Photocyclizations. I. 4,5-Dihydro-1H-naphth[1,8-*de*]azocin-2(3H)-one

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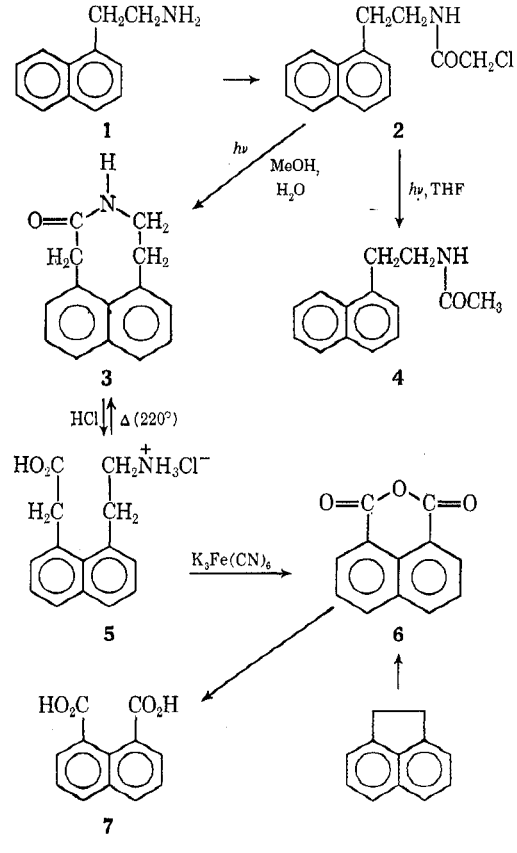
Photolysis of 1-(2-chloroacetamioethyl)naphthalene (**2**) in aqueous methanol has given naphthazocine **3** in 40–45% yields. The structure of **3**, assigned from nmr, uv, ir, and mass spectral data along with steric considerations, was rigorously confirmed by its degradation to 1,8-naphthalic anhydride (**6**), also obtained from acenaphthene. Photolysis of **2** in tetrahydrofuran gave chiefly hydrogenolysis product **4** and no **3**.

The photolysis of N-chloroacetyl derivatives of a variety of pharmacodynamic amines as well as some aromatic amino acids has been studied extensively by Yonemitsu and Witkop.[1-3] Among the many reactions observed, cyclization with release of hydrogen chloride seems to be the major pathway in neutral, aqueous medium leading to the formation of tricyclic indoles, benzazepines, and azaazulenes in yields ranging from 20 to 70%. As part of a study designed to explore the synthetic potentialities of such intramolecular cyclizations, it was of interest to us to examine the behavior of similar compounds incorporating aromatic systems other than a hydroxyphenyl or indole system. In this paper we report the photolysis of 1-(2-chloroacetaminoethyl)naphthalene (**2**) and the characterization of products obtained therefrom.

1-(2-Aminoethyl)naphthalene (**1**) prepared by the method of Schleigh, *et al.*[4] (or less satisfactorily by reduction of 1-naphthylacetonitrile with metal hydrides), was best converted to **2** in a nonpolar solvent in the presence of powdered potassium carbonate, with either chloroacetyl chloride or the anhydride. Irradiations of **2** were generally carried out in dilute solutions through which nitrogen was bubbled to remove dissolved oxygen. Vycor filters ($\lambda > 210$ mμ) were used in conjunction with a high-pressure mercury immersion lamp. In a methanol–water solution, the chloroacetamide, **2**, was rapidly consumed and a photoproduct, **3**, was isolated to which the empirical formula $C_{14}H_{13}NO$ could be assigned on the basis of its mass spectrum and combustion analyses. The ir spectrum of **3** taken in condensed phase showed carbonyl absorption at 1670 cm^{-1} and an NH band at 3170 cm^{-1}, both at higher frequencies than those of the corresponding **2**. In the uv spectrum of **3** was a main band at 287 mμ compared with 281 for **2**, a bathochromic shift attributable to the transverse polarization of the naphthalene nucleus.[5]

