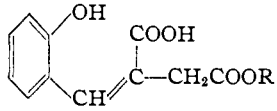
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

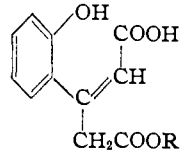
# Coumarins. II. Derivatives of Coumarin-3- and -4-Acetic Acids

BY S. C. LASKOWSKI AND R. O. CLINTON

A previous communication[1] described a series of derivatives of coumarin-3- and -4-carboxylic acids, with particular reference to their local anesthetic activity. The present paper extends this investigation to derivatives of coumarin-3-acetic acid and coumarin-4-acetic acid. If coumarin-3- and coumarin-4-acetates are written in the hypothetical non-cyclic forms (I, II), it is apparent

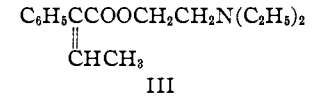


I

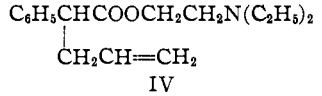


II

that they are, respectively, a substituted phenylvinylacetic ester and a substituted phenylpropionic ester. A number of investigators have reported[2] that the basic esters of phenylpropionic acids have little or no local anesthetic activity, and although no basic esters of phenylvinylacetic acids have been prepared, it might be inferred that the non-conjugation of the double bond with the carboxyl group would obviate a high potency.[3] Gilman, *et al.*,[4] have indicated that the compounds III and IV are of a very low order of activity, while on the other hand the compound 2-diethylaminoethyl 2,2-diphenylpro-



III



IV

pionate hydrochloride possessed a definitely greater local anesthetic activity. A similar observation in the case of 2-diethylaminoethyl 2,2-diphenyl-2-hydroxypropionate hydrochloride has been reported by Lehman and Knoefel.[5] The analogy to the known basic esters of dibenzylacetic acid is also apparent.

If we therefore consider the double bond in II to confer a degree of "aromaticity," the analogy with a 2,2-diarylpropionic acid is closer, and a certain degree of local anesthetic activity might be predicted in this series. No similar analogy exists for I, and other than the general rule that local anesthetic activity may be ascribed to the basic esters of higher molecular weight acids, regardless of "aromaticity,"[6] no prediction is justified in this series.

The literature contains no references to basic derivatives of coumarin-3- or -4-acetic acids, other than a single *bz* derivative, *viz*, 7-dimethylaminocoumarin-4-acetic acid.[7] No pharmacological investigations appear to have been made in these series.

The coumarin-4-acetic acids necessary as precursors in the present work were prepared by the v. Pechmann reaction[8,9] (*cf.* also Dey[7]) from a *m*-substituted phenol and acetone dicarboxylic acid (prepared *in situ* from the citric acid). In general these syntheses offered no difficulty, although in certain cases the yields were poor. However, in our hands the v. Pechmann reaction failed with *m*-thiolcresol, *m*-trifluoromethylphenol and *p*-hydroxydiphenyl, and we were unable to prepare the pharmacologically interesting 7-methylthiocoumarin and 7-trifluoromethylcoumarin-4-acetic acids.

The ethyl coumarin-3-acetates were prepared by the reaction between a *m*-substituted phenol and ethyl acetosuccinate in concentrated sulfuric acid,[10] analogous to the v. Pechmann synthesis of the coumarin-4-acetic acids. The yields were very poor (5 to 8%), except in the special case of resorcinol. These results prevented an extensive investigation in the coumarin-3-acetic acid series.

The coumarin-4-acetic acids could not be converted to the basic esters by reaction with an ω-dialkylaminoalkyl halide in isopropyl alcohol[11]; similar lack of reactivity with acetic acid types has been previously observed. A further complication in this reaction arises from the extreme case of decarboxylation observed in the coumarin-4-acetic acid series[7]; a similar phenomenon was observed in the related esterification reaction between a coumarin-4-acetic acid and a basic alcohol. In both reactions the chief product was the 4-methylcoumarin.

Dey[7] attempted to prepare coumarin-4-acetyl chlorides from the acids and phosphorus pentachloride with no success; only deeply colored decomposition products were obtained. We were able to isolate acyl chlorides from the reaction

(1) Clinton and Laskowski, THIS JOURNAL, **71**, 3602 (1949).

