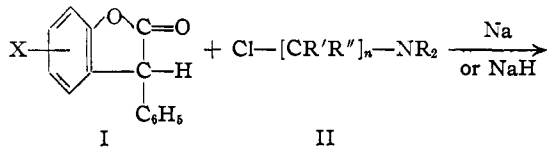
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Antispasmodics. Derivatives of 3-Phenyl-2-benzofuranone[1]

BY ARTHUR W. WESTON AND WM. B. BROWNELL

A series of 3-aminoalkyl-3-aryl-2-benzofuranones, prepared for the most part by direct alkylation of the parent 3-aryl-2-benzofuranones with the appropriate N,N-disubstituted aminoalkyl chloride, is described. These products have been evaluated as antispasmodics and were found to possess appreciable activity.

Within recent years, many diverse types of compounds have been investigated in an effort to find a synthetic antispasmodic drug which would combine both the musculotropic action of papaverine and the neurotropic activity of atropine without exhibiting the undesirable effects of the latter. For the most part, the substances found to possess this dual activity to any appreciable degree have been esters.[2] The present paper[3] describes the synthesis of a new series of compounds, the 3-aminoalkyl-3-aryl-2-benzofuranones (III), which may be regarded as cyclic esters. The general method of preparation may be schematically illustrated as



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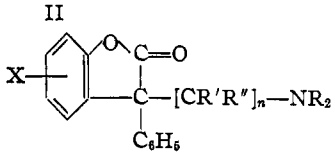
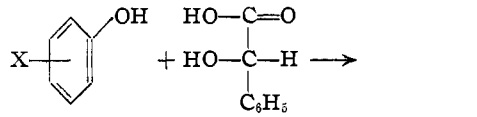
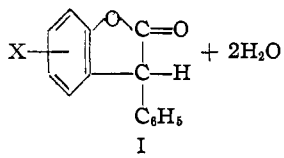


II III

The parent 3-phenyl-2-benzofuranones (I) were prepared according to the original directions of Bistrzycki by heating the appropriately substituted





I

phenol with mandelic acid[4a] or mandelonitrile[4b] in the presence of sulfuric acid, or by the direct fusion of mandelic acid and the phenol as described by Arventi.[5] Substitution in the 3-phenyl group was achieved by condensation of *m*-methylmandelic acid with phenol which gave 3-(*m*-tolyl)-2-benzofuranone.

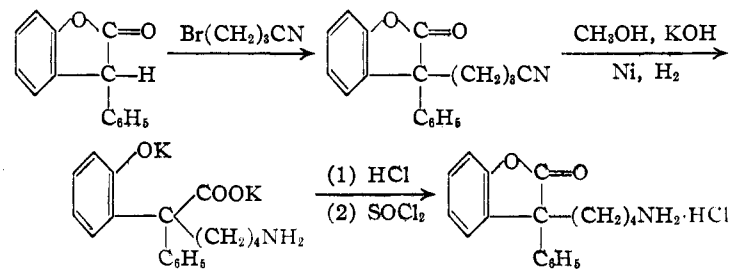
Subsequent reaction of the sodio derivatives of I with the N,N-disubstituted aminoalkyl chlorides produced the desired products (III, see Table I). Proof that C-alkylation than O-alkylation occurs in such a reaction has been previously furnished by Lowenbein and Simonis[6] who employed other types of halides.

The temperature at which the condensation took place and the nature of the basic alkyl chloride had distinct effects on the amount of final compound obtained. This was due, apparently, to the competitive side reaction which involved the formation of quaternary ammonium salts[7] from the basic alkyl chlorides.

An alternate synthesis of one of these compounds, 3 - (γ - morpholinopropyl) - 3 - phenyl - 2 - benzofuranone, was also investigated. From 3-phenyl-2-benzofuranone and trimethylene chlorobromide there was obtained the 3-(γ-chloropropyl) derivative which yielded the desired product upon condensation with excess morpholine in boiling benzene.

