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Alkylation and acylation of basic salts of anthranilic acid

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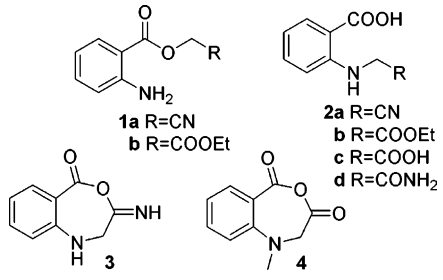
Abstract—The O-nucleophilicity of basic anthranilic acid salts was documented, analyzed, and utilized in synthesis. Specifically substitutions leading to esters instead of secondary amines, and formation of anthranilic acid anhydrides were studied.

Anthranilic acid (2-aminobenzoic acid) is the biochemical precursor of the amino acids tryptophan, phenylalanine, and tyrosine[1] and is present as part of the core structure of certain alkaloids[2] and synthetic drugs such as the sedative methaqualone[3] and the NSAIDs fenamate, and glafenine.[4] It is therefore of importance to report on all aspects of the chemical behavior of anthranilic acid. In the course of other projects we have discovered a strong inherent tendency for basic salts of anthranilic acid to give O-alkylation or O-acylation in reactions with electrophiles. In the literature anthranilic acids are normally assumed to react nucleophilically at the amino group. As a response to recent publications we report our findings in this field. Anthranilic acid is in broad terms a β-amino acid and derivatives similar to those reported here may be useful as peptides or peptidomimetics, or as precursor building blocks for pharmaceutics.



When anthranilic acid was stirred with chloroacetonitrile in DMF with one equivalent $NaHCO_3$, the O-alkylated compound **1a** was formed and could be isolated in a high yield. The same components in aqueous (basic) solution gave a moderate yield of the N-alkylated compound **2a**.[5] Very recently it was claimed that the seven-membered cyclic compound **3** is the product of reaction between anthranilic acid and chloroacetonitrile in DMF using *N*,*N*-diisopropylethylamine as base.[6] The authors' analysis of the HMBC spectral data for this compound is clearly erroneous (see Table 1 for a correct assignment). The product is in fact spectroscopically identical to **1a**. The authors were misled by the fact that the IR-spectrum of this compound does not show a significant cyano absorption, actually a common situation in aliphatic cyano compounds.[7] It is also highly unlikely that a compound of the structure **3** would survive aqueous work up when the related anhydride **4**[8] does not.

A recent study aimed at new anti-inflammatory agents from anthranilic acid was based on the assumption that reaction of anthranilic acid with ethyl chloroacetate under anhydrous conditions will yield the ester **2b**.[9] Comparison of the physical data for this product with those of the already described compound **2b**,[10] make it clear that the reaction in question actually gives the O-alkylation product **1b**.† The mono ester **2b** is readily prepared by Fischer esterification of the

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† **1b** can be prepared like **1a** (Table 1) substituting chloroacetonitrile for ethyl chloroacetate.

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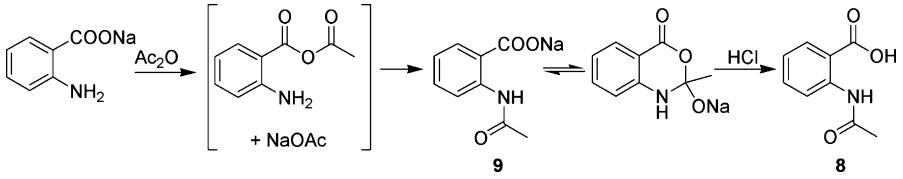


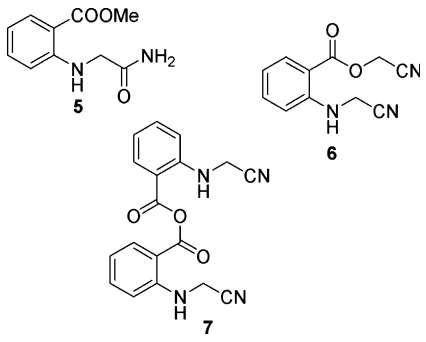
Scheme 1. Acetylation of sodium anthranilate.

well-known diacid **2c**, or by reaction of anthranilic acid with ethyl chloroacetate in basic aqueous solution (vide infra).[11] A similar confusion about phenacyl anthranilate has been resolved.[12]

