INDOLE DERIVATIVES

LXXXVII.* IMPROVED METHODS FOR THE SYNTHESIS OF SKATYL- AND SUBSTITUTED SKATYLMALONIC ESTERS

N. N. Suvorov, V. S. Velezheva, and V. V. Vampilova

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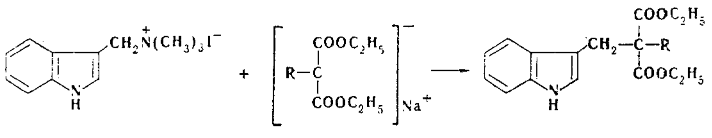
An improved method is proposed for obtaining skatyl- and substituted skatylmalonic esters by the alkylation of sodiomalonic esters with gramine methiodide in dimethylformamide in an inert-gas atmosphere, which leads to yields exceeding 90%. To obtain a skatylmalonic ester uncontaminated with the diskatylmalonic ester a method is proposed which involves the catalytic hydrogenation of a skatylidenemalonic ester over $Pd/CaCO_3$; yield 96%.

According to a method developed by Snyder, ethyl α-ethoxycarbonyl-α-(indol-β-ylmethyl)propionate (skatylmalonic ester) is obtained by the alkylation of sodiomalonic ester with gramine methiodide in dibutyl ether. Although the skatylmalonic ester is obtained by this method with a yield of 85%, this is in the form of an oily product difficult to purify. Another defect of the method is the necessity for using the explosion-hazardous dibutyl ether and the long duration of the process. In the absence of a solvent, the time of the reaction lengthens still further, and an even more contaminated product is obtained [2].

On the basis of the available information on the mechanism of the reaction [2, 3], it appeared desirable to use dimethylformamide (DMFA) as a solvent in this case; we have previously used it successfully for performing the Michael reaction [4].

According to the method that we have developed, the alkylation of the sodiomalonic esters (I-IV) with gramine methiodide (V) is performed in DMFA in an inert-gas atmosphere at a temperature of 100-120°C. The time of the reaction is 4 h-4 h 30 min.



V I-IV VI-IX

I, VI R = H; II, VII R = C_2H_5; III, VIII R = C_4H_9; IV, IX R = C_6H_5

The methiodide (V) for performing the alkylation can be prepared by a known method [2] from gramine and methyl iodide in absolute ethanol with its subsequent isolation. We have succeeded in simplifying this stage and preparing the methiodide (V) from the same starting materials in DMFA and using it in the reaction without isolation. The yields of the skatylmalonic esters (VI-IX) exceed 90%, and the ester (VI) is obtained directly from the reaction mixture in the form of a white crystalline compound in a purer state than by Snyder's method [2].

Our attempt to use an equimolar ratio of the reactants led to the formation, in addition to the ester (VI), of another compound to which, on the basis of the results of elementary analysis and those of IR, UV, and PMR spectroscopy, we have ascribed the structure of diskatylmalonic ester (X).

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On checking the purity of the skatylmalonic ester (VI) synthesized by Snyder's method [2] by thin-layer chromatography on Al_2O_3, we found that it contains a considerable amount of the ester (X), which remains even after one or two recrystallizations from ethanol. The ester (VI) synthesized by our modified method contains only traces of the ester (X) which are eliminated in the process of crystallization. In order to obtain the ester (VI) free from contamination with the ester (X), we have used a method [5] of the indirect alkylation of malonic ester which consists of the preparation of the skatylidenemalonic ester (XI) and its subsequent catalytic reduction over PtO_2 at 50 atm with a yield of the ester (VI) of 62%.

According to our modified method, the reduction of the ester (XI) was performed at a temperature of 50°C and at atmospheric pressure using $Pd/CaCO_3$ as catalyst, whereupon the yield of the ester (VI) was 96%. The ester (VI) that we synthesized by the two modified methods was identical with the compound obtained by Snyder's method [2].

We confirmed the structure of the ester (VI) by IR, UV, and PMR spectroscopy, since Snyder used only the results of elementary analysis for this purpose and the formation of compounds of a similar type is frequently accompanied by rearrangements [3].

The structures of the substituted skatylmalonic esters (VII-IX) were also confirmed satisfactorily by IR, UV, and PMR spectroscopy.

