*Anal.* Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.21; H, 4.45; N, 24.33.

β-(2-Benzimidazolyl)-β-alanine did not form a hydantoin under similar conditions.

*Reactions of monobasic α-amino acids with o-phenylenediamine. 2-Aminomethylbenzimidazole dihydrochloride* (XI). A solution of 10.8 g. (0.1 mole) of *o*-phenylenediamine and 11.25 g. (0.15 mole) of glycine in 100 ml. of 5.5*N* hydrochloric acid was refluxed for 30 hr. At this point paper chromatography indicated that little *o*-phenylenediamine remained. The solution was allowed to stand in the cold overnight and the hydrochloride then removed by filtration. It was recrystallized from ethanol with the aid of decolorizing carbon; yield 12.1 g. (56%), m.p. 263° dec. Two melting point values are reported in the literature, 263°[9] and 267°.[11] The sample for analysis was dried for 6 hr. over potassium hydroxide at 110° and 2 mm. Longer drying at 110° causes the loss of hydrogen chloride.

*Anal.* Calcd. for $C_8H_9N_3 \cdot 2HCl$: C, 43.65; H, 5.04; N, 19.09; Cl, 32.22. Found: C, 43.77; H, 5.11; N, 18.92; Cl, 31.94.

Infrared: 1630 (s), 1488 (s), 1430 (s), 1220 (s), 900 (s), 878 (s), 770 (s). Ultraviolet: 270 mμ (log ε 4.14), 277 mμ (4.09).

*2-(β-Aminoethyl)benzimidazole dihydrochloride* (XII). A solution of 10.8 g. (0.1 mole) of *o*-phenylenediamine and 13.4 g. (0.15 mole) of β-alanine in 100 ml. of 5.5*N* hydrochloric acid was refluxed for 24 hr. At this time the diamine was barely detectable by paper chromatography. The solution was cooled overnight and the hydrochloride removed by filtration. It was recrystallized from 90% ethyl alcohol with the aid of decolorizing carbon; yield 15.8 g. (68%), m.p. 268–309° dec. Sorb and Urban[12] reported 270–325°. The observed melting point is in reality a mixed m.p. due to a mixture of mono- and dihydrochlorides. Paper chromatography showed two spots: $R_f$ 0.49 fluorescing weakly in the ultraviolet and giving a golden yellow color with ninhydrin (due to the monohydrochloride); and $R_f$ 0.28 fluorescing strongly blue in the ultraviolet and giving a golden yellow color with ninhydrin (due to the dihydrochloride). $R_f$ 0.49 disappeared when an ethanol solution of XII was saturated with hydrogen chloride before chromatograming.

A sample for analysis was recrystallized from ethanol saturated with hydrogen chloride and dried over phosphorus pentoxide for 18 hr. at 76° and 2 mm.

*Anal.* Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95; Cl, 30.29. Found: C, 46.22; H, 5.70; N, 18.17; Cl, 29.95.

Infrared: 1640 (m), 1570 (m), 1525 (m), 1480 (m), 1470 (m), 1225 (m), 1160 (m), 965 (m), 895 (m), 745 (v.s.). Ultraviolet: 269 mμ (log ε 3.99), 276 mμ (4.00).

*2-(α-Aminoethyl)benzimidazole dihydrochloride* (XIII). A solution of 5.4 g. (0.05 mole) of *o*-phenylenediamine and 6.68 g. (0.075 mole) of L-(+)-alanine in 50 ml. of 5.5*N* hydrochloric acid was refluxed for 72 hr. At this time only a very small amount of diamine was detectable. The solution was evaporated and the solid residue taken up in a minimum amount of 4*N* hydrochloric acid. After cooling overnight, the solid was removed by filtration. It was recrystallized from ethanol with the aid of decolorizing carbon, yield 4.95 g. (42%), m.p. 132–138°. Paper chromatography showed the presence of a small amount of monohydrochloride ($R_f$ 0.62) with the dihydrochloride ($R_f$ 0.39). The $R_f$ 0.62 spot disappeared when an ethanol solution of the product, saturated with hydrogen chloride, was chromatogramed.

A sample for analysis was recrystallized from ethanol saturated with hydrogen chloride. It was dried over potassium hydroxide for 6 hr. at 110° and 2 mm., $\alpha_D^{24}$ −6.3° in 1*N* HCl.