A 100-MHz nmr spectrum of **3** in dimethyl sulfoxide-d_6 showed signals for six aromatic protons with two centered at δ 7.75, and the other four at δ 7.35, indicative of two α and four β protons. The slightly broadened singlet at δ 7.1 which vanished upon shaking with D_2O was apparently due to the NH proton. Signals from the six alicyclic protons are not clearly defined; they appeared as a very broad band in the region of δ 3.0–3.9. The broadness of lines may be due in part to overlapping or some unresolved long-range coupling; also, it may be a result of incomplete averaging if the rate of ring inversion in the alicyclic system is not very fast.[6]



Thus, it would seem that cyclization of **2** has occurred at one of the α positions of the naphthalene nucleus, and the photoproduct formed could be a derivative of azocine fused to the naphthalene ring at the 1,8 positions, or it could be derivatives of other tricyclic systems formed by cyclization at C-4 or C-5. The last two possibilities were ruled out from spatial considerations, for the bond angles and chain lengths are such that formation of an aliphatic bridge across the naphthalene ring at 1,4 or 1,5 would be virtually impossible. This can be amply demonstrated with models.

A final, unequivocal assignment of structure **3** to the photoproduct was made on the basis of chemical evidence. Refluxing **3** with dilute hydrochloric acid led to an amino acid, **5**, whose nmr spectrum showed a now-sharpened methylene signal at δ 4.3 in addition to a symmetrical AA'BB'-type multiplet at 3.15–3.80.

(1) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3941 (1966).

(2) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *ibid.*, **90**, 776 (1968).

(3) O. Yonemitsu, Y. Okuno, Y. Kanaoka, I. Karle, and B. Witkop, *ibid.*, **90**, 6522 (1968).

(4) W. R. Schleigh, A. Catala, and F. D. Popp, *J. Heterocycl. Chem.*, **2**, 379 (1965).

(5) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1965, p 305.

(6) F. A. L. Anet and M. A. Brown *Tetrahedron Lett.*, 4881 (1967).

When **5** was heated at temperatures above 200° with or without the application of vacuum, a change in crystalline structure took place, and the product isolated was found to be identical with the original photoproduct, **3**, in all respects. The ease with which the thermal ring closure proceeded provided additional support for the *peri*-fused structure in **3**. Numerous attempts were made to oxidize **5** selectively to a known naphthalenedicarboxylic acid. While potassium permanganate, under a variety of conditions, gave mainly a benzenetricarboxylic acid, oxidation with neutral sodium dichromate at 250°, usually found satisfactory for converting dimethylnaphthalenes to naphthalenedicarboxylic acids,[7,8] yielded only naphthoquinone derivatives. Potassium ferricyanide, however, was found to attack slowly the saturated α carbons when used in large excess and in an alkaline medium,[9] leaving the aromatic moiety intact. After 5 days at 75°, compound **5** was thus converted to a thermally unstable dicarboxylic acid which, upon standing or heating, readily lost water to form the anhydride **6**; this was accompanied by a shift of carbonyl frequency from 1690 cm^{-1} to two bands at 1775 and 1740 cm^{-1}. Compound **6** was readily identified as 1,8-naphthalic acid anhydride (**6**) by comparison of its melting point and ir, uv, and nmr spectra with those of an authentic sample, obtained either commercially[10] or by oxidation of acenaphthene.

The photolysis of **2** in an aprotic solvent was also studied. When irradiation was carried out in dilute tetrahydrofuran (THF) solution, the chloroacetamide **3** was consumed at a much slower rate, and the product isolated was mainly 1-(2-acetaminoethyl)naphthalene (**4**) besides some unreacted amide and polymeric materials. Such a dualism of photolytic behavior was also observed by Schaffner[11] and by Witkop[3] who proposed that in nonpolar solvents a radical mechanism initiated by the homolysis of a carbon–halogen bond would be favored; the free radical thus formed could then undergo hydrogen abstraction to yield the acetamide, **4**. In polar solvents, however, cyclization was likely to proceed through an ionic intermediate which, in the present case, was probably preceded by the $\pi-\pi^*$ excitation of naphthalene.[12]

Experimental Section

All melting points were determined on a Kofler hot-stage and are uncorrected; ir spectra were recorded with a Perkin-Elmer spectrophotometer, Model 421 (chloroform solutions or KBr pellets). Unless otherwise stated, nmr spectra were taken on a Varian A-60 spectrometer using TMS as internal standard.

