Chemistry of Heterocyclic Compounds, Vol. 32, No. 8, 1996

NAPHTHOINDOLES.
7. SYNTHESIS OF 4,11-DIMETHOXYNAPHTHO[2,3-f]INDOLE-5,10-DIONE AND 4-METHOXYNAPHTHO[2,3-f]-INDOLE-5,10-DIONE

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4,11-Dimethoxynaphtho[2,3-f]indole-5,10-dione and 4-methoxynaphtho[2,3-f]indole-5,10-dione have been synthesized by the Leimgruber–Batcho reaction from 1,4-dimethoxy-2-methyl-3-nitroanthraquinone.

Many compounds of the anthraquinone series are widely used as antitumor agents. Adrianycin, discovered in 1969 [2], is one of the most effective medicinal preparations, acting against various forms of tumor with a moderate toxicity. The 4-demethoxy analog of rubomycin, assigned the name "carminomycin," was isolated from *Actinomadura carminata* in 1973 by G. F. Gauze and is also widely used as an antitumor preparation [3].

On the other hand it is known that among indole derivatives there is a large group of both natural and synthetic antitumor preparations. The indole alkaloids vincristine and vinblastine [3] and the antitumor antibiotic mitomycin [3] are widely used in clinical practice. Consequently the search for new biologically active substances with antitumor activity and containing in their structure indole and anthraquinone fragments is of significant interest. Methods of synthesizing naphthoindolediones have been described [4-9], however no naphthoindolediones of linear structure containing donor substituents in the benzene ring annelated with the pyrrole fragment have been obtained in good yield by any of these methods.

The Leimgruber–Batcho reaction, used successfully to obtain condensed systems in [10], was applied by us to construct the pyrrole ring in the synthesis of 4,11-dimethoxynaphtho[2,3-f]indole-5,10-dione. 1,4-Dimethoxy-2-methylanthraquinone (I) obtained by the method of [11] was selected as starting material.

On nitrating the anthraquinone (I) with fuming nitric acid (d 1.5 g/ml) in glacial acetic acid, demethylation of one of the methoxy groups takes place leading to 4-hydroxy-1-methoxy-2-methyl-3-nitroanthraquinone (II) in 72% yield. Compound (II) was converted subsequently into 1,4-dimethoxy-2-methyl-3-nitroanthraquinone (III) in 88% yield by alkylation with dimethyl sulfate in the presence of potassium carbonate in dry acetone. The anthraquinone (III) was treated with the diethylacetal of N,N-dimethylformamide (DEADMF) in dry DMF in a current of argon and 1,4-dimethoxy-2-[2-(N,N-dimethylamino)vinyl]-3-nitroanthraquinone (IV) was obtained in 79% yield. The target naphthoindoledione (V) was obtained in 62% yield and its demethoxylated analog 4-methoxynaphtho[2,3-f]indole-5,10-dione (VI) in 10% yield by the reductive cyclization of enamine (IV) with iron in an mixture of ethanol and glacial acetic acid (1:1). A similar demethoxylation of methoxyanthraquinones was observed previously in the synthesis of anthracyclines [12].

The structure of products (I)-(VI) was confirmed by data of PMR, IR, UV, and mass spectrometry. In the PMR spectra of compounds (II) and (III), one [in compound (II)] and two [in compound (III)] singlets for protons of the methoxy group near 4 ppm were observed in addition to multiplets for four aromatic protons at low field and a singlet for the protons of the methyl

*For communication 6, see [1].

Russian University of Chemical Technology, Moscow 125190. Center for Drug Chemistry, All-Russian Scientific Research Institute for Pharmaceutical Chemistry, Moscow 119815. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1050-1054, August, 1996. Original article submitted March 20, 1996.

