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# SYNTHESIS AND MOLECULAR STRUCTURE OF A SUBSTITUTED 8-OXA-10-AZATRICYCLO-[7.3.1.0]TRIDECATETRAENE

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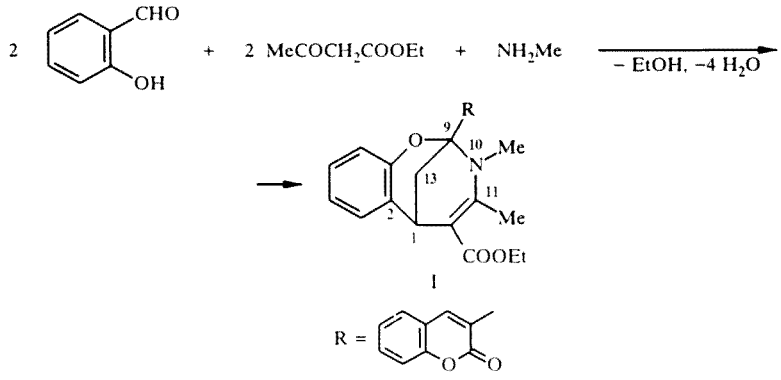
*10,11-Dimethyl-9-(coumarin-3-yl)-12-ethoxycarbonyl-8-oxa-10-azatricyclo[7,3,1.$0^{2,7}$]trideca-2,4,6-11-tetraene was isolated from the mixture of products from the condensation of salicyl aldehyde with acetoacetic ester and methylamine. Its molecular structure has been established by x-ray crystallography.*

The Hantzsch method has been widely used for the synthesis of biologically active 1,4-dihydropyridines [1]. However, when salicyl aldehyde is used, complex mixtures of products are formed the structure of which is determined to considerable degree by the nature of the CH active and amine components and the reaction conditions [2-6]. We have isolated the basic product of the condensation of salicyl aldehyde with acetoacetic ester and methylamine: the polycyclic compound (I), the structure of which has been established from $^1$H NMR, IR and mass spectroscopy and x-ray crystallography.




The IR spectrum of product (I) contains bands at 1730 and 1677 cm$^{-1}$ corresponding to ester and lactone carbonyl groups and also a band at 1622 cm$^{-1}$ assigned to an isolated double bond. The $^1$H NMR spectrum contains singlets for two methyl substituents in positions 10 and 11, plus the characteristic triplet ($CH_3$) and quartet ($CH_2$) of an OEt group. The presence of a $-CHCH_2-$ group is indicated by two doublets of doublets at 1.94 and 2.62 ppm plus a triplet at 4.38 ppm with coupling constants of 12.5, 3.7, and 2.6 Hz. There are two overlapping ABCD spectra of *ortho*-substituted benzene rings in the aromatic region (7.0-7.8 ppm). A singlet of a single proton at 8.41 ppm may be assigned to 4'-H of the coumarinyl substituent. The mass spectrum of compound I contains a molecular ion peak at *m/z* 417 (18%) with fragment ions which confirm the presence of methyl, carbonyl, and ethoxycarbonyl groups in its structure.

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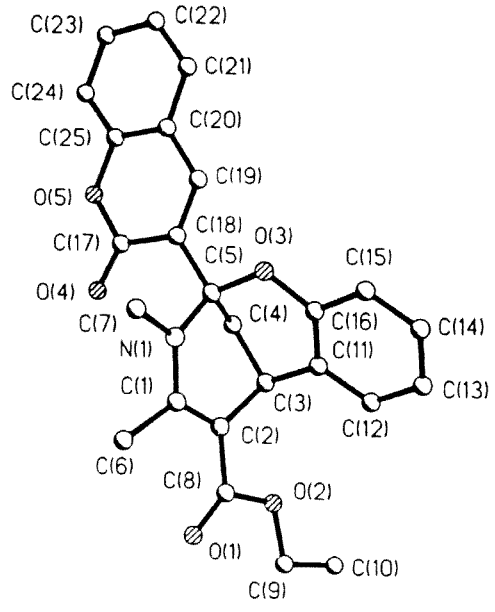


Fig. 1. Overall view and numbering of the atoms in the molecule of compound I.