*Anal.* Calcd. for $C_9H_{11}N_3 \cdot 2HCl \cdot 1H_2O$: C, 42.87; H, 6.00; N, 16.67; Cl, 28.12. Found: C, 42.78; H, 6.19; N, 16.47; Cl, 27.98.

Infrared: 1615 (m), 1480 (s), 1460 (m), 1228 (m), 1144 (m), 758 (s). Ultraviolet: 270 mμ (log ε 4.03), 277 mμ (3.97).

The benzoyl derivative prepared from equivalent quantities of XIII and benzoyl chloride in pyridine solution was recrystallized from ethanol–ether, m.p. 254–256.5°.

*Anal.* Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.32; H, 5.85; N, 15.82.

PHILADELPHIA 4, PA.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

# Benzofuro[3,2-*b*]indoles

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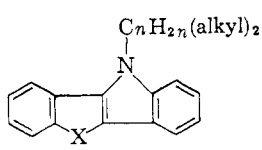
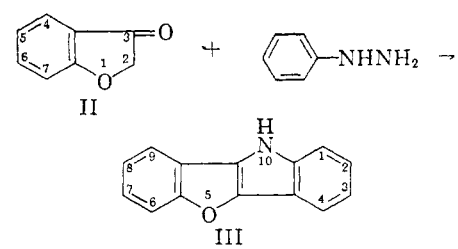
Several benzofuro[3,2-*b*]indoles have been synthesized and some of the intermediates involved were investigated.

The interesting pharmacological activity of certain 10-substituted thianaphtheno[3,2-*b*]indoles (Ia)[1] led us to investigate the synthesis of the corresponding benzofuro[3,2-*b*]indoles (Ib).




Ia. X = S; Ib. X = O

A search of the literature revealed only three references to this class of compounds[2–4] and in all




(1) L. H. Werner, D. C. Schroeder, and S. Ricca, Jr., *J. Am. Chem. Soc.*, 79, 1675 (1957).

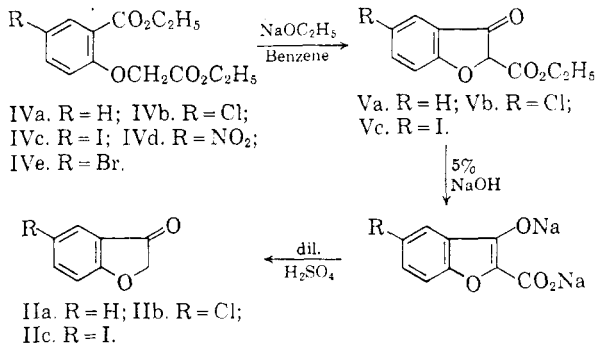
(2) S. R. Cawley and S. G. P. Plant, *J. Chem. Soc.*, 1214 (1938).

(3) J. W. Cornforth, G. K. Hughes, F. Lions, and R. H. Harraderie, *J. Proc. Roy. Soc., N.S. Wales*, 71, 486 (1938); *Chem. Abstr.*, 33, 588 (1939).

(4) D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.*, 4814 (1956).

cases benzofuro[3,2-*b*]indole (III) was prepared by a Fischer indole reaction of phenylhydrazine with 3(2*H*)-benzofuranone (II).

Many different syntheses of II have been reported. We investigated a number of these[5-12] and found them unsatisfactory. Yields were low and the product so badly contaminated that purification was tedious. The most effective method we found was a Dieckmann reaction performed on ethyl *O*-carbethoxymethylsalicylate (IVa).[13]




IVa. R = H; IVb. R = Cl; IVc. R = I; IVd. R = $NO_2$; IVe. R = Br.

Va. R = H; Vb. R = Cl; Vc. R = I.

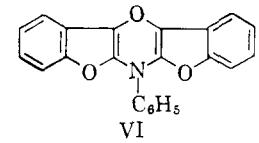
IIa. R = H; IIb. R = Cl; IIc. R = I.

This gave us a pure product in a reasonable yield and was adaptable for the preparation of certain substituted 3(2*H*)-benzofuranones.

IVa was prepared in good yield by esterification of the commercially available *O*-carboxymethylsalicyclic acid. However, we prepared the substituted diesters (IVb, IVc, IVd, and IVe) by *O*-alkylating the appropriate ethylsalicylate with ethyl bromoacetate in ethanolic potassium hydroxide.[14]

Ring closure to Va, Vb, and Vc went readily, but we were unable to accomplish this with the 5-$NO_2$ compound. We tried to accelerate the hydrolysis step by varying the concentration of the alkali and the temperature, but 5% sodium hydroxide at room temperature proved to be the optimum conditions. Solubility seems to be an important factor in this step. Thus, Vc, which is the least soluble, took the longest to hydrolyze. Acidification with dilute sulfuric acid causes immediate decarboxylation to the corresponding 3(2*H*)-benzofuranone.

