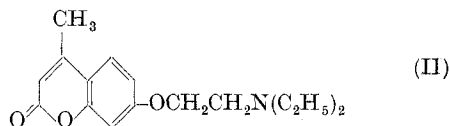
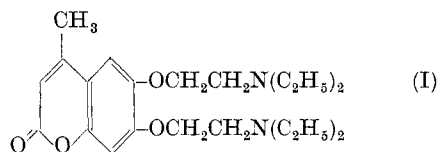


## New Orally Active Derivatives of $\alpha$ -Pyrone possessing Anti-capillary Fragility Activity—III

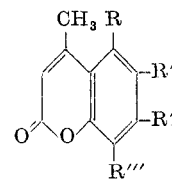
E. MASSARANI, D. NARDI, P. MANTEGAZZA, M. RIVA and G. CAVALLINI, *Medicinal Chemistry Research Laboratories, Vister-Casatenovo Brianza (Como), Italy*

It is well known that the derivatives of 4-methylesculetin possess a remarkable capillary-protective activity in the test of Borbély.<sup>1</sup> Cavallini and Mazzucchi<sup>2</sup> had synthesized the sulphuric acid ester of 4-methyl-6,7-dihydroxycoumarin and of 4-methyl-7-hydroxycoumarin, and these proved to exhibit considerable activity upon the capillary permeability in man.<sup>3,4</sup> In a subsequent study Massarani<sup>5</sup> prepared the  $\beta$ -diethylaminoethyl ethers of 4-methyl-6,7-dihydroxycoumarin (I) and of 4-methyl-7-hydroxycoumarin (II).



These products proved to have a higher capillary-protective activity in comparison with that of the analogous sulphuric acid esters, especially when the substances were given orally. This may be due to the difference in chemical bonds in the two types of compounds, the sulphate esters being probably more easily hydrolysable in the stomach. Mead and co-workers<sup>6</sup> have recently proved that the sulphuric acid esters of 4-methyl-7-hydroxycoumarin and of other coumarins which have hydroxyl

Table I



| Compound no. | R                                                         | R'                                                        | R''                                                                               | R'''                                                      | Method         | % Yield  |
|--------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------|----------------|----------|
| (I)          | H                                                         | H                                                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$                                  | H                                                         | A              | 80       |
| (II)         | H                                                         | H                                                         |                                                                                   | H                                                         | A              | 50       |
| (III)        | H                                                         | H                                                         |                                                                                   | H                                                         | A              | 60       |
| (IV)         | H                                                         | H                                                         |                                                                                   | H                                                         | A              | 55       |
| (V)          | H                                                         | H                                                         | $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$              | H                                                         | A              | 70       |
| (VI)         | H                                                         | H                                                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$              | H                                                         | B              | 70       |
| (VII)        | H                                                         | H                                                         | $\text{OCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ | H                                                         | C              | 50       |
| (VIII)       | H                                                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ | H                                                                                 | H                                                         | A              | 70       |
| (IX)         | H                                                         |                                                           | H                                                                                 | H                                                         | A              | 82       |
| (X)          | H                                                         |                                                           | H                                                                                 | H                                                         | A              | 73       |
| (XI)         | H                                                         |                                                           |                                                                                   | H                                                         | D              | 15       |
| (XII)        | H                                                         |                                                           |                                                                                   | H                                                         | D <sup>d</sup> | 25       |
| (XIII)       | H                                                         | H                                                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ | A              | 35       |
| (XIV)        | H                                                         | H                                                         |                                                                                   |                                                           | D <sup>e</sup> | 25       |
| (XV)         | H                                                         | H                                                         |                                                                                   |                                                           | E              | 40       |
| (XVI)        | $\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ | H                                                         | $\text{OCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$                         | H                                                         | A              | 20       |
| (XVII)       |                                                           | H                                                         |                                                                                   | H                                                         | D <sup>e</sup> | 45       |
| (XVIII)      |                                                           | H                                                         |                                                                                   | H                                                         | F              | 55<br>50 |

<sup>a</sup> IS = Isopropyl alcohol; E = Ethanol; EA = Ethyl acetate; M = Methanol; W = Water.

<sup>b</sup> Water was determined by the Fisher method.

<sup>c</sup> Decomposition.

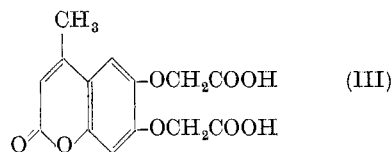
<sup>d</sup> Acetone was used as solvent.