EXPERIMENTAL

The IR spectra of the compounds obtained were recorded on a UR-10 instrument and the UV spectra on an SF-4 spectrophotometer in ethanol. The PMR spectra were taken on a JNM-4H-100 instrument using tetramethylsilane as internal standard; the following abbreviations are used: s – singlet; d – doublet; t – triplet; q – quartet; m – multiplet.

Skatylmalonic Ester (VI). a) Preparation of gramine methiodide. To a solution of 4.52 g (2.5 mmoles) of gramine in 15 ml of DMFA was added, by drops, 3.69 g (2.5 mmoles) of methyl iodide, and the mixture was left for 10-12 h.

b) Alkylation with gramine methiodide. To the sodium ethoxide prepared from 0.57 g of Na (2.48 mg-atoms) and 10 ml of absolute ethanol was added 10 g (5.9 mmoles) of malonic ester, the mixture was stirred, and the ethanol was distilled off to dryness in vacuum. The resulting sodiomalonic ester was dissolved with stirring in 10 ml of DMFA and the gramine methiodide prepared previously was added. The reaction mixture was heated at 110-120°C with stirring in a strong current of nitrogen for 4-5 h, and was then treated with water and extracted with ether. The ethereal extracts were washed with 10% HCl and with water and were dried with $MgSO_4$. The ether was distilled off, and the residual oil crystallized on the addition of petroleum ether. Yield 7.17 g (95%); mp 63-64°C (from aqueous ethanol). According to the literature [2], mp 60-61°C. IR spectrum in paraffin oil, cm^{-1}: 1720, 1750, C=O in an ester, 3360 (NH in an indole). UV spectrum, nm: λ_{max} 282, 290; log ε 3.80, 3.75. PMR spectrum in $(CD_3)_2CO$, δ, ppm: 1.18 (t) and 9.97 (q) – two ester C_2H_5 groups; 3.29 (unsym. d) – CH_2 of skatyl; 3.76 (q) – CH of a malonic ester; 6.93-7.25 (m) and 9.87 (s) – NH; intensity ratio 6 : 4 : 2 : 1 : 5 : 1.

Skatylmalonic Ester (VI). With heating, 2 g (0.7 mmole) of skatylidenemalonic ester (XI) [5] was dissolved in 20 ml of ethanol and hydrogenated in the presence of 0.3 g of $Pd/CaCO_3$ at 50°C. Hydrogenation was complete after 1 h 30 min-2 h, the theoretical amount of hydrogen having been absorbed. The catalyst was filtered off and washed with ethanol, and the filtrate was evaporated to give 2.05 g (96%) of the ester (VI), mp 63-64°C; a mixture with the ester (VI) obtained by the method described above gave no depression of the melting point.

Diskatylmalonic Ester (X). This was obtained from 0.57 g of Na (2.48 mg-atoms), 4.8 g (3.0 mmoles) of malonic ester, 4.35 g (2.5 mmoles) of gramine, and 3.54 g (2.5 mmoles) of methyl iodide in 20 ml of DMFA by a method analogous to the synthesis of the ester (VI) with the exception of the fact that the ester (X) was isolated by chromatography on a column of Al_2O_3 with successive elution by chloroform and chloroform–acetone (20 : 1). The separation was monitored by thin-layer chromatography on Al_2O_3 using chloroform–acetone (1 : 1). This gave the ester (VI), mp 63-64°C, R_f 0.82, and the ester (X), mp 130-132°C (from ethanol), R_f 0.54. IR spectrum in paraffin oil, cm^{-1}: 1720 s and 1740 s (two ester C=O groups) and 3380 s cm^{-1} (NH). PMR spectrum in $(CD_3)_2CO$, δ, ppm: 1.04 (t) and 3.92 (q)–two ester C_2H_5 groups; 3.52 (s)–two skatyl CH_2 groups; 6.93-7.25 (m)–aromatic CH groups; 10.04 (s)–NH; intensity ratio 6 : 4 : 4 : 5 : 1.

