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INDOLE DERIVATIVES. I. β-(3-INDOLYL)KETONES

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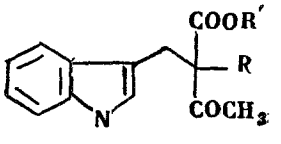
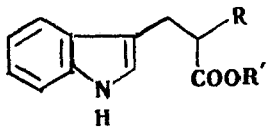
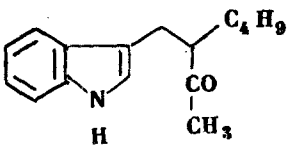
A number of α-skatyl-α-substituted acetoacetic esters (ethyl, tert.-butyl, and benzyl) are prepared by treating gramine with sodium derivatives of α-substituted acetoacetic esters. When ethyl α-alkyl-α-skatylacetoacetates are heated with dilute alkali, they are split into indole and a substituted acetoacetic ester, while saponification with concentrated alcoholic alkali gives α-substituted β-(3-indolyl)propionic acids. 3-Skatyl-heptan-2-one can be obtained by pyrolysis of 3-skatyl-3-carbo-tert.-butoxyheptan-2-one, or by hydrogenolysis of 3-skatyl-3-carbobenzoxyheptan-2-one over a palladium catalyst. Alkylation of cycloheptanone and cyclohexanone enamines by gramine gives cyclic β-(3-indolyl)ketones, viz., 2-skatylcyclopentanone and 2-skatylcyclohexanone.

The literature describes two methods of synthesizing β-(3-indolyl)ketones, namely addition of indole derivatives to vinylketones [1], and decarboxylation of skatylacetoacetic esters (lacking a second substituent in the α position of the acetoacetic acid), which are obtained by alkylating acetoacetic acid with compounds of the gramine type [2]. An attempt to pass to 2-skatylcycloalkanones by saponification of the corresponding cyclic ketoesters gave only dibasic acids [3]. 2-(2-Carbethoxyskatyl)cyclohexanone was synthesized by hydrogenolysis of 2-(2-carbethoxyskatyl)-2-carbobenzoxycyclohexanone [3].

A number of new skatylacetoacetic esters have been synthesized, and the conditions under which they suffer ketonic decomposition investigated, with a view to preparing α-substituted β-(3-indolyl)ketones. Starting materials were 3-skatyl-4-phenyl-3-carbethoxybutan-2-one (I), 3-skatyl-3-carbethoxyheptan-2-one (II), and 2-skatyl-2-carbethoxycyclopentanone (XI), obtained by the action of gramine methiodide on the corresponding substituted β-keto esters in the presence of sodium ethoxide. When an attempt was made to synthesize the ester III, only its deacetylation product, skatylmalonic ester, was isolated.



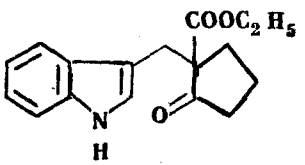




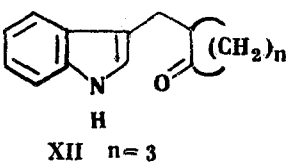
X

I R=$CH_2C_6H_5$; R′=C_2H_5
II R=C_4H_9; R′=C_2H_5
III R=$COOC_2H_5$; R′=C_2H_5
IV R=C_4H_9; R′=$C(CH_3)_3$
V R=C_4H_9; R′=$CH_2C_6H_5$

VI R=$CH_2C_6H_5$; R′=H
VII R=C_4H_9; R′=H
VIII R=C_4H_9; R′=CH_3
IX R=$(CH_2)_3COOH$; R′=H

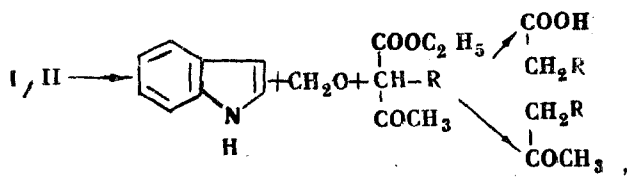


XI



XII n=3
XIII n=4

The resultant skatylacetoacetic esters were extremely unstable in acid medium, and hence could be submitted only to alkaline hydrolysis. However, it was shown that when esters I and II are treated with dilute alkali, they decompose according to the equation



while the cyclic analog XI gives α-skatyladipic acid. The requisite ketones are obtained only in inadequate amounts, and cannot be isolated pure from the reaction mixture.

Concentrated alcoholic alkali splits the keto esters I, II, and XI to the corresponding acids, α-skatyl-β-propionic acid (VI), α-skatylcapronic acid (VII), and α-skatyladipic acid (IX). The acid VII is a liquid which oxidizes rapidly in air (characterized by its stable methyl ester).

