this compound was still potent against 5-HT. Since quantitative aspects of this interaction were not studied, suggestions regarding the relation of cholinergic stimulation to 5-HT blockade produced by the same agent at the ganglia cannot be made. When cholinergic stimulation and blockade of the ganglia is produced by different specific agents (*i.e.*, DMPP or hexamethonium), and stimulation and blockade of the 5-HT receptors by other distinct agents (*i.e.* 5-HT and 5 hydroxy-3-indoleacetamidine), a clear separation of effects regarding stimulation as well as blockade can be obtained between the two different types of ganglionic receptors. Thus, their independence from each other can be established. The situation with molecules which combine cholinergic and 5-HT-like ganglionic stimulant properties (*i.e.*, bufotenine)[16] or cholinergic stimulant and 5-HT blocking properties (members of the present series) is not so clear. It is obvious that further studies are needed in order to clarify certain points in the ganglionic action of this novel type of agents.

Some members of the above series proved to be the most potent agents of their class, and, therefore, in spite of their incompletely known mode of action, will merit further interest as pharmacological tools.

**Acknowledgment.**—The author wishes to express his thanks to the Microanalytical Department (Dr. Schneller) for the analytical data, to Miss Y. Yosh, Mr. E. Bindler, and Mr. L. Soffer for their technical help.

(16) L. Gyermek, L. Bindler, and L. Soffer, *Federation Proc.*, **21**, 335 (1962).

# Syntheses of Some 4-Hydroxycoumarins and Their Condensation Products with Aldehydes and Carboxylic Acids. The Anticoagulant Activity of Some 4-Hydroxycoumarin Derivatives

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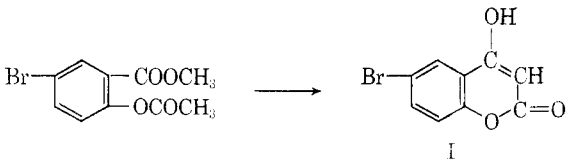
The syntheses of 6-bromo-4-hydroxycoumarin and 4-hydroxy-6,7-benzocoumarin and their condensation products with various aldehydes and carboxylic acids are described. Some of these compounds show anticoagulant activity in experimental animals.

Many compounds of the dicoumarin type have been prepared[1-3] by condensing 4-hydroxycoumarin with aldehydes. A great number of them show an intensive anticoagulant activity and therefore they are used in the therapy of thromboembolisms. This article describes analogous condensations with 6-bromo-4-hydroxycoumarin and 4-hydroxy-6,7-benzocoumarin, prepared in the hope that they may yield new substances with improved anticoagulant activity.

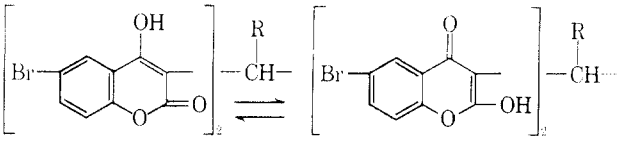
The starting material for the synthesis of 6-bromo-4-hydroxycoumarin was methyl 5-bromosalicylate[4] which on acetylation furnished methyl 2-acetoxy-5-bromobenzoate.[5] From this ester 4-hydroxy-6-bromocoumarin (I) was prepared according to a modified Pauly–Lockemann method.[6]




I

On introducing bromine into position 6 of the aromatic nucleus of 4-hydroxycoumarin its reaction with aldehydes was not essentially changed, so that we were able to prepare 3,3′-alkylidenebis(6-bromo-4-hydroxycoumarin) and 3,3′-arylidenebis(6-bromo-4-hydroxycoumarin) in the usual way. All the compounds obtained are shown in Table I. One of the compounds (3,3′-methylenebis-6-bromo-4-hydroxycoumarin) had been prepared by Huebner and Link.[7]

Because of the coumarin–chromone tautomerism[8] these compounds can be represented in two tautomeric structural formulas (IIa and IIb).




IIa IIb

4-Hydroxy-6,7-benzocoumarin (III) was synthesized starting from methyl 3-hydroxy-2-naphthoate, which by acetylation gave the acetyl derivative.[9] The reaction of methyl 3-acetoxy-2-naphthoate with sodium in hot liquid paraffin caused the lactone ring to close, giving III.