<sup>e</sup> Ethanol was used as solvent.

| b.p.,<br>°C/mm Hg | m.p., °C                   | Solvent<br>of cryst. <sup>a</sup> | Empirical formula                                                          | Calcd.         |              |              |       | Found          |              |              |       |
|-------------------|----------------------------|-----------------------------------|----------------------------------------------------------------------------|----------------|--------------|--------------|-------|----------------|--------------|--------------|-------|
|                   |                            |                                   |                                                                            | C              | H            | N            | Cl    | C              | H            | N            | Cl    |
| 185/1             | 221-222                    | IS                                | $C_{14}H_{17}NO_5$<br>$C_{14}H_{17}NO_5 \cdot HCl$                         | 59.26          | 6.39         | 4.93         | 12.49 | 59.26          | 6.55         | 4.75         | 12.50 |
| 194/0.3           | 166-168                    | E                                 | $C_{18}H_{19}NO_5$<br>$C_{18}H_{19}NO_5 \cdot HCl$                         | 62.02          | 6.50         | 4.52         | 11.44 | 62.25          | 6.45         | 4.45         | 11.00 |
| 195/0.3           | 181-183                    | E                                 | $C_{17}H_{21}NO_5$<br>$C_{17}H_{21}NO_5 \cdot HCl$                         | 63.05          | 7.32         | 4.32         | 10.95 | 63.05          | 6.96         | 4.29         | 10.90 |
| 198/0.3           | 102                        | EA                                | $C_{16}H_{19}NO_4$                                                         | 66.42          | 6.62         | 4.84         |       | 66.09          | 6.50         | 4.79         |       |
|                   | 203                        | E                                 | $C_{16}H_{19}NO_4 \cdot HCl \cdot \frac{1}{2}H_2O^b$                       | 57.40          | 6.32         | 4.18         | 10.59 | 57.82          | 6.33         | 4.43         | 10.90 |
|                   | 195                        | E                                 | $C_{17}H_{21}NO_5$<br>$C_{17}H_{21}NO_5 \cdot HCl$                         | 62.66          | 7.42         | 4.28         | 10.88 | 62.38          | 7.40         | 4.12         | 10.80 |
|                   | 146                        | E                                 | $C_{16}H_{21}NO_5 \cdot HCl \cdot H_2O^b$                                  | 53.35          | 6.40         | 3.84         | 9.80  | 53.82          | 6.35         | 3.96         | 10.00 |
| 176/0.1           | 231-233                    | M                                 | $C_{18}H_{23}N_2O_8 \cdot 2HCl$                                            | 55.24          | 7.21         | 7.16         | 18.13 | 55.37          | 7.47         | 7.19         | 17.80 |
|                   | 155                        | IS                                | $C_{16}H_{21}NO_5$<br>$C_{16}H_{21}NO_5 \cdot HCl$                         | 61.62          | 7.11         | 4.66         | 11.67 | 62.05          | 7.07         | 4.49         | 11.40 |
|                   | 95<br>216-217 <sup>c</sup> | IS                                | $C_{17}H_{21}NO_5$<br>$C_{17}H_{21}NO_5 \cdot HCl$                         | 63.05          | 7.32         | 4.82         | 10.95 | 62.70          | 6.80         | 4.53         | 10.90 |
|                   | 85<br>265-267 <sup>c</sup> | E                                 | $C_{15}H_{19}NO_4$<br>$C_{15}H_{19}NO_4 \cdot HCl \cdot \frac{1}{2}H_2O^b$ | 57.40          | 6.32         | 4.18         | 10.59 | 57.72          | 6.60         | 4.08         | 10.45 |
| 195/0.5           | 263                        | E                                 | $C_{24}H_{31}N_2O_4 \cdot 2HCl$                                            | 58.90          | 7.41         | 5.74         | 14.55 | 58.50          | 7.40         | 5.70         | 14.80 |
|                   | 271-272                    | WE                                | $C_{22}H_{30}N_2O_8 \cdot 2HCl \cdot 2H_2O^b$                              | 50.10          | 6.87         | 5.31         | 13.45 | 49.68          | 7.02         | 5.15         | 13.46 |
|                   | 234-236                    | E                                 | $C_{22}H_{31}N_2O_4$<br>$C_{22}H_{31}N_2O_4 \cdot 2HCl \cdot H_2O^b$       | 54.88          | 7.95         | 5.82         | 14.73 | 55.04          | 8.04         | 5.89         | 14.85 |
|                   | 212                        | IS                                | $C_{24}H_{34}N_2O_4 \cdot 2HCl \cdot 2H_2O^b$                              | 55.06          | 7.70         | 5.35         | 13.54 | 55.43          | 7.40         | 5.35         | 13.10 |
| 195/0.2           | 230-231                    | E                                 | $C_{22}H_{30}N_2O_8 \cdot 2HCl$                                            | 53.76          | 6.56         | 5.70         | 14.43 | 53.56          | 6.67         | 5.67         | 13.90 |
|                   | 230                        | IS                                | $C_{22}H_{34}N_2O_4$<br>$C_{22}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O^b$       | 54.88          | 7.95         | 5.82         | 14.73 | 54.80          | 7.96         | 6.17         | 14.90 |
|                   | 265-267 <sup>e</sup>       | E                                 | $C_{24}H_{34}O_4N_2 \cdot 2HCl \cdot H_2O$                                 | 57.02          | 7.57         | 5.54         | 14.03 | 57.25          | 7.50         | 5.81         | 14.30 |
|                   | 131<br>195                 | E<br>E                            | $C_{22}H_{30}N_2O_8$<br>$C_{22}H_{30}N_2O_8 \cdot 2HCl \cdot H_2O^b$       | 63.14<br>51.77 | 7.23<br>6.71 | 6.69<br>5.49 | 13.90 | 63.03<br>51.53 | 7.34<br>6.79 | 6.57<br>5.17 | 13.50 |