(2) Leffler and Brill, *ibid.*, **55**, 365 (1933); Brill and Cook, *ibid.*, **55**, 2062 (1933); Kuwahata, Ochiai and Nukita, *Folia Pharmacol. Japan*, **7**, 408 (1928) (*Chem. Abstr.*, **23**, 5236 (1929)).

(3) Kamm, THIS JOURNAL, **42**, 1030 (1920); Gilman and Pickens, *ibid.*, **47**, 245 (1925); Gilman, Heckert and McCracken, *ibid.*, **50**, 437 (1928).

(4) Gilman, *et al.*, *J. Pharm. Exper. Ther.*, **74**, 290 (1942).

(5) Lehman and Knoefel, *ibid.*, **74**, 274 (1942).

(6) Cano and Ranedo, *Anales soc. españ. fis. quim.*, **18**, 184 (1920) [*Chem. Abstr.*, **15**, 2672 (1921)]; Bachman, THIS JOURNAL, **57**, 2167 (1935); Brill and Bulow, *ibid.*, **55**, 2059 (1933); *cf.* also 2-diethylaminoethyl 1-phenylvalerate hydrochloride in ref. 5.

(7) Dey, *J. Chem. Soc.*, **107**, 1606 (1915).

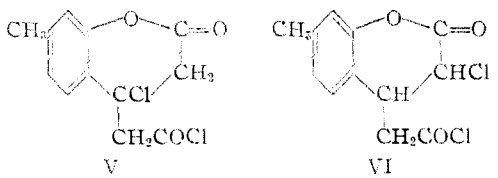
(8) v. Pechmann and Duisberg, *Ber.*, **16**, 2119 (1883).

(9) A comprehensive summary appears in the review by Sethna and Shah, *Chem. Revs.*, **36**, 1 (1945).

(10) Dey and Sankaranarayanan, *J. Indian Chem. Soc.*, **8**, 817 (1931).

(11) Hörenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

between coumarin-4-acetic acids and thionyl chloride, but the acyl chlorides, as shown by subsequent reactions, contained a second chlorine atom. We have tentatively assigned the structure of a chlorodihydrocoumarin-4-acetyl chloride (V or VI) to these compounds. It is reported[9] that such compounds as hydrogen cyanide,



V VI

sodium bisulfite, and cyanoacetamide add to the 3,4-double bond in coumarins, but there is no known example of the addition of a hydrogen halide. In the case of simple coumarin-3-carboxylic acids, thionyl chloride gives only the normal acyl chlorides. Furthermore, in opposition to the proposed structures, we may cite experimental evidence that hydrogen chloride, either alone or in the presence of sulfur dioxide and/or traces of thionyl chloride, does not add to the 3,4-double bond in coumarin-4-acetic acids. However, there is no analogy for the assumption that thionyl chloride will chlorinate either the pyrone ring or the activated methylene group in these or related coumarin types. In addition, the relative instability of the products obtained points to the 3,4-dihydrocoumarin structure. Of the two tentative structures proposed, structure V appears preferable when addition rules are considered.

For the preparation of the basic esters of the coumarin-4-acetic acids, recourse was therefore had to the synthesis *via* ω-haloalkyl coumarin-4-acetates, which were readily obtained by esterification of the acids with an ω-haloalkanol. Replacement of the ω-halogen group by reaction with a secondary amine gave excellent results if the condensations were carried out in an appropriate solvent (*i.e.*, toluene with bromo esters and xylene with chloro esters). However, an exception to this general method was observed in the case of 7-hydroxycoumarin-4-acetic acid derivatives. With these compounds anomalous results were obtained; these results will be made the subject of a subsequent communication.

The coumarin-4-acetamides were easily prepared by amination of the corresponding ethyl coumarin-4-acetates with a primary amine in boiling xylene. The reactions were straightforward, but in certain cases quite slow.

