

Synthesis of Naphth[1,8-*bc*]azepine Derivatives (1)

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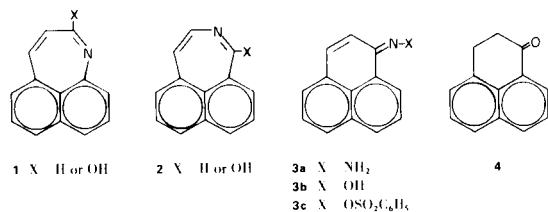
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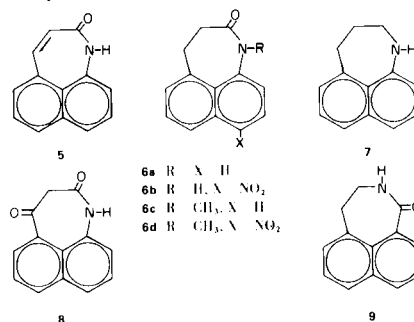
There are few reports in the literature regarding the synthesis and chemistry of the naphth[1,8]azepine ring system (2, 3). The fully unsaturated systems (1 and 2) are apparently unknown. The corresponding carbocyclic unsaturated system has been known for a long period of time (4), and recently a convenient synthesis of the latter was published (5). Various derivatives of 5-methyldihydro- and 5-methyltetrahydronaphth[1,8]azepinones were reported by Evans and Waite (2) and by Jones (3). In each case the cycloalkanone ring of 2,3-dihydrophenalen-1-one was expanded *via* Schmidt and Beckmann rearrangements, respectively. As part of an overall program designed to provide synthetic routes to a variety of bridged aromatic systems we investigated ring expansion reactions of **3** as a possible direct route to the unsaturated systems (1 and 2) (6). The previously studied Schmidt reaction of **4** was examined also. It was anticipated that the product from the latter reaction would serve as a precursor of **1** *via* dehydrogenation (7). The ring nitrogen atom provides a potential point of attachment of side chains, and thus derivatives of **1** analogous to clinically useful antidepressants may be synthesized (8). Since we have terminated our efforts in this area we wish to report our findings.

Reaction of **3a** with acidic reagents containing nitrite ion led to intractable materials that were not identified, except that the hydrolysis product (the corresponding ketone **3d**) was recovered. Also, **3c** resisted Beckmann rearrangement and/or fragmentation under conditions that normally lead to reaction of analogous acyclic oxime sulfonates (9). Thus **3c** could be recovered unchanged from refluxing chloroform, acetonitrile, benzene, or xylene.



However, treatment of **3b** with phosphorus pentachloride in dry ether or dry benzene followed by hydrolysis yielded an unstable material of undetermined structure (10). The unsaturated lactam **5a** was produced in 50% yield *via* de-

hydrogenation of the corresponding dihydronaphtho[1,9]azepin-2(1*H*)one (**6a**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane (10). The appearance of a pair of doublets at δ 5.70 and 6.65 ($J = 12$ Hz) indicated the presence of the dehydrogenation product **5**, and also provided a basis for determining the extent of reaction. Also, the low voltage mass spectrum of the mixture (**5** and **6a**) contained a major peak at m/e 195 (for **5**). This peak is absent in the mass spectrum of **6a**. The dihydrolactam **6a** was obtained from the Schmidt reaction (sulfuric acid-sodium azide) of 2,3-dihydrophenalen-1-one (**4** in acetic acid or chloroform). Amine **7** was obtained *via* lithium aluminum hydride reduction of **6a**.



Attempted oxidation of **6a** (or **6c**) at the benzylic position with a mixture of nitric and acetic acids yielded the nitro compound **6b** (or **6d**) instead of the desired oxidized system **8** (11). No useful product could be isolated when either ceric ammonium nitrate or chromic oxide in acetone was used as oxidizing agent. Structures of new compounds were assigned on the basis of spectral data (ir, nmr and selected mass spectra) and elemental analyses. Physical data for the various compounds are summarized in Table I.

