

# Succinimido[3,4-b]indan-8-one Derivatives

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## Introduction

A few years ago 3a,4,5,6-tetrahydrosuccinimido[3,4-b]acenaphthen-10-one (**1**) was found to be a potent anticonvulsant of low toxicity (**2**). The high activity of **1** was thought to be due, at least in part, to its rigid structure. In order to test this hypothesis a series of succinimido[3,4-b]indan-8-ones (**2**) were prepared. These compounds are structurally very similar to **1**, but lack some of its rigidity due to the lack of the fused six-membered ring.

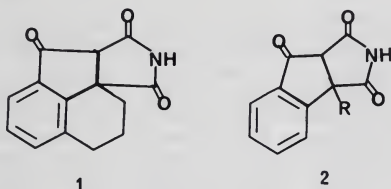
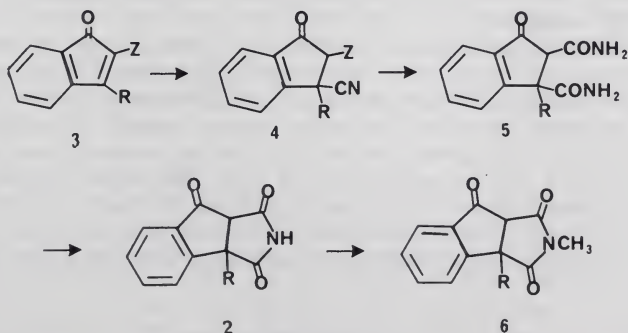


FIGURE 1.

## Chemistry

Compounds **2** were prepared in a sequence of three steps from 3-substituted-2-carboxamido (or 2-cyano)-1-indenones **3** (**1**). The Michael addition of cyanide ion to compounds **3** afforded the corresponding adducts **4**. Treatment of compounds **4** with concentrated sulfuric acid gave 3-substituted-2,3-dicarboxamido-1-indanones **5**. Heating the diamides **5** with acidified diethylene glycol yielded the desired imides **2**. The N-methyl derivative of **2d** (**6**) was prepared by treating **2d** with methyl iodide and potassium carbonate in dimethylformamide. The preparation and properties of compounds reported in this paper are summarized in Table. 1.

SCHEME 1.



a)  $R = C_2H_5$ ,  $Z = CONH_2$ ; b)  $R = i-C_3H_7$ ,  $Z = CONH_2$ ;  
c)  $R = t-C_4H_9$ ,  $Z = CN$ ; d)  $R = C_6H_5$ ,  $Z = CONH_2$

The indanones **4** and **5** were soluble in aqueous sodium carbonate, gave positive ferric chloride tests, and their infrared and ultraviolet spectra indicated that they existed to a large extent in the enol form. This is in agreement with the findings of Koelsch for a series of 2-carbethoxy-3-phenyl-1-indanones (**4**).