Since the instability of the β-*n*-butylaminoethyl and γ-aminobutyl chlorides precluded their direct introduction into the benzofuranone molecule, indirect methods were employed to obtain the benzofuranones containing these side chains. For the *n*-butylamino derivative, condensation of 3-phenyl-2-benzofuranone with β-(benzyl-*n*-butylamino)-ethyl chloride, followed by reductive cleavage of the benzyl group proved satisfactory.

The approach to the δ-aminobutyl compound is indicated in the scheme



The lactone ring of these 3,3-disubstituted benzofuranones shows considerable stability toward acids and bases, a property of distinct advantage in therapeutic agents of this type. Actually, lactonization of the corresponding *o*-hydroxyphenylphenylacetic acid derivatives occurs in strong acid solution and some of the hydrochlorides of these basic benzofuranones may be crystallized from dilute (6 *N*) hydrochloric acid. The ring is also relatively stable toward alkali; the free bases dissolve in al-

(1) Presented, in part, before the Medicinal Division of the American Chemical Society, Atlantic City, N. J., April, 1946.

(2) Reviews of the previous research in this field have been published by A. L. Raymond, *J. Am. Pharm. Assoc., Sci. Ed.*, **32**, 249 (1943) and F. F. Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

(3) For related papers see A. W. Weston, THIS JOURNAL, **68**, 2345 (1946); A. W. Weston and R. W. DeNet, *ibid.*, **73**, 4221 (1951).

(4) (a) A. Bistrzycki and J. Flatau, *Ber.*, **28**, 989 (1895); (b) A. Bistrzycki and H. Simonis, *ibid.*, **31**, 2812 (1898).

(5) B. I. Arventi, *Ann. sci. univ. Jassy.*, **24**, 72 (1938); *C. A.*, **33**, 1693 (1939).

(6) A. Lowenbein and H. Simonis, *Ber.*, **57**, 2040 (1924.)

(7) See C. F. Gibbs and C. S. Marvel, THIS JOURNAL, **56**, 725 (1934), and previous papers.

kali only after prolonged heating. It has also been observed that no opening of the ring occurs upon refluxing a benzene solution of some of the bases with excess of an amine, such as morpholine.

Most of these basic benzofuranones exhibit a musculotropic action comparable to that of papaverine and, in many cases, strong neurotropic activity is also present. Some of the members of this series also have a local anesthetic effect, a property often associated with antispasmodic drugs. The most promising compound, AP-43, 3-(β-diethylaminoethyl)-3-phenyl-2-benzofuranone (Amethone), possesses approximately $^1/_{10}$ the activity of atropine against acetylcholine and twice the activity of papaverine against barium chloride spasms of the isolated rabbit ileum. A detailed report on the pharmacological properties of several of these compounds has previously appeared.[8]

Experimental

N,N-Disubstituted Aminoalkyl Chlorides.—The β-dimethylaminoethyl,[9a] β-diethylaminoethyl,[9a,10] β-dibutylaminoethyl,[11] β-piperidinoethyl,[11,12] β-morpholinoethyl,[9b,11] β-diethylaminopropyl,[13] γ-diethylaminopropyl,[9a,14] γ-dibutylaminopropyl,[9c,12,14b,15] γ-morpholinopropyl[14b] and ω-diethylaminoundecyl[16] chlorides have been described previously.

β-(Benzyl-*n*-butylamino)-ethanol.—A mixture of 64 g. (0.5 mole) of benzyl chloride and 117 g. (1.0 mole) of β-*n*-butylaminoethanol in 400 cc. of dry benzene was refluxed 20 hours. The benzene layer was washed with water, concentrated at reduced pressure and the residue distilled. The product boiled at 138–140° at 4 mm., $n^{25}D$ 1.5072, and amounted to 89.4 g. (86%).