1-(2-Chloroacetaminoethyl)naphthalene (2).—A solution of 2.08 g (0.01 mol) of 1 hydrochloride in 10 ml of water was made basic with 2 *N* sodium hydroxide. The separated soil was dissolved in 30 ml of benzene and dried (sodium sulfate). After filtration, the benzene extract was refluxed with 2.08 g of anhydrous potassium carbonate, while a solution of 1.7 g (0.015 mol) of chloroacetyl chloride in 30 ml of benzene was slowly added over 60 min. Heating and stirring were continued for an additional 2 hr. The mixture was cooled and filtered. The filtrate was washed and dried (sodium sulfate). Evaporation of the benzene *in vacuo* left a colorless oil which upon standing yielded 1.9 g (77%) of fine needles: mp 109–110° (benzene–hexane); ν_{max}^{KBr} 3250 (NH), 1645 (amide I), 1560 (amide II) cm^{-1}; nmr ($CDCl_3$) δ 3.15–3.85 (m, 4, AA'BB', $-CH_2CH_2-$), 4.0 (s, 2, $-COCH_2Cl$), 7.60–8.10 (m, 7, aromatic protons).

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.86; H, 5.69; N, 5.65. Found: C, 67.90; H, 5.89; N, 5.70.

Photolysis of 2. A. In Aqueous Methanol. 4,5-Dihydro-1H-naphth[1,8-*de*]azocin-2(3H)-one (3).—A solution of 1.24 g (5 mmol) of 1-(2-chloroacetaminoethyl)naphthalene in 300 ml of methanol and 300 ml of water was irradiated for 2 hr with a 200-W Hanovia, high-pressure mercury immersion lamp and a Vycor filter. Nitrogen was bubbled through the solution during the irradiation and the quartz well was kept water cooled. The mixture was evaporated to dryness *in vacuo* at 30°, and the residue was triturated in 5 ml of methanol. After keeping in the cold overnight, the colorless crystals were filtered, 500 mg (47%), mp 275–284°. Recrystallization from methanol–water gave shining platelets: mp 284–286°; ν_{max}^{KBr} 3170 (NH), 1670 (CONH) cm^{-1}. The mass spectrum showed *m/e* 211 (molecular peak), 182 (loss of $NHCH_2$), 169 (loss of CH_2CO).

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.55; H. 6.20; N, 6.63. Found: C, 79.74; H, 63.7; N, 6.40.

B. In THF. 1-(2-Acetaminoethyl)naphthalene (4).—A solution of 1.24 g of **2** in 600 ml of THF was irradiated with a 200-W high-pressure mercury lamp at room temperature for 2 hr. After evaporation of the solvent *in vacuo* at 30°, a yellowish oil remained which, upon column chromatography on silica gel (eluted with a 0–5% gradient mixture of ethyl acetate–chloroform), yielded one major product (345 mg, 32%) in addition to 265 mg of unchanged **2**. The former, mp 91°, showed *m/e* 213 (molecular peak), 198 (loss of CH_3), 170 (loss of CH_3CO), and 155 (loss of CH_3CONH); the nmr spectrum ($CDCl_3$) exhibited a sharp singlet at 1.98 ppm corresponding to the three protons of an acetyl group.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.82; H, 7.08. Found: C, 79.01; H, 6.38.

1-(2-Aminoethyl)-8-carboxymethylnaphthalene Hydrochloride (5).—Compound **3** (211 mg, 1 mmol) and 4 ml of 2 *N* hydrochloric acid were refluxed until a clear solution resulted. Excess acid was removed by vacuum distillation to leave a white crystalline mass weighing 218 mg (82%): mp 194–196° (recrystallization from ethanol–water raised this to 198°); ν_{max}^{KBr} 3050 (NH_3^+), 1710 (COOH) cm^{-1}; nmr (D_2O) 3.15–3.80 (m, 4, AA'BB', $-CH_2CH_2-$), 4.3 (s, 2, CH_2CO), 7.51 (m, 4, β-naphthalene protons), 7.80 (m, 2, α-naphthalene protons) ppm.

Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.25; H, 6.06; N, 5.27. Found: C, 63.41; H, 6.06; N, 5.15.