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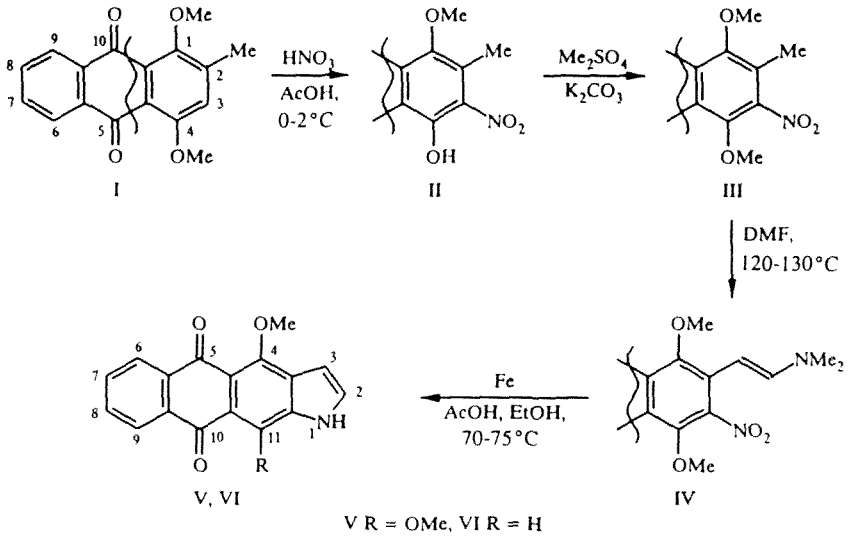


I II III IV V, VI

V R = OMe, VI R = H

group at high field. Measurement of the nuclear Overhauser effect (NOE) showed that in the case of compound (III) the NOE at the methyl group was +2.5% on saturating one of the methoxy groups and less than 0.5% on saturating the other. A similar difference between NOE was obtained in the reverse experiment, when measuring the NOE at the methoxy groups under conditions of saturating the methyl group signal. The positive NOE at the methyl and one of the methoxy groups of compound (III) indicates their spatial proximity and suggests that the ortho disposition of the methyl and methoxy groups in similar systems corresponds to an NOE of +2.5% and a meta disposition to an NOE of less than +0.5%. In the case of compound (II) the NOE was +5% at the methyl group on saturating the signal of the methoxy group and it was +4% at the methoxy group on saturating the signal of the methyl group. In view of the NOE data from compound (III) it may be affirmed that this corresponds to an ortho disposition of the methyl and methoxy groups in compound (II). Its structure follows from this. Signals were observed in the PMR spectrum of enamine (IV) for the α and β protons at a C=C double bond with a coupling constant J_{trans} = 13.4 Hz characteristic of trans disposition. Signals were present in the PMR spectra of naphthoindole-diones (V) and (VI) for N–H and C–H protons of a pyrrole ring with chemical shifts and coupling constants in agreement with the literature data for indoles [13]. These were in addition to the multiplets for the aromatic protons. Singlets were also observed in the spectrum of the dimethoxynaphthoindoledione (V) for the protons of two methoxy groups. In the spectrum of methoxynaphthoindole-dione (VI) there was a singlet for the protons of one methoxy group and a doublet for the aromatic proton of the indole ring (with a chemical shift of 8.10 ppm, J = 0.8 Hz) caused by interaction with the 3-H proton of the pyrrole ring. According to the literature data on coupling constants in indole $^5J_{3,7}$ is about 0.7 Hz greater than $^4J_{3,4}$ [14]. It may be suggested on this basis that the coupling constant observed in the demethoxylation product (VI) for the proton of the benzene ring of the indole fragment corresponds to $^5J_{3,11}$ and consequently [2] the demethoxylation product is 4-methoxynaphtho[2,3-f]indole-5,10-dione. This hypothesis was confirmed unequivocally by NOE experiments in which the significant positive NOE indicated the spatial proximity of the N–H and 11-H protons. The NOE effect was +18% at the 11-H signal on saturating the N–H proton signal. A positive NOE of 16% was also observed at the signal of the 2-H proton and a negative NOE of –3% was observed at the signal for the 3-H proton. A significant positive NOE (+11%) was observed at the 3-H proton signal on saturating the methoxy group signal which indicates their spatial proximity and gives additional confirmation of the structure of the demethoxylation product (VI) indicated above.

Intense absorption bands were observed in the IR spectra of compounds (II)-(VI) at 1600-1690 cm^{-1} caused by the stretching vibrations of a C=O group, and intense absorption bands were observed in the spectra of compounds (II)-(IV) at 1500-1550 and 1320-1330 cm^{-1} corresponding to the stretching vibrations of the nitro group.

Characteristic absorption frequencies for the N–H group of compounds (V) and (VI) were found at 3150-3350 cm^{-1} which agrees with the position of the corresponding bands in the indole spectrum.