groups in positions 3, 4, 5, 6, 7 and 8 are readily hydrolysed at pH 5.9 by an arylsulphatase which is obtained from the gastric juice of Roman snails (*Helix pomatia*).

Because we felt that the activity of (I) and (II) was probably due to the functional nature of the ether side chain, we compared the capillary-protective activity of (I) with that of 4-methyl-6,7-bis-(carboxymethoxy)-coumarin (III).



Since (III) was much less active, the basic nature of the bond may be considered a determinant factor for a higher oral activity. It therefore appears important to consider the following factors in order to obtain substances with higher activity and a better therapeutic index: (a) the nature of the basic ethers, and (b) the position of the hydroxyl groups.

We have now synthesized a series of basic ethers of 4-methyl-6-hydroxycoumarin, 4-methyl-7-hydroxycoumarin, 4-methyl-5,7-dihydroxycoumarin, 4-methyl-6,7-dihydroxycoumarin and 4-methyl-7,8-dihydroxycoumarin, containing the following ether chains: *N,N*-dimethylaminoethoxy, *N*-pyrrolidinoethoxy, *N*-piperidinoethoxy, *N*-morpholinoethoxy,  $\gamma$ -*N,N*-diethylaminopropoxy, *N,N*-bis( $\beta$ -hydroxyethyl)ethoxy, and *N,N*-diethylaminoethylaminoethoxy.

### Chemical Synthesis

The hydroxylated 4-methylcoumarins were prepared by Pechmann condensations of ethyl acetoacetate with suitable polyphenols in the presence of sulphuric acid.<sup>7</sup> The basic ethers were obtained by condensation of 4-methyl-hydroxycoumarins with a suitable chloroalkylamine in the presence of alkali carbonates or bicarbonates in ethyl alcohol, isopropyl alcohol, acetone and methyl ethyl ketone.

By condensation of 4-methyl-7-hydroxycoumarin with ethylene bromide in aqueous-alcoholic solution in the presence of NaOH,

4-methyl-7- $\beta$ -bromoethoxycoumarin was obtained, which by condensation with diethanolamine and *N,N*-diethylethylenediamine gave compounds (VI) and (VII), respectively. The hydrochlorides of many of the products often crystallized with water of hydration and were soluble in water. They showed a characteristic fluorescence under ultraviolet light. Mono-dimensional ascendent chromatography of the substances has been performed. The obtained  $R_f$  values are listed in Table II.

