# Benzoxazone Formation in the Reaction of Anthranilic Acid with Isocyanates

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The reactions of anthranilic acid with ethyl and phenyl isocyanates have been shown to yield, among other products, the previously unobserved 2-ethylamino-3,1,4-benzoxazone and 2-anilino-3,1,4-benzoxazone, respectively. The product distribution and relative yields have been shown to be dependent on the molar ratio of reactants. The mechanism of these reactions is discussed. The product of the reaction of 2-ethylamino-3,1,4-benzoxazone with ethyl isocyanate has been shown to be 2-(ethylcarbamyl)ethylamino-3,1,4-benzoxazone.

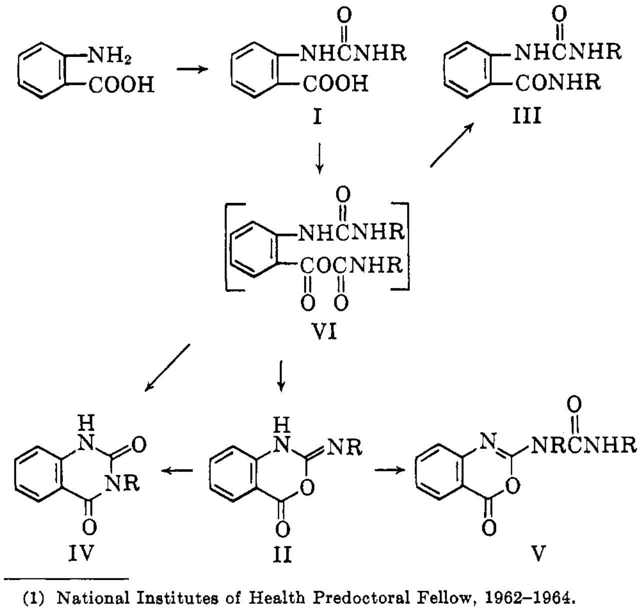
In connection with a study of the reactions of benzyne with isocyanates[2] in which diazoanthranilic acid was generated *in situ*, followed by thermal decomposition in the presence of ethyl isocyanate, a condensation product of anthranilic acid (present in the reaction mixture owing to incomplete diazotization) and ethyl isocyanate were isolated. When a search of the literature failed to disclose this compound, an investigation of the reaction was undertaken.

Treatment of anthranilic acid with excess ethyl isocyanate (phenyl isocyanate reacted similarly) yielded several products, among which was the originally isolated unknown material. This material was distinctly different from the only previously described condensation product of anthranilic acid and ethyl isocyanate, 3-ethyl-2,4-quinazolinedione[3] (IV, R = Et). The unknown compound was identified as 2-ethylamino-3,1,4-benzoxazone[4] (II, R = Et) by comparison of its infrared absorption spectrum with those of known 2-alkyl-3,1,4-benzoxazones, which exhibit characteristic absorption bands[5] in the region of 1775–1660 cm.$^{-1}$. For example, the spectrum of 2-methyl-3,1,4-benzoxazone shows bands at 1760, 1640, and 1605 cm.$^{-1}$, while 2-ethylamino-3,1,4-benzoxazone (II, R = Et) exhibits corresponding absorption bands at 1760, 1645, and 1605 cm.$^{-1}$. The infrared spectrum of 2-anilino-3,1,4-benzoxazone[6] (II, R = Ph) is similar.

Although the literature contains intermittent reports,[7–16] some dating back more than 75 years, of investigations of the reactions of anthranilic acid and its derivatives with various isocyanates and isothiocyanates, the formation of benzoxazone or benzthiazone[16] products has not previously been noted.

It has been reported[9] that the reaction of anthranilic acid with phenyl isocyanate in a 1:1 molar ratio produced exclusively N-(phenylcarbamyl)anthranilic acid (I, R = Ph). Gumpert,[8] however, treated 2 moles of phenyl isocyanate with 1 mole of anthranilic acid and obtained, in unspecified yield, N-(phenylcarbamyl)anthranilanilide (III, R = Ph) although this structure was not assigned.[17] In our hands, when three or more molecular portions of phenyl isocyanate were used, 2-anilino-3,1,4-benzoxazone[7] (II, R = Ph) was isolated. The reaction of anthranilic acid with ethyl isocyanate gave similar results. A total of five products (I–V, R = Et) were obtained with product distribution and relative

CHART I



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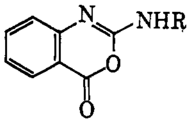
(1) National Institutes of Health Predoctoral Fellow, 1962–1964.

