droxyl). RD $[\alpha]_{589}$ +59°, $[\alpha]_{450}$ +70°, $[\alpha]_{350}$ +440° (*c* 0.04); $[\alpha]_{325}$ +1550°, $[\alpha]_{312}$ +800°, $[\alpha]_{308}$ +910°, $[\alpha]_{305}$ −580° (*c* 0.02).

Dihydroelatericin B.—In order to prepare a purified sample of dihydroelatericin B, the crude hydrogenation product of elatericin B[15] (one mole of hydrogen) was extracted in 4% aqueous sodium hydroxide solution, which was then acidified and re-extracted in chloroform. The residue crystallized from a solvent mixture of ether–benzene–hexane, m.p. 158–160° dec. (sinters ~135°); $[\alpha]_D$ −44° (*c* 0.91).

Acetylation of Tetrahydroelatericin B.—Tetrahydroelatericin B (VIa) (8.80 g.) was acetylated in a mixture of acetic anhydride (50 ml.) and dry pyridine (50 ml.) overnight at room temperature. The solution was decomposed with ice–water. The precipitate of tetrahydroelatericin B diacetate (9.64 g.) was filtered and washed with water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −24° (*c* 1.07); λ_{infl} at 270 mμ (ε 250); ν_{max} 1724 (esters) and 1700 cm.$^{-1}$ (overlapping of C-11 and C-22 carbonyls).

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.21; H, 8.38; CH_3CO, 14.92.

Acetylation of Dihydroelatericin A.—Dihydroelatericin A (Va)[10] (100 mg.) was acetylated in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.) overnight at room temperature. The solution was decomposed with ice–water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −11° (*c* 1.16); λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); ν_{max} 1724, 1700, 1240, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.15; H, 8.53; CH_3CO, 14.78.

Dihydroelatericin A (Va).[10]—RD $[\alpha]_{589}$ +83° (*c* 1.27); $[\alpha]_{400}$ +300°, $[\alpha]_{350}$ +732° (*c* 0.045); $[\alpha]_{325}$ +2200°, $[\alpha]_{302}$ −1870°, $[\alpha]_{290}$ −3130° (*c* 0.011).

Ultraviolet Absorption Spectra.—In order to indicate the effect of acetylation on the ultraviolet absorption, the following data are presented: dihydroelatericin A (Va), λ_{infl} 273 mμ (ε 300); dihydroelatericin A diacetate, λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); tetrahydroelatericin B (VIa), λ_{max} 278 mμ (ε 180), λ_{min} 256 mμ (ε 130); and tetrahydroelatericin B diacetate, λ_{infl} 270 mμ (ε 250).

Dihydrohexanorelaterin-2-methyl Ether-3,20-Bisethylenedithioketal (XI).—Hexanorelaterin-2-methyl ether (X)[19b] (680 mg.) was hydrogenated in ethanol solution (50 ml.) over 10% palladium-on-carbon catalyst. The filtered solution was evaporated *in vacuo* to dryness to give the **dihydro X** derivative which was crystallized from ether, m.p. 166–168°, $[\alpha]_D$ +165° (*c* 1.21); ν_{max} 1728 and 1705 cm.$^{-1}$.

To a mixture of dihydro X (400 mg.) and 1,2-ethanedithiol (0.5 ml.) in an ice bath, boron trifluoride etherate (0.2 ml.) was added as catalyst. The solution was stirred for 5 min. and then left at room temperature for 5 hr. Chloroform was added and any unchanged dithiol was removed by shaking with a 10% sodium hydroxide aqueous solution. Upon evaporation of the solvent the residue crystallized, it was collected (450 mg.) and washed with ether, m.p. 215–225°; ν_{max} 1698 cm.$^{-1}$.

Desulfurization of XI to VIII.—To the substance XI (440 mg.) in dioxane solution (100 ml.), Raney nickel (prepared from 25 g. of alloy) in dioxane suspension was added. The mixture was stirred and maintained at reflux temperature overnight. The Raney nickel was removed and the filtrate evaporated *in vacuo* leaving an oily residue. It was crystallized several times from ether, m.p. 161–170°, and then sublimed at 140° (0.5 mm.), ν_{max} 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +182° (*c* 1.69); $[\alpha]_{322.5}$ +4043°, $[\alpha]_{280}$ −3436°, $[\alpha]_{270}$ −3120° (*c* 0.083).

Oxidation of VIII to IX.—To a stirred ice-cooled solution of VIII (150 mg.) in purified acetone (50 ml.), 0.3 ml. of a chromium trioxide solution (68 g. of chromium trioxide and 57 ml. of concentrated sulfuric acid diluted to 250 ml. with water) was added dropwise during 30 min. The excess oxidant was destroyed with methanol, water was added, and the product extracted with chloroform. The solution was washed and dried. Evaporation of the solvent left a residue which crystallized from ether, m.p. 184–187°; ν_{max}^{KBr} 1750 and 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +55° (*c* 0.9); $[\alpha]_{360}$ +212°, $[\alpha]_{330}$ −99°, $[\alpha]_{320}$ +1147°, $[\alpha]_{315}$ +500°, $[\alpha]_{307.5}$ +1448°, $[\alpha]_{280}$ +672° (*c* 0.116).

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.50; H, 9.93.

Monoketone XII.[2b]—RD $[\alpha]_{589}$ +127° (*c* 0.94); $[\alpha]_{358}$ +1000°, $[\alpha]_{320}$ +3806°, $[\alpha]_{275}$ −4085°, $[\alpha]_{260}$ −3484° (*c* 0.14).

A(2)-Norhexanorelatericin A (XIII).[11]—RD $[\alpha]_{589}$ +66° (*c* 1.65); $[\alpha]_{335}$ +461°, $[\alpha]_{322.5}$ +303°, $[\alpha]_{305}$ +2091°, $[\alpha]_{270}$ −856°, $[\alpha]_{250}$ −371° (*c* 0.13).

Acknowledgment.—We thank Mrs. R. Tugenhaft for technical assistance; Mlle. H. Hermann, Université de Strasbourg, for taking the optical rotatory dispersion curves; and Professor G. Ourisson for stimulating and helpful discussions pertaining to their interpretation.