III

(1) R. Anschütz, *Ann.*, **367**, 212 (1909).
(2) W. R. Sullivan, C. F. Huebner, M. A. Stahmann, and K. P. Link, *J. Am. Chem. Soc.*, **65**, 2288 (1943).
(3) J. Klosa, *Arch. Pharm.*, **285**, 327 (1952).
(4) A. Cahours, *Ann.*, **52**, 328 (1844).
(5) L. Henry, *Ber.*, **2**, 275 (1869).
(6) H. Pauly and K. Lockemann, *Ibid.*, **48**, 28 (1915).
(7) C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.*, **66**, 656 (1944).
(8) F. Arndt, L. Loewe, R. Ün, and E. Ayca, *Ber.*, **84**, 319 (1951).
(9) F. Cohen and A. Dudley, *J. Chem. Soc.*, **97**, 1748 (1910).

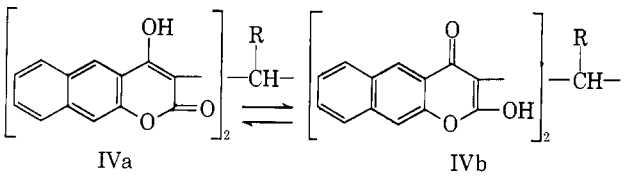
TABLE I

ALDEHYDE CONDENSATION PRODUCTS OF 6-BROMO-4-HYDROXYCOUMARIN AND 4-HYDROXYCOUMARIN

| Derivative of bis(6-bromo-4-hydroxycoumarin) | Yield, % | M.p., °C. | Formula | Calcd. / Found % Carbon | Calcd. / Found % Hydrogen |
|---|---|---|---|---|---|
| 3,3′-Methylene-[a] | 88 | 327 | $C_{19}H_{10}Br_2O_6$ | 46.19 | 2.04 |
| | | | | 45.93 | 2.12 |
| 3,3′-Ethylidene-[b] | 81 | 221 | $C_{20}H_{12}Br_2O_6$ | 47.28 | 2.40 |
| | | | | 47.42 | 2.55 |
| 3,3′-Propylidene- | 75 | 244 | $C_{21}H_{14}Br_2O_6 \cdot 0.5H_2O$ | 47.50 | 2.85 |
| | | | | 47.76 | 3.04 |
| 3,3′-*n*-Butylidene- | 75 | 187–188 | $C_{22}H_{16}Br_2O_6 \cdot 0.5H_2O$ | 48.48 | 3.14 |
| | | | | 48.91 | 3.15 |
| 3,3′-β-Phenylpropylidene- | 70 | 262–263 | $C_{27}H_{18}Br_2O_6 \cdot 0.5H_2O$ | 53.37 | 3.13 |
| | | | | 53.38 | 3.40 |
| 3,3′-Benzylidene-[b] | 87 | 220–222 | $C_{25}H_{14}Br_2O_6 \cdot 0.5H_2O$ | 51.81 | 2.61 |
| | | | | 51.64 | 2.76 |
| 3,3′-(*p*-Toluidene)- | 77 | 241 | $C_{26}H_{16}Br_2O_6 \cdot 0.5H_2O$ | 52.61 | 2.88 |
| | | | | 52.56 | 3.00 |
| 3,3′-(*m*-Hydroxybenzylidene)- | 83 | 224 | $C_{25}H_{15}Br_2O_7 \cdot 0.5H_2O$ | 50.38 | 2.71 |
| | | | | 50.40 | 2.94 |
| 3,3′-Piperonylidene-[c] | 71 | 232–233 | $C_{26}H_{14}Br_2O_8 \cdot 0.5H_2O$ | 50.07 | 2.39 |
| | | | | 50.02 | 2.13 |
| 3,3′-(*p*-Dimethylaminobenzylidene)-[d] | 76 | 229 | $C_{27}H_{19}Br_2NO_6$ | 52.83 | 3.09 |
| | | | | 52.68 | 3.44 |
| 3,3′-Vanillidene- | 57 | 215–217 | $C_{26}H_{16}Br_2O_8$ | 50.64 | 2.59 |
| | | | | 50.67 | 2.89 |
| 3,3′-Ethylvanillidene- | 46 | 236–238 | $C_{27}H_{18}Br_2O_8$ | 51.42 | 2.88 |
| | | | | 51.69 | 3.13 |
| 3,3′-Pyridiniliden-(2)-[e] | 91 | 276–278 | $C_{24}H_{13}Br_2NO_6 \cdot 0.5H_2O$ | 49.70 | 2.43 |
| | | | | 49.96 | 2.87 |
| 3-[6-Oxo(1)benzopyrano[4,3-*b*]-(1)-benzopyran-7-yl]-4-hydroxy-6-bromocoumarin | 42 | 291–293 | $C_{25}H_{12}Br_2O_6 \cdot 0.5H_2O$ | 51.99 | 2.28 |
| | | | | 51.84 | 2.28 |
| 3,3′-(*m*-Hydroxybenzylidene)bis-(4-hydroxycoumarin)[f] | 100 | 232–234 | $C_{25}H_{16}O_7 \cdot 0.5H_2O$ | 68.71 | 3.87 |
| | | | | 69.00 | 3.45 |
| 3,3′-Piperonylidene-bis(4-hydroxycoumarin) | 97 | 258–260 | $C_{26}H_{16}O_8 \cdot 0.5H_2O$ | 67.15 | 3.69 |
| | | | | 67.15 | 3.90 |
| 3,3′-(*p*-Toluidene)bis(4-hydroxycoumarin) | 80 | 268 | $C_{26}H_{18}O_6$ | 73.26 | 4.22 |
| | | | | 73.51 | 3.92 |

