the reaction temperature. Refluxing for 26 hr. gave a 40% yield, and allowing the reaction to proceed at room temperature for 116 hr. produced 39% of IIe.

Preparation of a mixture of IId *and* IIe. Allowing 86.5 g. (0.55 mole) of 1-bromo-3-chloropropane to react with a solution of the sodium derivative, prepared from 105 g. (0.5 mole) of I in 400 ml. of dimethylformamide, at room temperature for 60 hr., gave, after removal of solvent, 113 g. of solid product, m.p. 80–81°. Several recrystallizations from ethanol did not raise the m.p. above 89–90°. Quantitative halogen analysis indicated that this product consisted of approximately 75% of the bromide IIe and 25% of the chloride IId.

Halogen exchange. Preparation of IIe *from* IId. Heating a mixture of 7.15 g. (0.025 mole) of IId, 3.1 g. (0.03 mole) of powdered sodium bromide and 50 ml. of dimethylformamide on the steam bath for 30 hr. gave, after isolation in the usual way, 6.8 g. (82%) of IIe, m.p. 92–93°, undepressed by mixing with a sample of authentic IIe.

3-(δ-Bromobutyl)-3-phenyl-2-benzofuranone (IIf). Reaction of 38.5 g. (0.175 mole) of 1,4-dibromobutane with the sodium derivative, prepared from 33 g. (0.157 mole) of I in 100 ml. of dimethylformamide, at room temperature for 16 hr. gave two products which were separated by fractional crystallization from ethanol. The less soluble compound (10.2 g.), m.p. 223–224° (from chloroform), had an analysis corresponding to the product resulting from displacement of both bromine atoms, *1,4-bis(3-phenyl-2-benzofuranon-3-yl)butane.*

Anal. Calcd. for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 80.45; H, 5.57.

The more soluble product (18.9 g.) proved to be the desired bromobutyl derivative IIf, m.p. 98–99°, $\lambda_{max}^{CHCl_3}$ 5.55 μ (>C=O).

Anal. Calcd. for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 63.07; H, 4.92.

Methyl 3-phenyl-2,3-dihydro-3-benzofurancarboxylate (IIIa). To a stirred suspension of 21.2 g. (0.07 mole) of 3-bromomethyl-3-phenyl-2-benzofuranone (IIa) in 100 ml. of dry methanol, containing three drops of a 1% solution of phenolphthalein in methanol, was added dropwise at room temperature over a period of 0.25 hr., a solution of sodium methoxide previously prepared by adding 1.6 g. (0.07 g.-atom) of sodium to 50 ml. of dry methanol. As evidenced by the absence of indicator color, the first 85–90% of the reaction occurred as rapidly as the addition of methoxide was performed. Purple color developed only during addition of the last 10–15% of base. Even after standing over a week-end, the reaction was still alkaline. It was then worked up by removing solvent under reduced pressurd using a rotating evaporator. The semisolid residue was treated with 50 ml. of water and the insoluble oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration, removal of the ether by evaporation, and distillation of the residue

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

gave 12.4 g. (70%) of methyl ester IIIa, b.p. 147° (1.2 mm.), n_D^{25} 1.5755, m.p. 48–49°, $\lambda_{max}^{CHCl_3}$ 5.79 μ (>C=O).

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; O, 18.88. Found: C, 75.49; H, 5.39; O, 18.92.

Replacing the sodium methoxide in the preceding procedure by an equivalent of sodium ethoxide in ethanol led to *ethyl 3-phenyl-2,3-dihydro-3-benzofurancarboxylate* (IIIb), b.p. 145–147° (0.6 mm.), n_D^{25} 1.5630, m.p. 73–75° (from ethanol), $\lambda_{max}^{CHCl_3}$ 5.79 μ (>C=O) in 87% yield (m.p. 69–72°).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.38; H, 6.27.

Methyl 4-phenyl-4-chromancarboxylate (IIIc). Treatment of 22.2 g. (0.07 mole) of the β-bromoethyl compound IIc with an equivalent of sodium methoxide in dry methanol, according to the above procedure for the preparation of IIIa, gave an 84% yield of IIIc, b.p. 160–163° (1.4 mm.), n_D^{26} 1.5833, λ_{max}^{liq} 5.77 μ (>C=O).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.33; H, 6.25.