The coumarin-3-acetic acid series, for reasons outlined above, was not extensively investigated. As with the corresponding 4-acetic acid series, esterification by means of the Hörenstein and Pählicke method[11] failed, as did attempted amination or transesterification. In this case the failure of transesterification or amination was not due, however, to decarboxylation, but to an unexpected inherent resistance of the esters toward reaction. Similar observations have been made by Dey and Sankaranarayanan.[10]

An interesting series of observations was made in connection with the quantitative estimation of the coumarin-3- and -4-acetic acids by means of titration with a base.[12] It was expected that the acetic acid portion of the molecule could be readily titrated by, *e.g.*, standard sodium carbonate solution, while standard sodium hydroxide solution would cause rupture of the lactone ring with consequent consumption of two equivalents of base. However, it was found that the ease of ring cleavage varied greatly among the individual coumarin acetic acids, as shown in Table I. The difference in ease of ring cleavage between a 7-hydroxy- and a 7-methoxycoumarinacetic acid is readily apparent from the table. A considerable difference is also evidenced between a coumarin-3- and a coumarin-4-acetic acid as regards ease of ring rupture. It will be noted that the data obtained by refluxing the coumarinacetic acid with an excess of standard base and back-titration have the same order of magnitude as the data obtained by direct titration with base; this therefore obviates the assumption that the 7-hydroxy group is being titrated to any extent (hydrolysis of the phenolate ion would be extensive).

TABLE I

TITRATION OF COUMARIN-ACETIC ACIDS

| Compound | Equivalents: Direct, NaOH to *p*H 8,[a] | Direct, $Na_2CO_3$ to *p*H 5.5,[b] | Refluxed, NaOH to *p*H 8,[c] |
|---|---|---|---|
| 7-Hydroxycoumarin-4-acetic acid | 1.90 | 1.00 | 1.95 |
| 7-Methoxycoumarin-4-acetic acid | 0.99 | 1.00 | 1.53 |
| 7-Hydroxy-4-methylcoumarin-3-acetic acid | 1.67 | 1.13 | 1.92 |
| 7-Methoxy-4-methylcoumarin-3-acetic acid | 0.98 | 1.03 | 1.15 |

[a] The sample was dissolved in neutral alcohol and titrated with 0.1 *N* sodium hydroxide solution to *p*H 8 (phenolphthalein). [b] The sample was dissolved in neutral alcohol and titrated with 0.1 *N* sodium carbonate solution to *p*H 5.5 (methyl red–methylene blue). [c] The sample was refluxed with excess 0.1 *N* sodium hydroxide solution for ninety minutes and the excess of base was back-titrated to *p*H 8 (phenolphthalein).

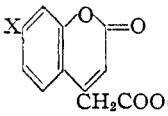
The basic esters and amides of the coumarin-4-acetic acids, and their precursors, are listed in Tables II and III. These compounds have been examined for local anesthetic activity by Drs. T. J. Becker and F. P. Luduena[13] of these laboratories. Most of the dialkylaminoalkyl coumarin-4-acetates showed a local anesthetic activity by infiltration approaching that of procaine. In contrast to procaine, however, they were also found to be topically active. For example, 3-(2-

(12) These titrations were performed by Mr. Morris E. Auerbach of these laboratories.

(13) A complete report will be published by these authors at a later date.

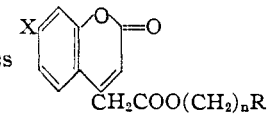
TABLE II

ω-HALOALKYL COUMARIN-4-ACETATES



| X | n | R | Yield,[a] % | M. p., °C. | Analyses, % Halogen Calcd. | Halogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 2 | Br | 82 | 96–98 | 24.62 | 24.58 | | |
| $CH_3$ | 3 | Br | 58 | 90–91 | 23.60 | 23.39 | | |
| $CH_3$ | 3 | Cl | 48 | 85–86 | 12.03 | 12.10 | | |
| $CH_3$ | 4 | Cl | 55 | 86–87 | 11.48 | 11.40 | | |
| $CH_3O$ | 2 | Br | 74 | 94–95 | 23.46 | 23.44 | | |
| $CH_3O$ | 3 | Br | 71 | 73–75 | 22.54 | 22.28 | | |
| HO | 2 | Br | 52 | 147–148 | 24.46 | 24.64 | | |
| HO | 3 | Br | 50 | 127–130 | 23.46 | 23.24 | | |
| $C_2H_5$ | 2 | Br | 86 | 57–58 | 23.56 | 23.6 | | |
| $C_2H_5$ | 3 | Cl | 75 | 94–96 | 11.48 | 11.71 | | |
| $C_2H_5$ | 4 | Cl | 40 | 75–76 | 10.98 | 11.02 | | |
| $C_4H_9O$ | 2 | Cl | 50 | 78–79 | 10.47 | 10.77 | | |

