Pergamon

Tetrahedron Letters 40 (1999) 7459–7462

TETRAHEDRON LETTERS

Synthesis and resolution of a C_2-symmetrical indolo-2,3-quinodimethane dimer

Khalid Diker, Michèle Döé de Maindreville and Jean Lévy *

Laboratoire de Transformations et Synthèse de Substances Naturelles, associé au CNRS, Université de Reims Champagne-Ardenne, Faculté de Pharmacie, 51 rue Cognacq-Jay, F-51096 Reims Cedex, France

Received 24 April 1999; accepted 8 June 1999

Abstract

Thermolysis of ethyl 3-dimethylaminomethyl-2-indolylacetate generated an indolo-2,3-quinodimethane as evidenced by its dimerization to a first '4+2' dimer, which rearranged at a higher temperature to a cyclooctadienic diester. Resolution of this last diester in the form of the amides derived from (–)-α-methyl-benzylamine proved it to be C_2-symmetrical.

Keywords: indoles; dimerisation; resolution; circular dichroism.

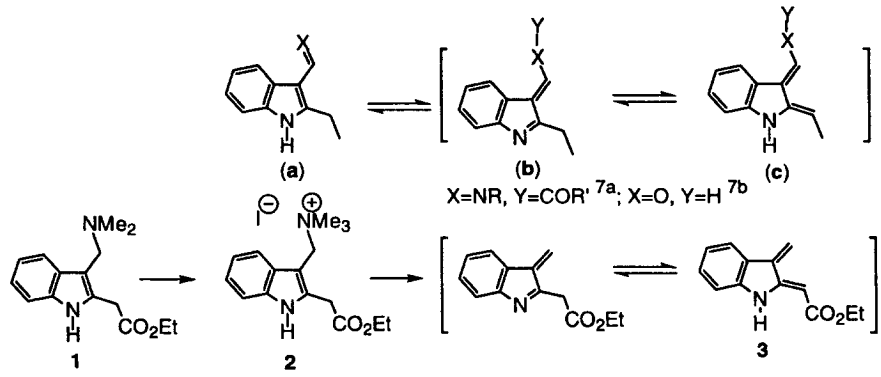
A number of indolo-2,3-quinodimethane intermediates (IQDMs) have been generated[1] and have proven their synthetic utility.[1–8] They give rise to self-condensations to '4+2' and to '4+4' dimeric species, and to Diels–Alder reactions in the presence of suitable dienophiles. Besides the extensive work of Pindur,[1a] Magnus,[7a] and later on Ciganek[7b] generated an IQDM (Scheme 1) through vinylogous enolization of a 2-substituted 3-formylindole derivative (**a**). This result shows that a 3-methylene-3-*H*-indole (**b**) can isomerize to an IQDM (**c**).

We then supposed that a 3-methylene-3-*H*-indole classically generated from a 2-substituted gramine, might easily isomerize to a reactive IQDM. In order to favor the process, we chose the gramine **1**, having an activated 2-methylene group. Thus, ethyl indole-2-acetate[9] was reacted with formaldehyde and dimethylamine in acetic acid to yield **1** (95%), which was methylated with methyl iodide to **2**. Heating **2** for 1 h in xylene gave two products that obviously resulted from the dimerization of the IQDM **3**.

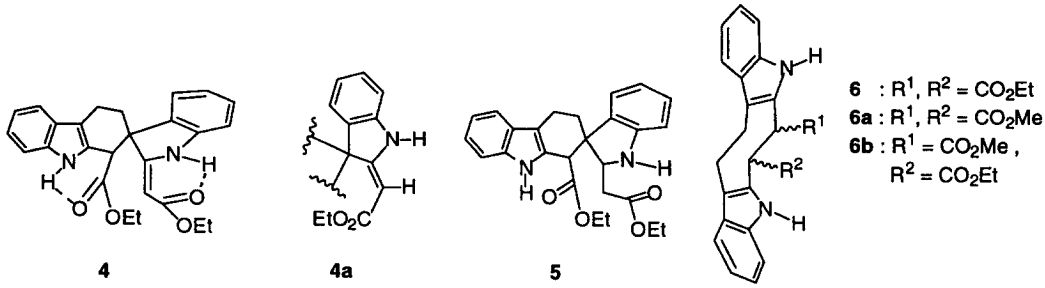
The less polar major product (92%) consisted of two compounds, the less abundant of which rapidly isomerized to the more abundant one upon standing. The structure **4** (Scheme 2) of this last compound was consistent with the following data: its UV spectrum (224, 292, 324 nm) agreed with the superimposition of both indole and anilinoacrylic chromophors.

* Corresponding author. Fax: 03 26 91 80 29; e-mail: jean.levy@univ-reims.fr

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01348-9



Scheme 1.