Yields of IIIc ranging from 86% to 95% could be obtained by treatment of IIc with the following bases in refluxing methanol for 16 hr.: two equivalents of morpholine, slight excess of triethylamine, one equivalent of sodium bicarbonate, or one equivalent of anhydrous sodium acetate. Two equivalents of morpholine at room temperature for 11 days gave the same yield (95%) as did the higher temperature and shorter reaction time. All of these reaction times could probably be shortened considerably with little influence on yield.

Ethyl 4-phenyl-4-chromancarboxylate (IIId). Treatment of 3-(β-chloroethyl)-3-phenyl-2-benzofuranone (IIb) with an equivalent of sodium ethoxide in ethanol gave a 90% yield of IIId, b.p. 175–178° (2.5 mm.), n_D^{25} 1.5730 λ_{max}^{liq} 5.78 μ (>C=O).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.29; H, 6.49.

Reaction of sodium ethoxide with the chloro compound IIb appeared to occur just as fast as with the corresponding bromide IIc.

Methyl 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylate (IIIe). To a solution prepared from 25.5 g. (1.11 moles) of sodium and 3 l. of dry methanol was added 367 g. (1.11 moles) of solid 3-(γ-bromopropyl)-3-phenyl-2-benzofuranone (IIe). After stirring at room temperature for 0.5 hr., the solid was completely dissolved, and after another 0.5 hr., sodium bromide began to precipitate. The mixture was allowed to stir over a week-end at room temperature. The solvent was then removed by distillation under reduced pressure. Water was added to the solid residue and the mixture was stirred for 2 hr. at room temperature. The product was collected at the filter, washed well with water, and dried. There was obtained 305 g. (97%) of IIIe, m.p. 108–110°. One recrystallization of a sample from methanol raised the m.p. to 110–111°, $\lambda_{max}^{CHCl_3}$ 5.79 μ (>C=O).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.55; H, 6.47; O, 16.89.

Treatment, according to the above procedure, of either the γ-chloropropyl compound IId or a mixture of IId and IIe, gave the ester IIIe, but in poorer yield. In this case reaction of the chloro analog appears to be more sluggish than the bromide. Use of an elevated temperature had little effect on the yield of desired product.

Ethyl 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylate (IIIf). A solution of 14.3 g. (0.05 mole) of 3-(γ-chloropropyl)-2-benzofuranone (IId) in 200 ml. of ethanol containing sodium ethoxide, prepared from 1.2 g. (0.05 g.-atom) of sodium, was stirred and refluxed over a week end. At the end of this time the reaction mixture was still alkaline, but the solvent was removed under reduced pressure, and the residue was taken up in a mixture of water and ether, and separated. After drying over anhydrous magnesium sulfate, the ether was removed by distillation and the residue (10 g.) was distilled to give two fractions, b.p. 190–200 (1.5 mm.) (3.0 g.) and b.p. 200–201 (1.5 mm.) (5.3 g.). Neither glasslike fraction could be crystallized. Infrared spectra indicated that the first fraction consisted of about 50% of an ester-carbonyl containing compound (present in less than 5% quantity in the second fraction). This fraction (3.0 g.) was triturated with 10 ml. of a cold 10% solution of potassium hydroxide in 95% ethanol. The solid (0.7 g., m.p. 80–85°) which formed was collected at the filter, washed with cold ethanol and dried. Recrystallization from ethanol gave pure IIIf, m.p. 100–101°, $\lambda_{max}^{CHCl_3}$ 5.79 μ (>C=O).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; O, 16.20. Found: C, 76.79; H, 7.08; O, 16.22.

The other fraction (5.3 g.) consisted mainly of 3-(γ-hydroxypropyl)-3-phenyl-2-benzofuranone (IX),[1] formed by hydrolysis of the chloride at some stage of the process. A better yield of IIIf could undoubtedly be obtained using the bromide IIe instead of IId, with a lower reaction temperature. This was not tried.