Since it proved impossible to obtain the β-(3-indolyl)ketones from the ethyl esters of skatylacetoacetic acids, attention was turned to other possible methods of synthesis. Recently [4], a simple and convenient method has been worked out for preparing ketones from tert.-butyl esters of acetoacetic acids by heating with a catalytic amount of p-toluenesulfonic acid. To find out whether it was possible to apply this method to indole derivatives, 3-skatyl-3-carbo-tert.-butoxyheptan-2-one (IV) was synthesized, and heated with p-toluenesulfonic acid. The result was complete destruction of the keto ester IV, which, however, was smoothly hydrolyzed when heated to 240° without a catalyst, giving a high yield of 3-skatylheptan-2-one (X), also prepared by hydrogenolysis of 3-skatyl-3-carbobenzoxyheptan-2-one (V) over a palladium catalyst. The benzyl α-acetocapronate required for synthesizing the keto ester V is obtained by transesterification of the corresponding ethyl ester.

Tert.-butyl and benzyl esters of cyclic β-ketoacids are accessible only with difficulty, so to prepare 2-skatylcycloalkanones use was made of a recently described [5] method of alkylating the cyclohexanone enamine with Mannich bases. 2-Skatylcyclopentanone (XII) and 2-skatylcyclohexanone (XIII) are obtained by heating the enamines of the corresponding ketones with gramine in the presence of catalytic amounts of p-toluenesulfonic acid followed by saponification of the condensation products by refluxing in aqueous dioxane.

EXPERIMENTAL

Benzyl α-acetylcapronate. 8 g ethyl α-acetylcapronate, 4.7 g benzyl alcohol, and 25 ml xylene are heated in a flask, fitted with a condenser for downward distillation, at a rate such that in four hours most of the xylene-alcohol azeotrope has distilled off. The residue is fractionated in a vacuum. Yield 8.50 g (79%), bp 132-134° (2 mm), 154° (5 mm). Found: C 72.31, 72.34; H 8.16, 8.14%. Calculated for $C_{15}H_{20}O_3$: C 72.56; H 8.12%.

Skatylacetoacetic esters

a) To 0.79 g sodium in 50 ml anhydrous alcohol was added an equimolecular amount of the substituted acetoacetic ester, followed by 6.0 g gramine. The mixture was stirred under nitrogen, 4.88 g methyl iodide in 10 ml alcohol were added dropwise, and the mixture left at room temperature for 18-20 hr. The mixture was then boiled thoroughly until trimethylamine ceased to be evolved. The reaction mixture was cooled and filtered, the solvent evaporated, 15-20 ml water poured in, and the solution extracted with chloroform. The organic layer was washed with dilute acetic acid, water, and soda solution. After distilling off the solvent, the residue was chromatographed over aluminium oxide. The oil obtained, which solidified on standing, was recrystallized from petroleum ether-benzene or carbon tetrachloride.

b) 1.84 g dimethyl sulfate were added to 2.25 g gramine in 17 ml anhydrous alcohol, the temperature being held at 0°, and after 30 min an equimolecular amount of the substituted acetoacetic ester was added, followed by a solution of 0.336 g sodium in 6 ml anhydrous alcohol. The mixture was heated for five hours under nitrogen, and the reaction products isolated as in method (a) above.

Skatylacetoacetic esters

Compound	Name	Synthesis method	Yield, %	Mp, °C	n_D^{20}	Mol. formula	Found, %	Calc., %
I	3-Skatyl-4-phenyl-3-carbethoxy-butan-2-one	a	80	66—67	1.5820	$C_{22}H_{23}NO_3$	C 76.06; 75.87 H 6.91; 6.80 N 4.16; 3.93	C 75.63 H 7.01 N 4.04
II	3-Skatyl-3-carbethoxy-heptan-2-one	a	76	65—66	—	$C_{19}H_{25}NO_3$	C 72.40; 72.11 H 8.05; 7.86 N 4.49; 4.52	C 72.31 H 7.97 N 4.46
XI	2-Skatyl-2-carbethoxycyclo-pentanone	a	70	—	1.4963	$C_{17}H_{19}NO_3$	C 71.96; 71.53 H 7.19; 7.00 N 4.50; 4.42	C 71.54 H 6.71 N 4.95
IV	3-Skatyl-3-carbo-tert.-butoxy-heptan-2-one	b	91	—	1.5260	$C_{21}H_{29}NO_3$	C 73.69; 73.94 H 8.42; 8.35 N 3.93; 3.81	C 73.44 H 8.51 N 4.08
V	3-Skatyl-3-carbo-benzoxy-heptan-2-one	c	69	89—90	—	$C_{24}H_{27}NO_3$	C 76.35; 76.68 H 7.14; 7.24 N 3.86; 3.97	C 76.63 H 6.92 N 3.74

c) 5.15 g gramine and an equimolecular quantity of the substituted acetoacetic ester was boiled in 25 ml xylene with 0.35 g sodium hydroxide. After eight hours the reaction mixture was cooled and washed with water, dilute acetic acid, and soda solution. After distilling off the solvent the residue was chromatographed on aluminum oxide.

The constants of the compounds obtained are given in the table.