(2) J. C. Sheehan and G. D. Daves, Jr., in press.

(3) R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **18**, 1427 (1953).

(4) The exocyclic double bond is indicated because this tautomer is that arrived at by mechanistic considerations (see Chart I). The compounds may actually exist as the other tautomer (IIa). See, however, the argument of Doleshall and Lempert.[7]



IIa

(5) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 6698 (1955).

(6) During the course of this investigation the preparation of this compound by other methods has been reported.[7]

(7) (a) G. Doleshall and K. Lempert, *Tetrahedron Letters*, 1195 (1963); (b) H. Herlinger, *Angew. Chem.*, **76**, 437 (1964).

(8) F. Gumpert, *J. prakt. Chem.*, **32**, 287 (1885).

(9) C. Paal, *Ber.*, **27**, 974 (1894).

(10) G. Fortmann, *J. prakt. Chem.*, **55**, 123 (1897).

(11) H. N. McCoy, *Am. Chem. J.*, **21**, 111 (1899).

(12) G. Rossi, *Gazz. chim. ital.*, **57**, 625 (1927).

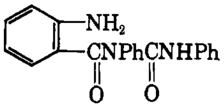
(13) T. N. Ghosh, *J. Indian Chem. Soc.*, **7**, 981 (1930).

(14) D. T. Elmore and J. R. Ogle, *Proc. Chem. Soc.*, 289 (1957).

(15) J. E. McCarty, E. L. Haines, and C. A. Vander Werf, *J. Am. Chem. Soc.*, **82**, 964 (1960).

(16) A benzthiazone structure has been assigned to the product obtained from the reaction of anthranilic acid with phenyl isothiocyanate [C. V. Gheorghiu, C. H. Budeanu, E. Budeanu and A. Toma, *Acad. R. P. R. Filiala Iasi, Studii Cercetari Stiint, Chim.*, **8**, 297 (1957)]; however, the authors presented no evidence to support this assignment and a comparison of their data with those reported by other investigators (for example, Doleshall and Lempert[7a]) indicates that the isomeric 3-phenyl-2-thio-4-quinazolone is the correct one.

(17) Gumpert[8] tentatively assigned structure IIIa to the compound he obtained. Consideration of the evidence (see Chart I) that initial reaction of isocyanate takes place at the amino group of anthranilic acid makes formation of this product, under the conditions of the reaction, appear highly unlikely. Compound III (R = Ph) has more recently been prepared by A. Darapsky and B. Gaudian [*J. prakt. Chem.*, **147**, 43 (1936)].



IIIa

TABLE I

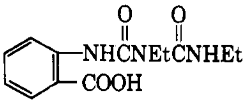
REACTION OF ANTHRANILIC ACID WITH ETHYL AND PHENYL ISOCYANATES

| Isocyanate | Mole ratio of isocyanate/ anthranilic acid | Product, % yield I | II | III | IV | V |
|---|---|---|---|---|---|---|
| Ethyl | 1 | 65 | | 15 | | |
| | 2 | 66 | *a* | *a* | | |
| | 3 | 26 | 30 | 5.7 | 2.2 | |
| | >3 | | | | | 80 |
| Phenyl | 1 | (100)[b] | | | | |
| | 2 | | | *c* | | |
| | 3 | 97 | 2.1 | | | |
| | >3 | 70 | 19 | | | |

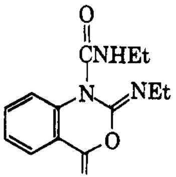
[a] Not isolated; shown to be present by thin layer chromatography. [b] See ref. 9. [c] See ref. 8; yield not reported.

yields dependent on the molar ratio of isocyanate used. Results obtained in this study are reported in Table I.