Table II. Chromatographic data<sup>a</sup>

| Compound                                 | Solvents <sup>b</sup> |                   |                   |
|------------------------------------------|-----------------------|-------------------|-------------------|
|                                          | A                     | B                 | C                 |
| 4-Methyl-7-hydroxycoumarin               | 0.86                  | 0.95              | 0.70              |
| 4-Methyl-7- $\beta$ -bromoethoxycoumarin | 0.88                  | 0.95              | 0.55 <sup>c</sup> |
| (I)                                      | 0.64                  | 0.88              | 0.60              |
| (II)                                     | 0.72                  | 0.90              | 0.53              |
| (III)                                    | 0.77                  | 0.90              | 0.54              |
| (IV)                                     | 0.65                  | 0.92              | 0.77              |
| (V)                                      | 0.77                  | 0.90              | 0.50              |
| (VI)                                     | 0.57                  | 0.90              | 0.77              |
| (VII)                                    | 0.55                  | 0.88              | 0.57              |
| 4-Methyl-6-hydroxycoumarin               | 0.86                  | 0.93              | 0.63              |
| (VIII)                                   | 0.67                  | 0.91              | 0.53              |
| (IX)                                     | 0.70                  | 0.90              | 0.52              |
| (X)                                      | 0.63                  | 0.92              | 0.74              |
| 4-Methyl-6,7-dihydroxycoumarin           | 0.78                  | 0.87 <sup>c</sup> | 0.60 <sup>c</sup> |
| (XI)                                     | 0.57                  | 0.80 <sup>c</sup> | 0.43              |
| (XII)                                    | 0.43                  | 0.90              | 0.76              |
| 4-Methyl-7,8-dihydroxycoumarin           | 0.85                  | 0.86              | 0.54 <sup>c</sup> |
| (XIII)                                   | 0.45                  | 0.87              | 0.41              |
| (XIV)                                    | 0.40                  | 0.84              | 0.75              |
| (XV)                                     | 0.62                  | 0.85              | 0.41              |
| 4-Methyl-5,7-dihydroxycoumarin           | 0.91                  | 0.95              | 0.58 <sup>c</sup> |
| (XVI)                                    | 0.45                  | 0.85              | 0.43              |
| (XVII)                                   | 0.54                  | 0.80              | 0.43              |
| (XVIII)                                  | 0.34                  | 0.90              | 0.74              |

<sup>a</sup> The table shows the  $R_f$  values of the ascending paper chromatography carried out on Whatman paper No. 1 at  $20^\circ \pm 1^\circ$ .

The length of the run was 25 cm. The spots were detected by examining fluorescence under ultraviolet light and spraying the strips with Dragendorff's  $\text{KBiI}_4$  reagent.

<sup>b</sup> A = *n*-butanol saturated with water and acetic acid; B = 60% ethanol; C = 25% ethanol.

<sup>c</sup> These compounds gave elongated spots.

### Experimental\*

*4-Methyl-7- $\beta$ -bromoethoxycoumarin.* A mixture of 4-methyl-7-hydroxycoumarin (88 g, 0.5 mole), ethanol (1350 ml), and ethylene bromide (30 ml) was refluxed with stirring, and a solution of sodium hydroxide (20 g) in water (150 ml) and ethylene bromide (70 ml) was simultaneously added dropwise over a period of 4 h, and the mixture was refluxed for 2 h. Evaporation of the solvent gave a residue which was washed with aqueous sodium hydroxide solution. By acidifying the mother liquors 24 g of 4-methyl-7-hydroxycoumarin was recorded. The residue was dissolved in hot ethanol and an insoluble product was filtered off. 4-Methyl-7- $\beta$ -bromoethoxycoumarin crystallized from ethanol on cooling; the yield was 46 g (30 per cent), m.p. 104–105°.

*Anal.* Calcd. for  $C_{12}H_{11}BrO_3$ : C, 50.90; H, 3.91; Br, 28.23. Found: C, 51.34; H, 3.90; Br, 28.30.

#### *General Methods for the Preparation of Basic Ethers of 4-Methyl-hydroxycoumarin (Table I)*

*4-Methyl-7-dimethylamino- $\beta$ -ethoxycoumarin. Method A.* A mixture of 4-methyl-7-hydroxycoumarin (2.2 g, 0.05 mole), sodium hydroxide (2 g, 0.05 mole) and acetone (80 ml) was refluxed with stirring for  $\frac{1}{2}$  h. Then 1-dimethylamino-2-chloroethane (8 g, 0.075 mole) was added dropwise over a period of 15 min, and the mixture was refluxed for 5 h. After evaporating the solvent, the residue was diluted with water and extracted with ethyl ether. The ethereal layer was washed with dilute aqueous sodium hydroxide solution and water, and on drying and concentration gave a residue which was distilled under reduced pressure.

