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# SYNTHESIS OF HETEROCYCLIC ANALOGS OF PROSTAGLANDINS FROM PYRROLE AND INDOLE

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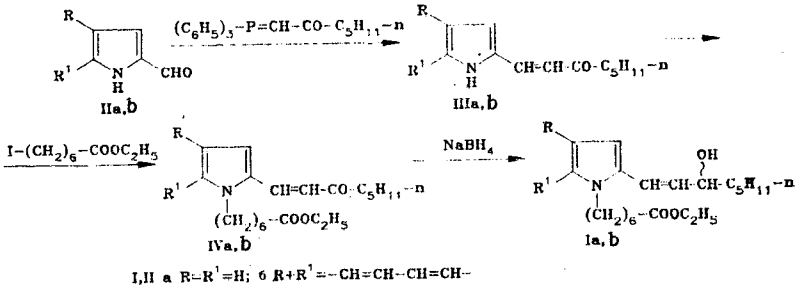
UDC 547.741'754'295'361.07

Heterocyclic analogs of prostaglandin, dl-2-(trans-3-hydroxyocten-1yl)-N-(6-ethoxycarbonylhexyl)pyrrole and -indole were obtained by the condensation of 2-formylpyrrole and 2-formylindole with 2-oxoheptylidenetriphenylphosphorane, followed by alkylation with ethyl 7-iodoheptanoate and reduction of the keto group by sodium borohydride.

In recent years, studies on the preparation of prostaglandin analogs, which are synthetically more accessible than the natural prostaglandins and have the same or comparable biological activity, received great impetus [1, 2]. Special attention is paid at present to the synthesis of analogs of prostaglandins in which the cyclopentane ring is replaced by a nitrogen-containing heterocycle, for example, derivatives of indole, pyrrolidine, oxazole, and others [1, 3-5]. This is mostly due to the fact that some of the azacyclic analogs of prostaglandin are strong inhibitors of the thrombocyte aggregation [6].

In search for new potential thrombocyte aggregation inhibitors, we were first to synthesize dl-2-(trans-3-hydroxyocten-1-yl)-N-(6-ethoxycarbonylhexyl)pyrrole (Ia) and dl-2-(trans-3-hydroxyocten-1-yl)-N-(6-ethoxycarbonylhexyl)indole (Ib), in which the side chains correspond to the side chains of natural prostaglandins. Commercially available 2-formylpyrrole (IIa) and 2-formylindole (IIb) served as the starting materials for the synthesis of these compounds. The synthesis of compounds Ia, b is shown by the following scheme:




I, II a R=R'=H; б R+R'=—CH=CH—CH=CH—

All-Union Scientific-Research Institute of Technology of Blood Substitutes and Hormonal Preparations, Moscow 109044. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 40-43, January, 1986. Original article submitted December 4, 1984.

0009-3122/86/2201-0033$12.50  

The condensation of aldehydes IIa, b by the Wittig condensation with 2-oxoheptylidenetriphenylphosphorane was carried out in carbon tetrachloride by boiling for several hours. 2-(trans-3-oxoocten-1-yl)pyrrole (IIIa) and -idole (IIIb) thus obtained had the required E-configuration of the double bond protons (the SSCC of olefinic protons is 16 Hz). Treatment of ketones IIIa, b by ethyl 7-iodoheptanoate in DMFA in the presence of NaH at 70-80°C leads to 2-(trans-3-octoocten-1-yl)-N-(6-ethoxycarbonylhexyl)pyrrole (IVA) and -indole (IVb). Reduction of the carbonyl group in ketones IVa,b by sodium borohydride in 70% aqueous isopropanol at room temperature took place nonselectively, but without the side-processes of 1,4-addition, and led to dl-Ia and Ib. The individual compounds dl-Ia and -Ib were isolated chromatographically on silica gel. Attempts to saponify the ester group in compounds Ia, b by alkaline or acid hydrolysis led to resinification.

The structure of the intermediate and final compounds was confirmed by IR, $^{13}C$ NMR and PMR spectroscopy. Some of the spectral characteristics of compounds Ia, b, IIIa, b, IVa,b are shown in Table 1.

Thus, a simple, three-step synthesis of nitrogen-containing prostaglandin analogs has been proposed, enabling obtention of dl-2-(trans-3-hydroxyocten-1-yl)-N-(6-ethoxycarbonylhexyl)pyrrole and dl-2-(trans-3-hydroxocten-1-yl)-N-(6-ethoxycarbonylhexyl)indole, whose activity in the thrombocyte inhibition test in a rabbit is equal to 40% of a standard (arachidonic acid).

