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Dilactams. Synthesis of nonsymmetrical dibenzodiazocinediones[1]

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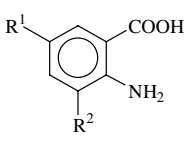
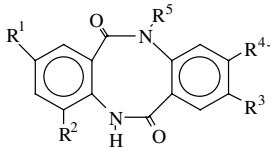
Abstract—We report the first examples of nonsymmetrical dibenzodiazocinediones, mono-, di-, tri- and tetra-substituted in the aromatic rings including a benzo pyridino diazocine, by a new short method without the requirement of protection. The procedure involves conversion of an anthranilic acid to its sulfinamide lactone followed by direct heating with a different *N*-alkylanthranilic acid.

Symmetrical dibenzo(*b*,*f*)(1,5)diazocine-6,12-diones for example, **2a**, also known as dianthranilides, are well known compounds because they are easily accessible from anthranilic acids **1** by condensation under various conditions.[2] Such dilactams have been of interest as chemosensitizers and drug resistance reversal agents,[3] as metal ion complexing agents,[4] as dipeptide analogues, and in conformational studies.[5] We were interested in the synthesis and chemistry of nonsymmetrically mono-, di-, tri- and tetra-substituted dibenzodiazocinediones like **2** and **3**, which are so far apparently unknown. One possible route to such compounds would be a peptide synthesis approach, involving coupling of an N-protected anthranilic acid with a differently substituted carboxy protected anthranilic acid requiring several protection and deprotection steps. This would be further complicated by the fact that many attempts to effect carboxy activation of anthranilic acid derivatives have led to symmetrical dibenzodiazocinediones.[6]

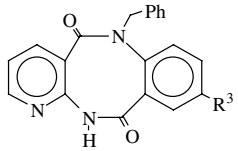
When we investigated such a protection–deprotection approach we were able to verify previous reports[2d] that *N*-anthranoylanthranilic acids for example, **4a**, expected intermediates in such reactions, undergo ring closure to six-membered ring lactones (cf. **5a**) rather than to eight-membered ring lactams **2**. Thus, treatment of (5-methyl-*N*-anthranoyl)anthranilic acid **4b** with DCC in pyridine or with EDC in DMF at rt produced only **5b** in good yield. To avoid six-membered ring formation an *N*-alkyl-*N*-anthranoylanthranilic acid like **4c** is required.



1a, $R^1 = R^2 = H$
1b, R^1 = Me; $R^2 = H$
1c, $R^1 = R^2$ = Ph
1d, $R^1 = H$; R^2 = Me
1e, $R^1 = R^2$ = Me
1f, R^1 = Me; R^2 = Br
1g, $R^1 = R^2 = NO_2$



2a, $R^1 = R^2 = R^3 = R^4 = R^5 = H$
2b, $R^1 = R^3 = R^4 = H$; $R^2 = R^5$ = Me (75%)
2c, $R^1 = R^2$ = Ph; R^3 = Me; $R^4 = H$; R^5 = Bn (88%)
2d, $R^1 = R^3 = R^4 = H$; R^2 = Me; R^5 = Bn (73%)
2e, $R^1 = R^4 = H$; $R^2 = R^3$ = Me; R^5 = Bn (72%)
2f, $R^1 = R^2$ = Me; $R^3 = R^4 = H$; R^5 = Bn (58%)
2g, $R^1 = R^3$ = Me; R^2 = Br; $R^4 = H$; R^5 = Bn (68%)
2h, R^1 = Me; R^2 = Br; $R^3 = R^4$ = OMe; R^5 = Bn (71%)
2i, $R^1 = R^2 = NO_2$; R^3 = Me; $R^4 = H$; R^5 = Bn (60%)



3, R^3 = Me

Keywords: Dilactam synthesis; Eight-membered ring; Diazocine; Dibenzodiazocine; Anthranilic acids.
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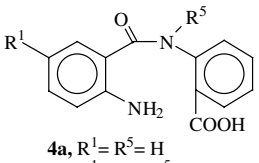
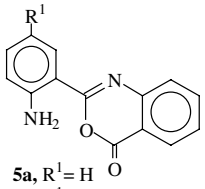
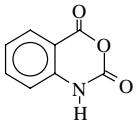
Another possible route to **2** via an isatoic anhydride **6** likewise proved unsuccessful, since we found **6** to be unreactive when heated with a differently substituted anthranilic acid or its *N*-alkyl derivative. For instance, **6** did not react with anthranilic acid **7b** in refluxing chloroform. Furthermore, isatoic anhydride **6** often reacts with amines at the amide carbonyl.[7]



