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The Bromination of Isatoic Anhydride

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Bromination of isatoic anhydride in acetic acid gives *N*-dibromoacetyl-3,5-dibromoanthranilic acid. Three new anthranils are described.

In connection with another problem we desired a series of anthranils substituted with halogen and nitro groups. Lesser and Weiss reported (1) that bromination of isatoic anhydride (I) in acetic acid gave a "tribromoanthranilic acid" (II), which with acetic anhydride was "dehydrated" to a "tribromoanthranil" (III). Such a dehydration is unlikely, for the reaction of anthranilic acids with acyl anhydrides gives 4-oxo-4*H*-3,1-benzoxazines (2) rather than anthranils.

We now show that II and III are *N*-dibromoacetyl-3,5-dibromoanthranilic acid and 2-dibromomethyl-6,8-dibromo-4-oxo-4*H*-3,1-benzoxazine, respectively. Elemental analyses and molecular weight determinations support the C_9 rather than the C_7 formulations. Spectral data (Table I) further support these assignments. The infrared spectrum of II shows N-H, O-H, and two C=O absorptions. Both the infrared and ultraviolet spectra are similar to those of 3,5-dibromo-*N*-acetylanthranilic acid (IV). The n.m.r. spectrum of II in dimethyl sulfoxide d_6 shows two aromatic protons situated *meta* to each other and one proton at 6.51 p.p.m. assigned to the single proton of the dibromoacetyl group. Possibly the carboxyl proton is lost by exchange with water in the solvent, and probably the amide NH proton resonance is so broad and weak as to be unobservable (3). The 6.51 p.p.m. assignment is in reasonable accord with the signals observed for the corresponding proton in α,α-dibromoacetanilide (5.96 p.p.m.), ethyl dibromoacetate (5.89 p.p.m.), and dibromoacetic acid (5.90 p.p.m.). The infrared spectrum of III has strong, sharp bands at 1795 and 1645 cm^{-1} attributable to the O=C-O-C=N grouping, is very similar to spectra of several authentic 4-oxo-4*H*-3,1-benzoxazines, and is very different from spectra of authentic anthranils (4) which have only moderate absorption near 1650 cm^{-1}. The ultraviolet spectrum