3-(δ-Bromobutyl)-3-phenyl-2-benzofuranone (IIf) *with sodium methoxide.* A mixture of 10 g. (0.029 mole) of powdered IIf in 100 ml. of methanol containing sodium methoxide, prepared from 0.67 g. (0.029 g.-atom) of sodium, was stirred at room temperature for 7 days. Part (2.3 g.) of the bromide remained undissolved. Removal of the solvent by distillation gave a residue that showed the presence of only a trace of ester-carbonyl in the infrared spectrum, which otherwise was qualitatively identical with that of starting material. A further 5.7 g. of IIf was actually recovered from this residue. Repetition of the reaction at reflux temperature likewise failed to give any desired ester in isolable amounts.

Direct synthesis of esters III *from 3-phenyl-2-benzofuranone* (I). *A. Ethyl 3-phenyl-2,3-dihydro-3-benzofurancarboxylate* (IIIb). To a stirred solution of sodium ethoxide prepared from 5.1 g. (0.22 g.-atom) of sodium in 100 ml. of ethanol was added, in one portion, a solution of 21.0 g. (0.1 mole) of I in 100 ml. of ethanol. After being refluxed for 1 hr., the solution was treated with 14.3 g. (0.11 mole) of bromochloromethane in one portion, and refluxing with stirring was continued for another 18 hr. The product was isolated in the usual way by distillation, followed by crystallization. There was obtained 10.3 g. (38%) of IIIb, m.p. 73–75°, identical (by infrared spectrum and mixed melting point) with the product obtained previously from IIa. Varying the temperature, the order and rate of addition of reactants, the quantity of sodium ethoxide (one mole instead of two), and the alkylating agent (dibromomethane in place of bromochloromethane) did not increase the yield appreciably.

B. Ethyl 4-phenyl-4-chromancarboxylate (IIId) was prepared in 30–35% yields when either 1,2-dibromoethane or 1-bromo-2-chloroethane was substituted for the bromochloromethane in the previous procedure. Attempts to better the yield by addition of the dihalide in two portions or by adding more than 2.0 moles of sodium ethoxide in multiple portions were unsuccessful. A somewhat better yield (55%) of IIId was obtained by a stepwise procedure: The benzofuranone I was alkylated with 1-bromo-2-chloroethane using sodium hydride in dimethylformamide; the solvent was removed by distillation at reduced pressure, and the residual mixture of halides (IIb and IIc) was treated with an equivalent amount of sodium ethoxide in ethanol.

C. Methyl 4-phenyl-4-chromancarboxylate (IIIc), b.p. 171–176° (2.4 mm.), n_D^{25} 1.5863, was obtained in 36% yield using sodium methoxide in methanol and 1-bromo-2-chloroethane as the alkylating agent in the above procedure (A). As in all of these one-step alkylations the crude product was contaminated by large amounts of starting material (I) which complicated the successful isolation of the desired product.

Proton magnetic resonance spectra of methyl esters IIIa,c, *and* e. These spectra were obtained on each of the there esters dissolved in carbon tetrachloride using tetramethylsilane as the internal standard. The Varian Model V-4311 instrument was used at 60 megacycles per second. The CH_3 peak was a sharp singlet at a chemical shift of δ =

3.94, 3.40, and 3.62 p.p.m. from tetramethylsilane for the five-, six-, and seven-membered ring esters, respectively. The two protons on position 2 of the dihydrobenzofuran IIIa gave nicely resolved identical doublets (J = 8.4 c.p.s.), one centered at δ = 4.55 and the other at 5.48. These coalesced to a quartet of about δ = 4.55 and the other at 5.48. These coalesced to a quartet of about δ = 3.78 for IIIc, the chroman derivative, and to a broad complex at about 3.98 for IIIe, the seven-membered ring compound. The two hydrogen atoms on position 3 of the chroman ring in IIIc gave similar septets, one centered at δ = 1.81, and the other at 2.55. For the seven-membered ring derivative IIIe, the four hydrogen atoms on positions 3 and 4 gave a broad complex centered at about δ = 2.34. The nine aromatic hydrogen atoms gave a broad complex of peaks different for each of the three compounds, but the strongest peak remained at δ = 7.17. Minor peaks fairly symmetrically placed about this strong peak in IIIa became progressively shifted to smaller δ-values in going to IIIc and IIIe, perhaps indicating a gradual increase in rotational restriction of the free phenyl group as the size of the heterocyclic ring is increased.