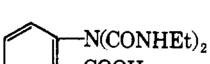
The cyclization of I (R = Et) in the presence of excess isocyanate to yield II (R = Et) and the further reaction of this material with ethyl isocyanate to produce V (R = Et) indicates the intermediacy of I and II in the formation of V. Since the mechanism for the reaction of a carboxylic acid and an isocyanate to produce an amide (*i.e.*, product III) *via* intermediate carbamoyl anhydride formation and subsequent elimination of carbon dioxide is well known,[18] a simple mechanism involving such an intermediate (VI) can be written for the formation of products II–V. The failure of ethyl anthranilate and ethyl isocyanate, under the conditions of these experiments, to produce II (R = Et) is evidence that a highly active leaving group is required for benzoxazone formation. It is not clear that 3-ethyl-2,4-quinazolinedione, (IV, R = Et) arose directly from VI; it is possible that IV (R = Et) was formed by rearrangement of II (R = Et) during work-up. In the presence of dilute acid the benzoxazones (II, R = Et and Ph) were readily converted to the more stable isomeric quinazolinediones (IV, R = Et and Ph). The production of VII upon treatment of V (R = Et) with acid is convincing evidence that structure V is correctly assigned since a compound of the alternate possible structure (VIII), under these conditions, would be expected to undergo rearrangement to a three-substituted 2,4-quinazolinedione analogous to that exhibited by II (R = Et and Ph). The other possible product (IX) which might be expected to result from acidic treatment of VIII is ruled out since the nuclear magnetic resonance spectrum of VII (see Experimental) clearly shows two nonequivalent ethyl substituents.



VII



VIII



IX

## Experimental[19]

**Reaction of Anthranilic Acid with Ethyl and Phenyl Isocyanates. General Procedure.**—In all cases a mixture of 1.37 g. (0.001 mole) of anthranilic acid and the appropriate molar quantity of either ethyl or phenyl isocyanate in 30 ml. of benzene was heated under reflux for 2 hr. The solvent was then evaporated under reduced pressure and the residue was triturated twice with 30-ml. portions of methylene chloride. The methylene chloride insoluble material[20] which was collected by filtration consisted of N-(ethylcarbamyl)anthranilic acid[8] (I, R = Et) or N-(phenylcarbamyl)anthranilic acid[21] (I, R = Ph) depending on the isocyanate used. Identity was confirmed by comparison with authentic material; the yields obtained are recorded in Table I. Following are the procedures for the isolation of products from the methylene chloride filtrates.

**Reaction of Anthranilic Acid with 1 Mole of Ethyl Isocyanate.**—The methylene chloride filtrate (see above) was concentrated to ∼10 ml. and petroleum ether was added to the cloud point. After 2 days 0.091 g. (15%) of N-(ethylcarbamyl)anthranilic acid, N-ethylamide (III, R = Et), m.p. 150–151°, was obtained. An infrared spectrum exhibited carbonyl maxima at 1650 and 1690 cm.$^{-1}$.

*Anal.* Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.3; H. 7.24; N, 17.9. Found: C, 61.6; H, 7.39; N, 18.2.

When 2 *M* portions of ethyl isocyanate were used, the results were substantially the same (see Table I).

**Reaction of Anthranilic Acid with 3 Moles of Ethyl Isocyanate.**—The methylene chloride solvent (see above) was removed and 15 ml. of ether and 5 ml. of petroleum ether were added to the residue. Following trituration, the solid material was removed by filtration to yield 0.571 g. (30%) of 2-ethylamino-3,1,4-benzoxazone (II, R = Et), m.p. 169–172°. A portion recrystallized from a mixture of methylene chloride and petroleum ether melted at 174–175°. An infrared spectrum exhibited intense bands at 1610, 1640, and 1760 cm.$^{-1}$.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.27; N, 14.7; mol. wt., 190. Found: C, 63.1; H, 4.97; N, 14.8; mol. wt., 190.

The remainder of the reaction mixture was chromatographed on 30 g. of neutral alumina. Two major bands were eluted. From the first (least polar) was obtained 0.133 g. (5.7%) of III (R = Et), m.p. 150–151°. From the more polar band was obtained 0.042 g. (2.2%) of 3-ethyl-2,4-quinazolinedione (IV, R = Et), m.p. 194–196° (lit.[3] m.p. 198°).

**Reaction of Anthranilic Acid with Excess (6 Moles) Ethyl Isocyanate.**—The solvent (see above) was removed, the residue was dissolved in petroleum ether (∼500 ml.), and a small amount of insoluble residue was removed. The solvent was again evaporated to yield 2.1 g. (80%) of 2-(ethylcarbamyl)ethylamino-3,1,4-benzoxazone (V, R = Et) as colorless crystals, m.p. 89–91°. A portion recrystallized from cyclohexane melted at 93–94°. Strong infrared maxima appeared at 1610, 1695, and 1760 cm.$^{-1}$.

*Anal.* Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.8; H, 5.75; N, 16.1. Found: C, 59.9; H, 5.32; N, 16.2.