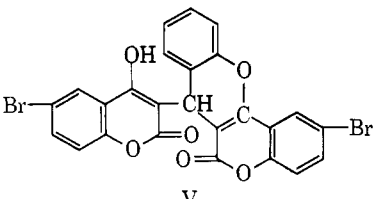
[a] Huebner and Link, ref. 7, prepared this compound; the reaction mixture was refluxed for 30 min. cooled, filtered, and the product recrystallized from cyclohexanone. [b] The reaction mixture was refluxed for 30 min. [c] The crude product washed with ethanol was analyzed. [d] This could not be recrystallized from any of the usual neutral solvents. The crude product was washed and analyzed. [e] The reaction mixture was refluxed for 30 min. and the crude product was washed and analyzed. [f] The reaction mixture was refluxed for 2 hr.

By refluxing an ethanolic mixture of 4-hydroxy-6,7-benzocoumarin with an aldehyde, 3,3′-alkylidenebis(4-hydroxy-6,7-benzocoumarin) or 3,3′-arylidenebis(4-hydroxy-6,7-benzocoumarin) (IVa, IVb) were obtained. All the compounds of this type are shown in Table II.

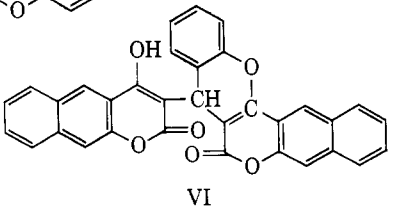


IVa IVb

Salicylaldehyde was condensed with 6-bromo-4-hydroxycoumarin and with 4-hydroxy-6,7-benzocoumarin, respectively, in an analogous way as with 4-hydroxycoumarin itself.[2] In this reaction one mole of water was eliminated between the 4-hydroxyl groups of the coumarin system and the phenolic group of salicylaldehyde, and 6-bromo-3-[6-oxo(1)-benzopyrano[4,3-*b*]-(1)benzopyran-7-yl]-4-hydroxycoumarin (V) or 4-hydroxy-3-[6-oxo(1)benzopyrano(4,3-*b*)-(1)benzo-pyran-7-yl]-6,7-benzocoumarin (VI) was obtained. This reaction occurred only with *o*-hydroxybenzaldehyde while with *m*- or *p*-hydroxybenzaldehyde no water was eliminated and a compound of the dicoumarin type was obtained.



V



VI

Derivatives of 4-hydroxycoumarin with monocarboxylic acids show bactericidal and anticoagulant activity[10] and therefore interest in these substances has

(10) T. Ukita, S. Nojima, and M. Matsumoto, *J. Am. Chem. Soc.*, **72**, 5143 (1950).

