Substituted Derivatives of 3a,4,5,6-Tetrahydrosuccinimido[3,4,-b]acenaphthen-10-one[1]

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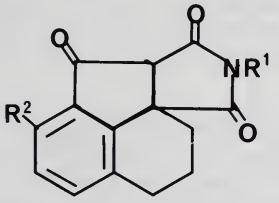
Introduction

3a,4,5,6-Tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (1a ,R^1 = R^2 = H) was shown to be a potent anticonvulsant of low toxicity (5) but with some undesirable side effects (1). It was therefore of considerable interest to prepare and test for biological activity various derivatives of the title compound, with the objective of discovering compounds with more selective activity. We wish to report here the synthesis and preliminary testing of compounds of structure 1 (figure I). The compounds reported include a series where R^2 = H, and R^1, substitution on the nitrogen, includes a variety of pharmacophoric groups such as dialkylaminoalkyl, acetonyl, and acetic acid, as well as simple alkyl, arylalkyl, etc. A second series includes the two compounds 1 where R^1 = H, and R^2 is methyl or methoxyl.



1

a. R^2 = H, R^1 = H
b. R^2 = H, R^1 = CH_3
c. R^2 = H, R^1 = $CH_2CH{=}CH_2$
d. R^2 = H, R^1 = $CH(CH_2)_4$
e. R^2 = H, R^1 = $CH_2C_6H_5$
f. R^2 = H, R^1 = $CH_2CH_2N(C_2H_5)_2$
g. R^2 = H, R^1 = $CH_2CH_2N(CH_2)_5$
h. R^2 = H, R^1 = $CH_2CH_2N(CH_2)_4$
i. R^2 = H, R^1 = CH_2COCH_3
j. R^2 = H, R^1 = $CH_2CO_2C_2H_5$
k. R^2 = H, R^1 = CH_2CO_2H
l. R^2 = H, R^1 = CH_2SCH_3
m. R^2 = H, R^1 = $(CH_2)_3CN$
n. R^2 = H, R^1 = CH_2-3-C_4H_3S
o. R^2 = H, R^1 = CH_2-2-C_4H_3S
p. R^2 = CH_3, R^1 = H
q. R^2 = OCH_3, R^1 = H

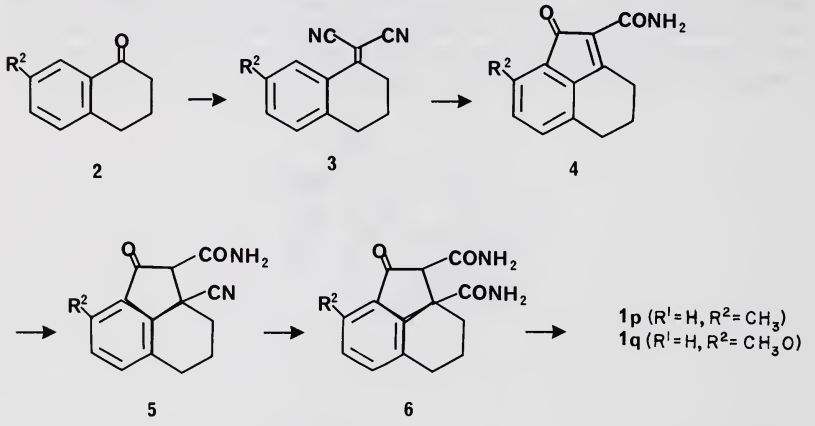
Figure 1.

Chemistry

The preparation of compounds 1b and 1c by alkylation of 1a has previously been reported (7). Compounds 1d to 1o were prepared in essentially the same way, by reacting the potassium salt of 1a with an appropriate organic halide, as described in the experimental section. Compound 1k was obtained by acid hydrolysis of the ester 1j in good yield.