**Reaction of Anthranilic Acid with 3 Moles of Phenyl Isocyanate.**—The solvent (see above) was removed and the residue was recrystallized from a mixture of chloroform and petroleum ether to give 0.052 g. (2.1%) of 2-anilino-3,1,4-benzoxazone (II, R = Ph) as needles, m.p. 190–192° (lit.[7] m.p. 192–193°). An infrared spectrum exhibited intense maxima at 1605, 1640, and 1760 cm.$^{-1}$.

*Anal.* Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.6; H, 4.20; N, 11.8. Found: C, 70.4; H, 4.13; N, 11.8.

**Reaction of Anthranilic Acid with Excess (6 Moles) Phenyl Isocyanate.**—The methylene chloride solution (see above) was

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[18] See A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953), and references cited therein.

[19] All melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237 recording spectrophotometer as 3–5% methylene chloride solutions unless otherwise specified. N.m.r. spectra were run on a Varian Associates A-60 spectrophotometer in deuteriochloroform using tetramethylsilane as an internal standard. Molecular weights were determined with a Mechrolab vapor pressure osmometer, Model 301A, using benzene solutions. We are indebted to Dr. S. M. Nagy and his associates for the microanalytical data.

[20] When a large excess (6 *M* portions) of ethyl isocyanate was used no methylene chloride insoluble product was obtained.

[21] C. D. Hurd, C. M. Buess, and L. Bauer, *J. Org. Chem.*, **19**, 1140 (1954).

evaporated and the resulting residue was recrystallized from hexane, to yield 0.331 g. (19%) of II (R = Ph), m.p. 190–192°.

**Reaction of 2-Ethylamino-3,1,4-benzoxazone (II, R = Et) with Ethyl Isocyanate.**—A solution of 0.050 g. of 2-ethylamino-3,1,4-benzoxazone and 2 ml. of ethyl isocyanate in 25 ml. of benzene was heated under reflux for 2 hr. The solvent was removed and the residue was recrystallized from hexane to yield 0.062 g. (95%) of V (R = Et), m.p. 93–94°.

**Reaction of N-(Ethylcarbamyl)anthranilic Acid (I, R = Et) with Ethyl Isocyanate.**—A mixture of 1 g. of N-(ethylcarbamyl)-anthranilic acid[3] and 5 ml. of ethyl isocyanate in 25 ml. of benzene was heated under reflux for 2 hr. The mixture was cooled and unreacted starting material, 0.47 g., m.p. 187–189°, was collected by filtration. The filtrate was evaporated and the residue was recrystallized from hexane to yield 0.190 g. (39% based on consumed starting material) of II (R = Et), m.p. 172–174°.

**Reaction of Ethyl Anthranilate with Ethyl Isocyanate.**—A mixture of 1.65 g. of ethyl anthranilate and 0.71 g. of ethyl isocyanate in 25 ml. of benzene was heated under reflux for 3 hr. An infrared spectrum of the reaction mixture showed no band near 1760 cm.$^{-1}$ attributable to benzoxazone carbonyl. The solvent was evaporated and the residue was dissolved in a minimum volume of ether. Petroleum ether was added to the cloud point and the product which crystallized was collected to yield 1.23 g. (53%) of ethyl N-(ethylcarbamyl)anthranilate as long needles, m.p. 98–99°.

*Anal.* Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.0; H, 6.78; N, 11.9. Found: C, 61.4; H, 6.82; N, 12.0.

**Reaction of 2-(Ethylcarbamyl)ethylamino-3,1,4-benzoxazone (V, R = Et) with Acid.**—A mixture of 0.20 g. of 2-(ethylcarbamyl)ethylamino-3,1,4-benzoxazone and 30 ml. of 10% sulfuric acid containing a few drops of ethanol was heated until solution was complete. The solution was filtered and allowed to cool. The product which crystallized was collected and recrystallized from a mixture of ethanol and hexane to yield 0.084 g. of 1-(*o*-carboxyphenyl)-3,5-bisethylbiuret (VII), m.p. 165–166°. The n.m.r. spectrum showed two nonequivalent ethyl substituents appearing as a triplet (3H) centered at $\delta$ 1.21, a triplet (3H) centered at 1.39, a multiplet (2H) at 3.38, and a quartet (2H) centered at 4.07.

*Anal.* Calcd. for $C_{13}H_{17}N_3O_4$: C, 56.0; H, 6.10; N, 15.0. Found: C, 56.0; H, 6.53; N, 14.9.