The electronic absorption spectra of compounds (III)-(V) are given in Fig. 1. The long wave maximum for the nitrosubstituted derivative (III) lies near 350 nm. Such a hyposochromic shift of this band compared with the spectrum of 1,4-dimethoxyanthraquinone is evidently linked with the electron-accepting effect of the nitro group reducing the electron-accepting electron density on the oxygen atoms. This effect disappears in the case of the naphthoindole(V) where the long wave maximum

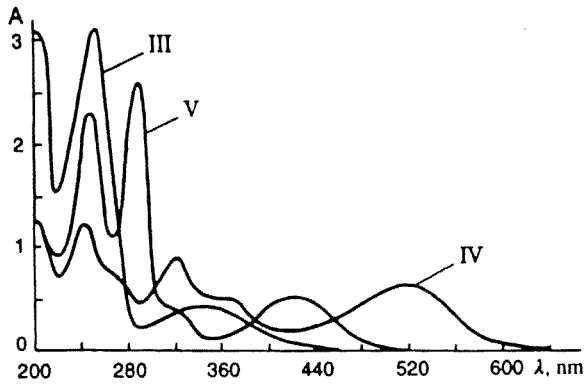
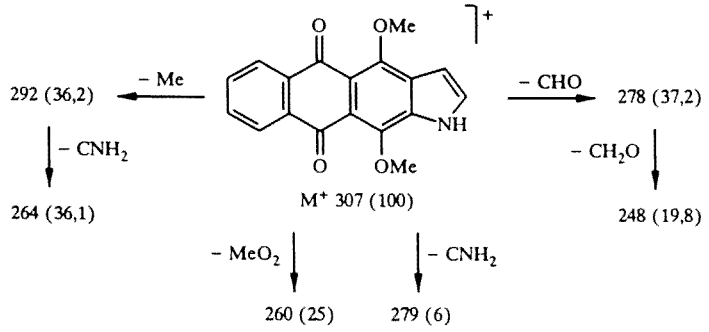


Fig. 1. Electronic absorption spectra of compounds (III)-(V).

is found near 420 nm. The absorption maxima of 1,4-dihydroxyanthraquinone derivatives are found in approximately the same region [15]. The bathochromic shift of the maximum of the long wave absorption band of enamine (V) is linked with the formation of an efficient conjugation system with the strongly electron-donating substituent (dimethylamino group) and the electron-accepting system (nitro group). In addition it is not possible to exclude the possibility of an interaction with the carbonyl groups of the anthraquinone ring.

There were intense peaks in the mass spectrum of the naphthoindolediones (V) and (VI) for the molecular ions M^+ at 307* and 277 respectively and the character of the further fragmentation confirmed by metastable transitions was not incompatible with the structure assigned to it.



The mass spectrum of naphthoindole (VI) was similar.

EXPERIMENTAL

The IR spectra of compounds were recorded on a Perkin-Elmer 599 spectrometer in Nujol. The PMR spectra were drawn on an Varian Unity +400 spectrometer with an operating frequency of 400 MHz. Chemical shifts were measured relative to TMS as internal standard. The mass spectra were recorded on a Varian Mat-112 chromato-mass spectrometer, ionizing voltage was 70 eV, cathode emission current was 1 mA, accelerating voltage 3 kV, and temperature 250°C. The UV spectra were drawn on a Specord M400 spectrophotometer in ethanol. A check on the progress of reactions and the purity of compounds was carried out with TLC on Silufol UV 254 plates. Compounds were chromatographed on silica gel type L 40/100.

4-Hydroxy-1-methoxy-2-methyl-3-nitroanthraquinone (II). 1,4-Dimethoxy-2-methylanthraquinone (I) (9.5 g: 33.5 mmole) was dissolved in a mixture of nitric acid (d 1.5 g/ml) (20 ml) and glacial acetic acid (20 ml) previously cooled to −5°C. The solution was maintained at this temperature for 15 min then poured onto ice (200 g). The resulting orange powder

*Here and subsequently values of *m/z* are given for ion peaks. The relative intensities of ion peaks as % maximum value are given in parentheses.was rapidly filtered off, dried, and crystallized from alcohol. Yield was 7.5 g (72%) of mp 168-171°C.