3-Phenyl-2,3-dihydro-3-benzofurancarboxylic acid (IVa). A solution of 6.2 g. (0.023 mole) of ethyl ester (IIIb) in 50 ml. of 10% potassium hydroxide in methanol was refluxed for 20 hr. The methanol was removed by distillation and replaced by 50 ml. of water. Any insoluble oil was removed by a single extraction with ether. The aqueous solution was acidified with dilute hydrochloric acid and the precipitated oil was taken up in ether and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave a residue which solidified on trituration with pentane. Filtration and drying gave 5.1 g. (92%) of IVa, m.p. 125–127°. Recrystallization of a sample once from 50% aqueous ethanol and once from benzene-hexane lowered the m.p. to 124–125°, $\lambda_{max}^{CHCl_3}$ 5.86 μ (>C=O).

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 74.98; H, 5.04. Found: C, 74.95; H, 5.32.

4-Phenyl-4-chromancarboxylic acid (IVb), m.p. 151–152° (from aqueous ethanol), $\lambda_{max}^{CHCl_3}$ 5.86 μ (>C=O), was prepared in 90% yield by hydrolysis of the corresponding methyl ester IIIc according to the above procedure.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; O, 18.88. Found: C, 75.44; 75.61, 75.77; H, 5.67, 5.78, 5.63; O, 18.68.

5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic acid (IVc). Refluxing 62 g. (0.22 mole) of the methyl ester IIIe in 500 ml. of a 10% solution of potassium hydroxide in 95% ethanol for 16 hr., followed by isolation in the usual way, gave 59 g. (100%) of IVc, m.p. 182–183°. One recrystallization from benzene gave analytically pure material (55 g., 93%), m.p. 183–184°, $\lambda_{max}^{CHCl_3}$ 5.86 μ (>C=O).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; O, 17.89. Found: C, 76.11; H, 5.95; O, 17.96.

5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylyl chloride, m.p. 106–107° dec. (from cyclohexane) was obtained in 97% crude yield (m.p. 100–101°) by refluxing the acid IVc with 1.7 equivalents of thionyl chloride in benzene for 16 hr.

Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27; Cl, 12.36. Found: C, 70.91; H, 5.47; Cl, 12.68.

Treatment of bromides II *with sodium hydroxide. A. 3-Bromomethyl-3-phenyl-2-benzofuranone* (IIa). To a solution of 2.0 g. (0.05 mole) of sodium hydroxide in 30 ml. of water was added 6.1 g. (0.02 mole) of powdered IIa. The mixture was stirred and heated on the steam bath for 1.5 hr. during which time dissolution occurred almost completely. Any remaining insoluble material was removed by ether extraction of the cooled reaction mixture. Acidification of the aqueous layer with hydrochloric acid precipitated 4.6 g. (96%) of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid (IVa), m.p. 121–123°. One recrystallization from a benzene-hexane mixture gave 3.0 g., m.p. 124–125°, identical (mixed melting point and infrared spectrum) with a sample of IVa prepared by hydrolysis of the corresponding ethyl ester. Although reaction of hydroxide ion with IIa at 100° progresses smoothly to give IVa exclusively, reaction at room temperature is extremely slow even when dioxan-water mixtures, which solubilize all reactants, are used. This lower reactivity of hydroxide ion is in marked contrast to alkoxide ion attack which, as was shown above, is extremely rapid even at room temperature.

B. 3-(β-Bromoethyl)-3-phenyl-2-benzofuranone (IIc). Treatment of 6.3 g. (0.02 mole) of IIc with aqueous sodium hydroxide according to the foregoing procedure gave 5.0 g. of crude product, m.p. 130–137°, from which, by fractional crystallization from cyclohexane, was obtained 3.6 g. (71%) of 4-phenyl-4-chromancarboxylic acid (IVb), m.p. 146–149°, identical (mixed melting point and infrared spectrum) with the IVb prepared by hydrolysis of the corresponding methyl ester. Although melting a few degrees low, it had a correct analysis.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.89; H, 5.64.