From a comparison of the spectroscopic data with information in the literature on the reaction of salicyl aldehyde with acetoacetic ester and amines [3-5], compound I may be assigned the structure of a 9-(coumarin-3-yl) substituted 10,11-dimethyl-12-ethoxycarbonyl-8-oxa-10-aza-tricyclotridecatetraene. A system with such a heterocyclic system was first described in 1987 [5], but unambiguous proof of its formation was not obtained. For additional confirmation of the structure, and to determine the conformation of the heterocyclic fragments and the orientation of the substituents in compound I, we undertook an x-ray crystallographic investigation. A general view of the molecule is shown in Figure 1 (the numbering of the atoms does not conform to IUPAC recommendations). The atomic coordinates, bond lengths, and bond angles are given in Tables 1-3.

The most interesting feature of the structure of molecule I is the conformation of the tetrahydropyridine and dihydropyran rings which make up the oxaazabicyclononane skeleton. The piperidine ring has a distorted boat conformation, while the dihydropyran ring has a distorted chair conformation. The least squares plane for the piperidine passes through $N_{(1)}-C_{(1)}-C_{(2)}-C_{(3)}$ with divergences of no more than 0.002 Å; atoms $C_{(4)}$ and $C_{(5)}$ diverge from the plane in the same direction by 0.916 and 0.284 Å respectively. The least squares plane for the dihydropyran ring passes through atoms $C_{(3)}-C_{(11)}-C_{(16)}-O_{(3)}$ with divergences of no more than 0.039 Å. Atoms $C_{(4)}$ and $C_{(5)}$ diverge from it by 0.618 and −0.167 Å respectively. The angle between the two planar parts of the oxaazabicyclononane fragment is 68.3°. The torsion angles are as follows: −105.3° for $C_{(1)}-N_{(1)}-C_{(5)}-O_{(3)}$, −79.3° for $N_{(1)}-C_{(5)}-O_{(3)}-C_{(16)}$, 80.5° for $C_{(1)}-C_{(2)}-C_{(3)}-C_{(11)}$, −92.6° for $C_{(2)}-C_{(3)}-C_{(11)}-C_{(16)}$, and −178.8° for $C_{(3)}-C_{(4)}-C_{(5)}-C_{(18)}$. There were no noteworthy distortions in bond lengths or bond angles within the rings [7]. Atoms $N_{(1)}$, $C_{(1)}$, $C_2$, $C_{(11)}$ and $C_{(16)}$ have planar trigonal configurations. The increase of the bond angle $C_{(2)}-C_{(3)}-C_{(11)}$ to 112.9° (in comparison with the tetrahedral angle) is probably connected to interference between the unshared pairs of the two cyclic heteroatoms and between the $\pi$-systems of the olefinic bonds in the two planar parts of the oxaazabicyclononane fragment. The $C_{(4)}-C_{(5)}-C_{(18)}$ angle is also increased to 112°, and the $C_{(18)}-C_{(5)}-O_{(3)}$ angle correspondingly decreased (to 104.2°) because of steric hindrance between the N-methyl group of the piperidine fragment and the carbonyl group of the coumarinyl substituent.

The N-methyl group has a cisoid position relative to the phenoxy substituent in the tetrahydropyridine ring which accounts for the strong deshielding effect of the unshared pair of the nitrogen atom on the resonance frequency of one of the protons (the *cis*-proton 13-H) of the methylene bridge (the difference in chemical shifts is about 0.7 ppm). Formation of the transoid isomer would evidently be less favorable because of repulsion between the unshared pairs of the cyclic nitrogen and oxygen atoms.

TABLE 1. Atom Coordinates ($\times 10^4$, for H $\times 10^3$) in the Molecule of Compound I