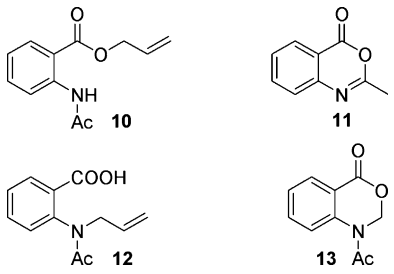
Many simple functionalized N-alkylated derivatives of anthranilic acids are known, such as the compounds **2a**,[5] **2b**,[11] **2c**,[13] and **2d**[14] as well as *N*-methyl-[15,16] and *N*-ethyl-**2c**.[16] All of these derivatives of anthranilic acid have been prepared in basic aqueous solution with the corresponding alkylating agent. There are also several reports of further alkylation of N-monosubstituted anthranilic acids giving mixtures of N- and O-alkylated products in basic aqueous solution.[17–19] Based on the observations above a hypothesis can be formulated: *Basic salts of anthranilic acid, and its N-substituted derivatives, undergo O-alkylation when reacting with alkylating agents. Given an excess of alkylating agent and base, the ester can subsequently be N-alkylated. Under aqueous conditions the ester can/will be hydrolyzed, leaving the carboxylate salt of the N-alkylated product in solution.*

The mono ethyl ester **2b** could thus be prepared in a moderate yield by reaction of sodium anthranilate with 2.3 equivalents of ethyl chloroacetate in the presence of one equivalent of Na_2CO_3 (i.e., effectively three equivalents of base in solution). When the reaction was completed the mixture was neutral (all base consumed). The ester could also be prepared by esterification (97% yield from **2c**).

This behavior of anthranilates can be utilized also in other ways. N-Alkylated derivatives can easily be transformed into the corresponding esters as exemplified by the O-methylation of **2d** to form **5**.[‡] The dialkylation product **6** was obtained in a low yield from reaction of sodium anthranilate with a large excess of chloroacetonitrile in aqueous Na_2CO_3. This compound could also be prepared in high yield from isatoic anhydride and chloroacetonitrile in hot DMF using K_2CO_3 as base (1 equiv NaH in DMF gives *N*-cyanomethyl isatoic anhydride)[20] and could in turn be hydrolyzed to give **2a**.



Reactions of basic salts of anthranilic acids with acylating agents are more complex, but it is fair to assume that also in these cases the carboxylic oxygen atom is the most nucleophilic and that it reacts first. This can be illustrated by the facile formation of the anhydride **7**. *N*-Acetyl anthranilic acid **8** can be prepared by dissolution of anthranilic acid in a slight excess NaOH in water, followed by addition of acetic anhydride.[21] The sodium salt **9** precipitates after only a few minutes. In order to obtain the free acid, concentrated hydrochloric acid must be added (a fact neglected by the original author). A direct N-acetylation cannot be ruled out, but in light of the documented O-nucleophilicity, intermediate anhydride formation, followed by transfer of the acetyl group to the nitrogen atom seems more likely. The insolubility of the sodium salt **9** is hard to explain, but a cyclic benzoxazinone salt form (as indicated in Scheme 1) of the product may contribute to this effect.



There are two published studies on the kinetics of O-alkylation of *ortho*-substituted benzoic acids, both of which include studies on **9**.[22,23] The known allyl ester

[‡] Treatment of **2d** with NaH (1 equiv) in DMF, followed by addition of MeI, afforded **5** in good yield after pouring the mixture into water.