Thermal Ring Closure of 1-(2-Aminoethyl)-8-carboxymethylnaphthalene Hydrochloride to 4.—When the above hydrochloride, **5** (133 mg, 0.5 mmol), was heated in an oil bath at 220–240°, the crystals melted and subsequently solidified to a grayish mass. Recrystallization from 80% methanol yielded 95 mg (85%) of colorless crystals, mp 282–284°. The ir, uv, and nmr spectra of this compound are superimposable on those of **3** obtained by direct photolysis of **2** in methanol–water. A mixture melting point determination of the two samples showed no depression.

Oxidation of 5 with Potassium Ferricyanide to 1,8-Naphthalic Acid Anhydride (6).—The oxidation was carried out by the general directions of Huisgen and Rietz.[9] A solution of 200 mg (0.75 mmol) of **5**, 40 g of potassium ferricyanide, and 10 g of potassium hydroxide in 160 ml of water was stirred at 70–75° for 5 days. The orange-colored solution was cooled and acidified with concentrated sulfuric acid until acidic to congo red. Extraction of the product was carried out with ether in a continuous extractor for 48 hr. After evaporation of the solvent, a semisolid residue remained which, upon heating with 5 ml of ethanol and chilling, yielded 43 mg (29%) of slightly yellowish needles: mp 274°; mass spectrum *m/e* 198 (molecular peak), 154 (loss of $-C(O)O$), 126 (loss of $-OC(O)O-$); ν_{max}^{KBr} 1775, 1740 cm^{-1} (conjugated cyclic anhydride); λ_{max}^{MeOH} 296 mμ (ϵ 7600).

Anal. Calcd for $C_{12}H_6O_3$ C, 72.71; H, 3.05. Found: C, 72.71; H, 3.15.

This compound proved to be 1,8-naphthalic acid anhydride (**6**) (melting point and ir and uv spectra identical with those of an authentic sample obtained either commercially or by oxidation of acenaphthene). The free dicarboxylic acid, **7**, was prepared by refluxing the above anhydride with 20% potassium hydroxide

(7) L. Friedman, D. L. Fishel, and H. Schechter, *J. Org. Chem.*, **30**, 1453 (1965).

(8) K. B. Wiberg in "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 90.

(9) R. Huisgen and U. Rietz, *Tetrahedron*, **2**, 271 (1958).

(10) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

(11) S. Iwasaki and K. Schaffner, *Helv. Chim. Acta*, **51**, 557 (1968).

(12) E. Grovenstein, Jr., T. C. Campbell, and T. Shibata, *J. Org. Chem.*, **34**, 2418 (1969).

followed by acidification at 0°. At higher temperature, the acid is readily cyclodehydrated. Recrystallization from cold acetone–hexane yielded white needles: mp 273°; ν_{max}^{KBr} 2650 (bonded OH), 1690 (COOH) cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.64; H, 3.72. Found: C, 66.42; H, 3.86.

Oxidation of Acenaphthene. By Potassium Ferricyanide.—Acenaphthene (308 mg, 2 mmol) was oxidized with 30 g of potassium ferricyanide and 10 g of potassium hydroxide in 160 ml of water in the same manner as described previously. After 5 days, the unreacted acenaphthene was removed by filtration and the filtrate acidified. Extraction with ether followed by evaporation yielded 46 mg (23%) of 1,8-naphthalic acid anhydride, mp 274–276°, mass spectrum *m/e* 198. The low yield of the oxidation product was probably due to the insolubility of acenaphthene in water.

Registry No.—**2**, 25055-69-0; **3**, 25055-70-3; **4**, 25055-71-4; **5**, 25055-72-5; **6**, 81-84-5; **7**, 518-05-8.

Reaction of Indole Derivatives with Bromine. Substitution, Oxidation, and Dimerization

