Chemistry of Natural Compounds, Vol. 47, No. 3, July, 2011 [*Russian original No. 3, May-June, 2011*]

SYNTHESIS OF CALONE DERIVATIVES

N. G. Kozlov,[1*] L. I. Basalaeva,[1]
O. G. Vyglazov,[2] and V. A. Chuiko[2]

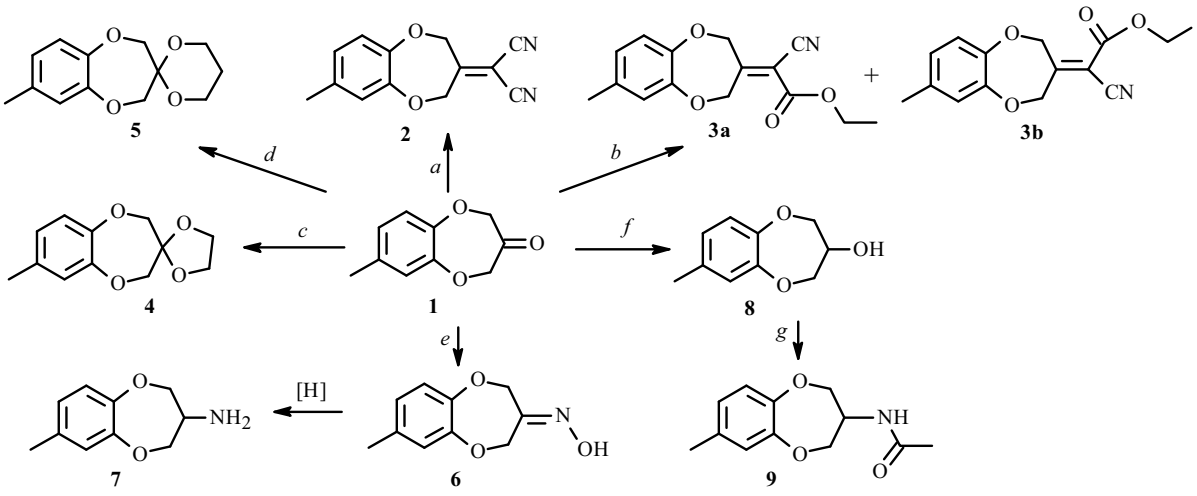
UDC 547.28.89+547.233

Compounds that were promising as fragrances were prepared by a series of transformations at the carbonyl group of 7-methyl-2H-benzo[b][1,5]dioxepin-3(4H)-one.

Keywords: calone, calone malonates, calone oxime, fragrances, organoleptic evaluation.

Greater than 900 named fragrances are currently produced worldwide, either through synthetic pathways or by isolation from natural essential oils. The demand for synthetic fragrances in perfumery, cosmetics, and food flavors exceeds by 5–6 times the use of natural products.

Herein we present results from a study of transformations of 7-methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-one (calone). Calone (**1**) or watermelon ketone was isolated from watermelon rind and is a valuable fragrance for preparing fresh, marine, and ozone aromas. Up to 25% of the worldwide assortment of modern perfumery contains calone. Calone, being an important indicator of marine aroma, contains in its molecule a constrained reaction center, the carbonyl. Performing reactions at this group enables the two methylenes immediately adjacent to the O atoms and the aromatic ring to be preserved. This is a potential feature of the marine aroma [1].



a. $NCCH_2CN$; *b*. $NCCH_2COOEt$; *c*. $HOCH_2CH_2OH$; *d*. $HOCH_2CH_2CH_2OH$; *e*. $NH_2OH{\cdot}HCl$; *f*. $NaBH_4$; *g*. CH_3CN

Reaction of **1** with malonic acid dinitrile and cyanoacetic acid ethyl ester in the presence of piperidine and acetic acid formed the condensation products 2-(7-methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-ylidene)malononitrile (**2**) and ethyl-2-cyano-2-(7-methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-ylidene)acetates **3a** and **3b**. Malononitrile **2** with a symmetric substituent is the only reaction product whereas addition of ethyl cyanoacetate forms the *cis*- (**3a**) and *trans*-isomers (**3b**) in a 1:2 ratio. This was confirmed by PMR spectroscopy.

1) Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, 220072, Minsk, e-mail: loc@ifoch.bas-net.by; 2) OOO Tereza-Inter, Moscow, Russia, e-mail: ilb_chuiko@mail.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 350–353, May–June, 2011. Original article submitted October 28, 2010.