*4-Methyl-7-( $\beta,\beta$ -dihydroxyethylamino)- $\beta$ -ethoxycoumarin. Method B.* A mixture of 4-methyl-7- $\beta$ -bromoethoxycoumarin (5.66 g, 0.02 mole), diethanolamine (6.30 g, 0.06 mole), sodium hydrogen carbonate (2.52 g, 0.03 mole) and ethanol (10 ml) was refluxed for 12 h. Evaporation of the solvent gave a residue which was washed with water and filtered. The product was dissolved in ethanol, the solution was cleared with charcoal and acidified with

\* All melting points are uncorrected.

hydrogen chloride. Ethyl ether was added until a faint permanent cloudiness was apparent. The crystals which separated were collected and recrystallized from ethanol.

*4-Methyl-7-N-(N,N-diethylethylendiamino)- $\beta$ -ethoxycoumarin. Method C.* A mixture of 4-methyl-7- $\beta$ -bromoethoxycoumarin (5.66 g, 0.02 mole), *N,N*-diethylethylendiamine (3.48 g, 0.03 mole), sodium hydrogen carbonate (2.52 g, 0.03 mole) and ethanol (10 ml) was refluxed for 20 h. The solvent was evaporated and the residue was dissolved in approximately 1 l. of water. An insoluble product was filtered off and the solution was evaporated under reduced pressure. The residue was dissolved in methylene chloride and the solution was washed with a small quantity of water, dried over sodium sulphate, and evaporated. The hydrochloride was prepared by dissolving the residue in ethanol and acidifying with hydrogen chloride. It was crystallized from methanol-ethyl ether.

*4-Methyl-6,7-bis-(N-piperidino- $\beta$ -ethoxy)-coumarin. Method D.* A mixture of 4-methyl-6,7-dihydroxycoumarin (9.6 g, 0.05 mole), sodium hydroxide (4 g, 0.1 mole) and methyl ethyl ketone (200 ml), was refluxed for  $\frac{1}{2}$  h, then 1-*N*-piperidino-2-chloroethane (14.76 g, 0.1 mole) was added dropwise and the mixture was refluxed for 10 h. After filtration and evaporation of the solvent, the residue was heated at 1 mm to 190° in order to remove unreacted 1-*N*-piperidino-2-chloroethane and its decomposition products. The residue was dissolved in aqueous hydrogen chloride, the solution was filtered with charcoal and made alkaline with aqueous sodium hydroxide. The base was extracted with methylene chloride and the solution was washed with dilute aqueous sodium hydroxide and water. After drying, the solvent was evaporated, the residue dissolved in ethyl ether, cleared with charcoal, filtered, and acidified with hydrogen chloride. The hydrochloride which separated was collected, washed twice with warm acetone and crystallized from ethanol.

*4-Methyl-7,8-bis-(N-morpholino- $\beta$ -ethoxy)-coumarin. Method E.* A mixture of 4-methyl-7,8-dihydroxycoumarin (9.6 g, 0.05 mole), sodium hydroxide (4 g, 0.1 mole) and 2-propanol (200 ml) was refluxed with stirring for  $\frac{1}{2}$  h. Then 1-*N*-morpholino-2-chloroethane (22 g, 0.15 mole) was added dropwise and the mixture was refluxed for 10 h. Sodium chloride was filtered off and the solvent

was evaporated under reduced pressure. The residue was heated at 1 mm up to 170° in order to remove the unreacted morpholino-2-chloroethane and its decomposition products; the residue was dissolved in anhydrous ethanol, the solution was cleared with charcoal and made acid with anhydrous hydrogen chloride. The hydrochloride was precipitated with ethyl ether, filtered, washed several times with warm acetone and crystallized from isopropyl alcohol.

*4-Methyl-5,7-bis-(N-morpholino- $\beta$ -ethoxy)-coumarin. Method F.* A mixture of 4-methyl-5,7-dihydroxycoumarin (9.6 g, 0.05 mole), sodium hydroxide (4 g, 0.1 mole) and isopropyl alcohol (200 ml) was stirred and refluxed for  $\frac{1}{2}$  h. Then 1-*N*-morpholino-2-chloroethane (22 g, 0.15 mole) was added dropwise over a period of 15 min and the mixture was refluxed for 10 h. After filtering from sodium chloride, the solution was cleared with charcoal, and on cooling yellow crystals separated and were collected. The hydrochloride was prepared by treating the ethanolic solution of the base with anhydrous hydrogen chloride and crystallizing from ethanol.