Anal. Calcd. for $C_{13}H_{21}NO$: N, 6.76. Found: N, 6.83.

β-(Benzyl-*n*-butylamino)-ethyl Chloride.—To a solution of 51 g. (0.43 mole) of thionyl chloride in 250 cc. of dry benzene, 89.4 g. (0.43 mole) of β-(benzyl-*n*-butylamino)-ethanol was slowly added while the temperature was maintained at 25–30°. The solution was stirred for 15 minutes at room temperature then refluxed for one hour. The product was removed from the benzene by washing with water. The aqueous washings were combined, filtered through Darco and made alkaline. The ether extracts of the liberated base were combined, dried and distilled whereupon 76.8 g. (79%) of material, b.p. 127–129° at 3 mm., was obtained.

Anal. Calcd. for $C_{13}H_{20}ClN$: N, 6.20. Found: N, 6.15.

γ-Morpholino-β,β-dimethylpropyl Chloride.—By treatment of 51.9 g. (0.3 mole) of γ-morpholino-β,β-dimethylpropanol[17] in the foregoing manner with excess (100 cc.) thionyl chloride in 200 cc. of dry benzene and refluxing the mixture for three hours the corresponding chloride was obtained. The excess reagent was removed before extracting the hydrochloride with water. The base was isolated as described above and boiled at 84–85° at 5 mm., $n^{27}D$ 1.4660. The weight was 48.4 g. (94%).

Anal. Calcd. for $C_9H_{18}ClNO$: Cl, 18.50. Found: Cl, 18.64.

3-Aryl-2-benzofuranones.—The 3-phenyl-,[4,5] 5-chloro-3-phenyl,[18] 5-bromo-3-phenyl-,[18] 5-methyl-3-phenyl-,[5] 7-methyl-3-phenyl-[5] and 4,5-benzo-3-phenyl-2-benzofuranone[19] have been reported previously.

5-Propyl-3-phenyl-2-benzofuranone.—The reaction product, obtained by heating 68 g. (0.5 mole) of *p*-*n* propylphenol[20] and 38 g. (0.25 mole) of mandelic acid in a bomb at 230° for 45 minutes, was cooled and poured with stirring into excess 10% sodium carbonate solution. The oil was extracted with ether. The combined extracts were washed with water, dried and the solvent evaporated. The excess *p*-*n*-propylphenol (34 g.) was recovered at reduced pressure. The residue which solidified on cooling was crystallized from alcohol whereupon 23 g. (36%) of product, m.p. 56–57° was obtained.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.92; H, 6.40.

3-(*m*-Tolyl)-2-benzofuranone.—A mixture of 10 g. (0.06 mole) of *m*-methylmandelic acid,[21] 10 g. (0.11 mole) of phenol and 30 cc. of 73% sulfuric acid was stirred and heated over a free flame to 120–130° and then poured on ice. The tarry product which separated was converted to crystalline material by stirring with 10% sodium carbonate solution. The solid was removed by filtration and crystallized from dilute alcohol. It weighed 3.6 g. (27%) and melted at 88°.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 80.40; H, 5.00.

3-Aminoalkyl-3-aryl-2-benzofuranones.—The following examples will serve to illustrate the general methods of preparation.

3-(β-Diethylaminoethyl)-3-phenyl-2-benzofuranone (AP-43).[22]—To a stirred suspension of 34.5 g. (1.5 moles) of finely divided sodium in 300 cc. of toluene, diluted with two liters of benzene, there was added portionwise 315 g. (1.5 moles) of 3-phenyl-2-benzofuranone.[4,5] The mixture was brought to reflux to ensure complete utilization of the sodium metal. To the resulting solution of the sodium salt, maintained at room temperature, 227 g. (1.67 moles) of β-diethylaminoethyl chloride was slowly added. Finally, the reaction mixture was stirred 60 hours at room temperature, then cooled and washed with water. The solvent layer was separated and extracted several times with dilute acid. The base, which was subsequently liberated by treatment of the combined acidic extracts with excess sodium carbonate solution, was extracted with ether. The combined extracts were dried, concentrated and distilled. The material boiling at 192–194° at 2 mm., $n^{24.5}D$ 1.5614, weighed 402 g. (87%). The base slowly solidified and after crystallization from petroleum ether, melted at 43–44°.