TABLE 1. Organoleptic Evaluation of Aromas of **2**–**9**

Compound	Aroma	
	1% alcohol solution	1% alcohol solution + 1% Hedione
2	Weak, woody-fruity	Flowery, natural jasmine, with indole-fruity note. Aroma increased 1.5 times
3	Woody-tobacco, notes of patchouli, leather	Natural "absolute" jasmine with animal note. Aroma increased 2 times
4	Fresh, fruity-berry, with musky note	Fresh, flowery-fruity, with tobacco-musky note. Aroma increased 3 times
5	Watery-flowery, with honey note	Fresh, flowery-fruity, with fougere and patchouli note. Aroma increased 1.5 times
6	Strong, fresh, ozone-marine, cooling, fruity-watermelon note	Fresh, flowery-ozone, cooling, fruity-powdery note. Aroma increased 4 times
7	Weak, woody-fruity	Fresh, flowery, jasmine flower with clear tobacco note. Aroma increased 3 times
8	Weak, flowery-woody	Flowery-powdery, jasmine with clear woody note. Aroma increased 2 times
9	Ozone-flowery with light animal note	Ozone-flowery, fresh fruity note with peach skin hint

The isomers were assigned by comparing in PMR spectra of **3a** and **3b** the chemical shifts of the C-2 and C-4 protons, which had different steric environments, with the chemical shifts of the analogous protons in the spectrum of **2**, the steric environments of which were the same in this compound. Thus, the chemical shifts of the C-4 protons in the NMR spectrum of *cis*-isomer **3a** were shifted to weak field compared with the shifts of the analogous protons in **2** (4.86, 4.92, and 4.61 ppm, respectively). The chemical shifts of the C-2 protons in both compounds were similar (4.66, 4.64, and 4.61, respectively). The chemical shifts of the C-2 protons were shifted to weak field in the spectrum of *trans*-isomer **3b** (4.70 and 4.80, respectively). However, the chemical shifts of the C-4 protons were similar to those of the analogous protons in **2** (4.68, 4.64, and 4.61, respectively). On this basis isomer **3a** was assigned the *cis*-configuration, i.e., the bulky ester substituent was located in the *cis*-position relative to the methylene group of the ketone fragment; isomer **3b**, the *trans*-configuration, in this instance the sterically less hindered C-4 atom. IR spectra of **2** and **3** contained absorption bands at 2211 and 2190 cm^{-1}, respectively, that belonged to stretching vibrations of the triple bond.

Calone reacted readily with ethyleneglycol and propyleneglycol to form a symmetric ether ring. As a result, the only reaction products were the corresponding ketals 7-methyl-3,4-dihydro-2*H*-spiro(benzo[*b*][1,5]dioxepin-3,2′-dioxolan-1′,3′) (**4**) and 7-methyl-3,4-dihydro-2*H*-spiro(benzo[*b*][1,5]dioxepin-3,2′-dioxan-1′,3′) (**5**). IR spectra of the synthesized ketals showed absorption bands at 1100 (**4**) and 1000 cm^{-1} (**5**) that were characteristic of C–O–C stretching vibrations.

The ketone of **1** reacted with hydroxylamine in the presence of CH_3CN to form the oxime [2]. The reaction was kept under control by the buffer-forming ability of sodium acetate in CH_3CN. The yield of 7-methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-one oxime (**6**) was 90%. Reduction of **6** occurred with $NaBH_4$ in the presence of HOAc [3], $LiAlH_4$ [4], and $NaBH_4$ in the presence of $TiCl_4$ [5]. The most effective was the last, which gave 7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-amine (**7**) in 55% yield. The formation of **7** was confirmed by the appearance of a resonance for the C-3 methine proton, which merged into a multiplet with the C-2 and C-4 resonances at 3.94–4.35 ppm in the PMR spectrum.

Analogously to the reduction of **6**, $NaBH_4$ in MeOH solution reduced **1** to 7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-ol (**8**). In this instance the C-3 methine proton appeared in the spectrum as a multiplet at 4.04–4.25 ppm.

A Ritter reaction of **8**:CH_3CN:H_2SO_4 (1:10:1 mole ratio) gave *N*-(7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-yl)acetamide (**9**).

An organoleptic evaluation of the aromas of the synthesized calone derivatives (**2**–**9**) was performed by the Taste-Test Panel of the Accredited Analytical Laboratory of OOO Tereza-Inter (Moscow).