PMR spectrum ($CDCl_3$): 13.18 (1H, s, OH), 8.18 and 8.20 (2H, m, 6-H, 9-H), 7.92 and 7.94 (2H, m, 7-H, 8-H), 3.82 (3H, s, OCH_3), 2.30 ppm (3H, s, CH_3). IR spectrum: 1665 (C=O), 1545 (NO_2), 1330 cm^{-1} (NO_2). Mass spectrum: 313 (100), 284 (10), 266 (12), 250 (15), 221 (10), 152 (12), 139 (26), 128 (8). Found, %: C 61.4; H 3.5; N 4.5. $C_{16}H_{11}O_6N$. Calculated, %: C 61.3; H 3.5; N 4.5.

1,4-Dimethoxy-2-methyl-3-nitroanthraquinone (III). A mixture containing the anthraquinone (II) (7 g: 22.3 mmole), calcined potassium carbonate (15.2 g: 110 mmole), and freshly distilled dimethyl sulfate (3.2 ml: 33 mmole) in dry acetone (800 ml) was boiled with vigorous stirring for 3 h in a current of argon, and then filtered. The filtrate was evaporated at reduced pressure, the residue washed with ethanol to remove the unreacted dimethyl sulfate, dried, and crystallized from benzene. Yield was 6.3 g (88%) as yellow crystals of mp 208-211°C. PMR spectrum (DMSO-D_6): 8.17 (2H, m, 6-H, 9-H), 7.77 (2H, m, 7-H, 8-H), 3.99 (H, s, OCH_3), 3.94 (3H, s, OCH_3), 2.32 ppm (3H, s, CH_3). IR spectrum: 1675 (C=O), 1538 (NO_2), 1330 cm^{-1} (NO_2). Mass spectrum: 327 (100), 280 (42), 252 (23), 200 (19), 238 (31), 223 (15), 195 (16), 181 (20), 165 (36), 152 (57), 139 (69), 126 (15), 104 (20), 91 (13), 76 (40), 67 (28), 63 (15). Found, %: C 62.4, H 4.0; N 4.3. $C_{17}H_{13}O_6N$. Calculated, %: C 62.4; H 4.0; N 4.2.

1,4-Dimethoxy-2-[2′-(N,N-dimethylamino)vinyl-3-nitroanthraquinone (IV). N,N-Dimethylformamide dimethylacetal (3.6 ml: 30 mmole) and dry DMF (50 ml) were added to the anthraquinone (III) (5 g: 15.2 mmole) and the mixture stirred in a current of argon at 125-130°C for 4 h. The reaction mixture was evaporated at reduced pressure and the residue recrystallized from ethanol. The enamine (IV) was obtained (4.6 g: 79%) as violet needle-shaped crystals having mp 170-172°C. PMR spectrum ($CDCl_3$): 8.21 and 8.15 (2H, m, 6-H, 9-H), 7.82 (1H, d, −CH=, J = 13.4 Hz), 7.75 and 7.71 (2H, m, 7-H, 8-H), 4.72 (1H, d, −CH=, J = 13.4 Hz), 3.98 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.95 ppm [6H, s, $N(CH_3)_2$]. IR spectrum: 1672 (C=O), 1620 (C=C), 1518 (NO_2), 1323 cm^{-1} (NO_2). Mass spectrum: 382 (57), 365 (100), 335 (14), 320 (16), 307 (22), 292 (13), 266 (19), 252 (40), 238 (12), 206 (16), 86 (45), 58 (79). Found, %: C 62.7; H 4.7; N 7.3. $C_{20}H_{18}O_6N$. Calculated, %: C 62.8; H 4.7; N 7.2.

4,11-Dimethoxynaphtho[2,3-f]indole-5,10-dione (V) and 4-Methoxynaphtho[2,3-f]indole-5,10-dione (VI). The enamine (V) (4 g: 10 mmole) was dissolved in a mixture of glacial acetic acid (100 ml) and ethanol (100 ml). Iron powder (2.8 g: 50 mmole) was added while stirring vigorously at 70-75°C. After 0.5 h the reaction mixture was filtered, the filtrate diluted with water, and the solid extracted with ether. The extract was washed three times with 20% KOH, and with water, dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel with a benzene−ether (10:1) mixture and needle-like yellow crystals of the naphthoindoledione (VI) (0.27 g: 10%) of mp 308-310°C (from alcohol) and yellow crystals of naphthoindoledione (V) (1.9 g: 62%) of mp 275-278°C (from alcohol) were obtained.