| Atom | x | y | z |
|---|---|---|---|
| O(1) | 1912(2) | 1817(5) | 4563(2) |
| O(2) | 1792(2) | 4733(4) | 4296(2) |
| O(3) | 2246(2) | 3244(5) | 1472(2) |
| O(4) | 4758(2) | 1476(5) | 2449(2) |
| O(5) | 5366(2) | 1703(5) | 1394(2) |
| N(1) | 2759(3) | 1220(5) | 2374(2) |
| C(1) | 2527(3) | 1292(6) | 3078(2) |
| C(2) | 2325(3) | 2878(6) | 3396(2) |
| C(3) | 2371(3) | 4549(6) | 2937(2) |
| C(4) | 3186(3) | 4353(6) | 2470(3) |
| C(5) | 2996(3) | 2813(6) | 1965(2) |
| C(6) | 2524(4) | -503(7) | 3452(3) |
| C(7) | 2750(5) | -491(7) | 1981(3) |
| C(8) | 2008(3) | 3013(7) | 4130(2) |
| C(9) | 1415(5) | 4991(9) | 4989(3) |
| C(10) | 1220(5) | 6934(10) | 5082(4) |
| C(11) | 1535(3) | 4812(6) | 2451(2) |
| C(12) | 764(3) | 5699(6) | 2666(3) |
| C(13) | 15(4) | 5926(7) | 2209(3) |
| C(14) | 26(3) | 5242(7) | 1514(3) |
| C(15) | 779(3) | 4357(7) | 1282(3) |
| C(16) | 1523(3) | 4129(6) | 1753(2) |
| C(17) | 4637(3) | 1860(7) | 1823(2) |
| C(18) | 3779(3) | 2464(6) | 1479(2) |
| C(19) | 3735(3) | 2800(6) | 766(2) |
| C(20) | 4504(3) | 2595(6) | 331(2) |
| C(21) | 4494(3) | 2947(7) | -414(2) |
| C(22) | 5262(4) | 2772(7) | -783(3) |
| C(23) | 6072(4) | 2289(7) | -431(3) |
| C(24) | 6100(3) | 1904(8) | 292(3) |
| C(25) | 5319(3) | 2068(6) | 659(2) |
| H(3) | 243(2) | 560(5) | 323(2) |
| H(41) | 325(3) | 537(6) | 216(2) |
| H(42) | 372(3) | 411(6) | 273(2) |
| H(61) | 309(3) | -115(6) | 330(2) |
| H(62) | 194(3) | -128(6) | 335(2) |
| H(63) | 243(3) | -28(6) | 397(2) |
| H(71) | 222(3) | -130(6) | 211(2) |
| H(72) | 337(4) | -100(9) | 205(3) |
| H(73) | 278(4) | 1(9) | 145(4) |
| H(91) | 91(3) | 421(7) | 500(3) |
| H(92) | 182(3) | 457(6) | 530(2) |
| H(101) | 95(3) | 703(7) | 549(3) |
| H(102) | 181(4) | 768(8) | 498(3) |
| H(103) | 83(4) | 726(9) | 470(3) |
| H(12) | 78(3) | 621(7) | 316(3) |
| H(13) | -52(3) | 647(6) | 237(2) |
| H(14) | -53(4) | 538(7) | 121(3) |
| H(15) | 84(3) | 401(7) | 80(3) |
| H(19) | 318(3) | 318(5) | 56(2) |
| H(21) | 394(3) | 326(6) | -64(2) |
| H(22) | 527(3) | 310(7) | -128(3) |
| H(23) | 663(3) | 220(6) | -69(2) |
| H(24) | 659(3) | 154(6) | 52(2) |

The coumarin fragment is effectively planar (to a precision of 0.067 Å) since the twist angle at the $C_{(20)}-C_{(25)}$ bond is just 1.8°. Its plane is at 68° to the plane of the piperidine ring. Bond lengths and bond angles in both rings of the coumarinyl unit are close to normal [7].

The COOEt group is planar, the angles $C_{(2)}-C_{(8)}-O_{(2)}-C_{(9)}$ and $C_{(8)}-O_{(2)}-C_{(9)}-C_{(10)}$ are 176.0 and 179.9° respectively, and it is coplanar with the least squares plane of the piperidine ring (the dihedral angles $C_{(1)}-C_{(2)}-C_{(8)}-O_{(1)}$ and $-O_{(2)}$ are 2.9 and −174.4° respectively). The benzene ring condensed with the oxaazabicyclononane unit is coplanar with the least squares plane of the dihydropyran ring (with a precision of 0.036 Å; the twist angle at the $C_{(11)}-C_{(16)}$ bond is 0.7°).