Neighboring Group Reactions. VIII. Reactions of 3-(ω-Bromoalkyl)-3-phenyl-2-benzofuranones with Ammonia and Primary Amines

H. E. ZAUGG, R. W. DENET, AND R. J. MICHAELS

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received January 11, 1963

Reactions of a series of ω-bromoalkylbenzofuranones I (*n* = 0–2) with ammonia and primary amines are described. The first member of the series (I, *n* = 0) reacts with ammonia and cyclohexylamine to give the α-amino amide V. With ammonia the two other homologs (I, *n* = 1,2) form only the rearranged amide VI (*n* = 1,2). Primary amines, however, yield appreciable quantities of a second product in addition to the rearranged amide VI (*n* = 1,2). From the bromomethyl homolog (*n* = 1), β-aminopropionamides VII are obtained and from the bromoethyl derivative (*n* = 2) five-membered ring imidates VIII are secured. Relative yields of the two products are found to depend on the amine used and on the solvent system. Both amino amides V and VII are weak bases ($pK_a \sim 4$) and acylate preferentially on the phenolic oxygen atom. Evidence is presented in support of a mechanism for the formation of VII which involves the intermediacy of the four-membered cyclic imidate A.

A previous paper[1] of this series described the reactions of 3-(ω-haloalkyl)-3-phenyl-2-benzofuranones (I) with secondary amines. Depending on the length of the haloalkyl side chain, the amine used, the temperature, and solvent, any one or several of three products was formed. With morpholine, for example, the bromomethyl homolog I (*n* = 1) under all conditions, gave only the rearranged amide II. The three extreme members of the series (*n* = 0,3,4), formed only the product III of direct halogen displacement. In excess morpholine at room temperature, the bromoethyl homolog I (*n* = 2) gave exclusively the trapped tetrahedral intermediate IV; but at raised temperatures (95–100°), or in dimethylformamide or dimethyl sulfoxide solution at room temperature, only the displacement product III (*n* = 2) was obtained. With other secondary amines more basic than morpholine, the bromoethyl derivative I (*n* = 2) gave varying amounts of the re-

(1) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567(1962).

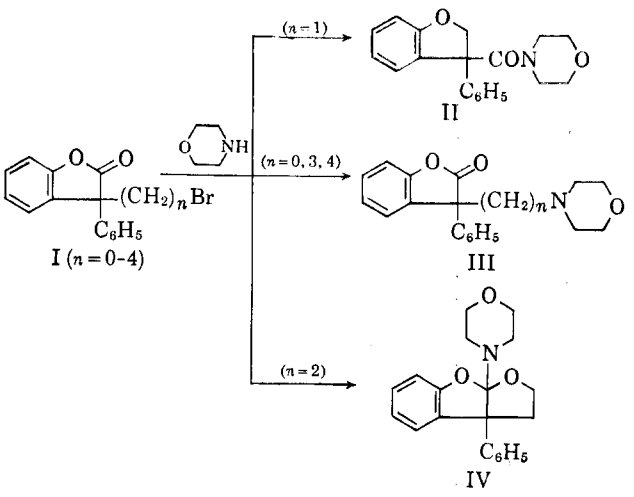
TABLE I

REACTION[a] OF 3-BROMOMETHYL-3-PHENYL-2-BENZOFURANONE WITH PRIMARY AMINES

I (n = 1) + RNH_2 ⟶ VII + VI (n = 1)

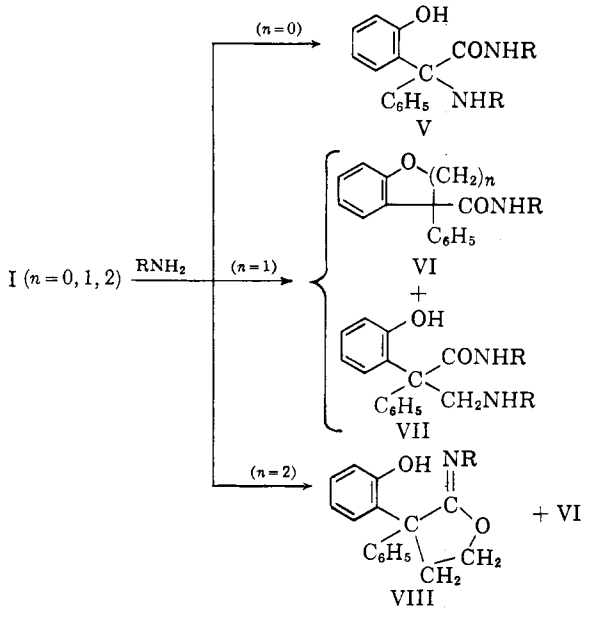
R	Yield of VII, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ C=O, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield of VI, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ C=O, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Cyclopropyl	46	188–190	6.06[b]	$C_{21}H_{24}N_2O_2$	74.97	75.25	7.20	7.27	8.33	8.44	10	133–134	5.96	$C_{18}H_{17}NO_2$	77.40	77.67	6.14	6.48	5.02	5.10
n-Propyl	10	143–144	5.97 6.08	$C_{21}H_{28}N_2O_2$	74.07	74.15	8.29	8.25	8.23	8.07	46	111–112	5.98	$C_{18}H_{19}NO_2$	76.82	76.81	6.80	6.69	4.98	5.09
Cyclobutyl	26	163–165	5.98	$C_{24}H_{28}N_2O_2$	75.79	76.08	7.74	8.06	7.69	7.59	27	153–154	6.00	$C_{19}H_{19}NO_2$	77.79	77.67	6.53	6.72	4.79	4.82
n-Butyl	7	117–119	5.96 6.07	$C_{23}H_{30}N_2O_2$	74.96	74.79	8.76	8.57	7.60	7.79	45	109–110	5.96[c]	$C_{19}H_{21}NO_2$	77.25	77.27	7.17	7.16	4.74	4.73
Cyclopentyl	18	146–147	5.99	$C_{25}H_{32}N_2O_2$	76.49	76.26	8.22	8.28	7.14	7.25	25	170–171	6.01	$C_{20}H_{21}NO_2$	78.14	78.07	6.89	6.70	4.56	4.62
Cyclohexyl	13	145–147[d] 178–179[e]	5.98	$C_{26}H_{34}N_2O_2$[f]	77.10	77.12	8.63	8.55	6.66	6.89	56	189–190	5.99	$C_{21}H_{23}NO_2$	78.47	78.73	7.22	7.06	4.36	4.40
Cycloheptyl	6	132–133[g]		$C_{31}H_{44}N_2O_4$[g]	66.88	66.41	7.97	7.75	5.03	5.05	39	151–152	6.01	$C_{22}H_{25}NO_2$	78.78	78.50	7.51	7.53	4.18	4.21
Benzyl	25	164–165	6.08	$C_{29}H_{28}N_2O_2$	79.79	79.69	6.47	6.46	6.42	6.21	...[h]									

[a] According to procedure 1. [b] In Nujol mull. [c] In carbon tetrachloride. [d] Metastable dimorph. [e] Stable dimorph. See Table IVD for the n.m.r. spectrum. [f] Hydrochloride, m.p. 215–216°, pK_a (water–extrapolated) 4.2: *Anal.* Calcd. for $C_{27}H_{27}ClN_2O_2$: C, 70.96; H, 8.16; N, 6.13. Found: C, 70.68; H, 8.19; N, 6.09. [g] Oxalic acid salt monohydrate. *Anal.* Calcd. O, 20.12. Found: O, 20.27. [h] No amide could be isolated in pure form from the neutral fraction.



arranged amide (corresponding to II), at the expense of the trapped tetrahedral intermediate (*e.g.*, IV).