The hydrochloride prepared in the usual manner melted at 152–153° after crystallization from isopropyl alcohol.

The methobromide salt was prepared by allowing a solution of 15.45 g. (0.05 mole) of the above base and 19 g. (0.10 mole) of methyl bromide in 100 cc. of absolute alcohol to stand six days. The oil which remained after removal of the alcohol was slurried with ether and on standing slowly solidified. This material was crystallized from ethyl methyl ketone and melted at 132–133°.

4,5-Benzo-3-(β-diethylaminoethyl)-3-phenyl-2-benzofuranone (AP-88).—In this instance, the sodium salt was obtained by employing 5.0 g. (0.104 mole) of sodium hydride[23] and 26.0 g. (0.10 mole) of 4,5-benzo-3-phenyl-2-benzofuranone[19] in a benzene medium. The sodio derivative formed rapidly accompanied by the evolution of hydrogen. Following the addition of 13.6 g. (0.1 mole) of β-diethylaminoethyl chloride, the reaction mixture was stirred one hour at room temperature then refluxed 15 hours. The benzene layer was washed with

(8) R. K. Richards, G. M. Everett and K. E. Kueter, *J. Pharmacol.*, **84**, 387 (1945).

(9) (a) K. H. Slotta and R. Behnisch, *Ber.*, **68**, 758 (1935); (b) J. P. Mason and H. W. Block, THIS JOURNAL, **62**, 1445 (1940); (c) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

(10) G. A. C. Gough and H. King, *J. Chem. Soc.*, 2436 (1928).

(11) F. F. Blicke and C. E. Maxwell, THIS JOURNAL, **64**, 429 (1942).

(12) F. F. Blicke and H. M. Kaplan, *ibid.*, **65**, 1970 (1943).

(13) J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, *ibid.*, **69**, 2961 (1947).

(14) (a) O. J. Magidson and I. Th. Strukow, *Arch. Pharm.*, **271**, 572 (1933); (b) R. R. Adams and F. C. Whitmore, THIS JOURNAL, **67**, 736 (1945); (c) H. Gilman and D. A. Shirley, *ibid.*, **66**, 889 (1944); (d) D. S. Breslow, *et al.*, *ibid.*, **67**, 1474 (1945).

(15) F. F. Blicke and E. L. Jenner, *ibid.*, **64**, 1723 (1942).

(16) O. J. Magidson, O. S. Madajewa and M. W. Rubzow, *Arch. Pharm.*, **273**, 331 (1935).

(17) L. C. Cheney and W. G. Bywater, THIS JOURNAL, **64**, 970 (1942).

(18) R. Sotermer, *Ber.*, **44**, 1863 (1911); B. I. Arventi, *Bull. soc. chim. France*, [5] **3**, 602 (1936).

(19) A. Bistrzycki and J. Flatau, *Ber.*, **30**, 124 (1897); H. Simonis, *ibid.*, **31**, 2821 (1898).

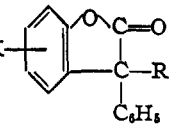
(20) E. Clemmensen, *ibid.*, **47**, 53 (1914).

(21) E. Bornemann, *ibid.*, **17**, 1469 (1884).

(22) This product, Amolanone Hydrochloride, is produced under the Abbott trademark, Amethone.

(23) This material was kindly supplied by the Electrochemicals Department, E. I. du Pont de Nemours and Company.