Also obtained, as the fraction insoluble in cyclohexane, was 0.33 g. (6.5%) of the direct displacement product, 2-(*o*-hydroxyphenyl)-2-phenyl-4-hydroxybutyric acid γ-lactone (X),[1] m.p. 158–160° (from benzene-hexane) identified by mixed melting point, infrared spectrum and microanalysis.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 75.57; H, 5.55. Found: C, 75.75; H, 5.49.

C. 3-(γ-Bromopropyl)-3-phenyl-2-benzofuranone (IIe). Powdered IIe (9.9 g., 0.03 mole) was stirred at room temperature for 2 weeks in 200 ml. of water containing 2.4 g. (0.06 mole) of sodium hydroxide. Unreacted IIe (0.7 g., 7%) was removed by filtration and the filtrate was acidified with normal hydrochloric acid. From the precipitated oil (8.0 g.), isolated by ether extraction, was obtained, by further extraction with aqueous sodium bicarbonate, 2.6 g. (35% based on unrecovered IIe) of 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic acid (IVc), m.p. 181–183°, identical (mixed melting point) with the material obtained from saponification of the corresponding methyl ester. The bicarbonate-insoluble fraction was distilled to give 4.2 g. (57% based on unrecovered IIe) of the direct displacement product, 3-(γ-hydroxypropyl)-3-phenyl-2-benzofuranone (IX),[1] b.p. 170–180° (0.5 mm.), n_D^{25} 1.5832, identified by its infrared spectrum.

Relative stabilities of the heterocyclic rings towards cleavage by hydrobromic acid. A. Tetrahydrobenzoxepin ring. A solution of 5 g. (0.0186 mole) of 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxylic acid (IVc) in 75 ml. of glacial acetic acid containing 25 ml. of 48% hydrobromic acid was refluxed for 40 hr. The residue, obtained after removal of volatile solvent and reactants by distillation, was taken up in ether and extracted with aqueous sodium bicarbonate solution. No acidic material was extracted by the aqueous layer. From the ether layer was obtained 5.7 g. (92%) of 3-(γ-bromopropyl)-3-phenyl-2-benzofuranone (IIe), m.p. 92–94°. One recrystallization from ethanol gave 5.0 g., m.p. 94–95°, identified by mixed melting point and infrared spectrum, $\lambda_{max}^{CHCl_3}$ 5.56 μ (> C=O).

B. Chroman ring. Treatment of 5 g. (0.0195 mole) of 4-phenyl-4-chromancarboxylic acid (IVb) in the foregoing manner gave 3 g. (60%) of unchanged IVb, 0.7 g. of a crude neutral solid, m.p. 55–80°, and 0.8 g. of a neutral oil. The fact that the 1.5 g. of neutral material contained at least 0.49 g. (8%) of 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (IIc) was proved by the formation from it of an equivalent amount (0.50 g.) of a characteristic product, m.p. 115–116°, obtained by reaction of IIc with morpholine (this type of reaction will be discussed in a future paper of this series).

C. Benzotetrahydrofuran ring. Treatment of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid (IVa) with hydrobromic acid in the usual manner led to no observable ring cleavage. The only product isolated (85% yield) was the starting acid in a state of near purity (m.p. 122–125°).

Preparation of carboxamides V. A. 3-Phenyl-2,3-dihydro-3-

benzofurancarboxamide (Va). A solution of the carboxylic acid IVa (7.2 g., 0.03 mole) in 40 ml. of dry benzene containing 5.4 g. (0.045 mole) of thionyl chloride was refluxed for 3 hr. The benzene and excess thionyl chloride were removed by distillation at reduced pressure, the residual oil was taken up in 30 ml. of dry ether and was added rapidly to a solution of approximately 50 ml. of liquid ammonia in 200 ml. of dry ether. The mixture was stirred for 3 hr. and was allowed to stand over a week-end. Evaporation of the reaction mixture to dryness gave a solid residue which was treated with a mixture of chloroform and water. The chloroform layer was separated and concentrated to dryness to give 6.6 g. (92%) of Va, m.p. 156–158°. Two recrystallizations from 95% ethanol gave pure amide, m.p. 158–159°, $\lambda_{max}^{CHCl_3}$ 5.91 μ (>C=O).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.12; H, 5.69; N, 5.94.