### Pharmacology

These products have been tested by establishing the critical petechial pressure by the method described by A. L. Bacharach *et al.*;<sup>8</sup> the only modification introduced consisted in the time interval between each depression, namely, 18–20 min, instead of 3–5 min.

The albino guinea-pigs of a selected stock which were used weighed from 350 to 450 g at the beginning of the treatment. In two weeks they were gradually adapted to Eddy's scorbutogenic diet. After 12–18 days of a complete scorbutogenic diet, the back of the guinea-pigs was depilated and 48 h after the depilation the necessary value of depression for the appearance of haemorrhagic petechia was determined for each animal.

The compounds under study were administered by intubation for three consecutive days, and 12 h after the last administration the necessary value of depression for the appearance of petechia was measured again in each animal to establish the difference between the data obtained before and after treatment. All the



compounds were administered as hydrochlorides, dissolved in water, at a dose of 0.0003 mole/kg per day per animal.

The activities of the compounds were compared with that of sodium rutin. The activities of derivatives of 4-methyl-7-hydroxycoumarin, of 4-methyl-6-hydroxycoumarin and of rutin were practically zero under our experimental conditions. The obtained values are reported in Table III, the activity of the most active product equalling 100.

Table III. Activity of methyl-hydroxycoumarin ethers in establishing the critical petechial pressure in guinea-pigs (sodium rutin = 1)



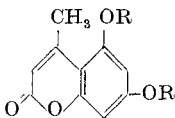
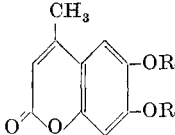
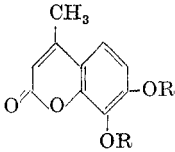
|                                                                                    | R<br>—CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> | R<br>—CH <sub>2</sub> CH <sub>2</sub> —N  | R<br>—CH <sub>2</sub> CH <sub>2</sub> —N  |
|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
|   | 5                                                                                    | 5                                                                                                                          | 100                                                                                                                          |
|   | 41                                                                                   | 5                                                                                                                          | 30                                                                                                                           |
|  | 18                                                                                   | 42                                                                                                                         | 34                                                                                                                           |

Table III shows clearly the importance both of the chemical nature of the basic ether and of the position of the two hydroxyls of the  $\alpha$ -pyrone nucleus. Maximum oral activity, according to our procedure, is reached for 4-methyl-5,7-bis-(*N*-morpholino- $\beta$ -ethoxy)-coumarin where the basic radical is represented by the  $\beta$ -*N*-morpholinoethyl group, and the position of the two hydroxyls is 5,7 as it occurs in most natural products showing the same activity.

*Summary.* A series of basic ethers of 4-methyl-6-hydroxycoumarin, 4-methyl-7-hydroxycoumarin, 4-methyl-5,7-dihydroxycoumarin, 4-methyl-6,7-dihydroxycoumarin and 4-methyl-7,8-dihydroxycoumarin, has been prepared and their activities, tested by critical petechial pressure, have been studied. 4-Methyl-5,7-bis-(*N*-morpholino- $\beta$ -ethoxy)-coumarin proved to be the most active derivative studied.

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### References

- <sup>1</sup> Borbély, F. *Z. Vitaminforsch.*, **14**, 207 (1944)
- <sup>2</sup> Cavallini, G. and Mazzucchi, F. *Farmaco*, **3**, 297 (1948)
- <sup>3</sup> Baserga, A. and Rovatti, B. *Haematologica*, **32**, 205 (1948)
- <sup>4</sup> Baserga, A. and De Nicola, P. *Le Malattie Emorragiche*. 1950. Milan; Soc. Ed. Libreria
- <sup>5</sup> Massarani, E. *Farmaco*, **12**, 691 (1957)
- <sup>6</sup> Mead, J. A. R., Smith, J. N. and Williams, R. T. *Biochem. J.*, **68**, 1957 (1958)
- <sup>7</sup> Pechmann, H.v. and Duisberg, C. *Ber. dtsh. chem. Ges.*, **16**, 2119 (1883)
- <sup>8</sup> Bacharach, A. L., Coates, M. E. and Middleton, T. R. *Biochem. J.*, **36**, 407 (1942)