In order to prepare the ring-substituted compounds 1p and 1q, where R^2 was methyl or methoxy, it was necessary to construct the complete ring system in each case, starting with the appropriately substituted 1-tetralone (see Scheme 1). In the case of 1p, the starting material, 7-methyl-1-tetralone (2a) was commercially available, while 7-methoxy-1-tetralone (2b) was synthesized as previously reported (8). The synthetic scheme is similar to that reported for 1a (5). The appropriate tetralone (2a or 2b) was condensed with malononitrile to give the ylidenemalononitrile (3a or 3b) which was then cyclized in polyphosphoric acid, as previously reported (3), to give the corresponding 7-substituted 2-carboxamido-3,4-trimethyleno-1-indenones (4a or 4b). The yield in the case of 4b was distinctly lower, perhaps due to the activating effect of the methoxy group, which could enhance side reactions.

SCHEME 1.



a) $R^2 = CH_3$; b) $R^2 = CH_3O$

Addition of cyanide to compounds 4 proceeded in good yield to give 5a or 5b, and hydration of the 2a-cyano group in sulfuric acid, as reported for 1a (4) gave yields of 6a or 6b in excess of 90%. Treatment of 6a or 6b with a small amount of sulfuric acid in diethylene glycol caused formation of the imides 1p and 1q in good yield.

Pharmacological Results

All of the compounds listed as structures 1 (a through q) have been submitted to Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, New York, for pharmacological evaluation.[2]

Compound 1a had an ED_{50} against electroshock of 35 mg/kg (mouse) and MED against electroshock of 10 mg/kg (mouse). The MED against metrazole-induced convulsions was 100 mg/kg (mouse) and the LD_{50} was greater than 3000 mg/kg (5). Compounds 1b- 1o were screened for anticonvulsant activity in the mouse, and were devoid of activity at doses of 300 mg/kg. A further broad screen for antihypertensive, analgetic, anti-inflammatory, autonomic, anti-allergic, endocrine, antibacterial and antifungal activity revealed no activity in these tests. It therefore appears that a free imide hydrogen is required in 1 for biological activity.

Compounds 1p and 1q were also screened for anticonvulsant activity in the mouse, and were found to be devoid of activity at doses of 300 mg/kg or below. This result was unexpected, but probably indicates that bulky groups at the 9-position of 1 interfere with receptor-site association. It would be interesting to test the activity of compounds 1 with groups at the 7- or 8-position.

Experimental

Melting points were determined in open capillary tubes in a Mel-Temp heating block and are corrected. A Perkin-Elmer Model 137 Infrared Spectrophotometer was used to record infra-red spectra in the range 2.5 to 15μ. Solids were measured in potassium bromide mulls, liquids as liquid films. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

N-Cyclopentyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one. (1d)

Following the procedure previously reported for the alkylation of 1a (7), a mixture of 5g (21 mmoles) of 1a (5), 2.85 g (21 mmoles) of potassium carbonate and 3.72 g (25 mmoles) of cyclopentyl bromide (Aldrich) was stirred in 25 mL of dimethylformamide (DMF) at room temperature for 20 hr. The mixture was then poured over 250 g of ice, and the resulting precipitate was collected, washed with water, and recrystallized from isopropanol, giving 3.11 g (48%) of white crystals melting at 115-117°.

Anal. Cald. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.52. Found: C, 73.65; H, 6.35; N, 4.53.

N-Benzyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one. (1e)

Using the above procedure, except that 2.1 g (25 mmoles) of benzyl chloride was added as the organic halide, 4.45 g (64%) of 1e, melting at 127-128° was obtained.

Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.11; H, 5.17; N, 4.23. Found: C, 76.06; H, 5.28; N, 4.37.

N-Diethylaminoethyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]-acenaphthen-10-one. (1f)

A mixture of 4.2 g (31 mmoles) of diethylaminoethyl chloride (prepared by the method of Burtner (2)), 7.5 g (31 mmoles) of 1a and 4.3 g (31 mmoles) of potassium carbonate in 25 mL of DMF, worked up as above, gave 9.6 g (91%) of colorless plates of 1f, melting at 103-104° after two recrystallizations from isopropanol: ir (cm^{-1}) 2900, 2790 (CH), 1770, 1720, 1700 (CO) and 1595 (C=C).

Anal. Calcd. for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.16; H, 6.97; N, 8.16.

