1,3-Substituted Benzocycloheptanes

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We describe some derivatives of benzocycloheptan-1-one-3-carboxylic acid (**2**) which was obtained by reduction of benzo[6,7]cyclohepta-3,6-dien-1-one-3-carboxylic acid (**1**).

On décrit quelques dérivés de l'acide benzocycloheptanone-1 carboxylique-3 (**2**) obtenus par réduction de l'acide benzo[6,7]cycloheptadiène-3,6 one-1 carboxylique-3 (**1**).

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Recently we reported the synthesis of benzo-[6,7]cyclohepta-3,6-dien-1-one-3-carboxylic acid (**1**) (1). We would now like to report some transformations of **1** directed at the synthesis of potentially biologically active compounds.

Reduction of **1** gave benzocycloheptan-1-one-3-carboxylic acid **2** (> 95%) which was converted to the methyl ester **3** (87%). Esterification of **1** went with enol ether formation to give methyl 1-methoxybenzo[6,7]-5-*H*-cycloheptatriene-3-carboxylate **4** (70%).

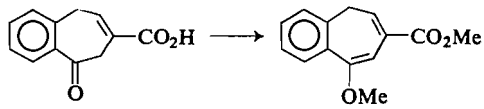
Treatment of **2** with phosphorous pentachloride gave **5** (unstable to distillation) which was readily converted to the amide **6** (45%). An excess of phosphorous pentachloride converted **2** into the trichloride 7 which gave **8** on distillation (50%). Treatment of either **7** or **8** with an excess of benzylamine gave **9** (85%).

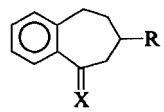
The acid chloride **5** was converted to its azide (2) and thence to the urethane **10** through the isocyanate. Urea **11** was also isolated. The overall conversion to **10** from **2** was 57%.

Reduction of **10** with sodium borohydride gave alcohol **12** (97%) which on treatment with sodium hydride gave 9-oxa-7-azabenzo[2,3]bicyclo[4.3.1]-decan-8-one (**13**) (77%). On this basis the *cis* configuration is assigned to **12** since formation of cyclic urethane **13** from the diaxial conformer (3) would be expected to be facile whereas the *trans* isomer would cyclize only with great difficulty, if at all.

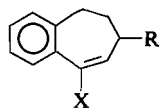
Reduction of **13** with lithium aluminum hydride gave *cis*-aminoalcohol **14**. Treatment of **10** with phenyl magnesium bromide followed by acidic work-up gave the olefin **15** rather than the desired alcohol.

Treatment of **10** with benzyl magnesium chloride gave **16** (46%) which on treatment with sodium hydride gave the cyclic urethane **17**

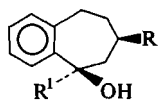




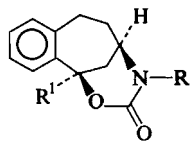
2 X = O; R = CO_2H
3 X = O; R = CO_2Me
5 X = O; R = COCl
6 X = O; R = CONHMe
7 X = Cl_2; R = COCl
10 X = O; R = $NHCO_2Et$