B. 4-Phenyl-4-chromancarboxamide (Vb). The crude acid chloride, prepared as above from 51.2 g. (0.2 mole) of 4-phenylchromancarboxylic acid (IVb) and 29.8 g. (0.25 mole) of thionyl chloride, was added to about 450 ml. of liquid ammonia. After washing the product free of ammonium chloride with water, the amide Vb (46 g., 90%) was obtained in analytically pure form, m.p. 180–182°, $\lambda_{max}^{CHCl_3}$ 5.95 μ (>C=O).

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.59; H, 5.85; N, 5.57.

C. 5-Phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-carboxamide (Vc), m.p. 154–155° (from benzene), $\lambda_{max}^{CHCl_3}$ 5.96 μ (>C=O), was prepared in 89% yield by the foregoing procedure, and in even better yield (95%) starting from the purified solid acid chloride (see above under preparation of IVc).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.61; H, 6.36; N, 5.24.

Preparation of amines VI *and carbamates* VII. *A. 3-Amino-3-phenyl-2,3-dihydrobenzofuran* (VIa). To a cold (5–10°) suspension of 6.1 g. (0.025 mole) in 3-phenyl-2,3-dihydro-3-benzofurancarboxamide (Va) in 45 ml. of water was added, dropwise with stirring over a period of 0.25 hr., a cold solution of potassium hypobromite, freshly prepared by the addition of 4.3 g. (0.027 mole) of bromine to 45 ml. of water containing 8.4 g. (0.15 mole) of potassium hydroxide. The mixture was then stirred at room temperature for 2 hr. during which time a clear yellow solution formed. Heating on steam bath for 0.5 hr. precipitated an oil. After cooling, the mixture was acidified with hydrochloric acid, insoluble material was removed by ether extraction, and the aqueous layer was made alkaline by the addition of 40% aqueous sodium hydroxide. The liberated oil was taken up in ether, dried and distilled to give a 75% yield of VIa, b.p. 139–140° (1.5 mm.), n_D^{25} 1.6078.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63; O, 7.58. Found: C, 79.75; H, 6.53; N, 6.49; O, 7.36.

VIa hydrochloride, m.p. 176° (from ethanol-ether), was prepared from this base by treatment with ethereal hydrogen chloride.

Anal. Calcd. for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.66. Found: C, 67.88; H, 5.60; N, 5.61.

Replacement of the potassium hypobromite in the above procedure by potassium hypochlorite gave VIa in very poor yield (<10%). Substitution of methanol for water in the above reaction gave, in 35% yield, *methyl 3-phenyl-2,3-dihydro-3-benzofurylcarbamate* (VIIa), m.p. 115–116° (from methylcyclohexane), $\lambda_{max}^{CHCl_3}$ 5.79 μ (>C=O).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.62; N, 5.20. Found: C, 71.51; H, 5.69; N, 5.19.

However, an attempt to convert VIIa to VIa by alkaline hydrolysis failed. Only a complex mixture was obtained.

Attempts to prepare VIa directly from the carboxylic acid IVa by a K. F. Schmidt reaction with hydrazoic acid failed. Also preparation of the corresponding acid azide (by action of the acid chloride of IVa on sodium azide) for subjection of it to the Curtius rearrangement was unsuccessful. Likewise, treatment of the ethyl ester IIIb with hydrazine in refluxing ethanol gave none of the desired hydrazide; and reaction of the acid chloride of IVa with hydrazine gave what appeared to be a small yield of desired hydrazide contaminated with a large quantity of the useless diacylhydrazine derivative.