The present paper reports the extension of these investigations to the reactions with ammonia and primary amines of the first three members of this homologous series. Similarities to and differences from the previous work were encountered. Results may be summarized as shown.



The reaction of I (n = 0) with aqueous ammonia gave[2] the α-amino amide V (R = H). However, with either liquid ammonia or ammonia in acetonitrile, the bromomethyl compound I (n = 1) produced only the rearranged amide VI (n = 1, R = H). From the bromoethyl derivative I (n = 2) the corresponding amide VI (n = 2, R = H) was the sole product with either aqueous or anhydrous ammonia and the main product with ammonia in acetonitrile.

With cyclohexylamine, the α-amino amide V (R = cyclohexyl) was again the only product obtained (85% yield) from I (n = 0). Unexpectedly, the bromomethyl homolog I (n = 1), with primary amines (unlike secondary amines[1] and ammonia), did not lead exclusively to the rearranged amides VI (n = 1). In addition, appreciable amounts of the β-amino amides VII

(2) G. Cramer, *Ber.*, **31**, 2813 (1898). We are indebted to N. F. Ryan for repeating this reaction.

TABLE II

EFFECT OF SOLVENT ON THE REACTION[a] OF 3-BROMOMETHYL-3-PHENYL-2-BENZOFURANONE WITH CYCLOHEXYLAMINE

$$I(n = 1) + C_6H_{11}NH_2 \longrightarrow VII\ (R = \text{cyclohexyl}) + VI\ (n = 1,\ R = \text{cyclohexyl})$$

Solvent	Yield of VII, %	Yield[b] of VI, %
Cyclohexylamine	18	42
Cyclohexane	33	42 (65)
Benzene	13	56
Ethyl ether	35	25 (59)
Tetrahydrofuran	30	51 (67)
1,2-Dimethoxyethane	21	58 (72)
Acetonitrile	13	67
Dimethylformamide	0	68
Dimethyl sulfoxide	0	54

[a] According to procedure 1. [b] Except for those in parentheses, numbers represent yields of isolated product. Parenthesized values are corrected yields based on infrared examination of the neutral residues (using the intensity of the 5.99-μ amide peak to estimate the amount of VI). Slight absorption at 5.55 μ in the neutral residues corresponded to the presence of from 2 to 5% of unchanged bromide I (n = 1).

were formed under mildly exothermic conditions. Relative yields of the two products varied with the amine and solvent used. Results are summarized in Table I (variation of amine) and Table II (variation of solvent).

Two products were obtained likewise from the bromoethyl derivative I (n = 2). In addition to the usual rearranged amide VI (n = 2), the cyclic imidate VIII was formed. Again, relative yields of the two products depended on the amine used (see Table III). It is interesting to note that of all the primary amines used in the reactions with both bromo homologs (n = 1,2), cyclopropylamine, which is the weakest base[3] of any of them, gave the lowest yields of rearranged amides VI (n = 1,2) and highest yields of VII and VIII. A similar phenomenon was encountered previously[1] in the reactions of I (n = 2) with secondary amines. Morpholine, the weakest base of the series, was the only amine that produced the trapped tetrahedral intermediate IV as the sole product. From the other amines, varying amounts of rearranged amides could be isolated. The anomalous behavior of 1,1-dimethylhydrazine toward I (n = 2) in which a 90% yield of cyclic imidate VIII was formed (Table III) may also be due to its relatively low (and optimal[1]) basicity ($pK_a \sim 7$).

The structure VII assigned to the products obtained from the bromomethyl derivative is based on microanalytical results (Table I), infrared spectra, n.m.r. spectra of the cyclohexyl derivative (Table IV D), and the surprisingly low pK_a's (4.0–4.2) of several hydrochlorides of the series, an abnormality shared by the hydrochloride of the α-amino amide V (R = cyclohexyl). In addition, lithium aluminum hydride reduction of VII (R = $n - C_3H_7$) gave a diamine IX capable of forming a dihydrochloride. Interestingly, but not surprisingly,[4] the corresponding cyclopropyl amino amide VII (R = cyclopropyl) was converted to the identical

(3) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951).

(4) C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, *J. Org. Chem.*, **27**, 768 (1962), have found that a number of cyclopropylamines possessing a replaceable hydrogen on the nitrogen atom undergo ring cleavage with lithium aluminum hydride. We have observed similar behavior in several other cases. Also, in agreement with these workers, we have found that N,N-disubstituted cyclopropylamines are resistant to lithium aluminum hydride cleavage.

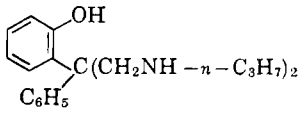
TABLE III

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

$$I(n = 2) + RNH_2 \longrightarrow VIII + VI\ (n = 2)$$

R	Yield of VIII, %	M.p., °C.	$\lambda_{max}^{CHCl_3}$ OH, μ[b]	$\lambda_{max}^{CHCl_3}$ C=N, μ	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
Cyclopropyl	52	130–131	3.8	5.88[c]	$C_{19}H_{19}NO_2$[d]	77.78	77.85	6.53	6.77	4.78	4.80	37	Oil[e]	5.97[f]
Cyclobutyl	47	99–101	4.0	5.91	$C_{20}H_{21}NO_2$	78.14	78.15	6.89	7.16	4.56	4.42	42	140–141[g]	6.02
n-Butyl[h]	16	62–64	3.9[i]	5.87[i]	$C_{20}H_{23}NO_2$	77.64	77.88	7.49	7.26	4.53	4.37	60	Oil[e]	6.00
Cyclohexyl	20	107–108	3.9[i]	5.88[i]	$C_{22}H_{25}NO_2$[j]	78.78	78.98	7.52	7.68	4.18	4.26	66	85–87[k]	6.02
Benzyl[k]	15	112–113	3.9[i]	5.90[i]	$C_{23}H_{21}NO_2$	80.44	80.77	6.16	6.15	4.08	4.03	70	87–88[l]	5.96[i]
d-$C_6H_5CH_2CH(CH_3)$-[m]	9	177–178	3.9	5.89	$C_{25}H_{27}NO_2$	80.82	80.89	6.78	7.03	3.78	3.76	[n]		
$(CH_3)_2N$[o]	90	165–166	3.7	5.97	$C_{18}H_{20}N_2O_2$[p]	72.93	72.86	6.80	6.89	9.45	9.39	<3[o]		