(Ethyl)(skatyl)malonic Ester (VII). Ethylmalonic ester was obtained by the catalytic hydrogenation of ethylidenemalonic ester [6] in the presence of Raney Ni. A purity analysis was performed by the GLC method on a Chrom-2 instrument using a copper column with $l = 23.5$ m, d=4 mm, with Chromosorb W, 80-100 mesh, as the solid phase and Tween-60 (12%) as the liquid phase, and nitrogen as the carrier gas at a rate of flow of 80 ml/min, at a temperature of 140°C. The ester (VII) was obtained from 0.57 g (2.48 mg-atoms) of Na, 9.3 g (4.95 mmoles) of ethylmalonic ester, 4.52 g (2.5 mmoles) of gramine, and 3.69 g (2.5 mmoles) of methyl iodide in 25 ml of DMFA at 100°C in a time of 4 h, as for the synthesis of the ester (VI). The oil obtained after the working up of the reaction mixture was washed several times with petroleum ether by decantation in order to eliminate the excess of ethylmalonic ester and was dried in a vacuum pistol. Yield 7.15 g (90.3%); n_D^{20} 1.5240. An analytically pure sample was obtained by preparative chromatography in a thin layer of Al_2O_3 with chloroform as the eluting solvent; R_f 0.45, n_D^{20} 1.5335. Found: C 68.1; H 7.3; N 4.1. $C_{18}H_{23}NO_4$. Calculated: C 68.2; H 7.3; N 4.4%. IR spectrum (in the form of a film), cm^{-1}: 1720-1740 s broad (two ester C=O groups), 3420 s broad (NH). UV spectrum: λ_{max} 280, 290 nm; log ε 3.80, 3.75. PMR spectrum in CCl_4, δ, ppm: 0.94 (t), 1.95 (q) – C_2H_5; 1.15 (t), 4.05 (q) – two ester C_2H_5; 3.35 (s) – skatyl CH_2; 6.68-7.45 (m) – aromatic CH; 8.48 (s) – H; intensity ratio 3:2:6:4:2:5:1.

<u>(Butyl)(skatyl)malonic Ester (VIII).</u> This was obtained from 0.57 g (2.48 mg-atoms) of Na, 10 g (4.62 mmoles) of butylmalonic ester previously distilled through a Widmer column (bp 132-136°C/20 mm, n_D^{20} 1.4240), 4.52 g (2.5 mmoles) of gramine, and 3.69 g (2.5 mmoles) of methyl iodide in 25 ml of DMFA at 100°C for 4 h. The oil formed as the result of the working up of the reaction mixture crystallized on the addition of petroleum ether, giving 5.46 g of the ester (VIII) with mp 60-61°C (from ethanol). An additional 2.3 g of the ester (VIII) was isolated from the filtrate by chromatography in a column of Al_2O_3 with elution by chloroform, R_f 0.48. The total yield was 7.76 g (90.5%). Found: C 69.6; H 7.9; N 3.8%. $C_{20}H_{27}NO_4$. Calculated: C 69.6; H 7.8; N 4.1%. IR spectrum in paraffin oil, cm^{-1}: 1720 s, 1740 s (two ester C=O groups), 3400 s (NH).

<u>(Phenyl)(skatyl)malonic Ester (IX).</u> This was obtained from 0.29 g (1.26 mg-atoms) of Na, 12 g (5.1 mmoles) of phenylmalonic ester (bp 160-168°C/20 mm, n_D^{20} 1.4925) [7], 2.28 g (1.31 mmole) of gramine, and 1.85 g (1.31 mmole) of methyl iodide in 15 ml of DMFA by analogy with the synthesis of the ester (VI). The alkylation time was 4 h and the temperature 100°C. Yield 4.21 g (92%), mp 93-94°C (from a mixture of benzene and petroleum ether and then from ethanol). Found: C 72.8; H 6.5; N 3.6%. $C_{22}H_{23}NO_4$. Calculated: C 72.4; H 6.3; N 3.8%. IR spectrum in paraffin oil, cm^{-1}: 1700 s, 1748 s (two ester C=O groups), 3380 (NH). UV spectrum: λ_{max} 280, 290; log ε 3.74, 3.68. PMR spectrum in $(CD_3)_2CO$, δ, ppm: 1.06 (t) and 3.95 (q) – two ester C_2H_5 groups; 3.74 (s) – skatyl CH_2; 6.87-7.78 (m) – aromatic CH; 9.82 (s) – NH.

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