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer, the PMR spectra of a BS-27 spectrometer (60 MHz) with reference to TMS as internal standard. The $^{13}C$ NMR spectra were recorded on a Bruker WP-80DS spectrometer. A qualitative analysis of the mixtures was carried out by TLC of Silufol UV-254 plates in the following systems of solvents: ethyl acetate—hexane, 2:3 (system A), acetone—chloroform, 1:19 (system B), ethyl acetate—heptane, 1:1 (system C). Brand L100/160, 40/100 silica gel was used for column chromatography.

2-(trans-3-Oxoocten-1-yl)pyrrole (IIIa). A 0.42 g (4 mmole) portion of 2-formylpyrrole was added with stirring to a solution of 3 g (8 mmoles) of 2-oxo-heptylidenetriphenylphosphorane in 25 ml of $CCl_4$. The reaction mixture was boiled for 6 h. The solvent was evaporated, and the yellow oil obtained was dissolved in 5 ml of ethyl acetate, and the solution was deposited on a column with silica gel (d 2.5 cm, $l$ 20 cm) L100/160, with elution by a 2:8 ethyl acetate—hexane mixture. The yield of ketone IIIa was 0.68 g (80%), mp 94-95°C, $R_f$ 0.63 (B).

2-(trans-3-Oxoocten-1-yl)indole (IIIb) was obtained and isolated in the same way as compound IIIa. A 0.2 g (18 mmole) portion of 2-formylindole was added to 1.4 g (3.7 mmoles) of 2-oxoheptylidenetriphenylphosphorane. After chromatographic purification, 0.37 g of ketone IIIb (88%) was obtained; mp 146-147°C; $R_f$ 0.78 (B).

2-(trans-3-Oxoocten-1-yl)-N-(6-ethoxycarbonylhexyl)pyrrole (IVa). A mixture of 0.1 g (4 mmoles) of NaH and 0.3 g (1.5 mmoles) of 2-(trans-3-oxoocten-1-yl)pyrrole in 5 ml of absolute DMFA was stirred for 1 h at room temperature. A solution of 0.6 g (2 mmoles) of ethyl 7-iodoheptanoate in 5 ml of absolute DMFA was added dropwise to the reaction mixture, with stirring, for 1 h at 70-80°C, followed by cooling, dilution with water, and acidification with 1 N $H_2SO_4$ to pH 5. The aqueous solution was extracted with ether (5 × 50 ml), and dried over $Na_2SO_4$. After distillation of the solvent, a yellow oil was obtained, which was deposited on a column (d 2.5 cm, $l$ 20 cm) with silica gel L40/100) with elution by a 2:8 ethyl acetate—hexane mixture. The yield of pure ketone was 0.51 g (94%), oil, $R_f$ 0.73 (A).

2-(trans-3-Oxoocten-1-yl)-N-(6-ethoxycarbonylhexyl)indole (IVb) was obtained in a similar way as compound IVa. A 0.6 g (2 mmole) portion a of ethyl 7-iodoheptanoate was added to a mixture of 0.1 g (4 mmoles) of NaH and 0.36 g (1.5 mmoles) of ketone IIIb. After chromatographic purification, 0.6 g of ketone IVb (77%) was obtailed. Oil, $R_f$ 0.64 (B).

dl-2-(trans-3-Hydroxyocten-1-yl)-N-(6-ethoxycarbonylhexyl)pyrrole (Ia). A suspension of 0.05 g (10.25 mmoles) of $NaBH_4$ in 3 ml of water was added to a solution of 0.14 g (0.41 mmole) of 2-(trans-3-oxoocten-1-yl)-N-(ethoxycarbonylhexyl)pyrrole in 7 ml of 2-propanol, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water, extracted by ethyl acetate (4 × 50 ml), the extract was washed with water, and dried over $Na_2SO_4$. After a chromatographic purification on a column with silica gel (d 2.5

TABLE 1. Spectral Characteristics of Compounds Ia,b, IIIa,b, IVa,b

| Compound | IR spectrum, $\nu$, $cm^{-1}$ | | | | | | PMR spectrum, $\delta$, ppm (J, Hz), in $CDCl_3$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CH-CH trans | C=C | C=O | COO | NH | OH | CH=CH | OH | $\overset{N-CH_2}{CO_2-CH_2-CH_3}$ | $CO-CH_2$ | $CH_3$ in side chain | NH | $COOCH_2-CH_3$ |
| IIIa | 975 | 1610 | 1670 | — | 3290 | — | 6,8 d (1H); 5,8 d, d (1H); $J$=16 Hz | | | 2,60 t (2H) | 0,90 t | 8,70 s | |
| IIIb | 960 | 1610 | 1650 | — | 3320 | — | 7,01 (1H); 6,85 d,d (1H); $J$=16 Hz | | | 2,65 t (2H) | 0,93 t | 8,20 s | |
| $IV_a$ | 970 | 1600 | 1680 | 1740 | — | — | 7,53 (1H); 6,35 (1H) | | 3,97 m (4H) | 2,28 m (4H) | 0,92 t | — | 1,20 t (3H) |
| IVb | 970 | 1600 | 1680 | 1740 | — | — | | | | | | | |
| Ia | 960 | 1650 | — | 1740 | — | 3200—3700 | 7,37 d (1H); 6,22 d,d (1H) | 3,27 м (1H) | 4,16 m (4H) | 2,28 t (2H) | 0,86 t | — | 1,22t (3H) |
| Ib | 960 | 1620 | — | 1740 | — | 3180—3600 | | | | | | — | |