Table 1. Preparation and analysis

Compound	Syntheses and yields	Mp (°C)	NMR ^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz
1a	Anthranilic acid (2.74 g, 20.0 mmol) was stirred at 120 °C in DMF (15 mL) with chloroacetonitrile (1.5 mL, 24 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) for 90 min. The mixture was poured into ice-water (150 mL) and stirred until a solid formed. The product was filtered off and allowed dry to yield an off-white solid (3.22 g, 91%).	63 (64)[31]	δ_H (acetone-d_6): 5.13 (s, 2H), 6.48 (2H, br s), 6.61 (1H, dt, *J* 0.7, 8.2), 6.85 (1H, dd, *J* 0.7, 8.4), 7.32 (1H, dt, *J* 1.5, 8.4), 7.79 (1H, dt, *J* 1.5, 8.2); δ_C (acetone-d_6): 48.4 (**C**H_2–CN), 107.5 (Ar**C**–COO), 115.3 (CH), 115.5 (**C**N), 116.7 (CH), 130.8 (CH), 135.0 (CH), 152.2 (Ar**C**–NH_2), 166.3 (Ar**C**OO). Assigment was based on DEPT/HMBC.
2a	*Method 1*: Compound **13** (11.5 g, 60 mmol) was stirred in DMSO (40 mL) at 80 °C with NaCN (3.0 g, 61 mmol) for 18 h. The mixture was poured into ice-water (250 mL) and acidified with concd HCl (10 mL). The solid, which slowly formed was filtered off and dried (8.01 g, 76%). *Method 2*: Compound **6** (1.08 g, 5.00 mmol) was partially dissolved in acetone (10 mL). NaOH (0.40 g, 10 mmol) dissolved in water (10 mL) was added and the mixture stirred for 15 h. The acetone was evaporated and the remaining solution was diluted with water, filtered, and acidified (HCl), upon which the product precipitated and could be filtered off (0.82 g, 93%).	185 (184)[32]	δ_H (DMSO-d_6): 4.48 (2H, d, *J* 6.4), 6.75 (1H, t, *J* 7.9), 6.89 (1H, d, *J* 8.3), 7.49 (1H, dt, *J* 1.5, 8.3), 7.86 (1H, dd, *J* 1.5, 7.9), 8.04 (1H, t, *J* 6.4), 12.89 (1H, br s); δ_C (DMSO-d_6): 30.9 (CH_2), 111.7 (CH), 112.0 (C), 116.5 (CH), 118.2 (C), 131.8 (CH), 134.5 (CH), 148.7 (C), 169.5 (C).
2b	*Method 1*: Anthranilic acid (2.74 g, 20.0 mmol) was dissolved in water (20 mL) containing NaOH (0.80 g, 20 mmol). A solution of $Na_2CO_3{\cdot}10\ H_2O$ (5.72 g, 20.0 mmol in 20 mL water) was added followed by ethyl chloroacetate (5.0 mL, 40.6 mmol). The mixture was heated under reflux for 15 h. On cooling, a crop of **2b** (2.05 g, 46%) precipitated from the neutral solution. *Method 2*: The diacid **2c** (19.5 g, 0.100 mol) was heated to reflux in abs EtOH (100 mL) with concd H_2SO_4 (1.5 mL) for 3 h. On cooling, the product **2b** precipitated and could be collected (21.6 g, 97%).	152 (152)[11]	δ_H (DMSO-d_6): 1.21 (3H, t, *J* 7.2), 4.14 (2H, q, *J* 7.2), 6.58–6.63 (2H, m), 7.35 (1H, dt, *J* 1.5, 7.9), 7.80 (1H, dd, *J* 1.1, 7.9), 8.17 (1H, br s), 12.72 (1H, br s); δ_C (DMSO-d_6) 14.1 (CH_3), 60.6 (CH_2), 110.7 (C), 111.5 (CH), 115.0 (CH), 131.7 (CH), 134.4 (CH), 150.0 (C), 169.8 (C), 170.5 (C).