It is significant that **6a** is dehydrogenated with difficulty in spite of the fact that the pi-bond being introduced is conjugated with an aromatic system (12, 13). Thus, the behavior of **6a** is reminiscent of the behavior of the corresponding carbocyclic system indicating that the pi-electron system of **5** (fourteen pi-electrons in a fused tricyclic system) is destabilized and may be properly labeled as anti-aromatic (14). The inertness of **3c** toward rearrangement might arise from the rigidity of the starting material or

Table I

Melting Points, Elemental Analyses and Nmr Spectral Data for Naphth[1,8]azepinones and Related Substances (a)

Compound	M.p. °C	Elemental Analyses			Nmr Data (f)
		C	H	N	
3c	151	68.04	3.91	4.18	7.0-8.3 (m)
		68.04	3.96	4.23	
5	(b,c)	79.98	4.65	7.17	5.70 (d, J = 12), 6.65 (d, J = 12)
		76.46	5.08	6.94 (g)	
6a	193	79.16	5.62	7.11	2.95 (m), 2.34 (m), 7.77 (m)
		79.25	5.54	7.10	
6b	236 (d)	64.46	4.16	11.57	2.86 (m), 3.36 (m), 7.1-8.5 (m)
		64.46	4.18	11.60	
6c	87	79.59	6.20	6.63	2.6-3.7 (s,m), 7.3 (m)
		79.45	6.26	6.48	
6d	159 (e)	65.62	4.72	6.48	2.85 (m) 3.45 (2,m), 7.2-8.5 (m)
		65.89	4.99		
7	73	85.21	7.15	7.64	2.05 (q), 3.29 (t), 3.40 (s), 6.60 (d,d), 7.0-8.0 (m)
		85.53	7.35	7.37	
9	165	79.16	5.62	7.10	2.8-4.0 (m), 7.0-8.5 (m)
		79.45	5.86	6.96	

(a) The first number in each column is the calculated percentage, followed by found. (b) Mixture contains **5** and **6a** in a 1:1 ratio. (c) M^+ observed at 195 and 197. (d) M^+ observed at 242. (e) M^+ observed at 256. (f) Chemical shifts are listed in δ values relative to tetramethylsilane in deuteriochloroform. Compounds **5**, **6a**, **6b**, and **9** showed ir carbonyl frequencies at ca 1670 cm^{-1} . (g) Pmr absorption bands for **6a** are omitted here.

reflect a high energy transition state leading to the anti-aromatic system (**5**). However, the behavior of oxime **3b** toward phosphorus pentachloride is somewhat similar to that of other cross-conjugated oximes in that it leads to destruction of the reactant (15, 16).

EXPERIMENTAL (17,18)

2,3-Dihydrophenalen-1-one (**4**).

This compound was prepared from α (1-naphthyl)propionic acid according to a general procedure for carrying out a Friedel-Crafts reaction (19). To a suspension of 42 g. (0.20 mole) of phosphorus pentachloride in 100 ml. of benzene was added in small portions 40 g. (0.20 mole) of α (1-naphthyl)propionic acid suspended in 100 ml. of benzene. After the vigorous reaction subsided the reaction mixture was heated with steam for 1/2 hour. Benzene and phosphorus oxychloride were removed under reduced pressure. The oily residue (light brown) was dissolved in 300 ml. of dry benzene and 27 g. (0.2 mole) of aluminum chloride was added in small portions (reaction temperature was moderated with an ice-bath and the mixture was hydrolyzed by dumping it on a slurry of ice and concentrated hydrochloric acid. Ethyl ether (100 ml.) was added, and the layers separated. The organic layer was washed successively with water and dilute sodium hydroxide solution, then dried and the solvents removed. The yellow oil which resulted was crystallized from benzene-hexane solution. Twenty-one g. (58%) of bright yellow crystals resulted, m.p. 69-74° (lit. (20,21) m.p. 83°).

3,4-Dihydronaphth[1,8-*bc*]azepin-2(1*H*)one (**6a**).

A 9.10 g. (0.50 mole) sample of 2,3-dihydrophenalen-1-one dissolved in 80 ml. of 1:1 (v/v) mixture of chloroform-sulfuric acid was treated in small portions with 3.90 g. (0.060 mole) of sodium azide (3,22). Gas evolution began immediately and the reaction temperature was moderated by the rate of addition of sodium azide and cooling with ice (the mixture was stirred throughout). After gas evolution ceased, the reaction mixture was dumped into a slurry of ice water. A yellow solid separated. The mixture was extracted with two 200 ml. portions of chloroform, the chloroform layer washed with dilute sodium hydroxide solution, dried, and evaporated. The yellow solid that resulted was recrystallized from methanol. A yellow crystalline material was obtained, 3.61 g. (37%), m.p. 187-188°. A crystalline bright yellow material (**9**) was obtained from the filtrate, and recrystallized from methanol several times, m.p. 165°.

1,2,3,4-Tetrahydronaphth[1,8-*bc*]azepine (**8**).