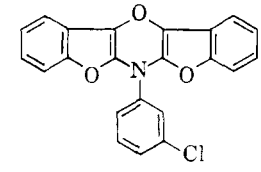
The method of Cawley and Plant[2] was used to convert II to III. Temperature control is essential, but difficult to maintain. The initial heating together of II and phenylhydrazine becomes quite exothermic at approximately 100° and is likely to get out of hand, especially when large quantities are involved. This leads to the formation of various by-products which seriously affect the yield. The desired benzofuroindole can be separated from such a mixture by means of column chromatography over neutral Woelm alumina.[15] Pure III comes off with benzene in the first few fractions. Further elution with benzene–methylene chloride carried down several by-products. One of these, consisting of yellow needles, m.p. 201–202°, has been tentatively assigned the structure VI.[16] Another material was




VI

isolated as red needles, m.p. 216–217°, has the empirical formula $C_{44}H_{32}N_4O_3$. A quantity of green, amorphous powder, m.p. 140–170°, was also recovered.

By limiting our batches to ten grams or less and using an ice bath to control the temperature, we were able to obtain III in good yields. In the same manner, IIb was converted to 8-chlorobenzofuro[3,2-*b*]indole (VII). Treatment of IIa with *meta*-nitrophenylhydrazine gave the 2-nitro derivative (VIII), but IIa and *meta*-chlorophenylhydrazine did not yield the expected 2-chloro compound. Instead, we isolated a product, m.p. 267–269°, which we believe has the structure IX.[17]

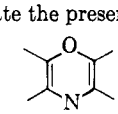



IX

III was converted to the sodio-derivative using sodium amide and treatment with piperidinoethyl chloride and dimethylaminoisopropyl chloride gave the 10-substituted compounds X and XI, respectively. The benzofuro[3,2-*b*]indoles which we prepared and their properties are given in Table III.

(5) R. Stoermer and F. Bartsch, *Ber.*, **33**, 3177 (1900).
(6) P. Friedlander and J. Neudörfer, *Ber.*, **30**, 1081 (1897).
(7) A. Blom and J. Tambor, *Ber.*, **38**, 3589 (1905).
(8) C. J. Schoot and K. H. Klaasens, *Rec. trav. chim.*, **75**, 190 (1956).
(9) K. Fries and W. Pfaffendorf, *Ber.*, **43**, 212 (1910).
(10) R. Stoermer and P. Atenstadt, *Ber.*, **35**, 3562 (1902).
(11) M. L. Kalinowski and L. W. Kalinowski, *J. Am. Chem. Soc.*, **70**, 1970 (1948).
(12) P. Pfeiffer and E. Enders, *Ber.*, **84**, 247 (1951).
(13) P. Friedlander, *Ber.*, **32**, 1867 (1899).
(14) R. W. Merriman, *J. Chem. Soc.*, **99**, 911 (1911).

(15) Alumina was used as received.
(16) *Anal.* Calcd. for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 77.67; H, 4.04; N, 4.26. Infrared spectra shows no —NH or —OH. A medium to strong band at 1635–1645 cm.$^{-1}$ could indicate the presence of the moiety




(17) *Anal.* Calcd. for $C_{22}H_{12}ClNO_3$: C, 70.84; H, 3.24; N, 3.75. Found: C, 70.20; H, 3.47; N, 3.49. Infrared spectra shows no —NH or —OH. A medium to strong band at 1635–1645 cm.$^{-1}$ could indicate the presence of the moiety.