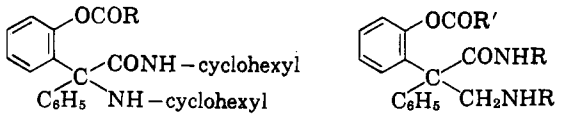
[a] According to procedure 2, unless otherwise noted. [b] None of the cyclic imidates VIII showed normal hydroxyl absorption either in the near (1.45-μ) or middle (2.7–2.9-μ) infrared region. However, they all absorbed broadly (and weakly) in the 3.5–5.0-μ region. The listed wave lengths give the approximate centers of these broad bands. [c] The presence of cyclopropyl was checked by its absorption in the near infrared: $\lambda_{max}^{CHCl_3}$ 1.63 μ. [d] See Table IVA for the n.m.r. spectrum. [e] The amide was not purified. The yield represents the entire neutral fraction. [f] Undiluted with solvent. [g] *Anal.* Calcd. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 78.26; H, 6.91; N, 4.46. [h] By procedure 3. [i] In carbon tetrachloride solution. [j] Hydrochloride, m.p. 167–168°, pK_a 9.15. *Anal.* Calcd. for $C_{22}H_{25}ClNO_2$: C, 71.05; H, 7.05; N, 3.77. Found: C, 71.19; H, 6.99; N, 3.86. $\lambda_{max}^{CHCl_3}$ 5.94 μ (C=N). [k] *Anal.* Calcd. for $C_{23}H_{23}NO_2$: C, 78.78; H, 7.52; N, 4.18. Found: C, 78.40; H, 7.78; N, 4.09. [l] *Anal.* Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.23; H, 6.39; N, 3.95. [m] *d*-Amphetamine was the base used. [n] Only 44% of the theoretical amount of *d*-amphetamine hydrobromide was formed after 19 days at room temperature. The corresponding amide could not be separated from unchanged bromide I. [o] Unsymmetrical dimethylhydrazine was the base using procedure 3. [p] See Table IVB for the n.m.r. spectrum.



IX

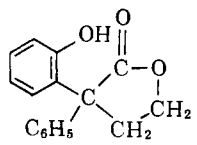
di-*normal* propylamine IX on similar treatment with lithium aluminum hydride.

Of some interest is the behavior of the α- and β-amino amides V and VII towards acylating agents. Compound V (R = cyclohexyl), with acetyl and propionyl chlorides in the presence of excess triethylamine, gives the O-acyl derivatives Xa and Xb, respectively, and from the requisite β-amino amides VII (R = cyclopropyl and cyclohexyl) the analogous products XIa–c were obtained (see Table IVC for the n.m.r. spectrum of XIb). The abnormally low basicity of these amines probably contributes to this preferential oxygen acylation. However, an attempt to effect, O,N-diacetylation using excess reagent under more drastic conditions failed. This suggests that a steric factor may also operate to prevent N-acylation in these compounds.



Xa. R = CH_3 XIa. R = cyclopropyl, R′ = OC_2H_5
Xb. R = C_2H_5 XIb. R = cyclohexyl, R′ = CH_3
XIc. R = cyclohexyl, R′ = C_2H_5

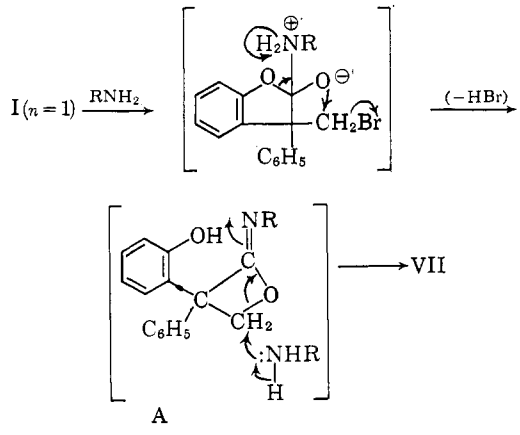
The structure VIII assigned to the basic products derived from the bromoethyl derivative is also based on microanalytical results (Table III), infrared spectra,[5] the n.m.r. spectrum of the cyclopropyl and 1,1-dimethylhydrazine derivatives of VIII (Table IV),[7] and on the products obtained from hydrolysis and aminolysis. Acid hydrolysis of VIII (R = benzyl) gave the lactone XII[9] (81% yield) and refluxing VIII (R = cyclohexyl) in morpholine containing morpholine hydrobromide led to the morpholinoethylbenzofuranone III (n = 2) in good yield (81%). Omission of the morpholine salt slowed but did not prevent aminolysis.



XII

Discussion

The unexpected displacement of a neopentyl-type bromine atom by primary amines [*i.e.*, I (n = 1) → VII] under mildly exothermic conditions is strong indication that, as is clearly the case in the formation of VI (n = 1), an intramolecular mechanism is involved.[10,12] The observation that the seemingly "direct" displacement of halogen in the production of VII is invariably accompanied by aminolysis of the lactone ring of I suggests that the intermediate involved is the four-membered cyclic imidate A analogous to the five-membered imidate VIII actually obtained from the higher homolog I (n = 2).[13] The mechanism can be represented as shown.



A

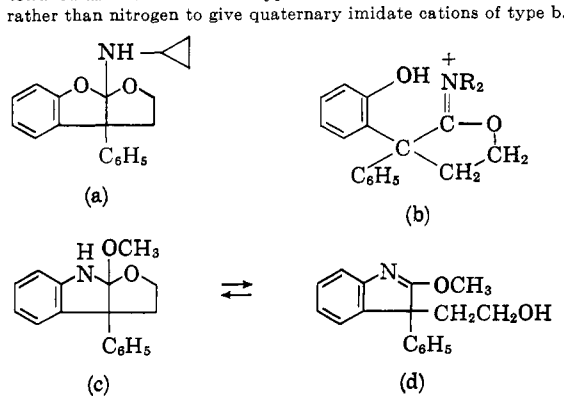
The process leading to A (and VIII) is undoubtedly the same as that by which the tetrahedral intermediates (*e.g.*, IV) are formed from I (n = 2) and secondary amines. This has been discussed previously[1] and will not be repeated. Considerable driving force leading

(5) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960), have reported $\lambda_{max}^{CHCl_3}$ 5.99 μ for the >C=NH group of a five-membered cyclic imidate. The range 5.87–5.91 μ observed (Table III) for compounds VIII is, therefore, consistent with an *N-alkylated* five-membered cyclic imidate structure. Substitution on nitrogen by the less electropositive $(CH_3)_2N$– group, as expected, gives a λ_{max}, 5.97 μ, closer to that of the unsubstituted model.