8 X = Cl; R = COCl
9 X = Cl; R = $CONHCH_2C_6H_5$
15 X = C_6H_5; R = $NHCO_2Et$



12 R = $NHCO_2Et$; R^1 = H
14 R = NHMe; R^1 = H
16 R = $NHCO_2Et$; R^1 = $CH_2C_6H_5$
19 R = NMe_2; R^1 = $CH_2C_6H_5$



13 R = H; R^1 = H
17 R = H; R^1 = $CH_2C_6H_5$
18 R = Me; R^1 = $CH_2C_6H_5$

TABLE 1. Infrared spectra and analytical data

Compound	The i.r. spectra (cm^{-1})	Calculated (%)			Found (%)		
		C	H	N	C	H	N
2	1700, 1645, 1600*	70.58	5.88	—	70.80	5.90	—
3	1730, 1680, 1600†	71.54	6.46	—	71.33	6.47	—
4	1725, 1720, 1600†	73.03	6.13	—	72.77	6.16	—
5	1785, 1680, 1595†			‡			
6	3340, 1680§	71.86	6.96	6.45	71.81	6.90	6.46
8	1785, 1620, 1595†	59.77	4.18	—‖	60.14	4.40	—
9	3420, 1670, 1515§	73.19	5.82	4.49	73.36	5.82	4.59
10	3320, 1712, 1680, 1600	68.10	6.88	5.67	67.73	6.82	5.74
11	3390, 1680, 1670(sh), 1600§	73.38	6.42	7.45	72.93	6.38	7.49
12	3600, 3420, 3280, 1710§	67.44	7.68	5.62	67.48	7.70	5.55
13	3430(s), 3245(b) 1700§	70.91	6.44	6.89	70.47	6.47	6.68
14	2400–3100(b), 3320(b)*	63.18	7.96	6.15	62.85	8.07	6.09
15	3330, 1715	78.14	6.89	4.56	78.01	6.90	4.52
16	1695, 1685§	78.14	6.89	4.56	77.78	6.95	4.51
17	3425(s), 3240, 1700§	77.79	6.53	4.78	77.58	6.59	4.64
18	1695, 1685§	78.14	6.89	4.56	77.88	6.95	4.51
19	3400b†	72.37	7.89	4.22¶	71.98	7.83	4.19

*Nujol mull.
†Neat.
‡Not analyzed.
§In $CHCl_3$.
‖Anal. Calcd. for Cl: 29.41. Found: 28.96.
¶Anal. Calcd. for Cl: 10.68. Found: 10.65.

(37%). The addition of methyl iodide to the sodium hydride reaction mixture gave *N*-methyl urethane **18** (80%). Reduction of **18** with lithium aluminum hydride gave *cis*-aminoalcohol **19** (96%). All attempts to esterify this alcohol have failed.

Summary

We have prepared a number of compounds (see Table 1) for biological evaluation as medicinal agents. None of the reported compounds exhibited significant activity although compound **15** did show marginal activity in the test for reversal of reserpine induced ptosis[1] (75 mg/kg in mice) and compound **19** showed slight C.N.S. stimulation (150 mg/kg in mice).

Experimental

The i.r. spectra were recorded on a Unicam SP-200G grating i.r. spectrometer. The n.m.r. spectra were determined on a Varian A60-A spectrometer using tetramethylsilane as an internal standard. Melting points are uncorrected and were determined on a Gallenkamp m.p. apparatus. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Benzocycloheptan-1-one-3-carboxylic Acid (2)

Benzocyclohept-3-en-1-one-3-carboxylic acid (**1**) (20.2 g, 0.10 mol) was hydrogenated over prehydrogenated platinum oxide in methanol to give 17.5 g (87%) of **2**; m.p. 132–134°. An additional 2.0 g (9.8%) of **2** was recovered from the mother liquors.

Methyl Benzocycloheptan-1-one-3-carboxylate (3)

Compound **2** (2.04 g, 0.01 mol) was esterified in methanol containing hydrogen chloride to give 1.75 g (82%) of **3** after distillation; b.p. 130–134°/0.1 mm.

Methyl 1-Methoxybenzo[6,7]-5-H-cycloheptatriene-3-carboxylate (4)

Esterification of compound **1** (2.02 g, 0.1 mol) gave 2.06 g of an oil. On distillation 1.60 g (70%) of the enol ester **4** was obtained; b.p. 138–140°/0.1 mm. The n.m.r. spectrum (CCl_4): 2.40 τ (m, 1H), 2.90 (m, 3H), 3.35 (t, J = 7.1 Hz, 1H), 3.87 (s, 1H), 6.18 (s, 3H), 6.34 (s, 3H), 6.98 (d, J = 7.1 Hz, 2H).[2]

N-Methylbenzocycloheptan-1-one-3-carboxamide (6)

A solution of 3.06 (0.015 mol) of **2** and 3.12 g (0.015 mol) phosphorous pentachloride in 50 ml of phosphorous oxychloride – ether (1:1) mixture was refluxed for 30 min. The solution was evaporated at reduced pressure to yield **5** as an oil.