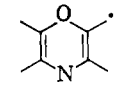
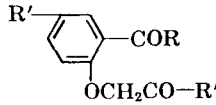
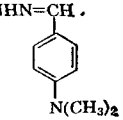
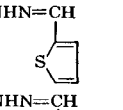
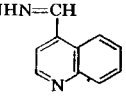


TABLE I

SUBSTITUTED *O*-CARBOXYMETHYLSALICYLIC ACIDS

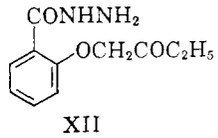



| Compound No. | R | R′ | R″ | Yield, % | M.P.[a] | Empirical Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IVa | —H | —H | $-OC_2H_5$ | 89 | B.p. 123–128 (0.1 mm.)[b] | $C_{13}H_{16}O$ | 61.88 | 61.30 | 6.39 | 6.21 | | |
| IVb | $-OC_2H_5$ | —Cl | $-OC_2H_5$ | 33 | 43–45 | $C_{13}H_{15}ClO_5$ | 54.45 | 54.19 | 5.27 | 5.26 | | |
| IVc | $-OC_2H_5$ | —I | $-OC_2H_5$ | 37 | 73–75 | $C_{13}H_{15}IO_5$ | 41.28 | 41.32 | 3.99 | 4.06 | | |
| IVd | $-OC_2H_5$ | $-NO_2$ | $-OC_2H_5$ | 76 | 70–71 | $C_{13}H_{15}NO_7$ | 52.52 | 52.51 | 5.09 | 5.20 | 4.71 | 4.76 |
| XIVa | $-OC_2H_5$ | —H | $-NHNH_2$ | 53 | 117–119[c] | $C_{11}H_{14}N_2O_4$ | 55.45 | 55.07 | 5.92 | 6.02 | 11.76 | 11.92 |
| XIVb | $-OC_2H_5$ | $-NO_2$ | $-NHNH_2$ | 25 | 153 | $C_{11}H_{13}N_3O_6$ | 46.64 | 46.50 | 4.67 | 4.83 | 14.84 | 14.71 |
| XIVc | $-OC_2H_5$ | —I | $-NHNH_2$ | 47 | 133–135 | $C_{11}H_{13}IN_2O_4$ | 36.30 | 36.39 | 3.60 | 3.75 | | |
| XVa | $-OC_2H_5$ | $-NO_2$ |  | 40 | 179–181 | $C_{20}H_{22}N_4O_6$ | 57.96 | 57.82 | 5.35 | 5.57 | 13.52 | 13.58 |
| XVb | $-OC_2H_5$ | $-NO_2$ |  | 93 | 212–213 | $C_{16}H_{15}N_3O_6S$ | 50.93 | 50.63 | 4.01 | 4.10 | 11.14 | 11.32 |
| XVc | $-OC_2H_5$ | —I |  | 77 | 217–218 | $C_{21}H_{18}IN_2O_4$ | 50.11 | 49.99 | 3.60 | 3.73 | 8.35 | 8.21 |
| XVIa | $-NHNH_2$ | —H | $-NHNH_2$ | 30 | 164–166 | $C_9H_{12}N_4O_3$ | 48.21 | 48.56 | 5.39 | 5.49 | 24.99 | 25.64 |
| XVIb | $-NHNH_2$ | $-NO_2$ | $-NHNH_2$ | 23 | 174–176 | $C_9H_{11}N_5O_5$ | 40.15 | 40.29 | 4.12 | 4.37 | 26.01 | 26.38 |
| XVII | $-NHN{=}CCl_3$ | —H | $-NHN{=}CCl_3$ | 75 | 201–202 | $C_{13}H_{10}Cl_6N_4O_3$ | 32.33 | 32.61 | 2.08 | 2.32 | 11.60 | 11.40 |
| XVIII | $-OC_2H_5$ | H | $-NHNHC_6H_5$ | 49 | 120–121 | $C_{17}H_{18}N_2O_4$ | 64.95 | 64.69 | 5.77 | 5.71 | 8.91 | 8.22 |
| XIX | $-OC_2H_5$ | Br | $-NHCH_2C_6H_5$ | 46 | 104–105 | $C_{18}H_{18}BrNO_4$ | 55.11 | 55.26 | 4.62 | 4.73 | 3.57 | 3.82 |
| XX | $-NHCH_2C_6H_5$ | Br | $-NHCH_2C_6H_5$ | 10[d] | 115 | $C_{28}H_{21}BrN_2O_3$ | 60.93 | 59.79 | 4.67 | 4.71 | 6.18 | 5.92 |

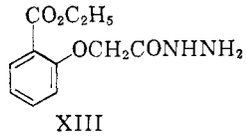
[a] Melting points are uncorrected. [b] Reported[14] b.p. 190–195° (25.0 mm.). [c] T. Curtius *et al.*, *J. prakt. Chem.*, 125, 106–138 (1930), reported m.p. 222°. [d] XX was obtained as a by-product in the preparation of XIX. No doubt the yield could be greatly improved by increasing the ratio of benzylamine to IVe.