TABLE I

3-AMINOALKYL-3-ARYL-2-BENZOFURANONES X- 

Code no.[a] (AP)	Ring subst. (X)	Side chain (R)	B.p. °C.	Mm.	Ref. index n_D	t, °C.	M.p.,[b] °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
45	None	$CH_2CH_2N(CH_3)_2$	165–166	3	1.5700	25	62–65[c]	24	$C_{18}H_{19}NO_2$	4.98	4.95
43	None	$CH_2CH_2N(C_2H_5)_2$	192–193	2	1.5614	24.5	43–44[c]	87	$C_{20}H_{23}NO_2$	4.53	4.46
89	5-Chloro	$CH_2CH_2N(C_2H_5)_2$					94–95[c]	70	$C_{20}H_{22}NO_2Cl$[d]	4.08	3.96
125	5-Bromo	$CH_2CH_2N(C_2H_5)_2$	205–206	4	1.5808	26	90–92[e]	71	$C_{20}H_{22}NO_2Br$[f]	3.61	3.58
60	5-Methyl	$CH_2CH_2N(C_2H_5)_2$	196	4	1.5591	24		76	$C_{21}H_{25}NO_2$	4.33	4.32
126	7-Methyl	$CH_2CH_2N(C_2H_5)_2$	193–194	4	1.5577	24		69	$C_{21}H_{25}NO_2$	4.33	4.27
127	3'-Methyl[g]	$CH_2CH_2N(C_2H_5)_2$	183–185	3	1.5585	25		33	$C_{21}H_{25}NO_2$	4.33	4.25
92	5-Propyl	$CH_2CH_2N(C_2H_5)_2$	207–208	3	1.5480	24	45–46[c]	75	$C_{23}H_{29}NO_2$[h]	3.99	3.97
88	4,5-Benzo	$CH_2CH_2N(C_2H_5)_2$					98.5–99.5[e]	59[i]	$C_{24}H_{23}NO_2$[j]	3.90	3.86
138	None	$CH_2CH_2NHC_4H_9$-n					103–104[k]		$C_{20}H_{23}NO_2$	4.54	4.53
56	None	$CH_2CH_2NC_4H_8O$[l]	225–227	4			95.5–96.5[e]	66	$C_{20}H_{21}NO_3$[m]	4.33	4.29
59	None	$CH_2CH_2NC_5H_{10}$[n]					88–89[e]	78	$C_{21}H_{23}NO_2$[o]	3.91	3.76
82	None	$CH_2CH_2N(C_4H_9$-$n)_2$	210–212	2	1.5383	28		74	$C_{24}H_{31}NO_2$	3.91	3.49
136	None	$CH_3CH_2N(C_4H_9$-$n)(CH_2C_4H_8)$	225–227	<1	1.5760	22		63	$C_{27}H_{35}NO_2$	3.50	3.46
66	None	$CH_2CH(CH_3)N(C_2H_5)_2$[p]	174–175	2	1.5581	25		81	$C_{21}H_{25}NO_2$	4.33	4.28
67	None	$CH_2CH_2CH_2N(C_2H_5)_2$	187–189	2	1.5510	24		16	$C_{21}H_{25}NO_2$	4.33	4.35
58	None	$CH_2CH_2CH_2NC_4H_8O$[l]					83–84[e]	64[q]	$C_{21}H_{23}NO_3$[r]	4.15	4.21
81	None	$CH_2CH_2CH_2N(C_4H_9$-$n)_2$	209–210	<1	1.5278	29		33	$C_{25}H_{41}NO_2$	3.79	3.79
118	None	$CH_2C(CH_3)_2CH_2NC_4H_8O$[l]	219–220	2	1.5622	24	94.5–95.5[e]	73[q]	$C_{23}H_{27}NO_3$	3.83	3.84
86	None	$CH_2CH_2CH_2CH_2NH_2$					115–116[s]	[t]	$C_{18}H_{19}NO_2$	4.98	4.93
132	None	$CH_2(CH_2)_2CH_2N(C_2H_5)_2$	205–210	0.1	1.5224	26		17[q]	$C_{23}H_{31}NO_2$	3.22	3.23