CHART I

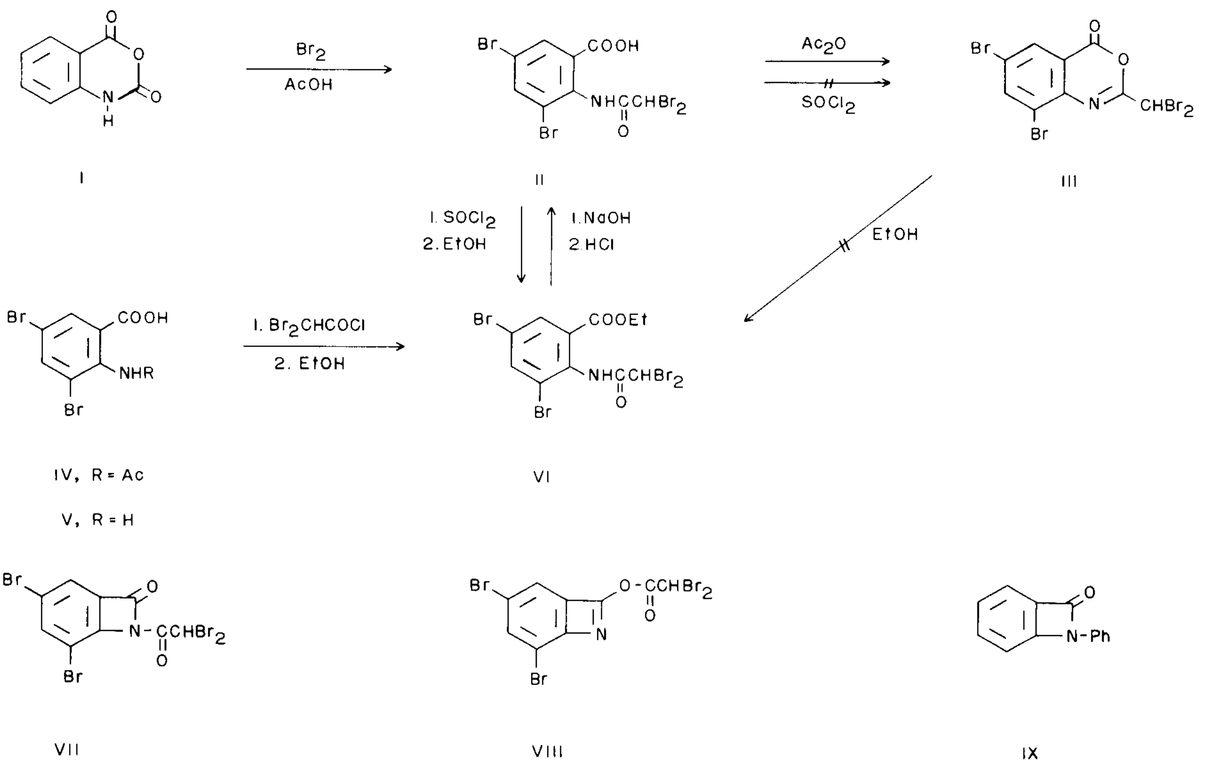

TABLE I

Spectral Properties of Some Anthranilic Acids, Benzoxazones, and Anthranils

Compound	λ max (EtOH), mμ, (ϵ) and ν max cm^{-1} (a, b)
II	219 (27,200); 251-263 (broad) (7,540-6,000); 298 (1,830). (KBr): 3450s; 3230m; 1710s; 1675s; 1530m; 1450m; 1305m; 880w.
IV	219 (28,200); 251sh (7,720); 302 (1,020). (KBr): 3450s; 3230m; 1710s; 1675s; 1525m; 1450m; 1305m; 880w.
III	244 (23,900); 266 (9,060); 281 (11,100); 293 (9,460); 324 (3,970); 335 (3,470). 1795s; 1645s; 1595m; 1560m; 1455s; 1440s; 1305m; 1280s; 1190m; 1045m; 990m; 890m; 815m.
6,8-Dibromo-2-methyl-4-oxo 4*H*-3,1-benzoxazine (21)	238 (25,400); 258 (7,250); 267 (7,810); 278 (6,220); 323 (2,910); 335 (2,500). 1760s; 1640s; 1580m; 1545w; 1445s; 1420m; 1300s; 1260s; 1190s; 1070s; 980s; 890s; 870m; 805m.
5,6,7,8-Tetrachloro-2-methyl-4-oxo-4*H*-3,1-benzoxazine (1)	244 (33,600); 264sh (6,240); 273sh (4,530); 283 (3,120); 332 (2,160); 345 (2,120). 1780s; 1660s; 1550s; 1405m; 1380s; 1270m; 1260s; 1075m; 1030w; 1000m; 895w; 815s.
5,6-Dichloroanthranil	263 (1,310); 276 (2,280); 285 (3,050); 298 (3,890); 316 (4,390). 1675m; 1650s; 1625m; 1545m; 1490m; 1465s; 1415m; 1330s; 1260m; 1125s; 1095s; 980s; 930m; 870s.
5,6,7-Trichloroanthranil	266 (1,300); 277 (2,070); 288 (2,870); 301 (3,700); 325 (5,400). 1675m; 1625m; 1605s; 1580m; 1520m; 1480s; 1460s; 1405m; 1320s; 1280m; 1255m; 1180m; 1135s; 1125s; 980m; 960m; 910m; 865s.
5-Chloro-6-nitroanthranil	257 (5,480); 286 (2,500); 301 (2,620); 325 (3,120). 1645w; 1550s; 1505m; 1460m; 1365m; 1330s; 1255m; 1120s; 1015s; 930m; 880m; 850m.
6-Nitroanthranil (18)	256 (17,600); 345 (2,410). 1645m; 1625w; 1555s; 1510s; 1460m; 1400m; 1380s; 1350s; 1300w; 1120s; 1070m; 950w; 930m; 895s; 845s; 830s.
4,6-Dinitroanthranil (c)	1650m; 1560s; 1545s; 1510s; 1470m; 1410m; 1400m; 1360s; 1340s; 1300m; 1250m; 1175w; 1120s; 1080w; 1020s; 925s; 905s; 840m; 830m.

