INDOLE DERIVATIVES

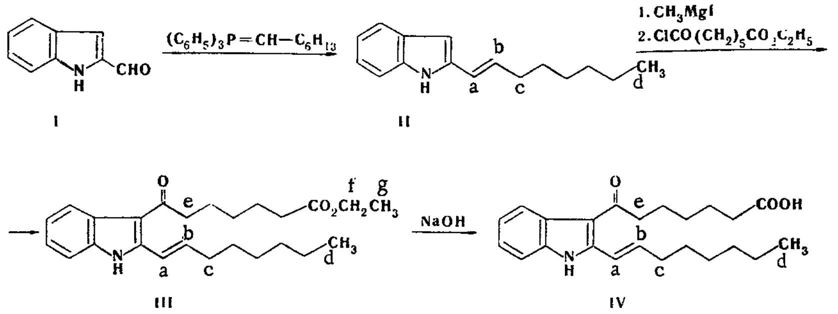
CIV.* SYNTHESIS OF 7-[2-(1-OCTEN-1-YL)-3-INDOLYL]-7-KETOHEPTANOIC ACID

V. G. Avramenko, N. N. Levinova,
V. D. Nazina, and N. N. Suvorov

UDC 547.752.757.07

2-(1-Octen-1-yl)indole was obtained by the Wittig reaction, and the product was used to prepare ethyl 7-[2-(1-octen-1-yl)-3-indolyl]-7-ketoheptanoate and the acid itself, which are possible model compounds in the synthesis of indole analogs of prostaglandins.

In developing our research involving a study of the Wittig reaction with formylindoles [2] and the synthesis of 3-indolylalkanoic acids [3] we obtained 7-[2-(1-octen-1-yl)-3-indolyl]-7-ketoheptanoic acid [4] and its ethyl ester [3]. These compounds may be used in the future for the synthesis of indole analogs of prostaglandins.



2-(1-Octen-1-yl)indole (II) is formed in good yield from 2-formylindole (I) and heptylidenephosphorane. The PMR spectrum (see Table 1) of II contains two doublets of triplets in the olefin proton region – at 5.80 ppm (spin–spin coupling constants $J_{H_bH_a}$ = 11.8 Hz and $J_{H_bH_c}$ = 7 Hz) and 6.12 ppm ($J_{H_bH_a}$ = 16.6 Hz and $J_{H_bH_c}$ = 6.8 Hz). The first doublet is related to the H_b signal of cis-2-(1-octen-1-yl) indole, and the second is related to the H_b signal of the trans isomer. The H_a signal appeared as doublets at 6.35 (cis) and 6.40 ppm (trans). The chemical shifts of the remaining protons differ to a lesser degree. In a quantitative respect, the PMR data show II is a mixture of 80% cis and 20% trans isomers.

Acylation of 2-(1-octene-1-yl)indole with the half-ester of pimeloyl chloride under the conditions recommended by A. N. Kost and V. N. Eraksina [4] gave ethyl ester III. Its 2,3-disubstituted indole structure was confirmed by the PMR spectrum (the 3-H signal of the indole ring is absent) and the mass spectrum, which contain peaks of $C_9H_{15}O_3^+$ (m/e 171) and $C_8H_{15}^+$ (m/e 111) ions, which correspond to fragments of the side chains. The ester is also a mixture of stereoisomers (55% trans and 45% cis forms).

Saponification of this ester with alcoholic alkali gives acid IV. We were able to isolate the trans isomer (probably) of the acid by means of thin-layer chromatography (TLC). The H_b signal in the PMR spectrum of this compound was detected only as one doublet of triplets at 6.55 ppm with $J_{H_bH_a}$ = 13.2 Hz and

---

*See [1] for communication CIII.

D. I. Mendeleev Moscow Chemical Engineering Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 204-206, February, 1975. Original article submitted May 25, 1974.

TABLE 1. PMR Spectra

Protons	Chem. shifts in ppm and signal character *		
	II	III	IV
Hd	0,96 t	0,80 t	0,92 t
Hg	—	1,20 t	—
Aliphatic protons	1,20—1,80 m	1,20—1,40 m Including H_b	1,10—2,60 m Including H_b
Hc	2,47 q		
He	—	2,96 m	3,00 t
Hf	—	4,04 q	—
Hb	5,80 t, cis 6,12 t, trans	5,80 m, cis 6,40 m, trans	6,55, trans
Ha	6,35 d, cis 6,40 d, trans		
Hh	6,62 s	—	—
Aromatic protons, except for H_4	7,10—7,55 m	6,60—7,60 m, Including H_a	6,90—7,70 m Including H_a
H_4	7,70 m	8,03 m, cis 7,80 m, trans	7,97 m
H_1	8,00 br s	9,96 br s, cis 10,23 br s, trans	8,00 m

---

*Symbols: t is triplet, d is doublet, q is quartet, s is singlet, br s is broad singlet, and m is multiplet.

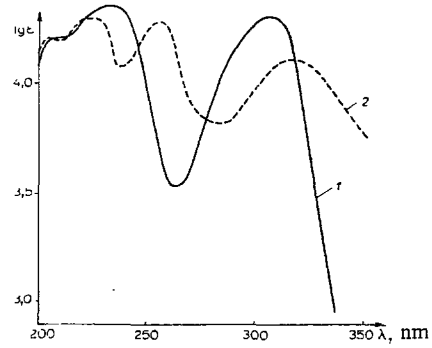


Fig. 1. UV spectra of ethanol solutions of: 1) 2-(1-octen-1-yl) indole (II); 2) ethyl 7-(2-[1-octen-1-yl]-3-indolyl) ketoheptanoate (III).