Treatment of the crude acid chloride with an excess of methylamine in ether gave 1.5 g (45%) crystalline amide **6**, m.p. 141–142 °C after one recrystallization from benzene.

1-Chlorobenzocyclohept-1-en-3-carboxoyl Chloride (8)

A solution of 1.02 g (0.005 mol) **2** and 3.12 g (0.015 mol) phosphorous pentachloride in 50 ml phosphorous oxychloride was refluxed for 20 min and let stand for 18 h. The solvent was evaporated at reduced pressure and the residue distilled (gas evolution was observed on

[1]The general screening procedure used has been described by Bergmann and Goldschmidt (4).

[2]For the n.m.r. spectra of a number of similar benzocycloheptatrienes see ref. 1.

heating the oil); b.p. 160–170°/0.3 mm, to give 0.60 g (50%) of **8**. The n.m.r. spectrum (CCl_4) 2.2–3.0 τ (m, 4H), 3.57 (d, J = 6 Hz, 1H), 6.5–8.0 (m, 5H).

N-Benzyl-1-chlorobenzocyclohept-1-en-3-carboxamide (9)

Treatment of crude trichloride **7** (prepared from 2.04 g, 0.01 mol **2** as above) with an excess of benzylamine in ether gave an oil which on trituration with ether and filtration yielded 1.75 g (56.5%) of **9**, m.p. 168–169 °C after recrystallization from methanol–water. An additional 0.9 g (29%) of amide was recovered from the mother liquors of trituration.

N-Carboethoxy-3-aminobenzocycloheptan-1-one (10)

The acid chloride **5** prepared as previously described from 2.41 g (0.12 mol) of **2** was added over a period of 20 min to a solution of 1.6 g sodium azide in 8 ml of a 1:1 mixture of dioxane–water precooled to 0–5 °C in an ice bath. The slurry was maintained at this temperature for 2 h, poured into 40 ml of cold water, and extracted with three 20 ml portions of chloroform. The extracts were dried over anhydrous $MgSO_4$ and concentrated below 15 °C at reduced pressure. The i.r. spectrum of the residual oil showed bands at 2135, 1700, and 1670 cm^{-1}.

The azide was then taken up in 20 ml of toluene and warmed gently until gas evolution commenced (~40 °C) after which the solution was brought to reflux for 20 min and evaporated to give 2.5 g of an oil the i.r. spectrum of which had bands at 2255 and 1672 cm^{-1}.

The isocyanate was taken up in 50 ml of benzene. To this solution, 5 ml of absolute ethanol was added and the solution then refluxed 18 h. Evaporation of the solvent gave 2.40 g of a brown oil which was chromatographed on 80 g of Florisil (60–100 mesh, Fisher Scientific) with benzene. The oil which was eluted crystallized on standing. Trituration with 5 ml of ether and filtration gave 1.40 g of white needles, m.p. 86–87.5 °C. The compound could not be recrystallized as the compound partially decomposed and darkened on heating.

In addition to **10** another compound was obtained from a large scale (40 g) experiment in < 2% yield which was identified as the urea **11**, m.p. 189–190 °C after recrystallization from ethanol–water.

N-Carboethoxy-1-hydroxy-3-aminobenzocycloheptane (12)

Reduction of **10** (1.25 g, 0.005 mol) with $NaBH_4$ (0.5 g) in ethanol at 0 °C for 30 min gave 1.20 g of a white solid, m.p. 184–187 °C (raised to 191–192 °C on recrystallization from methanol). The compound was homogeneous by t.l.c. on both silica gel and alumina plates using a number of solvent systems.