TABLE II

ALDEHYDE CONDENSATION PRODUCTS OF 4-HYDROXY-6,7-BENZOCOUMARIN

| Derivative of bis(4-hydroxy-6,7-benzocoumarin) | Yield, % | M.p., °C. | Formula | Calcd. / Found % Carbon | % Hydrogen |
|---|---|---|---|---|---|
| 3,3′-Methylene-[a] | 70 | 297–299 | $C_{27}H_{16}O_6 \cdot 0.5H_2O$ | 72.80 | 3.78 |
| | | | | 72.91 | 3.65 |
| 3,3′-Ethylidene- | 40 | 249–251 | $C_{28}H_{18}O_6 \cdot 0.5H_2O$ | 73.26 | 4.16 |
| | | | | 73.41 | 4.26 |
| 3,3′-Propylidene- | 30 | 253–255 | $C_{29}H_{20}O_6 \cdot 0.5H_2O$ | 73.63 | 4.40 |
| | | | | 73.96 | 4.10 |
| 3,3′-*n*-Butylidene- | 18 | 230–232 | $C_{30}H_{22}O_6 \cdot 0.5H_2O$ | 73.98 | 4.65 |
| | | | | 74.24 | 4.71 |
| 3,3′-Benzylidene- | 28 | 275–277 | $C_{32}H_{20}O_6 \cdot 0.5H_2O$ | 75.91 | 3.95 |
| | | | | 75.60 | 3.91 |
| 3,3′-(*p*-Toluidene)- | 35 | 264–266 | $C_{34}H_{29}O_6$ | 77.49 | 4.22 |
| | | | | 77.32 | 4.38 |
| 3,3′-(*p*-Dimethylaminobenzylidene)-[b] | 31 | 240–243 | $C_{33}H_{27}NO_6$ | 75.66 | 4.54 |
| | | | | 75.40 | 4.38 |
| 3,3′-(*m*-Hydroxybenzylidene)-[c] | 33 | 266 | $C_{33}H_{26}O_7 \cdot 0.5H_2O$ | 73.70 | 3.90 |
| | | | | 73.25 | 3.52 |
| 3,3′-Vanillidene- | 31 | 251–253 | $C_{34}H_{22}O_8$ | 73.18 | 3.97 |
| | | | | 73.19 | 3.83 |
| 3,3′-Ethylvanillidene- | 24 | 212–213 | $C_{35}H_{24}O_8$ | 73.41 | 4.19 |
| | | | | 73.02 | 4.20 |

[a] The reaction mixture was refluxed for 0.5 hr. and the crude product was washed with ethanol and analyzed. [b] Soluble in alkali, but could not be recrystallized from any of the usual neutral solvents. The reaction mixture was refluxed for 1 hr. and the crude product washed with ethanol. [c] The reaction mixture was refluxed for 1.5 hr.

TABLE III

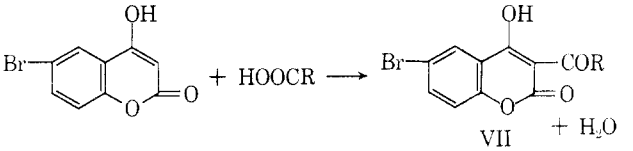
CONDENSATION PRODUCTS OF 4-HYDROXYCOUMARIN, 6-BROMO-4-HYDROXYCOUMARIN, AND 4-HYDROXY-6,7-BENZOCOUMARIN WITH CARBOXYLIC ACIDS