| | $^{13}C$ NMR spectrum, $\delta$, ppm in $CCl_4$ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $C_{(1)}$ | $C_{(2)}$ | $C_{(3)}$ | $C_{(4)}$ | $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$, $C_{(22)}$ | $C_{(9)}$ | $C_{(10)}$ | $C_{(11)}$ | $C_{(12)}$ | $C_{(13)}$ |
| IV b | 14,33 | 59,71 | 172,38 | 41,97 | 24,70; 26,60; 28,70; 29,70; 30,42 | 33,88 | 125,28 | 121,46 | 127,55 | 129,55 |
| I b | 13,20 | 59,25 | 172,76 | 42,05 | 23,75; 25,75; 27,75; 29,03; 30,76 | 33,21 | 119,88 | 118,69 | 120,42 | 120,88 |

| | $C_{(14)}$ | $C_{(15)}$ | $C_{(16)}$ | $C_{(17)}$ | $C_{(18)}$ | $C_{(19)}$ | $C_{(20)}$ | $C_{(21)}$ | $C_{(23)}$ | $C_{(24)}$ | $C_{(25)}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IV b | 138,55 | 134,37 | 120,36 | 123,46 | 109,45 | 103,54 | 197,85 | 43,07 | 31,61 | 22,51 | 13,96 |
| I b | 136,26 | 134,53 | 117,78 | 119,42 | 108,32 | 100,58 | 71,81 | 42,59 | 31,49 | 21,56 | 13,01 |

cm, l 25 cm) L40/100 with elution by a 1:19 acetone–chloroform mixture, 0.08 g (52%) of compound Ia was isolated. Oil, $R_f$ 0.78 (B).

dl-2-(trans-3-Hydroxyocten-1-yl)-N-(6-ethoxycarbonylhexyl)indole (Ib) was obtained and isolated in the same way as Ia. A 0.1 g (20 mmole) portion of $NaBH_4$ and 20 ml of 70% 2-propanol were added to 0.32 g (0.8 mmole) of ketone IVb. After chromatographic purification, 0.18 g (56%) of compound Ib was obtained. Oil, $R_f$ 0.73 (B).

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# NEW SYNTHESIS OF INDOLE-7-CARBOXYLIC ACID


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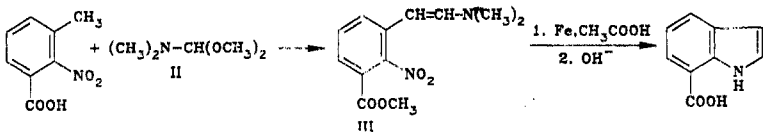
UDC 547.757.07



A new preparative method for the synthesis of indole-7-carboxylic acid has been developed, consisting in reductive cyclization of β-(dimethylamino)-3-carbomethoxy-2-nitrostyrene by the action of iron in acetic acid.


Indole-7-carboxylic acid is used in the synthesis of optical filter dyes, used for the protection of an exposed light-sensitive material fogging during its treatment in light [1, 2]. The known methods for the preparation of this compound are multistep and proceed with a low overall yield, which does not exceed 20% [3, 4].

In developing a new variant of the synthesis of indole-7-carboxylic acid [5], free of the above drawbacks, we used the method of constructing the indole ring, consisting in a reductive cyclization of β-(dialkylamino)-2-nitrostyrenes [6]. The latter compounds are most conveniently obtained by the condensation of substituted o-nitrotoluenes with DMFA dialkyl acetals [7]. In accordance with this, we selected 2-nitro-m-toluic acid (I) as the starting compound.




When acid I is heated with dimethyl acetal (II) in DMFA, an esterification of the carboxyl group takes place together with the formation of an enamine grouping. Reduction of enamine III by iron in acetic acid gives methyl indole-7-carboxylate, which, without purification, is hydrolyzed by boiling with an aqueous solution of sodium hydroxide. The overall yield of indole-7-carboxylic acid is thus 60%.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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 44-45, January, 1986. Original article submitted December 4, 1984.




0009-3122/86/2201-0036$12.50