A number of the intermediates involved in these syntheses have not been previously reported. In other instances their chemical properties were obscure. We performed a number of reactions with these compounds in order to become more familiar with their characteristics.

Treatment of IVa, IVc, and IVd with hydrazine hydrate in ethanolic solution gave both the mono- and the dihydrazides. As might be expected, increasing the amount of hydrazine, reaction time, and temperature favored the formation of the disubstituted compound. Two isomeric forms, XII



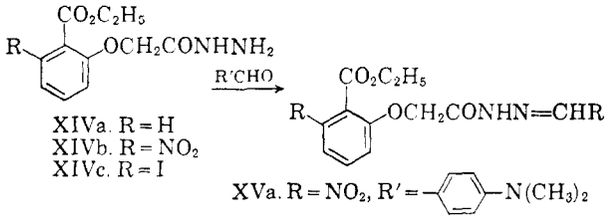
XII



XIII

and XIII, are possible for the monohydrazide. Merriman[14,18] prepared the monoamide of IVa in 1911 and concluded that it was the amide of the benzoic acid moiety as in XII. However, in our previous work, we had observed that phenoxyacetic acids react more readily with hydrazines than do benzoic acids and so we favored structure XIII. This belief has been confirmed by infrared data.[19]

As chemical evidence that we had obtained true hydrazides and not polymeric or cyclic materials, we condensed several of our hydrazides with aldehyes and obtained the expected *N*-acylhydrazones, *i.e.*,

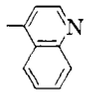


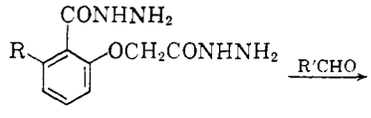
XIVa. R = H
XIVb. R = $NO_2$
XIVc. R = I



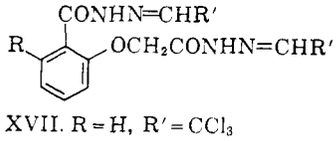
XVa. R = $NO_2$, R' = 

XVb. R = $NO_2$, R' = 

XVc. R = I, R' = 



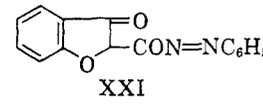
XVIa. R = H, XVIb. R = $NO_2$



XVII. R = H, R' = $CCl_3$

Infrared spectra of the monophenylhydrazide prepared from IVa (XVIII) and the monobenzylamide from IVc (XIX) indicate that they have the same isomeric structures as the monohydrazides.[20] The treatment of IVe with benzylamine gave, in addition to XIX, a small yield of the dibenzylamide (XX).

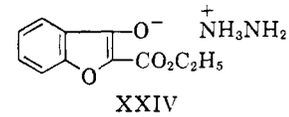
Merriman[14,18] found that an unusual azo compound (XXI) resulted when Va was treated with an equivalent amount of phenylhydrazine in ethanolic solution. This compound exists as yellow needles, m.p. 182–183°, and is readily soluble in dilute ammonium hydroxide. We repeated his experiment and obtained a small yield of XXI. However, our main product was a buff-colored material, m.p. 126–128°, which was insoluble in dilute ammonium hydroxide. These properties, plus its elemental analysis, indicate that it is identical with a product which Merriman had isolated on two rare occasions from the reaction of Va and phenylhydrazine in ethanol–acetic acid. He identified this compound as the phenylhydrazone of 2-carbethoxy-3(2*H*)-benzofuranone (XXII) but made no mention of its being formed along with XXI. Infrared leaves some doubt as to its true identity, as it shows a band at 1645 cm.$^{-1}$ rather than the normal ester band at 1710 cm.$^{-1}$



XXI

When Va was treated with an excess of phenylhydrazine in ethanolic solution, we obtained lustrous red needles, m.p. 189–190° (XXIII). Merriman obtained this compound in the same manner and identified it as the phenylhydrazone of XXI. Our observations confirm this.

Considerable heat is evolved when Va is mixed with hydrazine hydrate in ethanol. The resulting product is water soluble and we have identified it as the hydrazinium salt of the enolic form of Va (XXIV). The ketonic properties of Va are dis-



XXIV

played by the preparation of the semicarbazone of Vb (XXV) and by the formation of XXII and XXIII.

Although the phenylhydrazone of IIa (XXVI) has been mentioned as an intermediate in the synthesis of III,[3] we were unable to find a report of its isolation. We prepared this compound in the customary manner[21] and found that it existed as red-

(18) R. W. Merriman, *J. Chem. Soc.*, **103**, 1838 (1913).