4a, $R^1 = R^5 = H$
4b, $R^1 = Me$; $R^5 = H$
4c, $R^1 = Me$; $R^5 = Bn$



5a, $R^1 = H$
5b, $R^1 = Me$

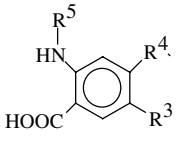


6

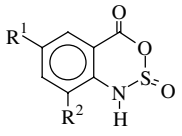
We report here a simple and effective synthetic method to couple nonsymmetrical anthranilic acids in order to obtain dibenzodiazocines of type **2**. Whereas reagents like $POCl_3$ react with anthranilic acids to produce symmetrical dibenzodiazocinediones, we found that **8**, the thio analogue of isatoic anhydride **6**, which can be prepared by heating an anthranilic acid with thionyl chloride, underwent reaction readily with a differently substituted *N*-alkylanthranilic acid, leading directly, often in one pot to an eight-membered dilactam **2**. For instance, heating the 3,5-diphenyl anthranilic acid **1c** with thionyl chloride in benzene led to **8d**, which on further heating with 5-methyl-*N*-benzylanthranilic acid **7c** in $CHCl_3$ afforded the nonsymmetrically trisubstituted dibenzodiazocinedione **2c** in 88% yield.

Kametami as well as others have reported[8] the synthesis of **8a** and its reaction with amides but apparently no reaction with amines, specifically with aromatic amines, had been attempted.

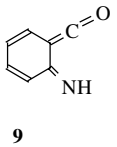
We surmise that the thio derivative **8** is either more reactive than **6** towards nucleophilic attack by the amino function of an anthranilic acid at the anhydride carbonyl or that **8** decomposes more readily to an intermediate iminoketene **9** as proposed by Kametami.[8]



7a, $R^3 = R^4 = H$; $R^5 = Me$
7b, $R^3 = R^4 = H$; $R^5 = Bn$
7c, $R^3 = Me$; $R^4 = H$; $R^5 = Bn$
7d, $R^3 = R^4 = OMe$; $R^5 = Bn$



8a, $R^1 = R^2 = H$
8b, $R^1 = Me$; $R^2 = H$
8c, $R^1 = R^2 = Me$
8d, $R^1 = R^2 = Ph$
8e, $R^1 = Me$; $R^2 = Br$
8f, $R^1 = R^2 = NO_2$



9

Using the methodology described above for the trisubstituted dibenzazocinedione **2c**, namely conversion of an anthranilic acid **1** to a sulfinamide lactone **8**, followed by reaction with an *N*-methyl- or *N*-benzylanthranilic acid **7**, we were able to obtain mono-, di- as well as tetrasubstituted dibenzodiazocinediones **2c–i** in good yields.

$$\mathbf{1} \xrightarrow{SOCl_2} \mathbf{8} \xrightarrow{7} \mathbf{2}$$

The aromatic substituents were both electron withdrawing or donating. In some cases a symmetrical dibenzodiazocinedione, derived by self-condensation–decomposition of **8**, was isolated as a side product in low yield. We also succeeded in synthesizing a nonsymmetrical diazocinedione in which one of the flanking aromatic rings was a heterocycle. Thus **3** was formed from 2-aminonicotinic acid via its sulfinamide lactone reacting with anthranilic acid **7c**.

Spectral properties readily distinguish between structures **2**, **4** and **5**. Typically dilactams **2** showed ^1H NMR peaks for the diastereotopic benzyl CH_2 group at ca. δ 5.1 ppm as an AB quartet, ^{13}C NMR amide carbonyls at ca. 168 and 170 ppm and IR absorptions near 1650 cm^{-1}. By contrast the isomeric lactones **5** showed IR absorptions near 1750 cm^{-1} and the open-chain anthranoylanthranilic acid **4** exhibited typical COOH absorption and a benzyl CH_2 singlet. Intermediates **8** were not purified but were used crude; they showed spectra consistent with those reported for **8a**.