9-Oxa-7-azabenzo[2,3]bicyclo[4.3.1]decan-8-one (13)

To 0.25 g of NaH (55% mineral oil dispersion washed free of oil using hexane) suspended in 50 ml of dry THF was added 1.21 g (0.00485 mol) of **12**. A vigorous gas evolution ensued. The solution was refluxed 10 min and let stand 18 h. To the solution was added 10 ml of 10% HCl followed by 200 ml water. The solution was extracted with ether, the extracts dried over anhydrous $MgSO_4$, and concentrated to give an oily solid 1.05 g (~ 100%). Trituration with 3 ml of ether and filtration gave 0.75 g (77%) of pure crystalline **13**, m.p. 184–185 °C.

N-Methyl-1-hydroxy-3-aminobenzocycloheptane (14)

To a solution of 0.8 g $LiAlH_4$ in 50 ml of THF was added 1.02 g (0.005 mol) of **13** in 10 ml THF. The solution was refluxed 3 h after which time 3 ml of water was added to the cooled solution. The solution was filtered and the filtrate evaporated. The resultant oil was taken up in 25 ml of ether and dry HCl gas bubbled in. The salt was then filtered and recrystallized from methanol–ethyl acetate to give 0.62 g of **14** as its hydrochloride, m.p. 196–197 °C.

N-Carboethoxy-1-phenyl-3-aminobenzocyclohept-1-ene (15)

To a solution of 1.235 g (0.005 mol) of **10** in 100 ml of ether was added (at 0 °C) 5 ml of a 2.14 M solution of phenyl lithium in benzene–ether (7:3). The solution was stirred for 10 min and then 25 ml of 10% HCl was added. The layers were separated, the ethereal extract dried over anhydrous $MgSO_4$, and concentrated to give an oil. The oil was chromatographed on alumina (Fluka, neutral activity grade 1) with benzene followed by ether–ethanol (95:5). An oil (1.15 g) was collected in the later fractions from the column. On standing, the oil crystallized, m.p. 114–115 °C.

N-Carboethoxy-1-benzyl-1-hydroxy-3-aminobenzocycloheptane (16)

To a solution of 0.052 mol benzylmagnesium chloride in 50 ml ether was added 4.22 g (0.017 mol) of **10**. After 1 h at reflux the reaction was worked-up by addition of 30 ml of 10% H_2SO_4 and extraction into ether. An oil was obtained which was chromatographed on florisil with benzene to remove toluene and bibenzyl. The column was flushed with ether to give 2.65 g of a pale yellow gum (46%), which could not be induced to crystallize nor could it be distilled.

1-Benzyl-9-oxa-7-azabenzo[2,3]bicyclo[4.3.1]decan-8-one (17)

Treatment of 0.90 g (0.00265 mol) of **16** with an excess of NaH in THF as before gave 0.51 g of an oily solid. Trituration with ether and filtration gave 0.29 g (37%) pure **17**, m.p. 227–228°.

1-Benzyl-7-methyl-9-oxa-7-azabenzo[2,3]bicyclo-[4.3.1]decan-8-one (18)

To a suspension of 2.0 g NaH (55% mineral oil dispersion) in 50 ml of THF was added 4.4 g (0.013 mol) of **16**. The solution was refluxed 10 min and 5 ml (large excess) of methyl iodide added. Reflux was continued for 1 h. The reaction was worked-up as described for compound **13** to give 4.8 g of an oil. Trituration with 10 ml of ether and filtration gave 2.2 g (55%) of pure **18**, m.p. 167–168° after recrystallization from methanol. An additional 1.0 g (25%) was obtained by column chromatography of the residue on Florisil (60–100 mesh) using benzene then ether as eluent.