Scheme 2.

Apart from the aromatic and NH protons, its ^{1}H NMR spectrum disclosed singlets at 4.23 and 4.94 ppm (protons adjacent to the saturated and unsaturated esters, respectively), and the 4-spin system of the two adjacent methylenes at 1.9–3.0 ppm.

The ^{13}C NMR spectrum[10] confirmed the structure, as did reduction of **4** with $NaBH_3CN$ in acetic acid, yielding **5** as a mixture of two isomers, whose UV spectrum had lost the long-wave maximum.

No efforts were made to determine the relative configuration of the spirotetrahydrocarbazole **4**. The unstable isomer of **4** might be the *E* derivative **4a**, equilibrating to **4** which is stabilized by hydrogen bond(s). Absence of stereoselectivity in the reduction of **4** to **5** reflects an almost equal access to both faces of the protonated anilinoacrylic ester.

The more polar minor product **6** from the thermolysis of **2** was chromatographically and spectroscopically unique. Compound **6**,[11] $M^{+\cdot}$ 430, had a pure indolic UV spectrum and its ^{13}C NMR spectrum disclosing only 13 signals demonstrated its symmetrical structure.

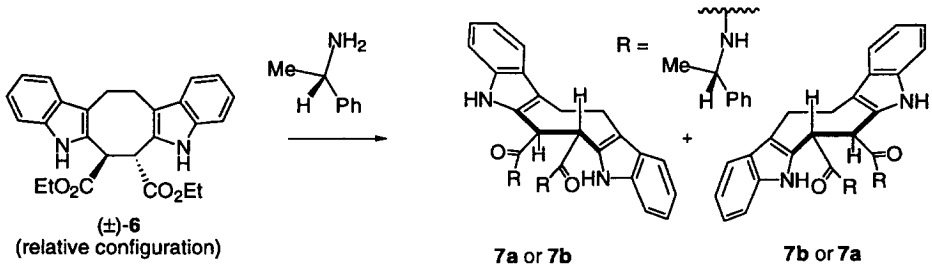
An interesting shortcut in the synthesis was found when gramine **1** (Scheme 1) was heated in refluxing xylene for 1 h, yielding **4** (92%) and **6** (5%) without the need to quaternize the amino group. Elimination of dimethylamine and generation of IQDM **3** are here thought to proceed through a thermal 1,5-shift of the hydrogen next to the ester group in **1**. More prolonged heating (4 days) raised the yield of **6** to 45%, to the detriment of that of **4** (27%), indicating a thermal rearrangement of **4** to **6**, in analogy with similar results in the furane series.[12] The spirocarbazole **4** was then refluxed for 4 days in xylene, giving the symmetrical dimer **6** with a 42% yield.

It was of interest to determine the relative configuration of the two esters in **6**, as a *cis* relationship would imply an achiral compound while a *trans* relationship would imply a C_2-symmetrical chiral racemic compound.

We attempted a desymmetrization aimed at distinguishing each of the two protons contiguous to the

ester groups. Thus, the mixed methyl/ethyl diester **6b** was prepared (simultaneously with the diethyl diester **6** and the dimethyl diester **6a**) starting from an equimolar mixture of gramine **1** and its methyl ester analog. However, after tedious separation on TLC (SiO_2, CH_2Cl_2), the ^1H NMR spectrum of **6b** did not allow the expected measurement of a clear coupling constant between the two above specified protons.

Diester **6** was then treated with *S*-(−)-α-methylbenzylamine, yielding the two amides[13] **7a** (less polar) and **7b** (more polar) (Scheme 3) which were easily separated by preparative TLC, and further purified by crystallization in methanol before measuring their optical rotations in pyridine: $[\alpha]_D$: **7a**, +150; **7b**, −230, and the CD curves in methanol (Fig. 1).



Scheme 3.

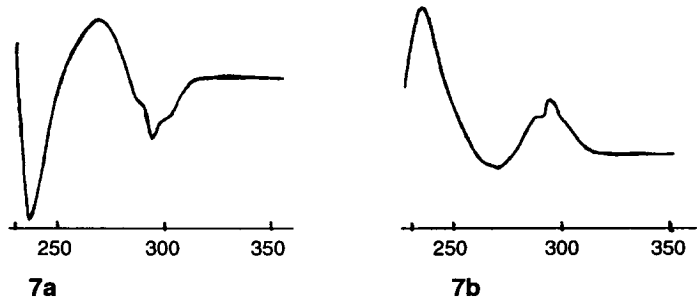


Figure 1. CD curves of **7a** and **7b** (MeOH)

Assuming that no epimerization had occurred during the transformation of **6** to **7a,b**, dimer **6** is then believed to be a racemate of a C_2-symmetric molecule, with its two ester groups in a *trans* relationship.