DIALKYLAMINOALKYL COUMARIN-4-ACETATE HYDROCHLORIDES



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 2 | $N(C_2H_5)_2$ | 44 | 144.6–145.8 | 10.04 | 10.12 | 3.96 | 3.90 |
| $CH_3$ | 2 | $NC_5H_{10}$[b] | 66 | 155–156.4 | 9.71 | 9.73 | 3.83 | 3.67 |
| $CH_3$ | 2 | $NC_4H_8O$[c] | 39 | 184.8–185.6 | 9.66 | 9.66 | 3.81 | 3.75 |
| $CH_3$ | 2 | $NC_6H_{12}$[d] | 36 | 86–87 | 9.35 | 9.62 | 3.69 | 3.55 |
| $CH_3$ | 3 | $N(C_2H_5)_2$ | 49 | 149–150.2 | 9.66 | 9.77 | 3.81 | 3.74 |
| $CH_3$ | 3 | $NC_5H_{10}$[b] | 71 | 177–180.6 | 9.35 | 9.09 | 3.69 | 3.58 |
| $CH_3$ | 3 | $NC_6H_{12}$[d] | 32 | 133–135 | 9.02 | 9.07 | 3.56 | 3.48 |
| $CH_3$ | 3 | $NC_4H_8O$[c] | 57 | 186.2–188.8 | 9.31 | 9.14 | 3.67 | 3.59 |
| $CH_3O$ | 2 | $N(C_2H_5)_2$ | 27 | 167.6–169.9 | 9.61 | 9.53 | 3.79 | 3.66 |
| $CH_3O$ | 2 | $NC_5H_{10}$[b] | 39 | 183–185 | 9.31 | 9.20 | 3.67 | 3.53 |
| $CH_3O$ | 2 | $NC_4H_8O$[c] | 53 | 155–155.8 | 9.26 | 9.08 | 3.65 | 3.53 |
| $CH_3O$ | 2 | $NC_6H_{12}$[d] | 34 | 164–166.4 | 8.98 | 9.00 | 3.54 | 3.33 |
| $CH_3O$ | 2 | $N(C_4H_9)_2$ | 50 | 75–80 | 8.34 | 8.15 | 3.29 | 3.26 |
| $CH_3O$ | 3 | $N(C_2H_5)_2$ | 47 | 134–136 | 9.26 | 9.08 | 3.65 | 3.58 |
| $CH_3O$ | 3 | $NC_5H_{10}$[b] | 65 | 145.8–148.2 | 8.98 | 9.00 | 3.54 | 3.58 |
| $CH_3O$ | 3 | $NC_6H_{12}$[d] | 37 | 130–133 | 8.67 | 8.59 | 3.42 | 3.39 |
| $CH_3O$ | 3 | $NC_4H_8O$[c] | 53 | 158.2–162.6 | 8.93 | 8.70 | 3.52 | 3.42 |
| $C_2H_5$ | 2 | $NC_5H_{10}$[b] | 35 | 149–151 | 9.33 | 9.45 | | |

[a] These yields represent percentage conversion without regard to recovered starting material. [b] 1-Piperidyl. [c] 4-Morpholinyl. [d] 2-Methylpiperidyl-1. [e] Calculated for $C_{20}H_{25}NO_4 \cdot HCl$: C, 63.23; H, 6.90. Found: C, 62.79; H, 7.21.

methylpiperidyl-1)-propyl 7-methylcoumarin-4-acetate hydrochloride was equal in activity to procaine by infiltration (external canthus of the rabbit's eye), and about one-half as active as cocaine topically. Its toxicity was about one-half that of cocaine. In general, the coumarin-4-acetic acid derivatives were much less toxic than the corresponding coumarin-3-carboxylic acid derivatives.[1] The coumarin-4-acetamides were found to be less active than the corresponding esters. In agreement with previous observations,[14] the morpholinyl terminus was found to impart greatly lowered toxicity; however, in contrast to Gardner, *et al.*,[14] activity also dropped more than proportionally. In view of previous work,[15] in which the morpholinyl terminus possessed little or no therapeutic advantage, it appears that this group confers no special benefits.