B. 4-Amino-4-phenylchroman (VIb). Treatment of 38.5 g. (0.152 mole) of the amide Vb with aqueous potassium hypobromite, as in the foregoing procedure, gave 21.6 g. (64%) of VIb, b.p. 153–160° (2 mm.), n_D^{25} 1.615. Redistillation for analysis gave b.p. 154–155° (1.5 mm.), n_D^{25} 1.6112.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.05; H, 6.83; N, 6.06.

VIb hydrochloride had a m.p. of 229–230° (from ethanol-ether).

Anal. Calcd. for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.54; H, 6.16; N, 5.47.

C. Methyl 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepinyl-5-carbamate (VIIb). To a solution of 10 g. (0.0375 mole) of the amide Vc and 0.082 mole of sodium methoxide in 150 ml. of dry methanol was added, dropwise with stirring, 6.1 g. (0.038 mole) of bromine. The mixture warmed exothermically to reflux temperature during the addition, refluxing was continued on the steam bath for another 2 hr., and then it was allowed to stand at room temperature overnight. Solvent was removed by distillation, and the residue was taken up in ether, washed with water, dried, and recovered from the ether again by concentration. The crude solid (14 g.) was recrystallized from cyclohexane (150 ml.) to give 10.0 g. (90%) of VIIb, m.p. 103–105°. Another recrystallization for analysis gave pure VIIb, m.p. 110–111°, $\lambda_{max}^{CHCl_3}$ 5.78 μ (>C=O)

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.44; H, 6.14; N, 4.65.

D. 5-Amino-5-phenyl-2,3,4,5-tetrahydro-1-benzoxepin hydrochloride (VIc). A solution of 8 g. (0.026 mole) of the carbamate VIIb in 150 ml. of 80% ethanol containing 15 g. of potassium hydroxide was refluxed for 16 hr. The residue obtained, after removal of solvent by distillation, was taken up in ether, washed with water and dried. Addition of a slight excess of ethereal hydrogen chloride to this solution precipitated 6.5 g. (87%) of VIc, m.p. 204–206°. Recrystallization from an ethanol-ether mixture gave a pure sample of VIc, m.p. 207–208°.

Anal. Calcd. for $C_{16}H_{18}ClNO$: C, 69.68; H, 6.58; N, 5.08. Found: C, 69.91; H, 6.40; N, 5.14.

Treatment of the amide Vc with aqueous hypobromite (as in procedure A above), in an effort to obtain the amine VIc in one step, led instead to a good yield of a crude neutral product, m.p. 120–125°, the infrared spectrum and analytical values of which approximated those required by the acylurea, RCONHCONHR (R = 5-phenyl-2,3,4,5-tetrahydro-1-benzoxepinyl).[19] This material was not investigated.

Proof of structure. Conversion of VIa *to 3-phenylbenzofuran* (VIII). Two grams of the hydrochloride salt of VIa was distilled under reduced pressure to give 1.2 g. (75%) of an oil, b.p. 112° (0.8 mm.), n_D^{28} 1.6296, which solidified, m.p. 40–42°. Recrystallization from pentane did not alter the melting point.

Anal. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19; O, 8.24. Found: C, 86.64; H, 4.94; O, 8.56.

This material proved to be identical (mixed melting point and infrared spectrum) with a sample of 3-phenylbenzofuran (VIII) prepared by treatment of ω-phenoxyacetophenone with polyphosphoric acid according to the method of Davies and Middleton.[2]

Many attempts to prove the structure of 3-phenyl-2,3-dihydro-3-benzofurancarboxylic acid (IVa) by direct decarboxylation to the known[20] 3-phenyl-2,3-dihydrobenzofuran were complete failures. Likewise, independent synthesis of IVa by carbonation of the metallation product, pre-

(19) Compare E. S. Wallis and J. F. Lane, *Org. Reactions*, **Vol. III**, 269, 279 (1946).

(20) C. O. Guss, *J. Am. Chem. Soc.*, **73**, 608 (1951).

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.

NORTH CHICAGO, ILL.

[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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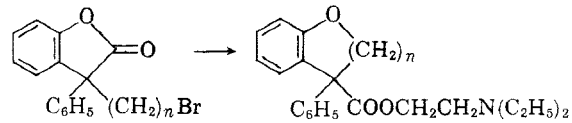
Received May 18, 1961

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