We have thus devised a novel and simple access to a reactive indolo-2,3-quinodimethane, whose Diels–Alder reactivity is exemplified in the accompanying Letter.

References

1. (a) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681–1689. (b) Collier, S. J.; Storr, R. C. *Progress in Heterocyclic Chemistry* **1998**, *10*, 25.
2. Vice, S. F.; Nandin de Carvalho, H.; Taylor, N. G.; Dmitrienko, G. I. *Tetrahedron Lett.* **1989**, *30*, 7289–7292.
3. (a) May, C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 247–250. (b) Nandin de Carvalho, H.; Dimitrienko, G. I.; Nielson, K. E. *Tetrahedron* **1990**, *46*, 5523–5532.
4. Marinelli, E. R. *Tetrahedron Lett.* **1982**, *23*, 2745–2748.
5. Magnus, P.; Gallagher, T.; Brown, P.; Papallardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.
6. Lévy, J.; Sapi, J.; Laronze, J.-Y.; Royer, D.; Toupet, L. *Synlett.* **1992**, *7*, 601–602.
7. (a) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242–2248. (b) Ciganek, E.; Schubert, E. M. *J. Org. Chem.* **1995**, 4629–4634.
8. Kurihara, T.; Hanakawa, M.; Wakita, T.; Yonida, R. *Chem. Pharm. Bull.* **1986**, *34*, 4545–4553.

9. Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673–679.
10. Compound **4**: ^{13}C NMR δ: 13.1, 14.5, 18.0, 36.1, 48.5, 52.4, 59.2, 61.2, 79.6, 108.9, 111.1, 111.2, 118.4, 119.4, 121.0, 122.2, 124.3, 126.5, 128.4, 128.5, 131.2, 136.7, 143.8, 169.9, 170.3, 170.5.
11. Compound **6**: UV: 220, 282, 291. MS: 430 ($M^{+\cdot}$, 54), 215 (100), 169 (96). ^1H NMR (DMSO-d_6) δ: 1.22 (t, *J*=6.7 Hz, 6H), 3.24 (s, 4H), 4.20 (m, 4H), 4.94 (s, 2H), 6.89 (t, *J*=8.0 Hz, 2H), 6.97 (t, *J*=8.0 Hz, 2H), 7.2 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 10.7 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 14.1, 22.6, 46.2, 61.3, 111.1, 111.2, 117.5, 118.4, 121.0, 128.2, 128.9, 135.5, 171.2.
12. Trahanovsky, W. S.; Huang, Y.-C. J.; Leung, M.-K. *J. Org. Chem.* **1994**, *59*, 2594–2598.
13. Compound **7a**: mp 287–288°C, $[\alpha]_D$=+150 (pyridine, *c* 5.2); MS: 581 (M+1, 65), 459 (19), 432 (23), 354 (23), 312 (26), 290 (37), 169 (28), 144 (27). ^1H NMR (pyridine-d_5) δ: 1.36 (d, *J*=6.8 Hz, 6H), 3.10 (d, *J*=10.0 Hz, 1H), 3.51 (d, *J*=10.0 Hz, 1H), 5.00 (s, 4H), 5.42 (qt, *J*=6.8 Hz, 2H), 7.08 (m, 10H), 7.28 (m, 2H), 7.41 (d, *J*=7.6 Hz, 4H), 7.59 (m, 2H), 9.42 (s, 2H), 10.87 (s, 2H). ^{13}C NMR (pyridine-d_5) δ: 21.8, 23.5, 48.2, 48.9, 111.1, 111.6, 118.0, 118.9, 121.9, 126.4, 126.7, 128.4, 129.7, 132.3, 136.2, 144.0, 170.9. Compound **7b**: mp 292–293°C, $[\alpha]_D$=−230 (pyridine, *c* 5.9); MS: 582 (M+2, 100), 461 (43), 434 (41), 355 (61), 312 (54), 291 (93), 284 (87), 270 (82). ^1H NMR (pyridine-d_5) δ: 1.53 (d, *J*=7.0 Hz, 6H), 3.08 (d, *J*=10.0 Hz, 1H), 5.50 (d, *J*=10.0 Hz, 1H), 5 (s, 4H), 5.54 (qt, *J*=7.0 Hz, 2H), 7.06 (m, 4H), 7.18 (m, 10H), 7.38 (m, 4H), 9.63 (d, *J*=6.5 Hz, 2H), 10.82 (s, 2H). ^{13}C NMR (pyridine-d_5) δ: 22.0, 23.5, 48.4, 49.2, 111.0, 111.7, 117.9, 118.8, 121.1, 126.3, 126.9, 128.5, 129.6, 132.1, 136.1, 144.5, 171.2.