In similar experiments II (R = Et) and II (R = Ph) were treated with acid to produce 72% of IV[3] (R = Et) and 48% of IV[21] (R = Ph), respectively.

# Oxidation Products of Vitamin E and Its Model, 6-Hydroxy-2,2,5,7,8-pentamethylchroman.

## VII. Trimer Formed by Alkaline Ferricyanide Oxidation[1]

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Additional evidence is presented for the structure of the trimers (II) produced by the oxidation of $\alpha$-tocopherol or 6-hydroxy-2,2,5,7,8-pentamethylchroman with alkaline ferricyanide. A structure analogous to that of trimers produced from other *o*-quinone methides is proposed. An improved procedure for the isolation of the trimer derived from 6-hydroxy-2,2,5,7,8-pentamethylchroman was developed.

The oxidation of $\alpha$-tocopherol with alkaline ferricyanide has been studied by a number of workers.[2–9] In addition, some of these workers[5–8] studied the oxidation of the model chroman, 6-hydroxy-2,2,5,7,8-pentamethylchroman. A dimer (I), whose structure was proposed by Nelan and Robeson,[5] proven by Schudel, *et al.*,[6] and further studied by Skinner and Alaupovic[7,8] and McHale and Green,[9] was produced in this reaction. A trimer,[7,8] designated as compound A, also was produced and structure II was proposed for it.[8] We now wish to report additional evidence confirming this proposed structure for the trimer (II).

Evidence of structure II for the trimer, compound A, is as follows: elementary analysis indicated the same empirical formula as the dimer (I); a molecular weight determination indicated it to be a trimer; the infrared absorption spectrum showed the presence of an $\alpha,\beta$-unsaturated ketone function and the absence of hydroxyl groups; the trimer could be prepared by heating monomer ($\alpha$-tocopherol or the model chroman) with the corresponding dimer (I); and the ultraviolet absorption spectrum of the trimer compared with spectra of the dimer (I) and monomer indicated the presence of an $\alpha,\beta$-unsaturated ketone function as in the dimer plus the addition of the aromatic absorption of the monomer. The spectrum of the trimer in isooctane, minus twice the absorption of the monomer, showed the typical absorption of an $\alpha,\beta$-unsaturated ketone [235 m$\mu$ ($\epsilon$ 14,800) and 310 m$\mu$ ($\epsilon$ 800)]. When absolute ethanol was used as solvent, the 235-m$\mu$ band showed a bathochromic shift of 3 and the 310-m$\mu$ band showed a hypsochromic shift of 5.

It would appear from this data that a quinone methide (III) was formed from the monomer ($\alpha$-tocopherol or model chroman) upon oxidation by either the alkaline ferricyanide or the dimer. The quinone methide then added to the dimer present to form the trimer (II). Two modes of addition of the quinone methide to the dimer are possible wherein an $\alpha,\beta$-unsaturated ketone is left in the adduct. One of these structures (IV) would be acid labile owing to the presence of a ketal grouping and the other (II) would be acid resistant. The trimer reported here proved to be stable toward acid.

Reductive acetylation of trimer II from the model chroman using zinc, acetic anhydride, and sodium acetate under reflux for 3 hr. afforded interesting results. The product isolated from this reaction was shown to be the acetate (V) of the dihydroxy dimer. Its melting point was 217–218.5° and a mixture melting point with a sample of V prepared from the dimer (I) by the

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[1] For the preceding paper of this series, see W. A. Skinner, *Biochem. Biophys. Res. Commun.*, **15**, 469 (1964).

[2] C. Martius and H. Eilingsfeld, *Ann.*, **607**, 159 (1957).

[3] H. H. Draper, A. S. Csallany, and S. N. Shah, *Biochim. Biophys. Acta*, **59**, 527 (1962).

[4] D. R. Nelan and C. D. Robeson, *Nature*, **193**, 477 (1962).

[5] D. R. Nelan and C. D. Robeson, *J. Am. Chem. Soc.*, **84**, 2963 (1962).

[6] P. Schudel, H. Mayer, R. Rüegg, and O. Isler, *Chimia* (Aarau), **16**, 368 (1962); P. Schudel, H. Mayer, I. Metzger, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **46**, 636 (1963).

[7] W. A. Skinner and P. Alaupovic, *Science*, **140**, 803 (1963).

[8] W. A. Skinner and P. Alaupovic, *J. Org. Chem.*, **28**, 2854 (1963).

[9] D. McHale and J. Green, *Chem. Ind.* (London), **29**, 366 (1964).