A 0.91 g. (5.0 mmoles) sample of **3a** was added to a slurry of 0.76 g. (20 mmoles) of lithium aluminum hydride in 75 ml. of dry ethyl ether. The reaction mixture was stirred magnetically at reflux temperature for 12 hours. Excess lithium aluminum hydride was destroyed with ethyl acetate; 50 ml. of water and 50 ml. of ethyl ether were added and the layers separated. The aqueous layer was extracted with an additional 50 ml. portion of ether. The ethereal solution was dried and evaporated. The white solid that separated was recrystallized from pentane, m.p. 72-73°.

Naphth[1,8-*bc*]azepin-2(1*H*)one (**5a**).

Via Dehydrogenation.

A 0.60 g. (3.0 mmoles) sample of lactam **6a** in 20 ml. of dioxane was allowed to react with 1.80 g. (8.0 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone for days (7). The reaction mixture was filtered to remove dark materials after the addition of 50 ml. of dichloromethane. The solid was washed with an additional 50 ml. of dichloromethane and the combined filtrate was evaporated under reduced pressure. This was extracted with 50 ml. of dichloromethane and again filtered. The filtrate was evaporated and chromatographed on an alumina column, eluting with chloroform. Nmr analysis indicated a 1:1 mixture of **5** and **6a**.

Phenalen-1-one Oxime Benzenesulfonate (**3c**).

A 1.95 g. (10 mmoles) sample of phenalen-1-one oxime (**3b**) (**23**) dissolved in 40 ml. of dimethoxyethane was allowed to equilibrate with 1.34 g. (12 mmoles) of potassium *t*-butoxide for 1/2 hour. The solution was treated with 2.12 g. (12 mmoles) of benzenesulfonyl chloride and the mixture was allowed to react for 12 hours. The solvent was removed under reduced pressure and the residue was taken up in 200 ml. of a 1:1 dichloromethane-water mixture. The organic layer was separated and dried. Solvent removal gave a yellow solid that was recrystallized from acetonitrile, 1.93 g. (58%), m.p. 151-152°.

Beckman Rearrangement of **3c**.

A 0.60 g. (3.0 mmoles) sample of phenalen-1-one oxime (**23**) and 1.0 g. (5 mmoles) of phosphorus pentachloride in 60 ml. of dry benzene were allowed to react at 80° for 2 hours. This was hydrolyzed by pouring over 60 g. of ice (change from bright yellow to brown) and extracted with 75 ml. of dichloromethane. The solvent was removed under reduced pressure to yield a dark brown semi-solid. Attempted crystallization from methanol failed. An unstable compound (**10**) of unknown structure was obtained (**16**).

N-Methylation of **6a**.

A 2.3 g. (12 mmoles) sample of **6a** dissolved in 100 ml. of dimethoxyethane was allowed to react with 2.5 g. (17 mmoles) of potassium *t*-butoxide for 1 hour. The reddish solution was treated with 12 g. (84 mmoles) of iodomethane and allowed to react for 18 hours. The solvent was removed under reduced pressure. The residue was taken up in 100 ml. of water plus 100 ml. of dichloromethane. The organic layer was separated and dried. Solvent removal gave an orange-brown oil that crystallized. Recrystallization from dichloromethane-petroleum ether yielded 1.4 g. (57%) of **6c**, m.p. 86-87°.

Nitration of *N*-Methyl Lactam (**6c**).

A 1.0 g. (4.7 mmoles) sample of **6c** was added to a solution of 1.0 ml. of concentrated nitric acid in glacial acetic acid and allowed to react with stirring at room temperature for 24 hours (**11**). The solvents were removed under reduced pressure to yield a brownish-red oil. This was taken up in a 1:1 mixture of water and dichloro-methane (100 ml.). The layers were separated and the organic layer dried. Solvent removal gave a brown solid that was recrystallized from methanol, 0.80 g. (66%), m.p. 159°.

Nitration of Lactam (**6a**).

A 3.0 g. (15.3 mmoles) sample of lactam **6a** was dissolved in 50 ml. of glacial acetic acid. To this was added 1.5 ml. of concentrated nitric acid in 20 ml. of glacial acetic acid (**11**). The mixture was stirred at room temperature for 15 hours. The solution was filtered to remove a small amount of yellow solid that was discarded. The solvents were removed under reduced pressure and the residue was taken up in 200 ml. of dichloro-

methane. The dichloromethane solution was washed with 50 ml. of water, 50 ml. of saturated sodium bicarbonate solution and dried. Solvent removal yielded a brown solid that was rinsed with hot methanol. The mixture was filtered to remove 1.3 g. (35%) of bright yellow solid. This compound was recrystallized from acetonitrile, m.p. 234-236°.

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