α-Skatyl-β-phenylpropionic acid (VI). A mixture of 2.35 g compound I and 6 ml 25% alcoholic potassium hydroxide solution was heated for 2 hr 30 min at 80-90° under nitrogen. The mixture was then cooled, 24 ml water added, and the whole extracted with ether. The aqueous layer was acidified with acetic acid, and the α-skatyl-β-phenylpropionic acid (VI), along with an unknown substance, extracted with ethyl acetate. Two methods were employed to separate them:

a) The ethyl acetate extract is extracted with (2 × 10 ml) sodium hydroxide solution, and by-products removed from the latter extract by extracting with ethyl acetate (10-15 × 4 ml). The aqueous extract is acidified with acetic acid, and a rapidly crystallizing oil extracted with ether. This is recrystallized from benzene-hexane, yield 1.407 g (74.4%).

b) 2.07 g of mixed acidic material extracted from the solution of reaction products is dissolved in methanol and chromatographed on 60 g silone [6]. 80% methanol elutes 1.52 g acid VI, mp 146-174°. Found: C 77.85, 77.62; H 6.32, 6.14; N 4.84, 4.92%. Calculated for $C_{18}H_{17}NO_2$: C 77.40; H 6.13; N 5.05%.

Methyl α-skatylcapronate (VIII). α-Skatylcapronic acid was prepared from the keto ester II in a way similar to that used for preparing acid VI. Diazomethane converted the acid to the methyl ester, which was purified on alumina and distilled. Yield 40%, bp 134-136° (0.05 mm), n_D^{20} 1.5433. Found: C 74.57, 74.32; H 8.44, 8.29; N 5.29, 5.37%. Calculated for $C_{16}H_{21}NO_2$: C 74.10; H 8.20; N 5.40%.

α-Skatyladipic acid (IX). 5.3 g compound XI, 21.5 ml alcohol, and 21.5 ml 5% aqueous sodium hydroxide solution were autoclaved at 150° for five hours.

The reaction product was evaporated in a vacuum to half volume, a saturated solution of sodium sulfate added, and the whole extracted with ether. The aqueous layer was acidified with acetic acid, extracted with ether, and recrystallized. Yield 2.65 g (63.9%). The acid IX can also be obtained in 62-63% yield by the method described for synthesis of acid VI. Mp 170-171° (from methanol). Found: C 65.19, 65.22; H 6.17, 6.06; N 5.08, 5.17%. Calculated for $C_{15}H_{17}NO_4$: C 65.44; H 6.23; N 5.09%.

3-Skatylheptan-2-one (X).

a) 4.32 g IV were heated at 240° (2-4 mm) for 30-40 min. The reaction product was extracted with ether, chromatographed on 40 g active carbon, and eluted with benzene, to give 2.65 g (86.5%) of a viscous yellow liquid, n_D^{20} 1.5369. Found: C 78.79, 78.60; H 8.65, 8.55; N 5.52, 5.71%. Calculated for $C_{16}H_{11}NO$: C 78.97; H 8.70; N 5.76%.

b) 0.795 g V, 8 ml alcohol, and 0.159 g 10% palladium on carbon were agitated in a current of hydrogen for 10 hr at room temperature. The catalyst was filtered off, and the solvent evaporated in a vacuum. 2.5 ml anhydrous alcohol, 2.5 ml pyridine, and 0.5 g hydroxylamine hydrochloride were added to the residue, and the mixture heated for five hours. The resultant solution was diluted with water and extracted with ether, the extract carefully washed with acetic acid and then with water until neutral and dried; the ether was distilled off, and the residue chromatographed on aluminum oxide, to give 360 mg (66%) of oxime X, mp 94° (from benzene-petroleum ether). Found: C 74.42; 74.76; H 8.60, 8.63; N 10.75%. Calculated for $C_{16}H_{22}N_2O$: C 74.42; H 8.58; N 10.84%.

2-Skatylcyclopentanone (XII). 1.805 g 1-morpholinocyclopentene, 2.060 g gramine, and 12 mg p-toluenesulfonic acid were heated in an inert atmosphere for 30 min/130-135°. The mixture was cooled, 4 ml dioxane and 0.5 ml water were added, and the whole was refluxed for 1 hr. The solvent was evaporated in a vacuum, the residue dissolved in methylene chloride, washed with dilute acetic acid, soda solution, and water, the solvent evaporated, and the product chromatographed on aluminum oxide to give 1.613 g (64%) of the compound, mp 61-62° (from benzene-petroleum ether). Found: C 79.07, 79.09; H 7.07, 7.09; N 6.46, 6.67%. Calculated for $C_{14}H_{15}NO$: C 78.84; H 7.09; N 6.57%.

2-Skatylcyclohexanone (XIII). Prepared similarly to XII. Yield 65%. Mp 71-72° (from benzene). Found: C 79.58, 79.68; H 7.46, 7.43; N 6.19, 6.33%. Calculated for $C_{15}H_{17}NO$: C 79.30; H 7.51; N 6.16%.

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