Several of the 7-substituted coumarin-3- and -4-acetic acids were tested for amebicidal activity *in vitro* against *E. histolytica*, with emetine hydrochloride as reference standard.[16] No appreciable activity was apparent for these compounds.

## Experimental[17]

**Coumarin-4-acetic Acids.**—The general method of v. Pechmann and Duisberg[7,8] was used for the preparation of the coumarin-4-acetic acids. Through numerous experiments it was found that the procedure was critical, especially as regards the *in situ* preparation of the acetone dicarboxylic acid. The following general procedure, of

(14) Gardner, Clarke and Semb, THIS JOURNAL, **55**, 2999 (1933).

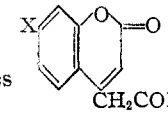
(15) Clinton, Salvador and Laskowski, *ibid.*, **71**, 3366 (1949).

(16) A complete report will be published by Dr. E. W. Dennis of these laboratories, at a later date.

(17) All melting points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

TABLE III

N-(ω-DIALKYLAMINOALKYL)-COUMARIN-4-ACETAMIDES



| X | R | Bases Yield, % | M. p., °C. | Nitrogen,[a] % Calcd. | Found | Hydrochlorides M. p., °C. | Nitrogen, % Calcd. | Found | Chlorine, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | 2-Diethylaminoethyl- | 50 | 118–120 | 4.43 | 4.26 | 150–151 | 7.94 | 7.38 | 10.05 | 9.70 |
| $CH_3$ | 3-Diethylaminopropyl- | 50 | 143–145 | 4.24 | 4.25 | 99–101 | 7.64 | 7.34 | 9.66 | 9.59 |
| $CH_3$ | 4-Diethylaminobutyl- | 51 | 154–155 | 4.07 | 4.12 | 146–150 | 7.36 | 7.18 | 9.31 | 9.33 |
| $CH_3$ | 4-Diethylamino-1-methylbutyl- | 25 | 160–163 | 3.91 | 3.83 | 153–154 | 7.09 | 6.86 | 8.98 | 9.00 |
| $CH_3$ | 3-Diethylamino-2-hydroxypropyl- | 30 | 144–145 | 4.04 | 3.85 | 173–175 | 7.32 | 7.14 | 9.26 | 9.41 |
| $CH_3$ | 2-(2-Diethylaminoethylmercapto)-ethyl- | 65 | 138–140 | 3.72 | 3.67 | 120–121 | 6.78[b] | 6.55 | 8.59 | 8.59 |
| $CH_3$ | 3-(2-Methylpiperidyl-1)propyl- | 50 | 147–148 | 3.93[c] | 3.94 | [d] | | | | |
| $CH_3O$ | 3-Diethylaminopropyl- | 47 | 122–123 | 4.04 | 4.03 | 150–151 | 7.31 | 7.16 | 9.26 | 9.36 |
| $CH_3O$ | 4-Diethylaminobutyl- | 86 | 140–141 | 3.89 | 3.92 | 164–165 | 7.06[e] | 6.87 | 8.93 | 8.95 |
| $CH_3O$ | 4-Diethylamino-1-methylbutyl- | 35 | 159–160 | 3.74 | 3.71 | 146–148 | 6.82 | 6.64 | 8.63 | 8.60 |
| $C_2H_5$ | 4-Diethylaminobutyl- | 71 | 120–122 | 3.91 | 3.93 | 174–175 | 7.09[f] | 6.91 | 8.98 | 9.06 |
| $C_2H_5$ | 4-Diethylamino-1-methylbutyl- | 40 | 151–152 | 3.76 | 3.78 | 154–158 | 6.85 | 6.65 | 8.67 | 8.70 |
| $C_2H_5$ | 3-Diethylamino-2-hydroxypropyl- | 40 | 127–128 | 3.89 | 3.88[g] | [d] | | | | |
| $C_2H_5$ | 2-(2-Diethylaminoethylmercapto)-ethyl- | 55 | 114–115 | 3.58 | 3.55 | 126–127 | 6.56 | 6.39 | 8.30 | 8.40 |