The abnormal hydroxyl absorption (3.7–4.0 μ) exhibited by these compounds (Table III, footnote *b*) is also consistent with the presence of strong intramolecular hydrogen bonding with the basic imino nitrogen atom.[6] (This displaced hydroxyl absorption is also characteristic of most of the β-amino amides VII, but to a less obvious degree.)

(6) Compare H. H. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).

(7) The n.m.r. spectrum of VIII (R = cyclopropyl) (see Table IVA) is best interpreted on the basis that, in carbon tetrachloride solution, structure VIII is in equilibrium with 10–15% of the tetrahedral intermediate (a). The clear preference shown for the imidate *vs.* the tetrahedral structure is consistent with the previous observations[8] that in the equilibrium c ⇄ d, the imidate tautomer (d) is favored by a factor of 3. Furthermore, protonation of tetrahedral intermediates of type IV has been found[1] to occur on oxygen rather than nitrogen to give quaternary imidate cations of type b.



(a) (b) (c) (d)

(8) H. E. Zaugg and R. W. DeNet, *J. Am. Chem. Soc.*, **84**, 4574 (1962).

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

(10) The facile reactivity of neopentyl(or neophyl)-type halides toward *intramolecular* displacement is well known.[11]

(11) (a) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley, and Son, Inc., New York, N. Y., 1956, p. 464; (b) J. L.Greene, Jr., and H. J. Hagemeyer, Jr., *J. Am. Chem. Soc.*, **77**, 3016 (1955); (c) H. E. Zaugg, *ibid.*, **72**, 2998 (1950).

(12) The effect of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) on the reaction of I (n = 1) with cyclohexylamine (Table II) further argues against a direct displacement mechanism. In these solvents, formation of the amino amide is completely suppressed in favor of the rearranged amide VI. Yet, in the reaction of morpholine with the bromoethyl homolog I (n = 2) where intermolecular displacement of bromide is possible, DMF and DMSO produce just the opposite effect.[1] Both *intramolecular* displacements [*i.e.*, I (n = 2) → IV + rearranged amide] are entirely suppressed in favor of the *intermolecular* displacement reaction [I (n = 2) → III (n = 2)].

(13) It must be stated that in contrast to secondary amines which are inert, primary amines (at 100°) readily aminolyze 3-phenyl-2-benzofuranones, containing an additional nonfunctional 3-substituent, to give the corresponding hydroxy amides. These reactions, however, are far from being even mildly exothermic (R. W. DeNet—unpublished).

to further reaction of A with amine should stem from two sources: strain energy of the four-membered ring[14] and acid catalysis by the phenolic hydroxyl. The latter effect is indeed demonstrable in the five-membered imidate series. Aside from infrared evidence[5,6] suggesting that, in VIII, the hydroxyl proton is strongly bonded to nitrogen, the observed reactivity of VIII toward morpholine to give III (n = 2) is firmly indicative of such catalysis. Although reaction is faster (80% yield *vs.* 40% in 22 hr. at 150°) in the presence of morpholine hydrobromide, it *does* occur even in its absence. By contrast, the reaction of the tetrahedral intermediate IV with morpholine requires the presence of amine salt for the same conversion.[1] The reactive species in this case is, in fact, the protonated form of IV, the imidate salt (b).[7]

The foregoing mechanism does not explain why ammonia behaves toward the bromomethyl compound I (n = 1) more like a secondary than a primary amine. The rearranged amide VI (R = H, n = 1) is the sole product formed under all conditions tried. But a clearly similar and equally puzzling preference for production of the amide VI (n = 2) is also exhibited toward the bromoethyl homolog I (n = 2). It would seem that we are dealing here with another example to add to the many already observed of the apparently quixotic behavior of ammonia and amines toward lactones[1,15] and esters,[16] a behavior probably stemming from the subtleties inherent in the nature and timing of proton transfer processes.[17]

Experimental

Reaction of 3-Bromomethyl-3-phenyl-2-benzofuranone with Cyclopropylamine and Other Primary Amines. Procedure 1.—To a stirred solution of 3-bromomethyl-3-phenyl-2-benzofuranone[18] (90.9 g., 0.3 mole) in dry benzene (450 ml.) was added over a period of 10 min., a solution of cyclopropylamine (51.3 g., 0.9 mole[19]) in dry benzene (50 ml.). An ice bath was used to maintain the reaction temperature below 35°. After standing at room temperature for 2 days, precipitated solid (99.4 g.) was removed by filtration and stirred vigorously with water (300 ml.) for 10 min., once again collected at the filter, and dried. The crude product (60.5 g., m.p. 173–176°); the difference in weight, 38.9 g., between this and the original 99.4 g., represented an 89% yield of the water-soluble cyclopropylamine hydrobromide), was recrystallized from dry ethanol to give 43.3 g. (43%) of **N-cyclopropyl-β-cyclopropylamino-α-(*o*-hydroxyphenyl)-α-phenylpropionamide (VII. R = cyclopropyl)**, m.p. 188–190°. (For microanalytical results, see Table I.)

The original benzene filtrate was extracted with two portions (100 ml.) of 10% hydrochloric acid which were combined and made alkaline by the careful addition of excess 40% sodium hydroxide solution. Filtration and drying of the resulting precipitate gave an additional quantity (3.7 g., 3%) of VII (R = cyclopropyl), m.p. 186–188°.

The neutral fraction in benzene solution was concentrated to dryness under reduced pressure. The resulting oil (30.7 g.), on trituration with isopropyl alcohol, partially solidified to give a solid substance (20 g., m.p. 104–109°). Two recrystallizations from ethanol produced 8.4 g. (10%) of **N-cyclopropyl-2,3-dihydro-3-phenylbenzofuran-3-carboxamide (VI. n = 1, R = cyclopropyl)**, m.p. 133–134°. (For microanalytical results, see Table I.)

By substituting the appropriate primary amine for cyclopropylamine in procedure 1 (in some cases with minor variations) the corresponding products of type VII and type VI (n = 1) were obtained. These are listed in Table I.

The effect of change in solvent on the outcome of procedure 1, as applied to cyclohexylamine, is summarized by the data listed in Table II.

N,N′-Di-*n*-propyl-2-(*o*-hydroxyphenyl)-2-phenyl-1,3-propanediamine (IX).—To a stirred suspension of lithium aluminum hydride (14.8 g., 0.39 mole) in dry 1,2-dimethoxyethane (500 ml.) solid VII (R = cyclopropyl) (43.7 g., 0.13 mole) was added portionwise over a 30-min. period. The mixture was then stirred and refluxed for 42 hr. Excess reducing agent was decomposed by successive addition of water (50 ml.) and 50% sodium hydroxide solution (50 ml.) followed by a period (1 hr.) of reflux. The organic layer was then decanted from the precipitate and concentrated to dryness under reduced pressure. The residual solid (41.9 g., m.p. 88–95°) was recrystallized twice from 95% ethanol to give 27.9 g. (67%) of IX, m.p. 102–103°, $\lambda_{max}^{CHCl_3}$ 1.54 μ (N–H), no absorption at 1.63 μ typical of a cyclopropyl CH_2 group.