1-Benzyl-1-hydroxy-3-dimethylaminobenzocycloheptane (19)

To 1.0 g of $LiAlH_4$ in 20 ml of dry THF was added 2.0 g (0.0065 mol) of **18**. The solution was refluxed for 3.5 h, cooled to 0 °C, and the excess hydride decomposed with 3.5 ml of 40% aqueous potassium hydroxide. The granular precipitate was filtered and the filter cake

washed thoroughly with ether. The filtrate was evaporated to yield 1.85 g (96%) of a pale yellow oil. This oil was taken up in 50 ml of ether and dry HCl bubbled in to give the hydrochloride salt, m.p. 229–230° recrystallized from methanol – ethyl acetate.

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1. T. W. DOYLE. Can. J. Chem. **48**, 1629 (1970); **48**, 1633 (1970).
2. M. A. GOLDBERG, E. P. ORDAS, and C. CARSCH. J. Am. Chem. Soc. **69**, 261 (1967).
3. E. L. ELIEL, N. L. ALLINGER, S. J. ANGYAL, and G. A. MORRISON. Conformational analysis. Interscience, New York, N.Y., 1965. p. 209–210.
4. E. D. BERGMANN and Z. GOLDSCHMIDT. J. Med. Chem. **11**, 1121 (1968).

On the Isolation of (+)3-Thujone

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Conditions necessary for the formation of the (+)3-thujone bisulfite adduct **1***a* and its utilization for the isolation of pure (+)-thujone have been established.

On a déterminé les conditions nécessaires pour former le complexe bisulfitique de la (+)-thujone-3 (**1***a*) et pour son utilisation afin d'isoler cette cétone à l'état pur.

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In our work on western red cedar [Thuja Plicata Donn] leaf oil we have been concerned with the isolation of (+)3-thujone (**1**)[1] and particularly with its separation from (−)3-isothujone (**2**). In regard to the larger amounts of **1** desired, fractional spinning band column distillation of the two ketones which differ in their b.p. by about 1°, proved tedious and time consuming. The same applied to large scale preparative g.l.c. Therefore we became interested in the use of $NaHSO_3$ for the separation of the two ketones.

Bruylants (1) observed that (+)3-thujone (**1**) formed an adduct **1***a* with $NaHSO_3$. Subsequent work has shown that (−)3-isothujone (**2**) does not form a $NaHSO_3$ adduct. Formation of the adduct **1***a* has been used repeatedly for the isolation of (+)3-thujone from various oils (tansy, cedar leaf, artemisia) and for its separation from (−)3-isothujone (3–7). Recently Eastman and Winn (8*a*, *b*) studied in detail the formation and decomposition of **1***a* and described the difficulties they met. However, none of the work recorded has dealt with the quantitative aspects of the (+)3-thujone bisulfite adduct formation. The implication has been that this method is generally applicable for the complete separation of (+)3-thujone from its isomer **2** and from a natural oil.

We now wish to report quantitative studies showing that this method has severe limitations with regard to the yield of adduct **1***a* and the necessary concentration of (+)3-thujone in the starting mixture.

In our work we used western red cedar leaf oil obtained by steam distillation of freshly harvested leaves. This oil contained 70–80% (−)3-isothujone and 5–10% (+)3-thujone. However, using either the conditions of Eastman and Winn (8*a*, *b*) or varying these conditions, we failed to obtain the bisulfite adduct **1***a* of (+)3-thujone from this oil. Subsequently, we utilized the known fact, (2, 7, 9, 10) that the base-catalyzed epimerization of either of the two ketones gives a mixture of (+)3-thujone and (−)3-isothujone in a ratio of 65:35 respectively, to enhance the (+)3-thujone content in our oil to about 55%. From this oil we then obtained the bisulfite adduct using the above mentioned conditions.

This result prompted us to investigate in detail the limits of the bisulfite adduct **1***a* formation using mixtures containing varying proportions of ketones **1** and **2** and cedar leaf oil samples containing varying amounts of **1**. Our results can be summarized as follows. Pure (+)3-thujone forms

[1]We have adopted the nomenclature proposal of H. C. Brown, see ref. 2.