Compound 1f was converted into its hydrochloride salt by dissolving 5.0 g (14.6 mmoles) in 80 mL of hot isopropanol, then adding 1.2 mL (14.9 mmoles) of aqueous concentrated hydrochloric acid. The resulting solution was cooled and 100 mL of ether added. Triturating the oil which precipitated with further cooling (ice bath) gave 4.9 g (91%) of a white powder, which was collected and recrystallized from isopropanol as colorless prisms of 1f.HCl, m.p. 150-152°; ir (cm^{-1}) 2910 (CH), 2610 (NH+), 1770, 1710, 1690 (CO) and 1610 (C=C).

Anal. Calcd. for $C_{20}H_{25}ClN_2O_3$: C, 63.57; H, 6.67; N, 7.42. Found: C, 63.72; H, 6.89; N, 7.36.

N-(1-Piperidinoethyl)-3a,4,5,6-tetrahydrosuccinimido[3,4-b]-acenaphthen-10-one. (1g)

A mixture of 5 g (21 mmoles) of 1a, 5.70 g (42 mmoles) of potassium carbonate in 25 mL of DMF was stirred in an ice bath while 3.86 g (21 mmoles) of 1-piperidinoethyl chloride hydrochloride was added in small portions. The resulting mixture was stirred at room temperature for 20 hr, and then poured over 250 g of ice, yielding a white

precipitate which was collected and recrystallized from isopropanol to give 6.65 g (90%) of 1g as white crystals, melting at 151-153°.

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.57; H, 6.92; N, 8.18.

N-(1-Pyrrolidinoethyl)-3a,4,5,6-tetrahydrosuccinimido[3,4,-b]-acenaphthen-10-one. (1h)

When 3.57 g (21 mmoles) of 1-pyrrolidinoethyl chloride hydrochloride was reacted with 1a as in the above procedure, 3.06 g (41%) of 1h was obtained as a crystalline hydrate, melting at 194-196°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74; N, 7.86. Found: C, 67.92; H, 6.47; N, 7.67.

N-Acetonyl-3a,4,5,6,-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one. (1i)

The procedure reported above for 1d, but substituting chloroacetone (2.2 g, 24 mmoles) for the alkyl halide, gave after two recrystallizations from isopropanol 4.86 g (78%) of 1i as white crystals, melting at 196-198°.

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.06; H, 4.47; N, 4.61.

N-Methylthiomethyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]-acenaphthen-10-one. (1l)

Using the procedure reported above for 1d, but substituting 2.32 g (24 mmoles) of chloromethyl methyl sulfide (Aldrich) for the alkyl halide, a yield of 1.21 g (19%) of 1l, melting at 149-150° after two recrystallizations from isopropanol, was obtained.

Anal. Calcd. for $C_{16}H_{15}NO_3S$: C, 63.78; H, 5.02; N, 4.65; S, 10.63. Found: C, 63.37; H, 5.04; N, 4.93; S, 10.45.

N-(3-Cyanopropyl)-3a,4,5,6-tetrahydroscuccinimido[3,4-b]-acenaphthen-10-one. (1m)

4-Chlorobutyronitrile (2.5 g, 24 mmoles) (Aldrich) was allowed to react with 5 g of 1a and potassium carbonate, as above to give 5.04 g (78%) of white crystals, after two recrystallizations from isopropanol, of 1m, melting at 118-119°.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.11. Found: C, 69.90; H, 5.36; N, 8.94.

N-(3-Thenyl)-3a,4,5,6-tetrahydrosuccinimido[3,4,-b]acenaphthen-10-one. (1n)

Following the above procedure, using 3.9 g (22 mmoles) of 3-thenyl bromide (6), a yield of 6.23 g (88%) of 1n, melting at 176-177° after two recrystallizations from isopropanol, was obtained.

Anal. Calcd. for $C_{19}H_{15}NO_3S$: C, 67.65; H, 4.48; N, 4.11; S, 9.50. Found: C, 67.86; H, 4.61; N, 4.17; S, 9.36.

N-(2-Thenyl)-3a,4,5,6-tetrahydrosuccinimido[3,4,-b]acenaphthen-10-one.(1o)

2-Chloromethylthiophene (2.9 g, 22 mmoles), prepared as previously reported (9), was allowed to react with 1a as above, to give 2.69 g (38%) of 1o, melting at 149-150° after two recrystallizations from isopropanol.