TABLE 2. Bond Lengths in the Molecule of Compound I

| Bond | $l$, Å | Bond | $l$, Å | Bond | $l$, Å |
|---|---|---|---|---|---|
| O(1)—C(8) | 1,212(6) | C(1)—C(6) | 1,507(7) | C(14)—C(15) | 1,377(7) |
| O(2)—C(8) | 1,359(6) | C(2)—C(3) | 1,513(6) | C(15)—C(16) | 1,388(6) |
| O(2)—C(9) | 1,436(7) | C(2)—C(8) | 1,462(6) | C(17)—C(18) | 1,468(6) |
| O(3)—C(5) | 1,445(5) | C(3)—C(4) | 1,518(6) | C(18)—C(19) | 1,347(6) |
| O(3)—C(16) | 1,375(5) | C(3)—C(11) | 1,513(6) | C(19)—C(20) | 1,428(6) |
| O(4)—C(17) | 1,204(5) | C(4)—C(5) | 1,501(6) | C(20)—C(21) | 1,407(6) |
| O(5)—C(17) | 1,370(5) | C(5)—C(18) | 1,518(6) | C(20)—C(25) | 1,386(6) |
| O(5)—C(25) | 1,391(5) | C(9)—C(10) | 1,49(1) | C(21)—C(22) | 1,355(7) |
| N(1)—C(1) | 1,366(5) | C(11)—C(12) | 1,389(6) | C(22)—C(23) | 1,387(7) |
| N(1)—C(5) | 1,459(6) | C(11)—C(16) | 1,391(6) | C(23)—C(24) | 1,372(7) |
| N(1)—C(7) | 1,469(7) | C(12)—C(13) | 1,379(7) | C(24)—C(25) | 1,368(7) |
| C(1)—C(2) | 1,359(6) | C(13)—C(14) | 1,388(8) | | |

TABLE 3. Bond Angles in the Molecule of Compound I

| Angle | $\omega$ (deg) | Angle | $\omega$ (deg) |
|---|---|---|---|
| C(8)—O(2)—C(9) | 115,6(4) | C(3)—C(11)—C(16) | 119,2(4) |
| C(5)—O(3)—C(16) | 117,0(3) | C(12)—C(11)—C(16) | 117,5(4) |
| C(17)—O(5)—C(25) | 123,0(3) | C(11)—C(12)—C(13) | 121,9(5) |
| C(1)—N(1)—C(5) | 122,8(4) | C(12)—C(13)—C(14) | 119,3(5) |
| C(1)—N(1)—C(7) | 120,8(4) | C(13)—C(14)—C(15) | 120,5(5) |
| C(5)—N(1)—C(7) | 116,4(4) | C(14)—C(15)—C(16) | 119,3(4) |
| N(1)—C(1)—C(2) | 121,2(4) | O(3)—C(16)—C(11) | 123,2(4) |
| N(1)—C(1)—C(6) | 114,3(4) | O(3)—C(16)—C(15) | 115,2(4) |
| C(2)—C(1)—C(6) | 124,5(4) | C(11)—C(16)—C(15) | 121,6(4) |
| C(1)—C(2)—C(3) | 117,0(4) | O(4)—C(17)—O(5) | 116,9(4) |
| C(1)—C(2)—C(8) | 123,3(4) | O(4)—C(17)—C(18) | 125,8(4) |
| C(3)—C(2)—C(8) | 119,5(4) | O(5)—C(17)—C(18) | 117,3(4) |
| C(2)—C(3)—C(4) | 107,3(4) | C(5)—C(18)—C(17) | 117,4(4) |
| C(2)—C(3)—C(11) | 112,9(4) | C(5)—C(18)—C(19) | 123,0(4) |
| C(4)—C(3)—C(11) | 108,6(4) | C(17)—C(18)—C(19) | 119,4(4) |
| C(3)—C(4)—C(5) | 107,3(4) | C(18)—C(19)—C(20) | 121,9(4) |
| O(3)—C(5)—N(1) | 108,5(3) | C(19)—C(20)—C(21) | 124,0(4) |
| O(3)—C(5)—C(4) | 110,2(4) | C(19)—C(20)—C(25) | 118,5(4) |
| N(1)—C(5)—C(4) | 109,8(4) | C(21)—C(20)—C(25) | 117,4(4) |
| O(3)—C(5)—C(18) | 104,2(3) | C(20)—C(21)—C(22) | 120,2(4) |
| N(1)—C(5)—C(18) | 112,0(4) | C(21)—C(22)—C(23) | 120,7(5) |
| C(4)—C(5)—C(18) | 112,0(4) | C(22)—C(23)—C(24) | 120,5(5) |
| O(1)—C(8)—O(2) | 120,6(4) | C(23)—C(24)—C(25) | 118,4(5) |
| O(1)—C(8)—C(2) | 128,1(4) | O(5)—C(25)—C(20) | 119,8(4) |
| O(2)—C(8)—C(2) | 111,3(4) | O(5)—C(25)—C(24) | 117,5(4) |
| O(2)—C(9)—C(10) | 108,6(5) | C(20)—C(25)—C(24) | 122,7(4) |
| C(3)—C(11)—C(12) | 123,3(4) | | |

The bond lengths in the benzene ring are within limits of 1.377-1.391 Å (mean 1.385 Å) and the bond angles within the ring are 117.5°-121.9° (mean 120°). The angle between the mean planes of the two benzpyrane systems of the molecule is 31.4°. Molecules of compound I in the crystal are associated by van der Waals forces.