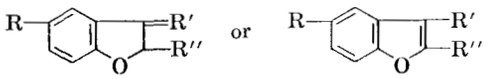
(19) A band at 1712–1720 cm.$^{-1}$ is characteristic of aromatic esters.

(20) XVIII and XIX both show bands at 1712–1720 cm.$^{-1}$ This is characteristic of aromatic esters.

(21) S. M. McElvain, *Characterization of Organic Compounds*, The MacMillan Company, New York, 1945, pp. 132 and 198.

TABLE II

3(2*H*)-BENZOFURANONES

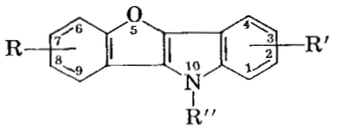


| Compound No. | R | R′ | R″ | Yield, % | M.P.[a] | Empirical Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | —H | =O | —H | 65 | 97[b] | $C_8H_6O_2$ | 71.64 | 71.24 | 4.47 | 4.42 | | |
| IIb | —Cl | =O | —H | 27 | 114.5–116[c] | $C_8H_5ClO_2$ | 56.99 | 57.06 | 2.99 | 3.02 | | |
| IIc | —I | =O | —H | 27 | 130–131 | $C_8H_5IO_2$ | 36.95 | 36.72 | 1.94 | 1.92 | | |
| Va | —H | =O | $—CO_2C_2H_5$ | 70 | 60–62[d] | $C_{11}H_{10}O_4$ | 64.07 | 63.87 | 4.89 | 4.83 | | |
| Vb | —Cl | =O | $—CO_2C_2H_5$ | 55 | 126–127 | $C_{11}H_9ClO_4$ | 54.89 | 54.69 | 3.77 | 4.85 | | |
| Vc | —I | =O | $—CO_2C_2H_5$ | 90 | 120–122 | $C_{11}H_9IO_4$ | 39.78 | 40.03 | 2.73 | 2.99 | | |
| XXI | —H | =O | $—CON{=}NC_6H_5$ | 7.5 | 180–181[e] | $C_{15}H_{10}N_2O_3$ | 67.67 | 67.67 | 3.79 | 3.88 | 10.52 | 10.61 |
| XXII | —H | $=NNHC_6H_5$ | $—CO_2C_2H_5$ | 60 | 126–128[f] | $C_{17}H_{16}N_2O_3$ | 68.90 | 68.68 | 5.45 | 5.53 | 9.45 | 9.63 |
| XXIII | —H | $=NNHC_6H_5$ | $—CON{=}NC_6H_5$ | 35 | 189–190[g] | $C_{21}H_{16}N_4O_2$ | 70.77 | 70.53 | 4.53 | 4.66 | 15.72 | 15.78 |
| XXIV | —H | $—O^-\overset{+}{N}H_3NH_2$ | $—CO_2C_2H_5$ | 74 | 137–138 | $C_{11}H_{14}N_2O_4$ | 55.45 | 55.34 | 5.93 | 6.05 | 11.78 | 11.81 |
| XXV | —Cl | $=NNHCONH_2$ | $—CO_2C_2H_5$ | 25 | 243–244 | $C_{12}H_{12}ClN_3O_4$ | 48.41 | 48.27 | 4.06 | 4.15 | 14.12 | 14.11 |
| XXVI | —H | $=NNHC_6H_5$ | —H | 48 | 168–170 | $C_{14}H_{12}N_2O$ | 74.98 | 75.05 | 5.39 | 5.46 | 12.49 | 12.42 |
| XXVII | —H | $=NNHCSNH_2$ | —H | 85 | 176–178 | $C_9H_9N_3O_3$ | 52.15 | 51.75 | 4.38 | 4.58 | 20.27 | 20.37 |
| XXVIII | —I | $=NNHCSNH_2$ | —H | 60 | 212–213 | $C_9H_9IN_3OS$ | 32.45 | 32.95 | 2.42 | 2.41 | 12.62 | 12.36 |

[a] Melting points are uncorrected. [b] Reported[6] m.p. 97°; reported[10] m.p. 101°; reported[5] m.p. 101–102°; reported[9] m.p. 102°; reported[11,12] m.p. 99–100°. [c] Reported[11] m.p. 115–116°; T. Minton and H. Stephen, *J. Chem. Soc.*, **2**, *Trans.* 2 (1922) 1598–1603, m.p. 113.5°; K. Fries, A. Hasselbach, and L. Schroeder, *Ann.*, **405**, 370 (1914) m.p. 117°. [d] Reported[13,14] m.p. 65°. [e] Reported[14] m.p. 182–183°. [f] Reported[14] m.p. 125–126°.