[a] Antispasmodic code number. [b] All melting points are uncorrected. [c] Crystallized from petroleum ether, b.p. 63–68°. [d] Calcd.: C, 69,86; H, 6.45. Found: C, 70.02; H, 6.25. [e] Crystallized from alcohol. [f] Calcd.: C, 61.86; H, 5.71; Br, 20.58. Found: C, 62.09; H, 5.67; Br, 20.32. [g] Prepared from 3-(*m*-tolyl)-2-benzofuranone. [h] Calcd.: C, 78.59; H, 8.32. Found: C, 78.76; H, 8.19. [i] Crude yield. [j] Calcd.: C, 80.19; H, 7.01. Found: C, 80.32; H, 6.91. [k] Crystallized from methanol. [l] NC_4H_8O represents the morpholino group. [m] Calcd.: C, 74.28; H, 6.55. Found: C, 74.48; H, 6.43. [n] NC_5H_{10} represents the piperidino group. [o] Calcd.: C, 78.47; H, 7.21. Found: C, 78.68; H, 7.24. [p] The structure of this product was not determined. The work of E. M. Schultz and J. N. Sprague, THIS JOURNAL, 70, 48 (1948), indicates that a mixture of the two possible side chain isomers, each of which exists in two racemic modifications, is probably present. [q] Corrected for recovered basic alkyl chloride. [r] Calcd.: C, 74.75; H, 6.87. Found: C, 74.71; H, 6.68. [s] Crystallized from dilute alcohol. [t] Isolated as hydrochloride salt, crude yield 87%.

water and extracted with dilute hydrochloric acid. During this extraction process, a solid began to separate. By cooling the acidic extracts in ice and collecting this solid by filtration, 23.3 g. (59%) of the hydrochloride of the desired product, m.p. 174–178°, was obtained. Crystallization of this material from absolute alcohol raised the melting point to 184–185°.

The free base liberated from an aqueous solution of the hydrochloride by sodium carbonate, melted at 98.5–99.5° after crystallization from alcohol.

3-(γ-Chloropropyl)-3-phenyl-2-benzofuranone.—The sodium salt from 105 g. (0.5 mole) of 3-phenyl-2-benzofuranone and 12.5 g. (0.50 mole) of sodium hydride in 400 cc. of dry benzene was prepared as previously described. Following the addition of 86.5 g. (0.55 mole) of trimethylene chlorobromide, the mixture was refluxed 36 hours, then cooled and washed with water. The solvent was removed and the residue distilled. A large forerun consisting of unreacted trimethylene chlorobromide and 3-phenyl-2-benzofuranone was followed by 60.3 g. (42%) of the chloropropyl derivative, b.p. 164–180° at 0.5 mm. Redistillation of this material gave 41.2 g. of oil, b.p. 170–173° at 0.5 mm. The product solidified on standing and melted at 75–76° after crystallization from alcohol.

Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 71.20; H, 5.27. Found: C, 71.52; H, 5.29.

3-(γ-Morpholinopropyl)-3-phenyl-2-benzofuranone Hydrochloride (AP-58).—A solution of 15 g. (0.05 mole) of the foregoing chloride and 18 g. (0.20 mole) of morpholine in 200 cc. of dry benzene was boiled for 90 hours. The morpholine hydrochloride (3.7 g.) which had separated during the reaction was removed by filtration and the benzene solution was extracted with dilute acid. Since the hydrochloride of the product began to precipitate from the acidic extracts, the aqueous mixture was cooled and the solid (11 g.) collected by filtration. Crystallization of this material from 100 cc. of dilute hydrochloric acid (1:1) gave 9 g. (48%) of product, m.p. 237–238°. There was no depression of the melting point when this substance was mixed with the material obtained from the condensation of 3-phenyl-2-benzofuranone with γ-morpholinopropyl chloride.