| Derivative of 4-hydroxycoumarin | Yield, % | M.p., °C. | Formula | Calcd., % C | H | Found, % C | H |
|---|---|---|---|---|---|---|---|
| 3-Acetyl-6-bromo-[a] | 95 | 198–200 | $C_{11}H_7BrO_4$ | 46.64 | 2.47 | 46.84 | 2.55 |
| 6-Bromo-3-propionyl | 84 | 185–187 | $C_{12}H_9BrO_4$ | 48.50 | 3.08 | 48.43 | 3.33 |
| 6-Bromo-3-*n*-butyryl- | 80 | 132–134 | $C_{13}H_{11}BrO_4$ | 50.20 | 3.57 | 50.24 | 3.61 |
| 6-Bromo-3-isobutyryl- | 92 | 160–162 | $C_{13}H_{11}BrO_4$ | 50.20 | 3.57 | 49.90 | 3.55 |
| 6-Bromo-3-isovaleryl- | 70 | 154–156 | $C_{14}H_{13}BrO_4$ | 51.74 | 4.03 | 51.72 | 4.22 |
| 3,3′-Oxalyl- | 33 | 96 | $C_{20}H_{10}O_8$ | 63.49 | 2.66 | 63.26 | 2.82 |
| 3-Malonyl- | 47 | 98 | $C_{12}H_8O_6$ | 58.06 | 3.22 | 58.13 | 2.99 |
| 4-Acetoxy-3-acetyl-6,7-benzocoumarin | 54 | 229–230 | $C_{17}H_{12}O_5$ | 68.98 | 4.05 | 69.00 | 3.75 |
| 4-Acetoxy-6,7-benzocoumarin | 33 | 231–232 | $C_{15}H_{10}O_4$ | 70.88 | 3.97 | 70.54 | 3.94 |

[a] This compound was prepared by E. Ziegler and H. Junek, ref. 13, by heating of diethyl(4-bromophenyl)malonate with $AlCl_3$, but the yield was small.

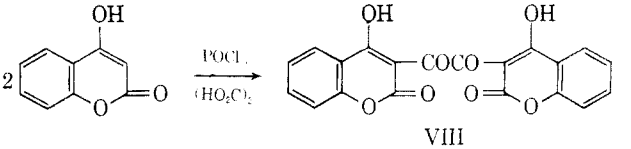
increased, while derivatives with dicarboxylic acids have not yet been described in the literature.

By applying the Fries' reaction with anhydrous aluminum chloride various authors[11–13] prepared 3-acyl-4-hydroxycoumarin from 4-acylhydroxycoumarins, but these methods are rather complicated and the yields are not always satisfactory. Klosa[14] introduced a new, much simpler method for the preparation of 3-acyl-4-hydroxycoumarin by the reaction of the corresponding acids with 4-hydroxycoumarin in the presence of phosphorus oxychloride. These reactions can be carried out easily and quickly with good yields, often higher than 90%. We used this method for preparing 3-acyl-6-bromo-4-hydroxycoumarins. These compounds behave like ketones and react with hydroxylamine and hydrazine. By means of polarographic measurements it was proved that they behave typically like alkyl aryl ketones.[15] Therefore they can be regarded generally as 3-acyl-(6-bromo-4-hydroxycoumarins) (VII, Table III).



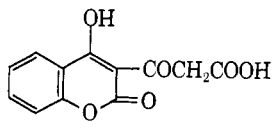

When these conditions were applied to the condensation of 4-hydroxycoumarin with dicarboxylic acids the expected reactions did not occur. This is due to the fact that dicarboxylic acids, especially the lower members of the homologous series, are sensitive to elevated temperature, so that decarboxylation takes place. Phosphorus oxychloride further increased this process of decomposition.

VIII was obtained by condensing oxalic acid with 4-hydroxycoumarin. However, in the case of malonic




(11) K. Vereš and V. Horak, *Collection Czech. Chem. Commun.*, **20**, 371 (1955).
(12) J. Klosa, *Arch. Pharm.*, **289**, 71 (1956).
(13) E. Ziegler and H. Junek, *Monatsh.*, **86**, 506 (1955).
(14) J. Klosa, *Arch. Pharm.*, **288**, 356 (1955).
(15) M. Deželić and M. Trkovnik, *Croat. Chem. Acta*, **33**, 209 (1961).

acid under the same conditions only one carboxylic group reacted, while the other remained free, giving IX.




IX

In the reaction of acetic acid on 4-hydroxy-6,7-benzocoumarin in the presence of phosphorus oxychloride, 4-acetoxy-3-acetyl-6,7-benzocoumarin (X) was obtained. 4-Hydroxycoumarin and 6-bromo-4-hydroxycoumarin always only gave the corresponding 3-acetyl-4-hydroxycoumarin.

**Pharmacology.**—A number of the compounds described in this paper were tested for their anticoagulant activity and toxicity.[16] All the substances tested behaved as anticoagulants with a rapid and strong activity of short duration, similar to ethyl biscoumarate.