TABLE III

BENZOFURO[3,2-*b*]INDOLES



| Compound No. | R | R′ | R″ | Yield, % | M.P.[a] | Empirical Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| III | —H | —H | —H | 90 | 197–199 | $C_{14}H_9NO$ | 81.14 | 80.74 | 4.37 | 4.28 | 6.76 | 6.98 |
| VII | 8-Cl | —H | —H | 25 | 185–187 | $C_{14}H_8ClNO$ | 69.58 | 69.11 | 3.34 | 3.33 | 5.80 | 5.78 |
| VIII | —H | $2\text{-}NO_2$ | —H | 4 | 255 | $C_{14}H_8N_2O_3$ | 66.67 | 66.69 | 3.20 | 3.61 | 11.11 | 11.02 |
| X | —H | —H | $—CH_2CH_2NC_5H_{10}$ | 76 | 109–110 | $C_{21}H_{22}N_2O$ | 79.21 | 78.79 | 6.96 | 6.92 | 8.79 | 8.77 |
| XI | —H | —H | $—CH_2CH(CH_3)N(CH_3)_2$ (as HCl) | 27 | 235–236 | $C_{19}H_{21}ClN_2O$ | 69.39 | 69.46 | 6.43 | 6.62 | 8.52 | 8.53 |

[a] Melting points are uncorrected. [b] Reported[2] m.p. 197°; reported[3] m.p. 198°.

brown needles, m.p. 168–170°. In addition, the thiosemicarbazones of IIa and IIc (XXVII and XXVIII) were prepared. Derivatives of 3(2H)-benzofuranone are listed in Table II.

All of the compounds in Tables I, II, and III were subjected to pharmacological screening.[22] The only interesting property observed was analgetic activity in the case of XXVII. Unfortunately, it also proved to be quite toxic. There was no correlation between the activities of X and XI and the corresponding thianaphthinoindoles.

We wish to express our gratitude to Mr. L. Dorfman and his associates for the analytical and infrared data and for the interpretation of the latter.

## EXPERIMENTAL

*Ethyl O-carbethoxymethylsalicylate* (IVa). To a solution of 7.1 g. (0.195 mole) of hydrogen chloride in 520 ml. of anhydrous ethanol and 117 ml. of dry benzene was added 75.0 g. (0. 38 mole) of *O*-carboxymethylsalicyclic acid. The mixture was heated at reflux for 3.5 hr. and then concentrated *in vacuo*. Distillation of the residue at 0.1 mm. gave pure IVa.

*Substituted ethyl O-carbethoxymethylsalicylates* (IVb, IVc, IVd, and IVe). Ethyl bromoacetate (0.03 mole) was added to a solution of potassium hydroxide (0.03 mole) and the appropriate ethyl salicylate (0.3 mole) in anhydrous ethanol. The reaction mixture was heated at reflux for 12 hr., cooled, and filtered. Concentration of the filtrate caused the product to precipitate. This material was collected by means of filtration and recrystallized from ethanol.

*2-Carbethoxy-3(2H)-benzofuranones* (Va, Vb, and Vc). The *O*-carbethoxymethylsalicylate (0.22 mole) was added dropwise with stirring to 0.22 mole of sodium ethoxide in 280 ml. of dry benzene. Stirring was continued and the reaction heated at reflux for 4 hr. After cooling to room temperature the reaction was poured with stirring into water (approx. 3.0 l.) and sufficient dilute sodium hydroxide was added to make the solution alkaline to litmus. The benzene and aqueous layers were separated and addition of dilute hydrochloric acid to the aqueous portion caused the product to precipitate. This material in most cases was quite pure. When necessary it was recrystallized from ethanol.

*3(2H)-Benzofuranones* (IIa, IIb, and IIc). The 2-carbethoxy-3(2*H*)-benzofuranone (0.1 mole) was suspended in approximately 500 ml. of 5% aqueous sodium hydroxide. This mixture was allowed to stand at room temperature with occasional stirring until all of the solid had dissolved. The length of time required for this varies with the compound. IIa took 1 week, IIb 2 weeks, and IIc had not completely dissolved after 4 wks. Dilute sulfuric acid is added cautiously to this bright red solution until there is no further evidence of decarboxylation. The product is extracted with benzene and isolated by removing the solvent *in vacuo*. Recrystallization of this crude product with ethanol gave pure 3(2*H*)-benzofuranone. In the case of IIc, we filtered off the insoluble material after 4 wks. and proceeded with the filtrate as indicated above.