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58; O, 4.91. Found: C, 77.27; H, 9.21; N, 8.71; O, 5.00.

IX dihydrochloride had m.p. 252–254° (from ethanol).

Anal. Calcd. for $C_{21}H_{32}Cl_2N_2O$: C, 62.99; H, 8.07; N, 6.84. Found: C, 62.75; H, 7.95; N, 7.25.

Reduction of VII (R = *n*-propyl) according to the foregoing procedure likewise gave IX (92%) identified by melting point, mixture melting point, infrared spectrum, and by conversion to the dihydrochloride, m.p. 252–254°.

Reaction of the Bromides I (n = 1,2) with Ammonia.—To anhydrous liquid ammonia (2.5 l.) was added portionwise with stirring over a period of 0.5 hr., 242.4 g. (0.8 mole) of solid 3-bromomethyl-3-phenyl-2-benzofuranone. The resulting green solution was stirred for 7 hr. and allowed to stand overnight at room temperature. The residue remaining after evaporation of the ammonia was partitioned between water and chloroform and separated. Removal of the chloroform by distillation gave a solid residue which was recrystallized from 95% ethanol to give 152 g. (79%) of 2,3-dihydro-3-phenylbenzofuran-3-carboxamide (VI, n = 1, R = H), m.p. 154–156°, identical with the material prepared from the corresponding acid chloride.[18] Similar treatment of the bromomethyl compound with ammonia in acetonitrile solution resulted in a quantitative conversion to rearranged amide VI (n = 1, R = H).

When 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I. n = 2) was subjected to the foregoing conditions, there was obtained a 93% yield of 4-phenyl-4-chromancarboxamide (VI. n = 2, R = H), m.p. 181–182°, identical (mixture melting point and infrared spectrum) with an authentic[18] sample.

When powdered bromoethyl derivative I (n = 2) was stirred with concentrated ammonium hydroxide for 21 hr. at room temperature, a 60% conversion to the corresponding amide VI took place. The remainder of the product appeared to be unchanged bromide. With ammonia in acetonitrile solution, however, the reaction deviated from a unidirectional course. From 6.3 g. (0.02 mole) of the bromoethyl derivative, in addition to a predominant neutral fraction (5.0 g.) consisting mainly of amide VI, there was obtained 1.93 g. of a basic oil. The structure of a pure compound obtained from it will be the subject of a future note.

Reaction of 3-(β-Bromoethyl)-3-phenyl-2-benzofuranone with Primary Amines. Procedure 2.—This procedure is exemplified by the reaction with cyclopropylamine. A solution of the bromide I (n = 2) (15.9 g., 0.05 mole) and cyclopropylamine (6.3 g., 0.11 mole) in dry benzene (100 ml.) was allowed to stand at room temperature for 6 days. The cyclopropylamine hydrobromide (6.6 g., 91%), m.p. 152–155°, was removed by filtration and washed with ether. The combined filtrate and ether washings were concentrated to dryness under reduced pressure; the residue was taken up in ether and extracted with two portions (50 ml.) of 10% sulfuric acid. From the neutral ether layer was obtained, in the usual way (procedure 1), the amide VI (n = 2, R = cyclopropyl) and from the acid extract (in the usual way), the cyclic imidate VIII (R = cyclopropyl). See Table III for further details.

(14) Facile displacements by amines at the β-carbon atom of β-lactones are well known.[15]

(15)(a) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951); (b) H. E. Zaugg in "Organic Reactions," Vol. VIII, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 305.

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

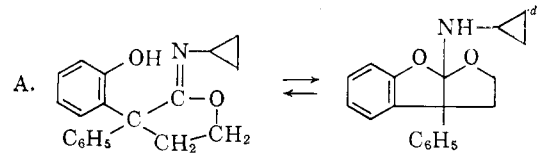
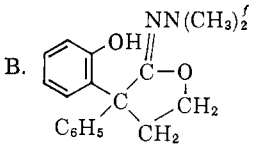
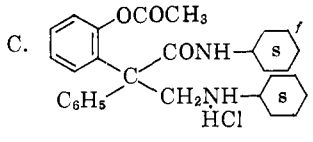
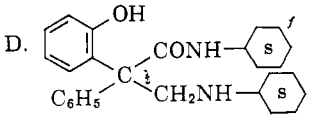
(17) M. L. Bender, *Chem. Rev.*, **60**, 91 (1960), and references cited therein.

(18) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **26**, 4821 (1961).

(19) One-third (0.3 mole) of the cyclopropylamine could be replaced by an equivalent quantity of triethylamine without affecting the course of the reaction.

TABLE IV

N.M.R. SPECTRA[a]

Chemical shift,[b] c.p.s.	Assignment	Relative area[c]	
A. 			
7–25	>NH	0.81[e]	
37–55	Cyclopropyl—CH_2CH_2—	3.65	5.13
125–160	Cyclopropyl—CH	1.48	
165–210	C—CH_2—C	2.02	
230–275	O—CH_2—C	2.04	
390–450	Aromatic H	9.00[e]	
653.2	OH	0.86	
B. 			
162.5	$N(CH_3)_2$	6.15	10.0
140–207	C—CH_2CH_2—O	3.85	
400–450	Aromatic H	9.00[e]	
618	OH	0.96	
C. 			
28–133	Cyclohexyl CH_2	20.00	27.5[g]
139	—$COCH_3$	3.32	
147–239	Cyclohexyl CH	2.23	
261	—N—CH_2—C	1.96	
370–398[h]	NH	0.98[e]	
398–504	Aromatic H	9.00[e]	
542–579[h]	NH	0.85[e]	
618–662[h]	NH	0.85[e]	
D. 			
40–120	Cyclohexyl CH_2	19.00	21.6[i]
120–150	Cyclohexyl CH	1.35	
185–250	Cyclohexyl CH	1.20	
214(4)	N—CH_2—C	1.85	
328–355[h]	OH	0.90	
400–460[j]	Aromatic H	9.00[e]	

[a] 60-Mc. [b] Tetramethylsilane as internal standard. Numbers denote range of frequencies of complex absorption except where digits in parentheses indicate the number of peaks in a symmetrical multiplet centered at the indicated frequency. A single frequency notation with no parenthetical digit following it represents a singlet. [c] Assuming 9 aromatic protons. [d] In CCl_4 solution. [e] Due to the quadrupole moment of nitrogen this area cannot be compared with the other areas. [f] In $CDCl_3$ solution. [g] Total required, 27.0. [h] Band disappears when D_2O is added. [i] Total required, 22.0. [j] No bands corresponding to the two NH protons could be identified. However, absorption at 1.49 μ in the near infrared provided firm evidence for the presence of the amide NH group; and, since both the near infrared and n.m.r. spectra of the corresponding acetyl derivative XIb indicate the presence of both NH groups, they must also both be present in the precursor of XIb.