3-(γ-Cyanopropyl)-3-phenyl-2-benzofuranone.—The sodio derivative from 50 g. (0.24 mole) of 3-phenyl-2-benzofuranone was prepared in the previously described manner from 6.5 g. (0.27 mole) of sodium hydride in 200 cc. of dry benzene. Following the addition of 36 g. (0.24 mole) of γ-bromobutyronitrile,[24] the solution was refluxed and stirred for 20 hours. The benzene layer was washed with water, dried, concentrated and the residue distilled. The yield was 45.0 g. (68%) of an oil, b.p. 227–228° at 4 mm., $n^{25}D$ 1.5765. The material solidified on standing and melted at 98–99° after crystallization from alcohol.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 5.11.

3-(δ-Aminobutyl)-3-phenyl-2-benzofuranone Hydrochloride (AP-86).—The above nitrile, 27.7 g. (0.1 mole), was dissolved in 100 cc. of methyl alcohol containing 12 g. of potassium hydroxide. This solution was shaken with Raney nickel, filtered, diluted to a volume of 150 cc. with methyl alcohol and hydrogenated in the presence of more Raney nickel at 120° using 900 lb. hydrogen pressure. The theoretical amount of hydrogen was absorbed in 15 minutes. The catalyst was removed by filtration and washed with methyl alcohol. The residue which remained after removal of the alcohol from the filtrate was dissolved in water. The resulting solution was extracted with ether and evaporated to dryness. To ensure the removal of traces of water, several volumes of chloroform were distilled from the residue. The final chloroform suspension was treated first with gaseous hydrogen chloride then with excess thionyl chloride. The solvent and excess reagent were removed on the steam-bath and water added to the residue. The resulting oil crystallized and the solid was removed by filtration and dried. The material weighed 27.8 g. (87%) and melted at 100–105°. Several crystallizations from ab-

(24) C. G. Derick and R. W. Hess, THIS JOURNAL, 46, 546 (1918).