6	Isatoic anhydride (16.3 g, 0.100 mol) was dissolved in DMF (120 mL). Chloroacetonitrile (14 mL, 0.22 mol) and K_2CO_3 (13.8 g, 0.100 mol) were added and the mixture was stirred at 100 °C for 90 min under evolution of gas (CO_2). After letting the mixture cool to rt, it was poured into water. The solid product, which soon formed, was collected (20.2 g, 94%).	105–106[a]	δ_H (DMSO-d_6): 4.50 (2H, d, *J* 6.4), 5.17 (2H, s), 6.81 (1H, t, *J* 8.3), 6.97 (1H, d, *J* 8.0), 7.59 (1H, dt, *J* 1.5, 8.0), 7.77 (1H, t, *J* 6.4), 7.87 (1H, dd, *J* 1.5, 8.3); δ_C (DMSO-d_6): 31.0 (CH_2), 49.4 (CH_2), 109.3 (C), 112.3 (CH), 116.2 (C), 116.9 (CH), 118.1 (C), 131.5 (CH), 135.9 (CH), 148.8 (C), 165.9 (C).
7	Compound **1a** (1.76 g, 10.0 mmol) was dissolved in dioxane (5 mL) with 2,6-lutidine (2.0 mL), and cooled to 0 °C. $SOCl_2$ (0.50 mL, 6.9 mmol) was added dropwise and the mixture stirred for 1 h at 0–25 °C. The mixture was poured into ice-water (100 mL), and the solid grayish product was filtered off (1.52 g, 91%).	202–204 (dec)[b]	δ_H (DMSO-d_6): 4.55 (2H, d, *J* 6.5), 6.85 (1H, t, *J* 7.8), 7.03 (1H, d, *J* 8.0), 7.67 (1H, dt, *J* 1.3, 8.0), 7.91 (1H, t, *J* 6.5), 7.98 (1H, dd, *J* 1.3, 7.8); δ_C (DMSO-d_6): 31.0, 109.4, 112.3, 117.0, 117.9, 132.5, 149.8, 163.8.
10	The salt **9** (2.01 g, 10.0 mmol) was stirred with allyl bromide (1.5 mL, 18 mmol) in DMSO (20 mL) for 5 h at 65 °C. The mixture was poured into ice-water (150 mL) and the solid that eventually formed was collected. After drying, this material was heated in heptane (150 mL). The acid **8** could be filtered off and the filtrate was evaporated to yield the product (1.68 g, 77%).	46–47 (49–49.5)[24]	δ_H (DMSO-d_6): 2.12 (3H, s), 4.79 (2H, dt, *J* 1.5, 5.4), 5.30 (1H, dd, *J* 1.5, 10.4), 5.41 (1H, dd, *J* 1.5, 17.1), 5.95–6.08 (1H, m), 7.19 (1H, dt, *J* 0.9, 7.8), 7.60 (1H, dt, *J* 1.6, 7.8), 7.92 (1H, dd, *J* 1.6, 7.9), 8.19 (1H, dd, *J* 0.9, 7.8); δ_C (DMSO-d_6): 24.5(CH_3), 65.4 (CH_2), 118.0 (C), 118.3(CH_2), 121.3 (CH), 123.2 (CH), 130.4 (CH), 132.4 (CH), 133.9 (CH), 139.6 (C), 166.7 (C), 168.4 (C).
13	*N*-Acetylanthranilic acid (17.9 g, 0.100 mol) was refluxed in AcOH (50 mL) with paraformaldehyde (4.0 g) for 3 h. The solvent was evaporated in vacuo (with addition of toluene). The residue was boiled in MeCN (200 mL), and the solution evaporated (after filtration) to yield a beige solid (16.7 g, 85%).	122[c]	δ_H (DMSO-d_6): 2.35 (3H, s), 5.78 (2H, s), 7.42 (1H, m), 7.73 (2H, m), 7.95 (1H, d, *J* 7.9); δ_C (DMSO-d_6): 22.3 (CH_3), 75.5 (CH_2), 119.3 (C), 123.6 (CH), 126.1 (CH), 129.6 (CH), 134.3 (CH), 141.0 (C), 162.8 (C), 169.4 (C).