*Benzofuro[3,2-b]indoles* (III, VII, and XIII). These compounds were prepared by the method of Cawley and Plant.[2] By limiting our batch size to 10 g. or less we were able to control the initial exothermic reaction when the benzofuranone was warmed with phenylhydrazine.

*N-Alkylation of benzofuro[3,2-b]indoles* (X and XI). Benzofuro[3,2-*b*]indole was *N*-alkylated in the same manner as previously described for thianaphtheno[3,2-*b*]indoles. X was isolated as the free base and XI as the hydrochloride.

*Hydrazides of O-carboxymethylsalicylic acids* (XIVa, XIVb, XIVc, XVIa, and XVIb). Monohydrazides were prepared in predominance by adding a slight excess of hydrazine hydrate to the ethyl *O*-carbethoxymethylsalicylate in ethanolic solution and allowing the reaction to stand 24 hr. at room temperature. When the quantity of hydrazine was increased to a 2 or 3 fold excess and the reaction time lengthened to 3 days (or refluxed 2–3 hr. on a steam bath) formation of the dihydrazide was enhanced. In both cases there was usually a mixture of products, but these were easily separated by fractional crystallization from ethanol. The dihydrazides are the least soluble and in the case of the 5-nitro compound this was so pronounced that XVIb could be purified by trituration with hot ethanol.

*Phenylhydrazide of ethyl O-carboxymethylsalicylate* (XVIII). This compound was prepared in the same manner as the hydrazides except that a reflux period (3 hr.) was required. Although two equivalents of phenylhydrazine was used for each equivalent of IVa, only the monophenylhydrazide was isolated.

*Benzylamides of 5-bromo-O-carboxymethylsalicylic acid* (XIX and XX). The same method of preparation was used as for the hydrazides. However, the products were separated in a different fashion. After the reaction was completed (24 hr. at room temperature), water was added to precipitate the monoamide. The diamide was isolated from the mother liquor.

*Acylhydrazones* (XVa, XVb, XVc, and XVII). XVa, XVb, and XVc were all prepared in the same manner. A slight excess of the aldehyde was added to the hydrazide in ethanol. The mixture was heated at reflux for 2–3 hr. during which time crystals started to form in the reaction flask. After cooling the product was collected by filtration and recrystallized from ethanol.

XVII was prepared by mixing 4.7 g. (0.021 mole) of the dihydrazide XVIa with 31.0 g. (0.21 *M*) of chloral in 70 ml. of isopropyl alcohol. After heating on a steam bath for 1 hr. and cooling, a white precipitate formed. This product was filtered and recrystallized from a mixture (1:1) of chloroform and isopropyl alcohol.

*Reactions of 2-carbethoxy-3(2H)-benzofuranone with phenylhydrazine* (XXI, XXII, and XXII). In duplicating the work described by Merriman[14] we obtained XXI which was soluble in dilute ammonium hydroxide. However, we also isolated a buff colored compound from this reaction which was insoluble in dilute ammonium hydroxide. It was recrystallized from ethanol and tentatively identified as XXII. We obtained XXIII when an excess of phenylhydrazine was used, as did Merriman.

*Hydrazinium salt of 2-carbethoxy-3-hydroxybenzofuran* (XXIV). Hydrazine hydrate (0.03 mole) was added to Va (0.02 mole) in ethanol solution. Some heat was evolved and white needles started to form immediately. When the reaction had cooled to room temperature, the product was filtered and recrystallized from ethanol.

*Thiosemicarbazones of 3(2H)-benzofuranone and 5-iodo-3-(2H)-benzofuranone* (XXVII and XXVIII). One equivalent of the ketone and one equivalent of thiosemicarbazide were dissolved in a minimum quantity of ethanol-water (80:20). After a reflux period of one hour, the reaction was chilled and the needles which formed were collected by filtration. Recrystallization from ethanol-water gave the pure thiosemicarbazones.

The semicarbazone (XXV) and the phenylhydrazone (XXVI) were prepared in the manner described by McElvain.[21]

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(22) Pharmacological testing was carried out by Dr. A. J. Plummer and associates of these laboratories.