The experiments were carried out on rats of both sexes weighing from 140 to 210 g. The substances suspended in propylene glycol were given perorally at a daily dose of 30 mg./kg. Blood was taken intracardially, from the eye, and 0.9 ml. of the blood was mixed with 0.1 ml. of a 3.8% solution of sodium citrate and centrifuged. The citrated plasma was used for the determination of the prothrombin time by the modified method of Quick.[17-19] The prothrombin times were determined 2, 3, and 4 days after the treatment of the animals with these substances. Fig. 1 shows the dependence of the prothrombin index (PI) on time, *i.e.*, on how many days these various substances acted on the animals. A PI value under 45 is a sign of hemorrhage.

Three of the substances (A, B, and D) showed maximal anticoagulant activity after 48 hr. In these substances no cumulation took place. D showed a much stronger anticoagulant activity than ethyl biscoumarate which is known as a powerful anticoagulant.

From Fig. 1 it can be seen that the PI of D was 49.5 after 2 days, while at the same time the PI of ethyl biscoumarate (E) was 68.8. After 3 days the PI of D approached the PI of E. After 4 days D was almost entirely excreted from the blood. It showed an intensive anticoagulant effect and was excreted so rapidly that the coagulation system became completely normal.

When the animals were treated for some days with dicoumarin (C), a strong decrease of the PI in the blood took place and the animals died of hemorrhage. This phenomenon took place because dicoumarin acted cumulatively and for a prolonged time.[20]

Substance B showed a significant anticoagulant effect, even stronger than that of E. The strongest anticoagulant effect was observed after 2 days (PI 57.8). After that time the PI increased quickly and its value reached 77.1. A is not so effective and shows the weakest anticoagulant activity of all the substances mentioned, but it is excreted very quickly from the circulation.

The toxicity of A, B, and D was tested in mice and compared with the toxicity of dicoumarin. The substances were suspended in propylene glycol and injected subcutaneously at a daily dose of 100 mg./kg. for 5 days. After 5 days 30% of the animals treated with A survived, and 70% of those treated with B and D. All mice treated with dicoumarin were dead after 3 days. The lethal dose of dicoumarin was found to be 270 mg./kg. Therefore, the toxicity of A, B, and D was lower than that of dicoumarin. Thus, the substances which showed the strongest anticoagulant effect (B and D) were the least toxic.

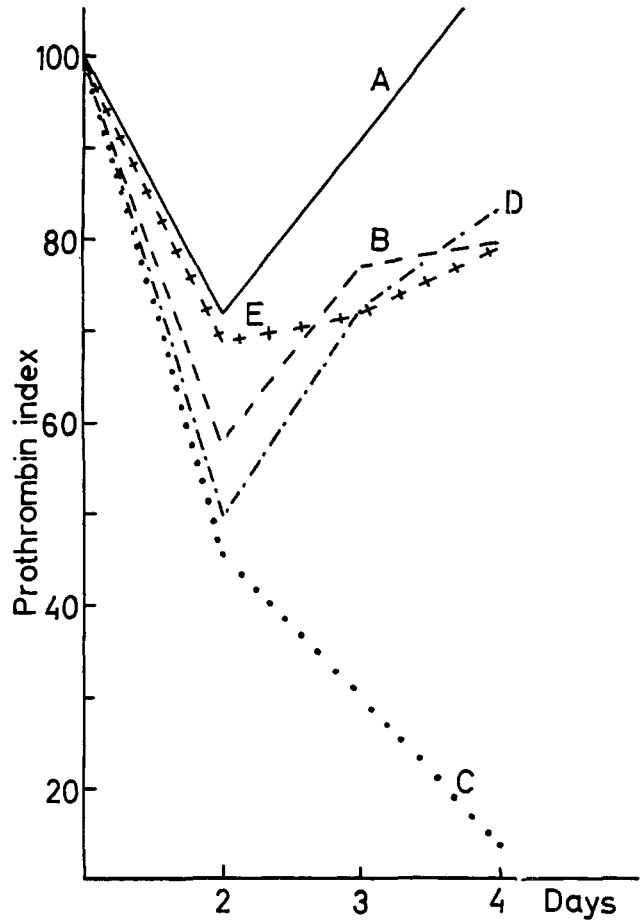



Fig. 1.—Prothrombin index (PI) for following substances: (A) 3,3′-oxalyl-bis-4-hydroxycoumarin, (B) 3,3′-methylenebis-4-hydroxy-5,6-benzocoumarin, (C) dicoumarin, (D) 3,3′-methylenebis-6-bromo-4-hydroxycoumarin, and (E) ethyl biscoumarate.