(a) In chloroform unless otherwise stated. (b) Relative intensities: s = strong, m = medium, w = weak.
(c) UV spectrum given in Ref. (20).

of III is very similar to those of the benzoxazones and is very different from those of anthranils or anthranilic acids. The n.m.r. spectrum of III shows only two *meta* aromatic protons and one proton at 6.30 p.p.m. attributable to the $\mathrm{Br_2C}H\text{-C=N}$ group.

Synthesis confirmed the assigned structure II. Dibromoacetyl chloride with 3,5-dibromoanthranilic acid (V) in ethereal pyridine gave a product which upon recrystallization from ethanol gave the ethyl ester VI. Apparently some of the expected II was converted to its acid chloride. The ester VI upon mild hydrolysis gave II. Conversely, II upon treatment with thionyl chloride and then ethanol gave VI (Chart I).

The synthesis of VI from V does not proceed through III and its alcoholysis during recrystallization (5), for III was recovered unchanged from refluxing ethanol. Moreover, treatment of II with thionyl chloride gave a product whose infrared spectrum indicated that it was the corresponding acid chloride, rather than III.

The dehydration of II could possibly give, instead of III, structures VII and VIII. The β-lactam carbonyl of VII might absorb at frequencies as high as 1795 cm^{-1} (6) and the O=C-O-C=N grouping is present in VIII, so neither structure can be eliminated *a priori* on the basis of infrared spectra. However, no such stable ring systems seem to be known (7), they should be highly reactive chemically (8), and their ultraviolet spectra should be quite different from that of III. Burgess and Milne (9) have apparently observed the transient formation of 7-phenyl-7-azabicyclo[4.2.0]octa-1,3,5-triene-8-one (IX), which had infrared absorption at 1830 cm^{-1}

and readily reacted with methanol to give the corresponding anthranilate ester. We therefore prefer structure III on the basis of the similarity of its ultraviolet and infrared spectra with those of authentic benzoxazones and its unreactivity towards ethanol.

The introduction of a dibromoacetyl group during a bromination in acetic acid is very unusual. The exact mechanism, remains speculative. However, we have some experimental evidence that appears to eliminate as possible intermediates the following compounds: dibromoacetic acid; *N*-acetylanthranilic acid; III; IV; 6,8-dibromo-2-methyl-4-oxo-4*H*-3,1-benzoxazine; and poly(anthranoyl)anthranilic acid.

EXPERIMENTAL (10)

N-Dibromoacetyl-3,5-dibromoanthranilic Acid (II).

Isatoic anhydride was brominated as described (1) to give a 61.3% yield of crude II, m.p. 209-227° (dec.). Four recrystallizations from acetic acid gave white needles of m.p. 242-245° (dec.); lit. (1) 245-246° (dec.).

Anal. Calcd. for $C_9H_5Br_4NO_3$: C, 21.84; H, 1.02; Br, 64.60; N, 2.83; Mol. wt., 495. Found: C, 22.04; H, 1.07; Br, 65.39; N, 2.85; Mol. wt. 513.

2-Dibromomethyl-6,8-dibromo-4-oxo-4*H*-3,1-benzoxazine (III).

Compound II was refluxed in acetic anhydride to give III, m.p. 143-145°; lit. (1) 145-146°.

Anal. Calcd. for $C_9H_3Br_4NO_2$: C, 22.67; H, 0.63; Br, 67.05; N, 2.94; Mol. wt., 477. Found: C, 22.46; H, 0.69; Br, 67.19; N, 2.99; Mol. wt. 505.

Ethyl 3,5-Dibromo-*N*-dibromoacetylanthranilate (VI).

A solution of 1.18 g. (0.005 mole) of dibromoacetyl chloride (11) in 100 ml. of dry ether was added to a mixture of 1.48 g. (0.005 mole) of 3,5-dibromoanthranilic acid (V) (12), 1 ml. of pyridine, and 100 ml. of ether. The mixture was allowed to stand overnight, filtered and the filtrate was evaporated *in vacuo*. The residue was crystallized from ethanol to give 0.83 g. of tiny crystals, m.p. 158-160°.