TABLE 1. Yields and Properties of Compounds Prepared

| Product                | Yield           | M.P., °C  | Formula                                                       | Calculated |      |       | Found |      |       |
|------------------------|-----------------|-----------|---------------------------------------------------------------|------------|------|-------|-------|------|-------|
|                        |                 |           |                                                               | C          | H    | N     | C     | H    | N     |
| <b>4a</b> <sup>a</sup> | —               | oil       | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | —          | —    | —     | —     | —    | —     |
| <b>4b</b>              | 78              | 136-137   | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | 69.40      | 5.82 | 11.57 | 69.69 | 6.10 | 11.45 |
| <b>4c</b>              | 100             | 140-142   | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O              | 75.60      | 5.92 | 11.76 | 75.51 | 5.99 | 11.88 |
| <b>4d</b>              | 98              | 171-173   | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | 73.90      | 4.38 | 10.14 | 73.80 | 4.52 | 10.00 |
| <b>5a</b>              | 45 <sup>b</sup> | 180-181.5 | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | 63.40      | 5.73 | 11.38 | 63.10 | 5.70 | 11.23 |
| <b>5b</b>              | 80              | 168.5-170 | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | 64.60      | 6.20 | 10.77 | 65.22 | 6.18 | 10.62 |
| <b>5c</b>              | 20 <sup>c</sup> | 157-158   | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | —          | —    | 10.21 | —     | —    | 9.97  |
| <b>5d</b>              | 95              | 195-196   | C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> | 69.38      | 4.79 | 9.52  | 69.34 | 4.80 | 9.66  |
| <b>2a</b>              | 42              | 181-182   | C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub>               | 68.11      | 4.84 | 6.11  | 68.18 | 5.04 | 6.09  |
| <b>2b</b>              | 86              | 236-237   | C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub>               | 69.12      | 5.39 | 5.76  | 69.05 | 5.62 | 5.81  |
| <b>2c</b>              | 70              | 243-244   | C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub>               | 70.02      | 5.88 | 5.44  | 70.06 | 5.92 | 5.47  |
| <b>2d</b>              | 94              | 180-181   | C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub>               | 73.64      | 4.00 | 5.05  | 73.41 | 4.19 | 4.96  |
| <b>6d</b>              | 67              | 169-170   | C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub>               | 74.22      | 4.50 | 4.81  | 74.52 | 4.68 | 5.06  |

(a) The oil obtained was converted directly to **5a**.

(b) Overall yield from **3a**.

(c) **2c** also formed in 35% yield.

### Pharmacological Results

Compounds **2a**, **2b**, **2c**, **2d**, **4d**, **5d** and **6** were evaluated for the following actions: central nervous system, antihypertensive, analgesic, anticoagulant, anti-inflammatory, autonomic, anti-allergic, endocrine, reticulothelial, antibacterial and antifungal. The pharmacological screening data, summarized in Table II, are through the courtesy of Dr. M.L. Pindell, of the Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, New York. The corresponding data previously reported (2) for **1** is included for comparison.

The activities observed were the following: (**2a**,) hypotensive; **2b**, smooth muscle relaxant in vitro; **2c**, motor stimulant and analgesic; **2d**, protectant against electrically induced convulsions and hypotensive. Of the compounds tested, therefore, only the imides **2** are active, the nature of the activity varying markedly with small changes in the substituent R. The phenyl derivative **2d** is the only one having anticonvulsant activity, but this is only one-twentieth that of **1**; the added rigidity afforded by the fused six-membered ring in **1** (as opposed to **2**) thus seems necessary for high anti-convulsant activity. It is interesting to note that when the imide hydrogen of **2d** was replaced by a methyl group, a compound (**6**) was obtained which was devoid of activity.

### Experimental

Melting points were taken on a Mel-Temp capillary melting point apparatus and

TABLE 2. Summary of Pharmacological Screening Results<sup>a</sup>

| Compound | Activity <sup>b</sup>  | MED/mg/kg        |
|----------|------------------------|------------------|
| 1        | CNS <sup>c</sup>       | 10               |
|          | CNS <sup>d</sup>       | 100 <sup>h</sup> |
| 2a       | Hypotensive            | 100              |
| 2b       | Autonomic <sup>e</sup> | 150              |
| 2c       | Motor stimulant        | 75               |
|          | Analgesic              | 100              |
| 2d       | CNS <sup>c</sup>       | 200              |
|          | Hypotensive            | 100 <sup>f</sup> |
| 4d       | g                      |                  |
| 5d       | g                      |                  |
| 6d       | g                      |                  |

(a) The pharmacological screening data are through the courtesy of Dr. M.L. Pindell, of Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, NY. (b) The activities observed are listed together with the minimal effective dose (MED) for oral administration. These compounds were evaluated for the following actions: central nervous system (CNS), antihypertensive, analgesic, anticoagulant, anti-inflammatory, autonomic, anti-allergic, endocrine, reticuloendothelial, antibacterial and antifungal. (c) A protectant against electrically induced convulsions. (d) A mild protectant against Metrazol-induced convulsions. (e) A smooth muscle relaxant *in vitro* (50 mcg/mL, bath concentration). (f) Two-thirds of the animals exhibited associated toxicity. (g) Devoid of significant pharmacological activity at 300 mg/kg. (h) Toxic dose >3050 mg/kg.

are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord, using potassium bromide mulls or liquid films.