In a typical procedure anthranilic acid **1f**, prepared by bromination of **1b**, was heated with 1.1 equiv of thionyl chloride in benzene or cyclohexane for 2 h. The solvent was evaporated in vacuum and the product **8e**, obtained as an oil, was dissolved in $CHCl_3$ and heated with *N*-benzyl-5-methylanthranilic acid **7c** for 5 h under reflux. Evaporation of the solvent left essentially pure dilactam **2g** in 68% yield. Chromatography over silica gel afforded **2g** as a solid, mp 248–250 °C.[†] ^1H NMR: δ 2.24 ppm (s, 3H), 2.26 ppm (s, 3H), 4.95 and 5.09 ppm (ABq, $J = 14.3$ Hz, 1H each), 6.79 ppm (d, $J = 8$ Hz, 1H), 7.01–7.32 ppm (m, 9H), 7.53 (s, 1H, NH). ^{13}C NMR: 20.63 and 20.86 ppm (CH_3), 53.37 ppm (CH_2), 126.29, 127.5, 127.84, 128.47, 128.60, 128.61, 128.81, 128.82, 132.01 and 134.25 (10 arom. CH), 120.62, 130.13, 132.52, 136.14, 136.26, 136.33, 139.05 and 139.76 ppm (8 arom. C), 167.52 and 169.51 ppm (C=O). IR: 1653 cm^{-1}. HRMS calcd for $C_{23}H_{19}N_2O_2Br$: 436.0609; found: 436.0590. Anal. Calcd for $C_{23}H_{19}N_2O_2Br$: C, 63.44; H, 4.37; N, 6.43. Found: C, 63.43; H, 4.55; N, 6.13.

Studies of the further scope of these reactions and biological tests on these new compounds are underway.

Acknowledgements

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[†] All new compounds are fully characterized by ^1H NMR, ^{13}C NMR and high resolution mass spectra.

References and notes

1. Synthetic Methods part 57. For part 56 see Hassner, A.; Usak, D.; Kumareswaran, R. *J. Org. Chem.* **2004**, *69*, 0000.
2. (a) Schroeter, G. *Liebig's Ann.* **1909**, *367*, 101; (b) Cooper, F. C.; Partridge, M. W. *J. Chem. Soc.* **1954**, 3429; (c) Jilek, J. O.; Pomykacek, J.; Svatek, E.; Seidlova, V.; Rajsner, M.; Pelz, K.; Hoch, B.; Protiva, M. *Coll. Czech Chem. Commun.* **1965**, *30*, 455; (d) Nadkarni, S. S.; Hosangadi, B. D. *Indian J. Chem.* **1988**, *27B*, 225.
3. Nonnenmacher, E.; Hever, A.; Mahamoud, A.; Aubert, C.; Molnar, J.; Barbe, J. *Org. Prep. Proced. Intern.* **1997**, *29*, 711.
4. Ru-Rehman, S.; Massod, A. *J. Chem. Soc. Pakistan* **1998**, *20*, 29.
5. Hoorfar, A.; Ollis, W. D.; Price, J. A.; Stephanidou, J.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1649.
6. (a) Corral, C.; Madronero, R.; Vega, S. *Indian J. Hetrocyc. Chem.* **1977**, *14*, 99; (b) Neda, I.; Fischer, A.; Kaukorat, T.; Jones, P. G.; Schmutzler, R. *Chem. Ber.* **1994**, *127*, 1579.
7. Guetschow, M. *J. Org. Chem.* **1999**, *64*, 5109.
8. (a) Kametami, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186; (b) Kametami, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306; (c) Kametami, T. M.; Fukumoto, K. *Acc. Chem. Res.* **1976**, *9*, 319; (d) Hermecz, I.; Vasvari-Debreczy, L.; Horvath, A.; Balogh, M.; Kokosi, J.; De Vos, C.; Rodriguez, L. *J. Med. Chem.* **1987**, *30*, 1543.