[a] Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.59; H, 4.22; N, 19.46.
[b] Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.26; H, 4.35; N, 16.34.
[c] Recryst. from diisopropyl ether. Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.80; H, 4.88; N, 7.25.

of **8**, that is **10**, could easily be prepared by addition of allyl bromide to the salt **9** (in warm DMSO). This ester, and several other anthranilate esters, have also been prepared by treatment of the benzoxazinone **11** with the corresponding alcohol (allyl alcohol).[24] Compound **11** is readily made by treatment of **8** with acetic anhydride.[25,26] The N-allylated counterpart **12** has been made by reaction of a dianion of **8** with allyl bromide.[27]

It is well known that *N*-alkyl and *N*-aryl anthranilic acids can be condensed with aldehydes to form 1,2-dihydrobenzoxazinones,[28,29] and it was discovered that **8** could be condensed with paraformaldehyde to form the useful dihydrobenzoxazinone **13**. These types of compound can be ring opened with cyanide ion,[30] but surprisingly after treatment of **13** with NaCN in warm DMF, the deacetylated cyanomethylated compound **2a** was isolated in a high yield (reaction in water gave hydrolysis to **8**). The deacetylation probably occurred during the aqueous work up.

In summary both N- and O-alkylated anthranilic acid derivatives can be prepared by different methods, but care needs to be taken to ensure that a compound of the desired structure is actually obtained. It is highly recommended to acquire ^{1}H NMR spectra in DMSO-d_6, where otherwise exchangable protons such as those of COOH, NH, and NH_2 are usually visible.

References and notes

1. Nelson, D.; Cox, M. *Lehninger Principles of Biochemistry*, 3rd ed.; Worth: New York, 2000.
2. Gröger, D. *Stud. Org. Chem.* **1984**, *18*, 165–190.
3. Patel, D. M.; Visalli, A. J.; Zalipsky, J. J.; Reavey-Cantwell, N. H. *Anal. Profiles Drug Subst.* **1975**, *4*, 245–267.
4. Brogden, R. N. *Drugs* **1986**, *32*, 27–45.
5. Giuliani, E.; Lembo, S.; Sasso, V.; Sorrentino, L.; Silipo, C.; Vittoria, A. *Farmaco, Ed. Sci.* **1983**, *38*, 847–864.
6. Mitchell, M. O.; Hurley, A. R. *J. Heterocycl. Chem.* **2003**, *40*, 552–553.
7. Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic Methods in Organic Chemistry*; Georg Thieme: Stuttgart, New York, 1997.
8. Wiklund, P.; Romero, I.; Bergman, J. *Org. Biomol. Chem.* **2003**, *1*, 3396–3403.
9. Sharma, S.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 689–697.
10. Stavropoulos, G.; Theodoropoulos, D. *J. Heterocycl. Chem.* **1977**, *14*, 1139–1143.
11. Vorländer, D.; von Schilling, R. *Ber.* **1900**, *33*, 553–554.
12. Gandhi, S. S.; Bell, K. L.; Gibson, M. S. *Tetrahedron* **1995**, *51*, 13301–13308.
13. Heumann, K. *Ber.* **1890**, *23*, 3431–3435.
14. Lempert, K.; Doleschall, G. *Chem. Ber.* **1963**, *96*, 1271–1276.
15. Guilbault, G. G.; Hieserman, J. E.; Sadar, M. H. *Anal. Lett.* **1969**, *2*, 185–196.
16. Thominet, M. L. USP 3573325/1971; FR 1503908/1967; *Chem. Abstr.* **1967**, *70*, 37651.
17. Cadogan, J. I. G.; Hutchison, H. S.; McNab, H. *Tetrahedron* **1992**, *48*, 7747–7762.
18. Edsall, J.; Wyman, J. *J. Am. Chem. Soc.* **1935**, *57*, 1964–1975.
19. Leardini, R.; McNab, H.; Nanni, D.; Parsons, S.; Reed, D.; Tenan, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1833–1838.
20. Hardtmann, G. E.; Koletar, G.; Pfister, O. R. *J. Heterocycl. Chem.* **1975**, *12*, 565–572.
21. Chattaway, F. D. *J. Chem. Soc.* **1931**, 2495–2496.
22. Ananthakrishnanadar, P. *Indian J. Chem., Sect. A* **1988**, *27A*, 343–346.
23. Srinivasan, C.; Shunmugasundaram, A.; Arumugam, N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 213–216.
24. Errede, L. A.; Ashley, P. E.; McBrady, J. J.; Yarian, D. R. *J. Org. Chem.* **1982**, *47*, 3825–3828.
25. Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12–18.
26. Detsi, A.; Bardakos, V.; Markopoulos, J.; Igglessi-Markopoulou, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2909–2913.
27. Crich, D.; Eustace, K. A.; Fortt, S. M.; Ritchie, T. J. *Tetrahedron* **1990**, *46*, 2135–2148.
28. Schwenker, G.; Chen, J. *Arch. Pharm.* **1991**, *324*, 821–825.
29. Legrand, L.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1967**, 2067–2074.
30. Hrib, N. J.; Jurcak, J. G.; Bregna, D. E.; Burgher, K. L.; Hartman, H. B.; Kafka, S.; Kerman, L. L.; Kongsamut, S.; Roehr, J. E.; Szewczak, M. R.; Woods-Kettelberger, A. T.; Corbett, R. *J. Med. Chem.* **1996**, *39*, 4044–4057.
31. Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Synthesis* **1995**, 1483–1484.
32. Bucherer, H.; Schwalbe, A. *Ber.* **1906**, *39*, 2796–2813.