Anal. Calcd. for $C_{19}H_{15}NO_3S$: C, 67.65; H, 4.48; N, 4.11; S, 9.50. Found: C, 67.34; H, 4.76; N, 4.31; S, 9.47.

7-Methyl-l-tetrylidenemalononitrile. (3a)

A mixture of 160 g (1.0 mole) of 7-methyl-l-tetralone (Aldrich), 80 g (1.2 moles) of malononitrile, 8 g of ammonium acetate, 24 mL of acetic acid and 400 mL of benzene was heated to reflux under a Dean-Stark trap with stirring for 6 hr, allowed to cool and poured into 800 mL of water. The aqueous layer was separated and extracted with 2 × 100 mL of benzene. The organic layers were combined, dried (sodium sulfate), evaporated and the solid residue recrystallized from 95% ethanol to give 119

g (57%) of 3a, melting at 87-90°. Two further crystallizations from ethanol gave yellow plates of analytical sample, melting at 92-94°: ir (cm^{-1}) 2880, 2800 (CH), 2200 (CN) and 1600 (C=C).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81. Found: C, 81.04; H, 5.89.

7-Methoxy-l-tetrylidinemalononitrile. (3b)

A mixture of 17.6 g (0.1 mole) of 7-methoxy-l-tetralone (2b) prepared by the method of Johnson and Glenn (8), 8.0 g (0.12 mole) of malononitrile, 0.8 g of ammonium acetate and 100 mL of benzene were refluxed until one equivalent of water (Dean-Stark trap) was collected (24 hr), then worked up as described for 3a. Several recrystallizations from 95% ethanol gave 8.74 g (39%) of yellow needles, melting at 98-99°; ir (cm^{-1}), 2880, 2810 (CH), 2205 (CN) and 1600 (C=C).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.97; H, 5.40; N, 12.49. Found: C, 75.07; H, 5.56; N, 12.43.

2-Carboxamido-7-methyl-3,4-trimethyleno-1-indenone. (4a)

A mixture of 5.0 g (24 mmoles) of 3a in 200 mL of polyphosphoric acid was heated on a steam bath for 5.5 hr (solution turned red, then purple), then poured into 1.5 L of ice water with stirring. Additional cold water (1.5 L) was added to the slurry of orange solid, and the mixture let stand for 2 days, then filtered to give 4.5 g (82%) of orange solid, melting about 180° when dry. Two recrystallizations from methanol gave orange needles of 4a, melting at 200-202° (dec.); ir (cm^{-1}) 3380, 3130 (NH), 1680 (CO), 1665 ($CONH_2$) and 1590 (C=C).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 74.00; H, 5.78; N, 6.28.

2-Carboxamido-7-methoxy-3,4-trimethyleno-1-indenone. (4b)

A mixture of 3.5 g (15.6 mmoles) of 3b and 70 mL of polyphosphoric acid, treated as above for the preparation of 4a, gave 1.54 g (41%) of 4b as orange needles, melting at 207-208° (dec.); ir (cm^{-1}) 3320, 3100 (NH), 2900, 2850 (CH), 1680 (CO), 1650 ($CONH_2$) and 1590 (C=C).

Anal. Calcd. for $C_{14}H_{13}NO_3$; C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.50; N, 6.16.

2-Carboxamido-2a-cyano-8-methyl-2a,3,4,5-tetrahydroacenaphthene-1-one. (5a)

A mixture of 15 g (66 mmoles) of 4a, 60 mL of water, 21 mL of *tert.* butyl alcohol and 6 g (0.12 mole) of sodium cyanide was stirred over a steam bath until a homogeneous clear orange solution was obtained (about 10 min), then let stand at room temperature for 1 hr. Some white precipitate was formed (probably the sodium salt of 5a), but dissolved when the solution was diluted with water to 750 mL. Addition of 23 mL of 20% sulfuric acid gave a light tan precipitate, and concentration of the filtrate to one-half volume gave additional precipitate. The combined solid was recrystallized once from 95% ethanol to yield 14.7 g (88%) of orange-yellow crystals of 5a, melting at 193-196°. Two more recrystallizations gave pale tan prisms of 5a, melting at 195-197°; ir (cm^{-1}) 3350, 3120 (NH), 2900 (CH), 2220 (CN), 1710 (CO), 1675 ($CONH_2$) and 1595 (C=C).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.55; N, 11.02. Found: C, 71.12; H, 5.78; N, 10.81.