The infrared spectrum (KBr) of VI shows strong absorptions at 1715, 1670, and 1280 cm^{-1}; the remainder of the spectrum is very similar to that of II.

Anal. Calcd. for $C_{11}H_9Br_4NO_3$: C, 25.27; H, 1.73; Br, 61.14; N, 2.68; Mol. wt. 523. Found: C, 25.39; H, 1.68; Br, 61.25; N, 2.72; Mol. wt. 536.

Dilution of the filtrate after the removal of VI gave 0.99 g. of material, m.p. 205-217°, identified as V by infrared spectral comparisons.

Comparison of VI with II.

The ester (VI) was treated with 10% sodium hydroxide in ethanol for 10 minutes at 60°. The mixture was cooled and acidified with dilute hydrochloric acid to precipitate a product which after washing with water and air-drying had m.p. 242-245° (dec.). This was identical with II by mixture melting point and infrared spectral comparisons.

The bromination product (II) was treated with thionyl chloride and then with ethanol to give a product of m.p. 158-160° which was identical with VI by mixture melting point and infrared spectral comparisons.

After having been refluxed 10 minutes in ethanol, III was recovered unchanged, as indicated by m.p., mixed m.p., and infrared spectrum.

A mixture of 1 g. of II and 10 ml. of thionyl chloride was refluxed for 1 hour, the excess reagent removed *in vacuo*, the residue taken up in benzene, the mixture filtered, and the filtrate concentrated and diluted with isooctane to give 0.7 g. of a tan powder, m.p. 180-185°. The infrared spectrum ($CHCl_3$) of this material shows no O-H absorption and strong absorption at 1795 cm^{-1} (COCl); the rest of the spectrum was very similar to that of II and quite different from that of III.

5,6-Dichloroanthranil.

2-Nitro-4,5-dichlorobenzaldehyde (13) was treated with granulated tin and acetic acid (14) to give a 55% yield of the anthranil, m.p. 132-133° (EtOH).

Anal. Calcd. for $C_7H_3Cl_2NO$: C, 44.72; H, 1.61; Cl, 37.72; N, 7.45. Found: C, 44.83; H, 1.63; Cl, 37.65; N, 7.26.

5,6,7-Trichloroanthranil.

A diazonium solution from 19.7 g. of 3,4,5-trichloroaniline (15) was allowed to react with formaldoxime (16) to give a 29% yield of 3,4,5-trichlorobenzaldehyde, m.p. 76-78°; lit. (17) m.p. 90-91°. Its phenylhydrazone had m.p. 146-147°; lit. (17) m.p. 147°. The cause of the melting point discrepancy is not known. The aldehyde was nitrated to give a 94% yield of 2-nitro-3,4,5-trichlorobenzaldehyde (m.p. 118-119°; lit. (17) m.p. 118.5-119°), which was reduced in 76% yield to 5,6,7-trichloroanthranil, m.p. 112-114° (EtOH).

Anal. Calcd. for $C_7H_2Cl_3NO$: C, 37.79; H, 0.91; Cl, 47.81; N, 6.30. Found: C, 37.82; H, 0.93; Cl, 47.88; N, 6.18.

5-Chloro-6-nitroanthranil.

The process for preparing 6-nitroanthranil (18) was applied to 2,4-dichloro-1,5-dinitrobenzene (19) to convert it, without purification of intermediates, in 62% overall yield into 5-chloro-6-nitroanthranil, m.p. 114-118° (EtOH).

Anal. Calcd. for $C_7H_3ClN_2O_3$: C, 42.34; H, 1.52; Cl, 17.86; N, 14.11. Found: C, 42.37; H, 1.80; Cl, 18.15; N, 14.54.

4,6-Dinitroanthranil.

Similarly, picryl chloride gave 60% overall yield of the anthranil, m.p. 122-123°; lit. (20) 122-124°.

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(4) Among the compounds we prepared the following are new: 5,6-dichloroanthranil; 5,6,7-trichloroanthranil; and 5-chloro-6-nitroanthranil.

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