Table 1 presents the statistical average taste-test data for aromas of the pure compounds as alcohol solutions (1%) and the same solutions with added (1%) Hedione [methyl-(3-oxo-2-pentylcyclopentyl)acetate]. Hedione is one of the most common perfumery components and alters and enhances the aroma of even slightly volatile compounds.

Judging from the results in Table 1, all synthesized compounds were promising for use as fragrances. Compound **3** with the fashionable woody-tobacco aroma was promising for male perfume. Compounds **4–6** and **9** could be used to create dynamic daily aromas. The effect of adding Hedione was extremely interesting. Even weakly aromatic compounds **2**, **7**, and **8** when mixed with it had enhanced and altered aromas with a flowery trend of various hints. An alcohol solution of Hedione itself (1%) had a weak flowery-jasmine aroma. Adding Hedione to a 1% solution of synthesized compounds **2–9** not only altered the aromas, making them rich and varied, but also enhanced them synergistically by 1.5–4 times. The synthesized compounds expand the choice of fragrances for creating fresh aromas with marine notes that are now fashionable and in demand in modern perfumery. The presence of flowery, fruity, and eastern notes and their modification by known industrial fragrances enables exotic and original perfumes to be produced. This is in demand on the market for fine perfumes and cosmetics.

EXPERIMENTAL

IR spectra were recorded on a Nicolet Protege-460 IR-Fourier spectrophotometer. PMR spectra were recorded on a Bruker AC-500 spectrometer (500 MHz). Concentrations of solutions were 2–5% in DMSO-d_6. Chemical shifts were determined relative to TMS internal standard. Mass spectra were obtained on an Agilent 6890N gas chromatograph with an Agilent 5975 Inert mass-selective detector operating in electron-impact ionization regime with 70-eV energy and tuned to the maximum sensitivity for the determined compounds. An HP-5MS capillary column (30 m × 0.25 mm × 0.25 μm) led directly into the mass spectrometer ion source. Samples were injected in CH_2Cl_2 solution.

Calone (watermelon ketone, Penta Manufacturing Co./Div. of Penta Int'l Corp.), mp 38–40°C, 98% purity, was used in the syntheses.

2-(7-Methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-ylidene)malononitrile (2). Calone (**1**, 1.78 g, 0.01 mol) and malonic acid dinitrile (0.8 g, 0.012 mol) in a mixture of acetic acid (0.8 mL), piperidine (0.4 mL), and benzene (20 mL) were refluxed with azeotropic removal of H_2O in a Dean–Stark trap. The mixture was washed with KOH solution (10%) and extracted with Et_2O. The extract was dried and evaporated. The resulting crystals were recrystallized from alcohol. Yield 1.17 g (52%), colorless crystals, mp 110–112°C. IR spectrum (ν, cm^{-1}): 3441, 3347, 3033, 2923, 2855, 2211 (C≡N), 1634, 1589, 1504, 1456, 1389, 1261, 1206, 1052, 815. PMR spectrum (DMSO-d_6, δ, ppm): 2.32 (3H, s, CH_3), 4.61 (4H, s, H_2-2, H_2-4), 6.40–6.50 ($2H_{arom}$, m), 6.84 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 226.23 (100) $[M]^+$, 200 (23), 135 (18), 123 (37), 121 (10). $C_{13}H_{10}N_2O_2$.

Ethyl-2-cyano-2-(7-methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-ylidene)acetates (3a, 3b) were prepared by the aforementioned method from **1** (1.78 g, 0.01 mol) and ethyl cyanoacetate (1.35 g, 0.012 mol). Yield 1.12 g (41%), colorless crystals, mp 116–117°C (EtOH). IR spectrum (ν, cm^{-1}): 3447, 3371, 3031, 2978, 2935, 2858, 2190 (C≡N), 1742, 1669, 1607, 1584, 1504, 1451, 1415, 1387, 1367, 1306, 1261, 1235, 1147, 1113, 1094, 1024, 947, 857, 810. PMR spectrum (DMSO-d_6, δ, ppm): 1.34 (3H, t, $OCH_2C\underline{H}_3$), 2.35 (3H, s, CH_3), 4.26 (2H, q, $OC\underline{H}_2CH_3$), 4.64 (2H, m, H_2-2, *cis*-isomer, 2H, H_2-4, *cis*-isomer), 4.66 (2H, s, H_2-2, *cis*-isomer), 4.68 (2H, s, H_2-4, *trans*-isomer), 4.70 (2H, s, H_2-2, *trans*-isomer), 4.80 (2H, s, H_2-2, *trans*-isomer), 4.86 (2H, s, H_2-4, *cis*-isomer), 4.92 (2H, s, H_2-4, *trans*-isomer), 6.45-6.50 ($2H_{arom}$, m), 6.87 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 273.28 (58) $[M]^+$, 211 (32), 135 (100). $C_{15}H_{15}NO_4$.