## EXPERIMENTAL

$^1$H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were measured with a Bruker WP-80 (80 MHz) spectrometer. IR spectra of KBr disks were recorded with a UR-20 spectrophotometer. Mass spectra were obtained with an

LKB-2091 by direct insertion of the sample into the ion source (ionizing electron energy 70 eV). The course of the reaction and the purity of the product were monitored by TLC on Silufol UV-254 plates with 9:1 benzene–acetone as eluent. Spots were revealed with iodine vapor.

Elemental analyses of compound I for C, H, and N agreed with calculated values.

**X-Ray Crystallographic Study of Compound I.** Crystals of compound I grown from chloroform were monoclinic with the following parameters at −80°C: $a$ = 14.771(5), b = 7.449(2), c = 18.575(7) Å, $\beta$ = 92.28(2)°; V = 2042(2) Å$^3$; $d_{calc}$ = 1.403 g/cm$^3$, $Z$ = 4, space group P2(1)/c. Unit cell parameters and the intensities of 2554 independent reflexions were measured on a four-circle automatic Syntex P21 diffractometer (λ Mo$K_\alpha$, $\beta$-filter, $\theta/2\theta$ scanning to $\theta_{max}$ = 26°). The structure was solved by direct methods which revealed all non-hydrogen atoms, and refined by full matrix least squares methods in the anisotropic approximation for non-hydrogen atoms using 1701 reflexions with $I > 3\sigma(I)$. All hydrogen atoms were revealed by difference Fourier syntheses and refined isotropically. The final value of the residual factor $R$ = 0.044 ($R_w$ = 0.044). All calculations were carried out using the SHELXTL program (PC version). Atom coordinates are given in Table 1, bond lengths and bond angles in Tables 2 and 3.

**10,11-Dimethyl-12-ethoxycarbonyl-9-(2-oxo-2H-1-benzopyran-3-yl)-8-oxa-10aza-tricyclo[7.3.1.0$^{2,7}$]trideca-2,4,6-11-tetraene (I).** A mixture of ethyl acetoacetate (10.4 g, 80 mmole), salicyl aldehyde (4.9 g, 40 mmole) and methylamine (3 g, 97 mmole) in ethanol (20 cm$^3$) and ethanoic acid (10 cm$^3$) was stirred for a day at room temperature. The precipitate was separated, washed with cold ethanol and dried to give compound I (5.17 g, 62%) as colorless crystals, mp 240-242°C (from chloroform). $R_f$ 0,67. Found, %: C 71.9, H 5.5, N 3.2. M$^+$ 417. Calc. for $C_{25}H_{23}NO_5$, %: C 71.9, H 5.5, N 3.2. IR spectrum: 1730, 1677, 1622 cm$^{-1}$. $^1$H NMR spectrum: 1.4 (3 H, t $CH_3CH_2$), 2.41 (3 H, s, 11−$CH_3$), 2.79 (3 H, s, 12−$CH_3$), 1.94 ( 1 H, dd, $J$ = 12.5, 3.7 and 2.6 Hz, *anti*-13-H), 2.62 (1 H, dd, *sin*-13-H), 4.25 (2 H, q, $CH_2CH_3$), 4.38 (1 H, t, 1-H), 6.95-7.65 (8 H, m $H_{arom}$), 8.41 ppm (1 H, s, 4′-H). Mass spectrum $m/z$ ($I$, %): M$^+$ 417 (18), [M − Me]$^+$ 402 (2), [M − CO]$^+$ 399 (2), [M − Et]$^+$ 388 (9), [M − OEt]$^+$ 372 (31), [M − H−OEt]$^+$ 371 (100), [M − COOEt]$^+$ 344 (50), 344 (47), 296 (23), 275 (17), 186 (10), 115 (16).

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