[a] Basic nitrogen by titration with perchloric acid in glacial acetic acid solution. [b] Calculated for $C_{20}H_{28}N_2O_3S\cdot HCl$: C, 58.16; H, 7.08. Found: C, 58.17; H, 6.97. [c] Calculated for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92. Found: C, 70.99; H, 7.88. [d] No crystalline derivative could be obtained. [e] Calculated for $C_{20}H_{28}N_2O_4\cdot HCl$: C, 60.52; H, 7.36. Found: C, 60.44; H, 7.29. [f] Calculated for $C_{21}H_{30}N_2O_3\cdot HCl$: C, 63.86; H, 7.91. Found: C, 63.83; H, 7.64. [g] Calculated for $C_{20}H_{28}N_2O_4$: N, 7.78. Found: N, 7.78.

all modifications tried, gave the highest yields and duplicability of results:

A mixture of 210 g. (1 mole) of citric acid monohydrate and 280 ml. of concentrated sulfuric acid was stirred at room temperature for sixty minutes, and then slowly heated (rate of heating governed by foaming) to 70°. After thirty-five minutes at this temperature, with stirring throughout, the evolution of carbon monoxide had slackened, and the clear solution was rapidly cooled to 0°. To this stirred solution was added 86.4 g. (0.8 mole) of redistilled *m*-cresol and 112 ml. of concentrated sulfuric acid, each in three equal portions, at such a rate that the internal temperature did not exceed 10°. The resulting mixture was stored at 0° for sixteen hours, poured into two liters of ice, and the resulting crystalline precipitate was filtered off and washed thoroughly with water. The precipitate was stirred with 1000 ml. of *N* sodium carbonate solution for fifteen minutes at 65°, filtered, and the insoluble material was washed with water. Acidification of the combined filtrate and washings gave 52.1 g. (31%) of 7-methylcoumarin-4-acetic acid, m. p. 191–192° (lit.,[18] m. p. 190°). The carbonate-insoluble portion (31.2 g.) was identified as 4,7-dimethylcoumarin.

The above procedure was varied by lengthening or shortening the period of heating, by variations in temperature during the condensation, by altering the proportion of sulfuric acid, and through use of sulfur trioxide–sulfuric acid mixtures. No improvement in yield was discernible in any of these modifications. By the above procedure, there were prepared the following coumarin-4-acetic acids:

**7-Hydroxycoumarin-4-acetic acid**, 61% yield, m. p. 201–202° (lit.,[7] m. p. 201°).

**7-Methoxycoumarin-4-acetic acid**, 51% yield, m. p. 175–176° (lit.,[7] m. p. 187°).

*Anal.* Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.27. Found: C, 61.54; H, 4.22.

**6-Methoxycoumarin-4-acetic acid**, 5% yield, m. p. 191–192° (from alcohol).

*Anal.* Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.27. Found: C, 61.33; H, 4.33.

**7-Ethylcoumarin-4-acetic acid**, 27.5% yield, m. p. 183–184° (from absolute alcohol).

*Anal.* Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17. Found: C, 67.38; H, 5.26.

**7-Butyloxycoumarin-4-acetic acid**, 81% crude yield, m. p. 91–97° (from alcohol–ether). This compound could not be obtained analytically pure, but was utilized successfully in the preparation of derivatives.

**7-Hexyloxycoumarin-4-acetic acid**, 80% yield, m. p. 131–133° (from ether). This compound proved difficult to purify, and yielded only waxy derivatives.

*Anal.* Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.68; H, 6.70.

**Coumarin-3-acetic Acids.**—The procedures of Dey and Sankaranarayanan[10] were used without modification for the preparation of the ethyl 7-substituted-4-methylcoumarin-3-acetates and the corresponding acids. Ethyl 7-hydroxy-4-methylcoumarin-3-acetate[10] and ethyl 7-methoxy-4-methylcoumarin-3-acetate[10] were obtained in crude yields of 64% and 57%, respectively.