2-Carboxamido-2a-cyano-8-methoxy-2a,3,4,5-tetrahydroacenaphthen-1-one. (5b)

When a mixture of 2.1 g (8.7 mmoles) of 4b, 10 mL of water, 3.5 mL of *tert.* butyl alcohol and 1.0 g (20 mmoles) of sodium cyanide was heated on a steam bath for 15 min, the contents of the flask solidified (sodium salt of 5b). About 100 mL of

water was added to give a clear yellow solution. Addition of 3 mL of 20% sulfuric acid with stirring gave a pale yellow precipitate, which after two recrystallizations from 95% ethanol gave 1.9 g (82%) of colorless needles of 5b, melting at 238-240°; ir (cm^{-1}) 3330, 3200 (NH), 2900, 2830 (CH), 2210 (CN), 1680 (CO), 1650 ($CONH_2$) and 1610 (C=C).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.47; H, 5.40; N, 10.47.

2,2a-Dicarboxamido-8-methyl-2a,3,4,5-tetrahydroacenaphthen-1-one. (6a)

Ten g (39 mmoles) of 5a was added in portions with stirring to 40 mL of conc. sulfuric acid maintained below 40° by intermittent cooling in an ice bath. The reaction mixture was then stirred at room temperature until a homogeneous red solution was obtained (1.5 hr), then poured over 200 g of crushed ice, yielding 10.5 g (98%) of a yellow precipitate which melted at 244-246° (dec.). one recrystallization from 95% ethanol gave colorless microcrystals of 6a, melting at 247-248° (dec.); ir (cm^{-1}) 3390, 3100 (NH), 2910 (CH), 1700 (CO), 1670, 1645 ($CONH_2$) and 1600 (C=C).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.96; N, 10.27. Found: C, 66.48; H, 6.16; N, 10.71.

2,2a-Dicarboxamido-8-methoxy-2a,3,4,5-tetrahydroacenaphthen-1-one. (6b)

A mixture of 2.88 g (10.67 mmoles) of 5b and 20 mL of conc. sulfuric acid was treated as above for the preparation of 6a, to yield 2.8 g (92%) of colorless crystals of 6b, melting at 234-236° (dec.); ir (cm^{-1}) 3300, 3080 (NH), 1680-1600 (CO and $CONH_2$).

Anal. Calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59. Found: C, 62.20; H, 5.87.

9-Methyl-3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one. (1p)

To a slurry of 5 g (18.4 mmoles) of 6a in 50 mL of diethylene glycol was added with stirring 1.5 mL of conc. sulfuric acid. The mixture was then heated to 120-130° for 45 min, and poured into 500 mL of ice water, yielding 3.7 g (79%) of white crystals, melting at 270-274°. Recrystallization from 95% ethanol gave colorless plates, melting at 276-278°; ir (cm^{-1}) 3130 (NH), 3000, 2910, 2740 (CH), 1770, 1710, 1695 (CO and CONH) and 1590 (C=C).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13; N, 5.49. Found: C, 70.64; H, 5.22; N, 5.38.

9-Methoxy-3a,4,5,6-tetrahydrosuccinimido[3,4,-b]acenaphthen-10-one. (1q)

A slurry of 2.5 g (8.7 mmoles) of 6b in 25 mL of diethylene glycol was stirred with 0.5 mL of conc. sulfuric acid, and heated to 120-130° for 45 min. The solution was then poured into 250 mL of ice water, to give 1.85 g (79%) of white solid, which twice recrystallized from 95% ethanol gave colorless needless of 1q, melting at 266-267.5°; ir (cm^{-1}) 3250 (NH), 2905 (CH), 1775, 1690 (CONH) and 1710 (CO).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.31; H, 4.73; N, 5.15.

Footnotes

1. Taken in part from a thesis submitted to Indiana University by R.F.W. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1965. This work was supported in part by a grant from Bristol Laboratories, Syracuse, N.Y.
2. We are indebted to Dr. M.H. Pindell of Bristol Laboratories for supplying selected preliminary test data.

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