TABLE II

SALTS OF 3-AMINOALKYL-3-ARYL-2-BENZOFURANONES

Code no.[a] (AP)	Formula	M.p.,[b] °C.	Solvent[c]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogn Calcd.	Nitrogn Found
45	$C_{16}H_{19}NO_2 \cdot HCl$	209–210	Ac-E	68.02	68.25	6.34	6.28	4.41	4.49
43	$C_{20}H_{23}NO_2 \cdot HCl$[d]	152–153	I	69.45	69.46	6.99	6.98	4.05	4.05
146	$C_{20}H_{23}NO_2 \cdot HBr$[d]	165–165	AA	61.54	61.76	6.20	6.22	3.59	3.50
135	$C_{20}H_{23}NO_2 \cdot HSO_4$[d]	136–137	AA	59.10	59.04	5.95	6.05	3.45[e]	3.21
124	$C_{20}H_{23}NO_2 \cdot CH_3Br$[d]	132–133	B	62.37	62.13	6.48	6.42	3.47[f]	3.37
89	$C_{20}H_{22}NO_2Cl \cdot HCl$	186–187	AA-E	63.10	63.38	6.10	5.86	3.68	3.64
125	$C_{26}H_{22}NO_2Br \cdot HCl$	178–179	Ac-E	56.55	56.81	5.46	5.31	3.30	3.22
60	$C_{21}H_{25}NO_2 \cdot HCl$	143–144.5	Ac-E	70.08	69.99	7.28	7.00	3.89	3.91
126	$C_{21}H_{25}NO_2 \cdot HCl$	171.5–173	Ac-E	70.08	70.36	7.28	7.41	3.89	3.88
127	$C_{21}H_{25}NO_2 \cdot HCl$	147.5–149	Ac-E	70.08	70.29	7.28	7.29	3.89	3.87
92	$C_{23}H_{29}NO_2 \cdot HCl$	131–133	Ec-E	71.20	71.13	7.80	7.65	3.61	3.50
88	$C_{24}H_{25}NO_2 \cdot HCl$	184–185	AA	72.80	72.54	6.62	6.80	3.54	3.49
138	$C_{20}H_{23}NO_2 \cdot HCl$[g]	136–137	Ac-E	61.54	...	6.20	..	4.05	3.99
137	$C_{20}H_{23}NO_2 \cdot HBr$[g]	158–159	Ac-E	61.54	61.77	6.20	6.12	3.59	3.56
56	$C_{20}H_{21}NO_3 \cdot HCl$	212–213	AA-E	66.75	66.81	6.16	5.93	3.89	3.80
59	$C_{21}H_{23}NO_3 \cdot HCl$	215–216	AA-E	70.48	70.64	6.74	6.61	3.91	3.76
82	$C_{24}H_{31}NO_2 \cdot HCl$	120–121	Ac-E	71.70	71.84	8.03	7.96	3.49	3.46
136	$C_{27}H_{30}NO_2 \cdot HCl$	134–136	Ac-E	74.22	74.54	7.15	6.97	3.21	3.20
66	$C_{21}H_{25}NO_2 \cdot HCl$	198–205[h]	Ac-E	70.08	70.11	7.28	7.12	3.89	3.83
67	$C_{21}H_{25}NO_2 \cdot HCl$	170–171	AA-E	70.08	70.29	7.28	7.29	3.89	3.86
58	$C_{21}H_{23}NO_3 \cdot HCl$	237–238	AA-E	68.03	67.85	6.62	6.49	3.75	3.70
81	$C_{25}H_{33}NO_2 \cdot HCl$	136–137	Ac-E	72.18	72.09	8.24	8.21	3.37	3.29
118	$C_{23}H_{27}NO_4 \cdot HCl$	219–220.5	I	68.73	68.99	7.02	6.78	3.49	3.40
86	$C_{18}H_{19}NO_2 \cdot HCl \cdot H_2O$	96–99	W	64.37	64.24	6.60	6.41	4.17	4.30

[a] Antispasmodic code number. [b] All melting points uncorrected. [c] Legend: Ac, acetone; E, absolute ether; AA, absolute alcohol; B, butanone-2; Ec, ethyl acetate; I, isopropyl alcohol; W, water. [d] Salts of the same base (AP-43). [e] *Anal.* Calcd.: S, 7.90. Found: S, 7.88. [f] *Anal.* Calcd.: Br, 19.76. Found: Br, 20.04. [g] Salts of the same base (AP-138). [h] See note *p*, Table I.

solute alcohol–ether gave m.p. 108–110°. Since the analyses indicated partial hydration, the product was crystallized from water with the subsequent formation of the monohydrate, m.p. 96–99°.

Addition of alkali to a solution of the hydrochloride salt precipitated the solid base which melted at 115–116° after crystallization from dilute alcohol.

3-(β-*n*-Butylaminoethyl)-3-phenyl-2-benzofuranone (AP-138).—3-(β-Benzyl-*n*-butylaminoethyl)-3-phenyl-2-benzofuranone, 24.0 g. (0.06 mole), was dissolved in 50 cc. of glacial acetic acid and reduced with 1% of its weight of platinum oxide at 70° with 45 lb. hydrogen pressure. The theoretical amount of hydrogen was taken up in five hours. The catalyst was removed by filtration and washed with acetic acid. The crystalline base, which separated on cooling the filtrate, was collected by filtration and crystallized from methanol. It melted at 103–104°.

Salts of the Basic Benzofuranones.—The hydrochlorides and sulfates were precipitated in the usual manner from ether and crystallized from a suitable solvent.

The hydrobromide salts were prepared by adding the base to concentrated hydrobromic acid (48%), evaporating the solution to dryness and crystallizing the residue from an appropriate solvent.

Pertinent data on these salts are contained in Table II.

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