**Ethyl 4,7-dimethylcoumarin-3-acetate** was prepared in 5% yield from *m*-cresol: white cottony needles from dilute alcohol, m. p. 103–104°.

*Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.20. Found: C, 69.45; H, 6.52.

Saponification of the crude esters gave, respectively, an 83% yield of 7-hydroxy-4-methylcoumarin-3-acetic acid,[10] m. p. 265–268°, and a 20% yield of **7-methoxy-4-methylcoumarin-3-acetic acid**, m. p. 196–197°.

*Anal.* Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.84. Found: C, 62.76; H, 4.71.

**Non-basic Coumarin-3- and -4-acetates.**—All of the esters of the coumarin-3- and -4-acetic acids were prepared by esterification of the acids with an alcohol or ω-haloalkanol in the presence of concentrated sulfuric acid, using benzene as water carrier. In general the esterifications were slow, due to the insolubility of the acids in the benzene mixture; however, the method gave better yields than the usual Fischer procedure. The proportions used and the general procedure are indicated in the case of **ethyl 7-ethylcoumarin-4-acetate.**

A mixture of 46.4 g. (0.2 mole) of 7-ethylcoumarin-4-acetic acid, 28.0 g. (0.6 mole) of ethanol, 6 ml. of concentrated sulfuric acid and 1250 ml. of dry benzene was refluxed under a water trap for twelve hours, at the end of which period the trapped aqueous layer amounted to 8.5

(18) Dey and Radhabai, *J. Indian Chem. Soc.*, **11**, 635 (1934).

ml. The cooled benzene solution was washed with sodium bicarbonate solution and with water, and evaporated to dryness *in vacuo*. Recrystallization of the solid residue from ethyl acetate (decolorization) gave a total (including material from the mother liquors) of 48.0 g. (92.5%) of product; white cottony needles, m. p. 103–104°.

*Anal.* Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.20. Found: C, 69.29; H, 6.25.

The same procedure was applicable to the chloro- and bromo-alkanols. Data on these compounds are given in Table II, and below.

By the above procedure there were obtained: ethyl 7-methylcoumarin-4-acetate, 88.5% yield, m. p. 125–126°,[19] ethyl 7-hydroxycoumarin-4-acetate, 66% yield (low yield due to insolubility of the acid; the yield was quantitative when based upon the recovered acid), m. p. 155–156°,[7] and ethyl 7-methoxycoumarin-4-acetate, 84% yield, m. p. 101–102°.[7]

**2-Bromoethyl 7-hydroxy-4-methylcoumarin-3-acetate** was obtained in 50% yield (95% yield based upon recovered acid), m. p. 164–165° (from ethyl acetate).

*Anal.* Calcd. for $C_{14}H_{13}BrO_5$: Br, 23.46. Found: Br, 23.38.

**2-Bromopropyl 7-methylcoumarin-4-acetate** was prepared in 53% yield (97% yield based on recovered acid), rosettes of white needles from alcohol, m. p. 90–91°.

*Anal.* Calcd. for $C_{15}H_{15}BrO_4$: Br, 23.60. Found: Br, 23.41.

3-Chloropropyl 7-butyloxycoumarin-4-acetate and 4-chlorobutyl 7-methoxycoumarin-4-acetate were oils. They could not be obtained analytically pure, and were not processed further.

**Basic Esters of Coumarin-3- and -4-acetic Acids.**—The basic esters were prepared by the reaction between an ω-haloalkyl coumarin-3- or -4-acetate and two mole proportions of a secondary amine. If the halogen was chlorine, xylene was used as solvent (toluene gave poor yields), but for bromine replacement toluene was satisfactory. When attempts were made to effect halogen replacement by heating with excess amine (no solvent), or in benzene, no perceptible reaction took place. A typical example is:

A mixture of 8.5 g. (0.025 mole) of 2-bromoethyl 7-methoxycoumarin-4-acetate, 4.3 g. (0.05 mole) of piperidine and 150 ml. of dry toluene was refluxed for seven hours. Piperidine hydrobromide separated slowly. The cooled reaction product was filtered and the filtrate was washed with 5 × 100 ml. of water (small amounts of sodium chloride were used to break emulsions). The toluene layer was dried and concentrated *in vacuo* (in several cases the bases crystallized at this point, but were not isolated). An excess of ethereal hydrogen chloride was added and the resulting semicrystalline oil was recrystallized from absolute alcohol.