7-Methyl-3,4-dihydro-2*H*-spiro(benzo[*b*][1,5]dioxepin-3,22-dioxolan-1′,3′) (4). A mixture of **1** (1.78 g, 0.01 mol) and ethyleneglycol (0.75 g, 0.012 mol) in the presence of *p*-toluenesulfonic acid (0.1 g) in benzene (30 mL) was refluxed with a Dean–Stark trap for 12 h. The products were extracted with Et_2O. The extract was washed with H_2O and dried over $MgSO_4$. Vacuum distillation afforded ketal **4** (0.9 g, 45%), bp 100–102°C (6 mm Hg), n_D^{20} 1.4756. IR spectrum (ν, cm^{-1}): 2977, 2932, 2886, 1581, 1504, 1442, 1305, 1267, 1178, 1147, 1100 (C–O–C), 1058, 919, 852, 813. PMR spectrum (DMSO-d_6, δ, ppm): 2.30 (3H, s, CH_3), 3.85 (4H, m, OCH_2CH_2O), 4.62 (4H, m, $2CH_2$), 6.43–6.52 ($2H_{arom}$, m), 6.90 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 222.24 (100) $[M]^+$, 194 (12), 179 (27), 163 (38), 135 (60). $C_{12}H_{14}O_4$.

7-Methyl-3,4-dihydro-2*H*-spiro(benzo[*b*][1,5]dioxepin-3,2′-dioxan-1′,3′) (5) was prepared by the aforementioned method using propyleneglycol (1 g, 0.013 mol). Vacuum distillation afforded ketal **5** (0.89 g, 38%), bp 104–105°C (6 mm Hg), n_D^{20} 1.4723. IR spectrum (ν, cm^{-1}): 3002, 2941, 2880, 1592, 1500, 1436, 1411, 1310, 1275, 1253, 1172, 1160, 1143, 1118, 1091, 1000 (C–O–C), 916, 850. PMR spectrum (DMSO-d_6, δ, ppm): 2.35 (3H, s, CH_3), 3.74 (6H, m, $OCH_2CH_2CH_2O$), 4.60 (4H, m, $2CH_2$), 6.45–6.50 ($2H_{arom}$, m), 6.84 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 236 (100) $[M]^+$, 210 (52), 195 (31), 180 (18), 135 (60). $C_{13}H_{16}O_4$.

7-Methyl-2*H*-benzo[*b*][1,5]dioxepin-3(4*H*)-one oxime (6) was prepared according to the literature method [2]. Calone (**1**, 1.78 g, 0.01 mol) was dissolved in CH_3CN (50 mL) with added H_2O (10 mL), treated dropwise with a solution of NaOAc (2.07 g, 0.025 mol) in H_2O (15 mL) and hydroxylamine hydrochloride (138 g, 0.02 mol) in H_2O (10 mL). The reaction mixture was stirred at 50°C for 24 h and poured onto ice (150 mL). The resulting crystals were filtered off, washed with H_2O (2×), and dried. Yield 1.74 g (90%), colorless crystals, mp 101–102°C. IR spectrum (ν, cm^{-1}): 3520 (OH), 3281, 3026, 2921, 1665 (C=N), 1580, 1507, 1450, 1415, 1307, 1264, 1201, 1149, 1114, 1054, 1025, 1000, 947 (N–O), 804. PMR spectrum (DMSO-d_6, δ, ppm): 2.24 (3H, s, CH_3), 4.80-4.85 (4H, m, H_2-2, H_2-4), 6.60–6.80 (3H, m, $2H_{arom}$, OH), 6.86 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 194.21 (100) $[M]^+$, 176 (52), 148 (40), 135 (23), 123 (24), 95 (17), 77 (12), 66 (20). $C_{10}H_{12}NO_3$.