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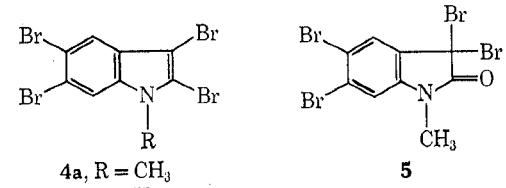
Bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**), in some solvents and with different mole ratios of bromine to indole, was investigated. Bromination of **1** in acetic acid, when 5:1 mol ratio of reactants was used, gave 2,3,5,6-tetrabromo-1-methylindole (**4a**) and, under somewhat different conditions, 2′,3,5,5′,6,6′-hexabromo-1,1′-dimethyl-2,3′-diindolyl (**6a**); in both cases 3,3,5,6-tetrabromo-1-methyloxindole (**5**) was also isolated. 5-Bromo-1-methylindole-3-carboxaldehyde (**12a**), compound **4a**, and 3,3,5-tribromo-1-methyloxindole (**10a**) were obtained by bromination of **2** (3:1 mol ratio) in acetic acid. Bromination of **3** in acetic anhydride gave mixture of 5- and 6-bromo derivatives (**14a** and **14b**) when a 2.5:1 mol ratio was used, whereas with a 4:1 mol ratio the 5,6-dibromo derivative (**14c**) was isolated in excellent yield. The structure of the compounds was proven on the basis of ir spectra and chemical evidence.

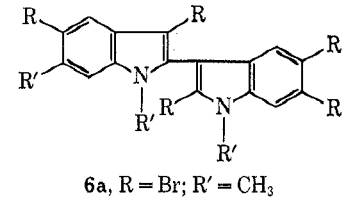
In the course of our work on the chemistry of indoles we have extensively investigated the nitration[1] and, more recently, the bromination[2] of indole derivatives. Although the action of brominating agents upon indoles in different media has been investigated to some extent,[3] comparatively little attention has been devoted to the reaction of indoles with bromine. In a previous paper on this subject we examined the reactions of indole-3-carboxaldehyde, 2-methylindole-3-carboxaldehyde, and ethyl indole-3-glyoxylate with bromine in acetic acid; it was seen that 5 and 6 positions are the normal sites of electrophilic substitution when electron-attracting substituents are present in the β position.[2] In order to extend our knowledge on this topic we have now investigated the bromination of 1-methylindole (**1**), 1-methylindole-3-carboxaldehyde (**2**), and ethyl 1-methylindole-3-glyoxylate (**3**) with bromine.

The bromination of **1**, when carried out in acetic acid with an equimolar amount of bromine, did not afford definite products; with a 5:1 mol ratio of reagent to substrate the course of the reaction was dependent on the temperature, and it was possible to isolate satisfactory amounts of solid compounds. When bromine was added to an ice-cold acetic solution of **1**, 1-methyl-2,3,5,6-tetrabromoindole (**4a**) (53% yield) and 1-methyl-3,3,5,6-tetrabromooxindole (**5**) (from the acetic mother liquor; 8.5% yield) were formed. When the reaction was carried out at room temperature, a product was isolated (42.8% yield) for which, on the basis of analytical data, molecular weight determination, and evidence outlined below, we suggest the dimeric structure **6a**; also in this case, **5** was produced (8.5% yield). The proposed structure **6a** was confirmed by its preparation, in 78% yield, through bromination of the dimer **6b**; the latter was prepared both by treating 1-methylindole (**1**) with dioxane–bromine complex in THF solution according to Kunori,[4] and by methylation of 2,3′-diindolyl (**6c**).[5] The latter synthesis of **6b**

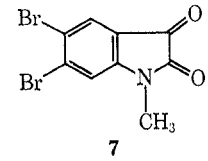


4a, R = CH_3
b, R = H

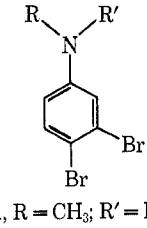
5



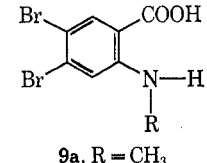
6a, R = Br; R′ = CH_3
b, R = H; R′ = CH_3
c, R = R′ = H



7



8a, R = CH_3; R′ = H
b, R = CH_3; R′ = tosyl
c, R = H; R′ = tosyl



9a, R = CH_3
b, R = H

(1) (a) G. Berti, A. Da Settimo, and O. Livi, *Tetrahedron*, **20**, 1397 (1964); (b) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 823 (1965); (c) A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 1923 (1965).

(2) A. Da Settimo, M. F. Saettone, E. Nannipieri, and P. L. Barili, *Gazz. Chim. Ital.*, **97**, 1304 (1967).

(3) See, *e.g.*, (a) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 5918 (1960); (b) R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).

(4) M. Kunori, *Nippon Kagaku Zasshi*, **83**, 836 (1962); *Chem. Abstr*, **59**, 1573c (1963).

(5) T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).