## Experimental

All melting points were determined with a Kofler heating microscope. Many of the described compounds crystallize with 0.5 molecule of water as proved by elementary analysis and by means of Kofler's methods.[21]

**6-Bromo-4-hydroxycoumarin (I).**—Methyl 2-acetoxy-5-bromobenzoate (30 g.) was suspended in liquid paraffin (200 ml.). The suspension was heated to 200° and at this temperature sodium (5 g.) was added in small amounts. Then the temperature was raised to 220–240° and kept at that point for some time (90–120 min.). During this reaction a dark brown crystalline mass was formed. After cooling, the brown granular solid substance was collected and washed with ether and petroleum ether. The dark brown mass was powdered and dissolved in water. Activated charcoal was added to the water solution, and the boiling solution was filtered and acidified to pH 5. A precipitate consisting of impurities was separated by filtration. Then the filtrate was acidified to pH 2 with 2 *N* HCl causing the

(16) M. Trkovnik, M. Deželić, and S. Hukovic, *Bull. Sci. Conseil Acad. RPF Yougoslavie*, **7**, 62 (1962).

(17) A. Quick, *J. Am. Physiol.*, **118**, 260 (1937); *J. Biol. Chem.*, **161**, 33 (1954).

(18) C. Montigel and R. Pulver, *Schweiz. Med. Wochschr.*, **82**, 132 (1952).

(19) E. Merck A.G., Darmstadt, "Medizinisch-chemische Untersuchungsmethoden," 9. Aufl., Verlag Chemie, Weinheim, 1958, p. 137.

(20) C. Montigel and R. Pulver, *Schweiz. Med. Wochschr.*, **85**, 586 (1955).

(21) L. Kofler and A. Kofler, "Thermo-Mikro-Methoden zur Kennzeichnung organischer Stoffe und Stoffgemische," Verlag Chemie, Weinheim, 1954, p. 28.

precipitation of I. The product was dissolved in 10% sodium hydroxide solution and the acidification to pH 5 was repeated. Then the filtrate from the precipitated impurities was again acidified to pH 2, giving a purer material; yield, 15.8 g. (60%); m.p. 255°. By recrystallization from glacial acetic acid yellow needles were obtained, m.p. 279°.

*Anal.* Calcd. for $C_9H_5BrO_3$: C, 44.85; H, 2.09. Found: C, 84.48; H, 1.89.

**4-Hydroxy-6,7-benzocoumarin (III).**—Methyl 3-acetoxy-2-naphthoate (97 g.) was suspended in liquid paraffin (600 ml.). The suspension was heated to 200° with stirring. At that temperature sodium (16 g.) was added in small amounts. The reaction mixture was heated to 220–230° and kept at this temperature for 2 hr. After cooling the extracted dark brown mass was separated by filtration from liquid paraffin and washed with ether and petroleum ether. After drying, the mass was powdered in a mortar and dissolved in 1.5 l. of water. The water solution was boiled with activated charcoal and filtered. The mass was then acidified with 2 *N* HCl to pH 2. III precipitated as yellow microcrystals. After recrystallization from water and ethanol 40.5 g. (48%) of a product with m.p. 225–230° was obtained. III is soluble in ethanol and acetic acid but insoluble in water. It is very soluble in alkali. The alcohol solution of this alkali salt gives a green color with $FeCl_3$.

Because III could be isolated in a pure state, we determined its composition by preparing its acetyl derivative and other derivatives, which could be isolated pure. The analysis of acetyl derivative was:

*Anal.* Calcd. for $C_{15}H_{10}O_4$: C, 70.88; H, 3.97. Found: C, 70.64; H, 3.94.