Procedure 3 differed from procedure 2 only in the omission of benzene as solvent. Instead, excess of the liquid amine (10 to 15 ml. per 0.01 mole of bromide) was used. The reaction mixture was then worked up by removing the amine under reduced pressure in a rotating evaporator, partitioning the residue between ether and water, separating, and treating the ether layer as in procedure 2.

Under the conditions of procedure 2, no reaction occurred with aniline. After 11 days, 90% of the bromide I (n = 2) was recovered unchanged.

N-Cyclohexyl-α-cyclohexylamino-α-(*o*-hydroxyphenyl)-α-phenylacetamide Hydrochloride (V. R = Cyclohexyl).—A solution of 10 g. (0.0346 mole) of 3-bromo-3-phenyl-2-benzofuranone[2] and 10 g. (0.1038 mole) of cyclohexylamine in benzene (150 ml.) was kept overnight at room temperature. The precipitated cyclohexylamine hydrobromide (6.2 g., m.p. 196–198°) was removed by filtration and washed with ether. The combined filtrate and washings were concentrated to dryness *in vacuo* and the residual oil (14.1 g.) was taken up in dry ether, decolorized with charcoal and treated with excess ethereal hydrogen chloride. Filtration and drying gave 13.0 g. (85%) of the hydrochloride of V (R = cyclohexyl), m.p. 160–161°. Recrystallization from an ethanol–ether mixture did not change the m.p., $\lambda_{max}^{CHCl_3}$ (μ) 1.49, 2.95, 5.94, pK_a (water) 4.1 (by titration with methanolic potassium hydroxide in different aqueous methanol solutions and extrapolating to 100% water).

Anal. Calcd. for $C_{26}H_{35}ClN_2O_2$: C, 70.49; H, 7.96; N, 6.32. Found: C, 70.44; H, 7.80; N, 6.48.

Aminolysis of VIII (R = Cyclohexyl) with Morpholine.—A mixture of 3.4 g. (0.01 mole) of the imidate VIII (R = cyclohexyl), 1.7 g. (0.01 mole) of morpholine hydrobromide, and 20 ml. of morpholine was refluxed for 22 hr. in an oil bath held at 150°. The solution was concentrated to dryness under reduced pressure and the residue was taken up in ether. After washing with water to neutrality, the ether solution was extracted with dilute (10%) hydrochloric acid. The cold acid extract was then treated with excess 40% sodium hydroxide solution and the precipitated base was taken up in ether and dried. Isolation by filtration and distillation of the ether gave a crude base (3.1 g., 97%), m.p. 85–90°. Recrystallization from isopropyl alcohol gave pure 3-(β-morpholinoethyl)-3-phenyl-2-benzofuranone (III. n = 2) (81%), m.p. 94–95°, identical (mixture melting point and infrared spectrum) with an authentic sample.[1]

When the foregoing procedure was repeated, but with the omission of morpholine hydrobromide, infrared examination of the crude reaction product (after 22 hr.) indicated that only 40% of the imidate had been converted to the benzofuranone III (n = 2). The remainder was unchanged.

When the β-amino amide VII (R = cyclohexyl) was submitted to the foregoing conditions (including morpholine hydrobromide) only starting material (> 70%) was recovered. No benzofuranone product (λ_{max} 5.55 μ) could be detected by infrared examination of the residues.

Hydrolysis of VIII (R = Benzyl).—The cyclic imidate VIII (R = benzyl) (0.50 g., 0.00146 mole) was refluxed for 2 hr. with 25 ml. of 10% hydrochloric acid. After cooling, solid product was removed by filtration and recrystallized from benzene to give 0.30 g. (81%) of 2-(*o*-hydroxyphenyl)-2-phenyl-4-hydroxybutyric acid γ-lactone (XII), m.p. 159–160°, identical with an authentic sample.[9] From the acid filtrate was obtained 0.10 g. (50% yield) of benzylamine hydrochloride, m.p. 259–261°.

N-Cyclohexyl-β-cyclohexylamino-α-(*o*-acetoxyphenyl)-α-phenylpropionamide Hydrochloride (XIb).—To a solution of 8.4 g. (0.02 mole) of the amino amide VII (R = cyclohexyl) in 100 ml. of 1,2-dimethoxyethane containing 4.0 g. (0.04 mole) of triethylamine was added dropwise with stirring over a period of 5 min. 1.6 g. (0.02 mole) of acetyl chloride dissolved in 10 ml. of 1,2-dimethoxyethane. The mixture was stirred at room temperature for 6 hr., refluxed and stirred for 1 hr. and then allowed to stand overnight at room temperature. The precipitated triethylamine hydrochloride (3.3 g., m.p. 259–260°) was removed by filtration and the filtrate was concentrated *in vacuo* on the steam bath. The residual oil [$\lambda_{max}^{CCl_4}$ (μ) 1.49 (amide NH), 1.53 (amine NH); $\lambda_{max}^{CHCl_3}$ (μ) 5.65 (ester >C=O), 6.01 (amide > C=O)] was taken up in dry ether and treated with excess ethereal hydrogen chloride. No precipitate resulted so the solution was concentrated to dryness and the residual solid was recrystallized from acetone to give 8.0 g. (80%) of XIb, m.p. 209–210°. One more recrystallization for analysis gave 6.6 g., m.p. 212–213°, $\lambda_{max}^{CHCl_3}$ (μ) 5.66 (ester >C=O), 5.96 (amide >C=O), pK_a (water—extrapolated) 4.0, for the n.m.r. spectrum see Table IVC.

Anal. Calcd. for $C_{29}H_{39}ClN_2O_3$: C, 69.79; H, 7.88; N, 5.61. Found: C, 69.81; H, 7.96; N, 5.58.

An attempt to prepare the O,N-diacetyl derivative by refluxing the amino amide VII (R = cyclohexyl) with excess acetyl chloride for 48 hr. failed. Only the mono-O-acetyl derivative could be obtained *even in the presence of excess triethylamine.*

Substituting propionyl chloride for the acetyl chloride in the foregoing procedure gave the similarly ether soluble **N-cyclohexyl-β-cyclohexylamino-α-(o-propionoxyphenyl)-α-phenylpropionamide hydrochloride (XIc)** in 53% yield, m.p. 190–191°, $\lambda_{max}^{CHCl_3}$ 5.69 μ (ester >C=O), 5.98 μ (amide >C=O).