**The Reaction of Thionyl Chloride with Coumarin-4-acetic Acids.**—A mixture of 21.8 g. (0.1 mole) of 7-methylcoumarin-4-acetic acid and 476 g. (4 moles) of pure thionyl chloride was refluxed with stirring for two hours under anhydrous conditions. Solution of the acid was slow. The excess thionyl chloride was removed *in vacuo* and the residual oil was taken down again *in vacuo* with 600 ml. of dry benzene. The oily product was dissolved in dry benzene and the solution was divided into two equal portions.

To one portion of the above benzene solution was slowly added a solution of 5 g. of 2-diethylaminoethanol in 50 ml. of dry benzene. A brown oil separated. This oil was triturated with Skellysolve A, dissolved in 100 ml. of absolute alcohol, and the solution was decolorized (Darco G-60). A small amount of a white solid (m. p. > 250°) separated. After filtration, the filtrate was concentrated to *ca.* 40 ml., cooled and the resulting crystalline precipitate was filtered off. Trituration of the product with acetone followed by recrystallization from absolute alcohol–acetone gave **2-diethylaminoethyl 4-chloro-7-methyl-3,4-dihydrocoumarin-4-acetate hydrochloride** (?) (*cf.* V. and VI), cream-colored needles, m. p. 175–176° (dec.). The compound darkened slowly on standing.

*Anal.* Calcd. for $C_{18}H_{24}ClNO_4 \cdot HCl$: N, 3.59; Cl (ionic), 9.10; Cl (total), 18.25. Found: N, 3.59; Cl (ionic), 9.10; Cl (total), 18.21.

To the second portion of the benzene solution (*vide supra*) was added a solution of 7.5 g. of diethylamine in 50 ml. of dry benzene. The mixture, after standing overnight at 0°, was concentrated to dryness *in vacuo*. The residual solid was dissolved in 50 ml. of alcohol and precipitated with water. Recrystallization (decolorization with Darco G-60) of the resulting solid from hot alcohol gave **N,N-diethyl-4-chloro-7-methyl-3,4-dihydrocoumarin-4-acetamide** (?) (*cf.* V and VI), golden yellow plates, m. p. 199–200°. The compound darkened on standing. It did not contain ionic chlorine.

*Anal.* Calcd. for $C_{16}H_{20}ClNO_3$: C, 62.03; H, 6.51; N, 4.52; Cl, 11.47. Found: C, 62.13; H, 6.41; N, 4.55; Cl, 11.30.

**N-(ω-Dialkylaminoalkyl)-coumarin-4-acetamides.**—The basic amides of the coumarin-4-acetic acids were prepared by the reaction between an ω-dialkylaminoalkylamine (1 mole) and an ethyl coumarin-4-acetate (1 mole) in boiling xylene. The mixture was refluxed for twenty to twenty-four hours, concentrated *in vacuo*, and the resulting solid bases were purified by solution in dilute hydrochloric acid, filtration, and precipitation with ammonium hydroxide. In general the bases could be satisfactorily recrystallized from benzene-Skellysolve mixtures or from ethyl acetate-Skellysolve mixtures. The use of toluene as solvent gave lowered yields.

Conversion of the bases to the hydrochlorides was effected by solution in an excess of warm absolute alcoholic hydrogen chloride followed by complete precipitation (usually as an oil) with absolute ether. Trituration with dry acetone or with boiling ethyl acetate usually effected crystallization. Absolute alcohol, or a mixture of absolute alcohol with ethyl acetate and/or ether, was satisfactory for recrystallization.

The N-(ω-dialkylaminoalkyl)-coumarin-4-acetamides and their hydrochlorides are listed in Table III.

## Summary

A series of basic esters and amides of coumarin-4-acetic acids has been prepared. Synthetic difficulties prevented extension of this investigation to the analogous coumarin-3-acetic acids. Anomalous results were obtained with 7-hydroxycoumarin-3- and -4-acetic acids.

RENSSELAER, N. Y. RECEIVED MARCH 23, 1950

(19) Fries and Volk, *Ann.*, **379**, 107 (1911).