**Condensation Products of Aldehydes with 4-Hydroxycoumarin. 6-Bromo-4-hydroxycoumarin (II, V) and 4-Hydroxy-6,7-benzocoumarin (IV, VI).**—By boiling 4-hydroxycoumarin or its derivatives (0.2 mole) with the corresponding aldehyde (0.1 mole) in ethanol under reflux, 3,3′-alkylidene- or 3,3′-arylidene-bis-4-hydroxycoumarin, -bis-6-bromo-4-hydroxycoumarin, or -bis-4-hydroxy 6,7-benzocoumarin was obtained. An excess of aldehyde (up to 2% above the theoretical amount) was used in the experiments reported here. The duration of this reaction was from 30 min. to 3 hr., whereas for the majority of compounds the reaction time was 1 hr. The reaction times are listed in Tables I and II. After cooling, the crystals were collected by filtration. Those soluble were recrystallized from glacial acetic acid; the insoluble ones were treated as shown in Tables I and II.

**3-Acyl-6-bromo-4-hydroxycoumarins (VII).**—6-Bromo-4-hydroxycoumarin (0.5 g.) was dissolved in 2 ml. of the corresponding acid, 0.5 ml. of phosphorus oxychloride was added, and the mixture refluxed for 35 min. The reaction mixture was kept for several hours at room temperature, and the separated crystals were removed by filtration. The compounds were recrystallized from ethanol with the aid of activated charcoal.

**Derivatives of 4-Hydroxycoumarin with Oxalic (VIII) and Malonic Acids (IX).**—The reactants for the preparation of derivatives of oxalic and malonic acid were used at a weight ratio of 1:1, except that 2–3 parts of phosphorus oxychloride had to be added. This reaction had to be carried out very carefully on a water bath in order to avoid pronounced resinification. The reaction mixture was refluxed for 2 hr. and evolved HCl. After that, the reaction mixture was kept for several hours at room temperature and carefully added to 5 volumes of cold water. After boiling, the substance was extracted 3 times from the dark mixture with warm ethanol. On adding water to the ethanolic extract, orange crystals of the new compound precipitated. Pure substances suitable for the analysis were obtained by repeated fractional recrystallization from ethanol and water.

**4-Acetoxy-3-acetyl-6,7-benzocoumarin (X).**—4-Hydroxy-6,7-benzocoumarin (0.6 g.) was dissolved in a mixture of 6 ml. of acetic anhydride and 2 ml. of pyridine and heated to boiling for 10 min. After standing for several hr., yellow crystals of 4-acetoxy-6,7-benzocoumarin separated. This compound (0.3 g.) was dissolved in 2 ml. of acetic acid and 0.8 ml. of phosphorus oxychloride was added. The mixture was kept for several hours at room temperature. The separated crystals were recrystallized from glacial acetic acid.

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# β-Hydroxyphenethylamino Derivatives of Various Nitrogen Heterocycles

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β-Hydroxyphenethylamino derivatives of pyridazine, pyrazine, triazine, thiazole, and triazole have been prepared for purposes of pharmacological comparison with their pyridine and pyrimidine analogs. Pharmacological properties ranging from analgesic and interneuronal blocking to antiinflammatory (on mustard-induced rat paw edema) have been observed and are discussed in the context of the relative basicities of the compounds. Optically active (−)-2-(β-hydroxyphenethylamino)pyridine has been synthesized and found to be equipotent to the racemate as an analgesic. In connection with this work a number of the corresponding mandelamido derivatives have been prepared. The physical properties, in particular the acidity of these secondary amides and the positions of their carbonyl stretching bands in the infrared, are discussed.

Continued interest in the analgesic and muscle relaxant (interneuronal blocking) properties of 2-(β-hydroxyphenethylamino)pyridine[1,2] and in the more potent muscle relaxant and sedative–hypnotic properties of the corresponding pyrimidine derivative, 2-(β-hydroxyphenethylamino)pyrimidine,[3,4] has encouraged further study of the effects of structural modification on pharmacological actions. A number of facets of this problem have been explored. This paper is concerned with one aspect which, in view of the striking shift in spectrum of biological effects in going from pyridine to pyrimidine derivative, seemed potentially most instructive, *viz.*, the pharmacological consequences of altering, particularly isosterically, the heterocyclic system attached to the nitrogen of the β-hydroxyphenethylamine moiety. To this end derivatives incorporating a variety of heterocyclic nuclei have been examined; many of these are described here.

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