Anal. Calcd. for $C_{30}H_{41}ClN_2O_3$: C, 70.22; H, 8.06; N, 5.46. Found: C, 70.18; H, 8.06; N, 5.67.

Substituting the amino amide VII (R = cyclopropyl) for the cyclohexyl analog and ethyl chloroformate for the acetyl chloride in the foregoing procedure gave **N-cyclopropyl-β-cyclopropylamino-α-(o-ethoxycarbonyloxy)-α-phenylpropionamide hydrochloride (XIa)**, m.p. 177–178°, $\lambda_{max}^{CHCl_3}$ 1.49 μ (NH), 1.63 μ (cyclopropyl), 5.69 μ (ester >C=O), 5.89 μ (amide >C=O).

Anal. Calcd. for $C_{24}H_{29}ClN_2O_4$: C, 64.77; H, 6.57; N, 6.30; O, 14.38. Found: C, 64.62; H, 6.39; N, 6.29; O, 14.57.

Treatment of the amino acetamide V (R = cyclohexyl) with acetyl chloride according to the above procedure and isolation of the product as the base gave, in 45% yield, **N-cyclohexyl-α-cyclohexylamino-α-(o-acetoxyphenyl)-α-phenylacetamide (Xa)**, m.p. 143–144°, $\lambda_{max}^{CHCl_3}$ (μ) 3.02 (NH), 5.67 (ester >C=O), 6.01 (amide >C=O).

Anal. Calcd. for $C_{28}H_{36}N_2O_3$: C, 74.97; H, 8.09; N, 6.24. Found: C, 75.07; H, 8.14; N, 6.31.

Likewise, from propionyl chloride and V (R = cyclohexyl) was obtained in 40% yield, **N-cyclohexyl-α-cyclohexylamino-α-(o-propionoxyphenyl)-α-phenylacetamide (Xb)**, m.p. 118–119°, $\lambda_{max}^{CHCl_3}$ (μ) 3.01 (NH), 5.68 (ester >C=O), 6.01 (amide >C=O).

Anal. Calcd. for $C_{29}H_{38}N_2O_3$: C, 75.29; H, 8.28; N, 6.05. Found: C, 75.74; H, 8.39; N, 5.77.

Acknowledgment—We wish to thank Mr. Dave 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 and Mr. N. F. Ryan for technical assistance; and Mr. T. F. Page, Jr., Battelle Memorial Institute, and Dr. R. W. Mattoon for the n.m.r. spectra.

Neighboring Group Reactions. IX. Some Cyclic Imidates and Related Lactones with Functional Substituents

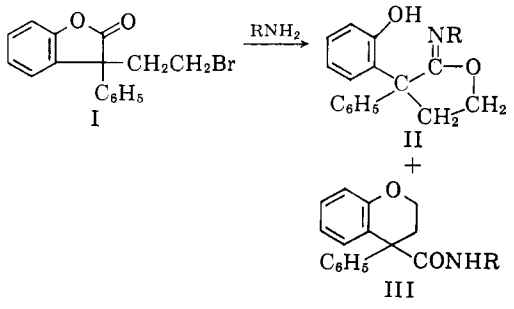
H. E. ZAUGG AND R. J. MICHAELS

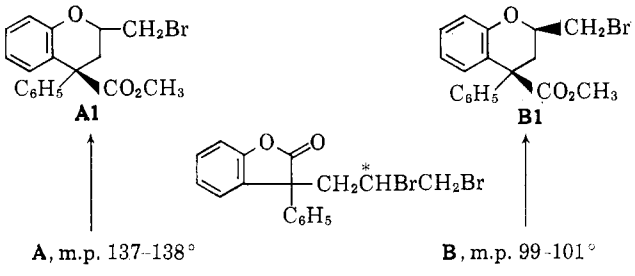
Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received January 11, 1963

Cyclopropylamine effects preferential and stereospecific intramolecular displacement of the 2′-bromine atom from the two diastereoisomers **A** and **B** of 3-(2′,3′-dibromopropyl)-3-phenyl-2-benzofuranone. Fair yields (60–70%) of the geometrically isomeric cyclic imidates **A2** and **B2** result. The multiplicity and variable proximity of functional groups in these compounds, as well as in the isomeric lactones (**A4** and **B4**) derived from them, lead to a variety of intramolecular reactions. These are summarized in the accompanying flow chart.

The purpose of the present work was the development of a synthetic sequence derived from the combination of results reported in two previous papers of this series. The accompaning paper[1] described the reaction of 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I) with primary amines. Products consisted of varying amounts of cyclic imidates II and rearranged amides III. Another report[2] described the reactions of the two diastereoisomeric dibromopropylbenzofuranones **A** and **B** with sodium methoxide. In each case preferential and stereospecific displacement of the secondary bromine atom occurred with rearrangement to give the geometrically isomeric bromo esters **A1** and **B1**,[3] respectively, in good yields (89–96%). Similar selective behavior of **A** and **B** toward primary amines, analogous to that of I to produce II, would be expected to yield products possessing an unusual combination of functional groups in a single molecule. Cyclopropylamine was chosen to verify this expectation because it, of all the primary amines used[1] in reactions with I, produced the best yields of II at the expense of III. Reactions of **A** and **B** with cyclopropylamine and subsequent transformations of the resulting products are outlined in the attendant chart.





Treatment of the isomeric dibromides **A** and **B** with cyclopropylamine at room temperature gave the expected cyclic imidates **A2** and **B2**, respectively, in 73% and 58% yields.[4] These products each contain two electrophilic carbon atoms (>C=N— and —CH_2Br)

(1) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *J. Org. Chem.*, **28**, 1795 (1963).

(2) H. E. Zaugg, R. W. DeNet, and E. T. Kimura, *J. Med. Pharm. Chem.*, **5**, 430 (1962).

(3) The notational convention used in this paper is designed to facilitate recognition of the steric relationships among isomers. For example, all products derived from **A**, m.p. 137–138°, by only one inversion at the carbon atom marked with an asterisk, are members of the **A** family. The **B** family derives similarly from **B**, m.p. 99–101°. It follows that two inversions at this asymmetric center effect family interconversion. Two compounds with the same number (*e.g.*, **A1**, **B1**) constitute diastereoisomeric pairs.

(4) The infrared spectra of these bases were typical of this structure (*i.e.*, II[1]), namely broad and weak absorption centered at 3.9 μ (bonded OH) and strong absorption at 5.87–5.88 μ (C=N). The neutral fractions of these reactions were not examined for the presence of rearranged amide [*i.e.*, the 2-bromomethyl derivative of III (R = cyclopropyl)].