4,11-Dimethoxynaphtho[2,3-f]indole-5,10-dione (V). PMR spectrum (DMSO-D_6): 12.38 (1H, m, NH), 8.08 (2H, m, 6-H, 9-H), 7.77 (2H, m, 7-H, 8-H), 7.41 (1H, m, 2-H), 6.83 (1H, m, 3-H), 3.97 (3H, s, OCH_3), 4.01 ppm (3H, s, OCH_3), $^3J_{1,2}$ = 2.8 Hz, $^3J_{2,3}$ = 2.8 Hz, $^4J_{1,3}$ = 1.8 Hz. IR spectrum: 3260 (N−H), 1660 cm^{-1} (C=O). Mass spectrum: 307 (100), 293 (36), 290 (16), 289 (16), 288 (10), 279 (6), 278 (37), 264 (36), 261 (12), 260 (25), 248 (19), 236 (14), 221 (11), 193 (19), 165 (10), 138 (12). Found, %: C 70.2; H 4.3; N 4.6. $C_{18}H_{13}O_4N$. Calculated, %: C 70.3; H 4.2; N 4.6.

4-Methoxynaphtho[2,3-f]indole-5,10-dione (VI). PMR spectrum (DMSO-D_6): 12.12 (1H, s, NH), 8.14 and 8.16 (2H, s, 6-H, 9-H), 8.10 (1H, d, 11-H), 7.82 and 7.86 (2H, m, 7-H, 8-H), 7.44 (1H, m, 2-H), 6.88 (1H, m, 3-H), 4.08 ppm (3H, s, OCH_3), $^3J_{1,2}$ = 2.8 Hz, $^3J_{2,3}$ = 3.24 Hz, $^4J_{1,3}$ = 1.85 Hz, $^5J_{3,11}$ = 0.8 Hz. IR spectrum: 3356 (N−H), 1670 cm^{-1} (C=O). Mass spectrum: 277 (85), 249 (20), 248 (100), 231 (16), 206 (25), 191 (14). Found, %: 73.6; H 4.0; N 5.1. $C_{17}H_{11}O_3N$. Calculated, %: C 73.7; H 4.0; N 5.0.

REFERENCES

1. I. E. Demidov, V. N. Buyanov, V. V. Negrebetskii, T. K. Efimova, and N. N. Suvorov, Chemistry and Technology of Biologically Active Compounds and Intermediates [in Russian], in: Scientific Proceedings of the Russian University of Chemical Technology (RKhTU), Moscow (1992), p. 37.
2. T. Arcamone, G. Granceschic, and S. Penco, Tetrahedron Lett., No. 13, 1007 (1969).
3. G. F. Gauze and Yu. V. Dudnik, Antotumor Antibiotics [in Russian], Moscow (1987), pp. 18-49, 116-127.
4. M. V. Gorelik and E. V. Mishina, Zh. Org. Khim., **19**, 2177 (1983).
5. A. M. Galushko and N. S. Dokunikhin, Zh. Org. Khim., **18**, 1539 (1982).
6. P. C. Shekar and S. Seshadri, Dyes and Pigments, **5**, 277 (1984).

7. M. S. Shvartsberg, A. A. Moroz, A. V. Piskunov, and I. A. Budzinskaya, 1st All-Union Conference on the Chemistry, Biochemistry, and Pharmacology of Indole Derivatives. Abstracts, Tbilisi (1986), p. 173.
8. A. A. Moroz, A. V. Piskunov, T. P. Galevskaya, and M. A. Mzhelskaya, 6th International Conference on Organic Synthesis. Abstracts. Moscow (1986), p. 150.
9. S. L. Vorob'eva, V. N. Buyanov, I. Yu. Levina, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 69 (1989).
10. E. P. Baberkina, R. N. Akhvlediani, V. N. Buyanov, and N. N. Suvorov, Zh. Org. Khim., **26**, 445 (1990).
11. F. Suzuki, S. Trenbeath, R. D. Gleim, and C. J. Sih, J. Org. Chem., **43**, 4164 (1978).
12. F. M. Hauser and N. V. Hewawasam, J. Org. Chem., **53**, 4516 (1988).
13. S. P. Hiremath and R. S. Hosmane, Advances Heterocycl. Chem., No. 15, 277 (1973).
14. B. I. Stepanov, Introduction to the Chemistry and Technology of Organic Dyestuffs [in Russian], Khimiya, Moscow (1984), p. 206.
15. U. H. Blak and N. F. Heffernan, Aust. J. Chem., **18**, 353 (1965).