#### 2-Carboxamido(or 2-Cyano)-3-cyano-1-indanones (4).

The method employed is similar to that of Koelsch (4) for the addition of cyanide ion to 2-carboxy-3-phenyl-1-indanone. A mixture of 5.0 g (20-30 mmoles) of a 2-carboxamido(or 2-cyano)-1-indanone 3 (1), 2.0 g (41 mmoles) of sodium cyanide, 7 mL of *t*-butyl alcohol and 20 mL of water was heated on a steam bath with stirring until a homogeneous solution was obtained (10-30 min). This solution was poured into a mixture of 50 mL of 20% aqueous sulfuric acid and 100 g of ice with vigorous stirring. Except for 4a (an oil), the products were obtained as solid precipitates, which were recrystallized to materials with the properties shown in Table I. The recrystallizing solvents used were the following: 4b, ethyl acetate-hexane; 4c, benzene-petroleum ether; and 4d, ethyl alcohol. Similar results were obtained when this reaction was scaled up by a factor of ten.

Compounds 4 exhibit a characteristic sharp nitrile absorption band at 2260-2210 cm<sup>-1</sup> in their infrared spectra.

#### 2,3-Dicarboxamido-1-indanones (5).

One gram of 4 was added in portions with stirring to 4 mL of concentrated sulfuric acid, with the temperature being maintained below 40° by the rate of addition. The resulting solution was stirred at room temperature for 1.5 hr, poured onto 40 g of ice and the mixture allowed to settle overnight, affording a precipitate. 5a and 5d were recrystallized from ethyl alcohol, 5c from benzene-petroleum ether, and 5b from ethyl alcohol, 30% aqueous ethyl alcohol and finally from benzene-petroleum ether. Similar results were obtained when this reaction was scaled up by a factor of twenty.

After four days of standing at room temperature, 0.38 g (35%) of 2c precipitated from the filtrate of 5c.

Succinimido[3,4-b]indan-8-ones (2).

A slurry of 5 g of a diamide 5 in 50 mL of diethylene glycol was made and 1 mL of concentrated sulfuric acid added with stirring. The mixture was heated with continued stirring to 120° and at 120-130° for 30 min. The resulting solution was poured onto 500 g of ice and the precipitate allowed to settle overnight. 2a and 2b were recrystallized from ethyl alcohol, and 2c and 2d from 50% aqueous ethyl alcohol. Similar results were obtained when this reaction was scaled up by a factor of four.

Compounds 2 exhibit a characteristic sharp imide absorption band at 1785-1770 cm<sup>-1</sup> in their infrared spectra.

N-Methyl-3a-phenylsuccinimido[3,4-b]indan-8-one (6).

The methylation of 2d was accomplished as previously reported (3) for similar imides. A mixture of 6.9 g (25 mmoles) of 2d, 4.47 g (32 mmoles) of methyl iodide, 3.51 g (26 mmoles) of potassium carbonate and 20 mL of dimethylformamide was stirred at room temperature for two days. The solution was diluted to 200 mL with water and extracted with chloroform. The chloroform extract was washed with 100 mL portions of water, 10% aqueous sodium hydroxide, then water, dried over sodium sulfate, and evaporated to dryness, yielding an oil, which crystallized from ethyl alcohol to give 4.9 g (67%) of colorless needles, m.p. 165-168°. Recrystallization from ethyl alcohol afforded material with the properties listed in Table I.

#### Literature Cited

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#### Note

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