7-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-amine (7). A cooled solution of $TiCl_4$ (0.4 g, 0.002 mol) in dry Et_2O (50 mL) under a dry N_2 atmosphere was treated in portions with $NaBH_4$ (3.4 g, 0.09 mol), stirred, treated with oxime **6** (1.94 g, 0.01 mol), stirred at room temperature for 24 h, and poured onto ice. The aqueous emulsion was extracted with Et_2O and dried by the literature method [5]. Yield 1.60 g (90%), colorless crystals, mp 121–122°C. IR spectrum (ν, cm^{-1}): 3360, 3295, 3033, 2925, 2878, 1612, 1588, 1505, 1459, 1417, 1394, 1373, 1305, 1260, 1202, 1148, 1114, 1092, 1033. PMR spectrum (DMSO-d_6, δ, ppm): 2.30 (3H, s, CH_3), 3.97–4.32 (5H, m, H_2-2, H-3, H_2-4), 4.15 (2H, s, NH_2), 6.60–6.70 ($2H_{arom}$, m), 6.89 ($1H_{arom}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 180 (19) $[M + 1]^+$, 179.22 (54) $[M]^+$, 150 (48), 135 (100), 122 (6), 108 (9), 94 (63), 77 (22), 56 (27). $C_{10}H_{14}NO_2$.

7-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-ol (8). A mixture of **1** (1.78 g, 0.01 mol) and $NaBH_4$ (1.14 g, 0.03 mol) in alcohol (20 mL) was refluxed for 1 h. The mixture was cooled and treated with H_2O (25 mL). The crystals that formed after 10 h were filtered off and recrystallized from alcohol. Yield 1.44 g (80%), colorless crystals, mp 60–62°C. IR spectrum (ν, cm^{-1}): 3274 (OH), 2961, 2923, 2857, 1578, 1506, 1450 (OH), 1343, 1300, 1261, 1136, 1115, 993, 817. PMR spectrum (DMSO-d_6, δ, ppm): 2.20 (3H, s, CH_3), 4.10–4.15 (1H, m, H-3), 4.30-4.55 (4H, m, H_2-2, H_2-4), 6.40–6.70 (3H, m, $2H_{arom}$, OH), 6.80 ($1H_{arpm}$, d). Mass spectrum (*m*/*z*, I_{rel}, %): 180.20 (100) $[M]^+$, 149 (13), 135 (48), 123 (27), 109 (11), 94 (9), 91 (10), 77 (12). $C_{10}H_{12}O_3$.

***N*-(7-Methyl-3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-3-yl)acetamide (9).** Alcohol **8** (1.8 g, 0.01 mol) was dissolved in CH_3CN (8 mL), treated slowly dropwise with conc. H_2SO_4 (0.5 mL), stirred at room temperature for 20 h, and neutralized with aqueous ammonia. The product was extracted by Et_2O. The extract was dried over $MgSO_4$ and evaporated. The resulting crystals were recrystallized from CH_2Cl_2. Yield 0.92 g (42%), colorless crystals, mp 67°C. IR spectrum (ν, cm^{-1}): 3320 (NH), 2923, 2864, 1669 (C=O), 1540 (NH), 1450, 1384, 1300, 1272, 1202, 1150, 1115, 1041, 992, 817, 713. PMR spectrum (DMSO-d_6, δ, ppm): 1.90 (3H, s, $COCH_3$), 2.38 (3H, s, CH_3), 3.68–3.93 (5H, m, H_2-2, H-3, H_2-4), 5.40 (H, br.s, NH), 6.60–6.85 ($3H_{arom}$). Mass spectrum (*m*/*z*, I_{rel}, %): 221.25 (13) $[M]^+$, 178 (65), 163 (20), 135 (100), 124 (14), 106 (13). $C_{12}H_{15}NO_3$.

REFERENCES

1. G. B. Frater and J. A. Kraft, *Tetrahedron*, **54**, 7633 (1998).
2. H. A. Dondas, R. Grigg, M. Hadjisoteriou, J. Markandu, W. A. Thomas, and P. Kennewell, *Tetrahedron*, **56**, 10087 (2000).
3. M. Periassamy and M. Thirumalaikumar, *J. Organomet. Chem.*, 137 (2000).
4. H. Spreitzer, G. Buchbauer, and C. Pueringer, *Tetrahedron*, **45**, 6999 (1989).
5. S. Kano, Y. Tanaka, E. Sugino, and S. Hibino, *Synthesis*, 695 (1980).