$J_{H_bH_c}$ = 5.5 Hz. The relatively low $J_{H_bH_a}$ value is possibly due to the effect of the protons of the methylene groups of the second side chain.

In contrast to the spectrum of indole itself, only two maxima at 234 and 307 nm are observed in the UV spectrum of indole II (Fig. 1). Both maxima are associated with $\pi-\pi^*$ polar transitions and are bathochromically shifted relative to the corresponding two bands of indole by 15 and 46 nm. The UV. spectrum of ester III in turn differs from the spectra of 3-acylindoles, particularly that of 3-acetylindole. It contains three maxima at 224, 256, and 319 nm. If the first are characteristic for the indole system, the last one is probably due to the electronic transitions in the new O=C−C=C−CH=CH−R system (λ_{max} calculated 318 nm, λ_{max} found 295 nm).

The authors sincerely thank Master of Chemical Sciences K. F. Turchin for his assistance in the interpretation of the PMR spectra.

EXPERIMENTAL

The UV spectra of ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The IR spectra of carbon tetrachloride solutions were recorded with a UR-10 spectrometer. The PMR spectra of deuterochloroform solutions were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples at (U = 50 eV).

2-(1-Octen-1-yl)indole (II). A few crystals of $FeCl_3$ and 0.67 g (29 mmole) of sodium metal were added to 150 ml of liquid ammonia, and the mixture was stirred until the blue coloration disappeared. Stirring was then continued for another 30 min, and 12.7 g (29 mmole) of heptyltriphenylphosphonium bromide [5] was added rapidly, during which a bright-orange coloration, which attests to the formation of heptylidenetriphenylphosphorane, appeared. The mixture was then diluted with 100 ml of absolute ether, the ammonia was evaporated, and a solution of 2.1 g (14.5 mmole) of 2-formylindole [6] in 100 ml of absolute ether was added dropwise. The mixture was then stirred for 1 h, the precipitated triphenylphosphine oxide was removed by filtration, the solvent was removed by distillation, and the residue was passed through a column filled with activity II Al_2O_3 with elution of petroleum ether to give 2.8 g (85%) of a light-yellow oil. IR spectrum: 3490 (NH), 1650 (C=C), and 960 cm^{-1} (γ_{CH} in CH=CH for the trans isomer). Found: C 84.5; H 9.4; N 6.4%. $C_{16}H_{21}N$. Calculated: C 84.6; H 9.2; N 6.2%.

Ethyl 7-[2-(1-Octen-1-yl)-3-indolyl]-7]ketoheptanoate (III). A solution of 1.7 g (7.5 mmole) of 2-(1-octen-1-yl)indole in 12 ml of ether was added dropwise to a solution of methylmagnesium iodide, prepared from 0.36 g (15 mg-atom) of magnesium and 2.56 g (18 mmole) of methyl iodide in 10 ml of ether, and the resulting yellowish mass was heated for 1 h, after which an ether solution of 1.5 g (7.5 mmole) of the ethyl ester of pimeloyl chloride [7] was added dropwise to it. The viscous oil that deposited on the bottom of the flask after 1 h was treated with 10.5 ml of ice water and 7.5 ml of 2N acetic acid. The ether layer was separated and dried with anhydrous magnesium sulfate. Purification with a column filled with Al_2O_3 [benzene–ether (1 : 1)] gave 2.4 g (80.5%) of ester III (yellow oil). IR spectrum: 3480 (NH), 1740 and 1680 cm^{-1} (CO). Found: C 75.0; H 8.8; N 3.5%. $C_{25}H_{35}NO_3$. Calculated: C 75.5; H 8.8; N 3.5%.

trans-7-[2-(1-Octen-1-yl)-3-indolyl]-7-ketoheptanoic Acid (IV). A 0.6-g (1.5 mmole) sample of ester III was refluxed with 2.4 ml of a 1 N alcohol solution of sodium hydroxide for 4 h, after which the alcohol was removed by distillation, and the residue was dissolved in water. The aqueous solution was acidified to pH 3 with hydrochloric acid, and the resulting oil was extracted with ether. The extract was dried with anhydrous magnesium sulfate, and the solvent was removed by distillation to give 0.36 g (64%) of an oily substance. The product was purified with a column filled with silica gel with elution by chloroform. IR spectrum: 3480 (NH), 1720 and 1650 (CO), 3530 (OH), and 2400-3600 cm^{-1} (OH of the dimer). Found: C 74.6; H 8.7; N 3.4%. $C_{23}H_{31}NO_3$. Calculated: C 74.8; H 8.4; N 3.8%.

LITERATURE CITED

1. N. N. Suvorov, B. Ya. Eryshev, L. E. Frumin, and A. G. Dubinin, Khim. Geterotsikl. Soedin., 1506 (1974).
2. N. N. Suvorov, I. A. Orlova, and K. F. Turchin, Khim. Geterotsikl. Soedin., 250 (1969).
3. V. G. Avramenko, G. N. Pershin, P. I. Mushulov, O. O. Makeeva, B. Ya. Eryshev, L. B. Shagalov, and N. N. Suvorov, Khim.-Farmats. Zh., No. 3, 15 (1970).
4. A. N. Kost, V. N. Mitropol'skaya (Eraksina), S. P. Portnova, and V. A. Krasnova, Zh. Obshch. Khim., 34, 2989 (1964).
5. C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, J. Org. Chem., 28, 372 (1963).
6. S. Siddappa and G. A. Bhat, J. Chem. Soc., C, 178 (1971).
7. E. E. Blaise and A. Koehler, Bull. Soc. Chim. France, 7, 218 (1910).