INDOLE CHEMISTRY

VII. New Method of Synthesizing Lilolidenes

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 4, pp. 704–707, 1967

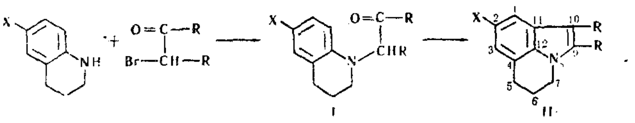
UDC 547.753+541.67

A new method of synthesizing lilolidenes (1,7-trimethyleneindoles), by reacting 1,2,3,4-tetrahydroquinolines with α-bromoketones, is given. PMR spectra of 2-substituted lilolidenes are obtained, and the effects of chemical substituents at positions 1 and 3 in the lilolidene ring on the chemical shift of protons is considered.

We previously developed a method of synthesizing lilolidene-type structures, i.e. 1,7-trimethyleneindole, from 1-amino-1,2,3,4-tetrahydroquinoline and carbonyl compounds, by a Fischer type reaction [1]. This method makes it possible to prepare lilolidenes with alkyl and aryl substituents [1, 2], and functional substituents [3] in the pyrrole part of the molecule. 6-Methyl-1,2,3,4-tetrahydroquinoline was used as the starting material for preparing the desired 2-methyllilolidenes (i.e. 5-methyl-1,7-trimethyleneindoles).

However, when at attempt was made to start from 6-methoxy-1,1,3,4-tetrahydroquinoline, great difficulties were encountered at the stage of preparing 1-amino-1,2,3,4-tetrahydroquinoline. Reduction of 1-nitroso-6-methoxy-1,2,3,4-tetrahydroquinoline under the most diverse conditions resulted in breaking of a N—N bond, and an almost quantitative yield of 6-methoxy-1,2,3,4-tetrahydroquinoline.

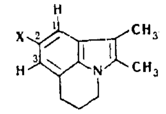
The required 2-methoxy-9,10-dimethyllilolid-9-ene was readily obtained by reacting 6-methoxy-1,2,3,4-tetrahydroquinoline with 3-bromobutan-2-one, the equation being:



II R = CH_3, X = H. III R = CH_3, X = CH_3O. IV R = $(CH_2)_4$, X = H. V R = $(CH_2)_4$, X = CH_3O.

Both unsubstituted tetrahydroquinoline and other α-bromoketones react readily. For example, α-bromocyclohexanone and tetrahydroquinoline or its 6-methoxy derivative react to give good yields of the corresponding lilolidenes. Actually the reaction takes place via the intermediate formation of aminoketone I, which it was not possible to isolate analytically pure, since on distillation it partly cyclized to give a lilolidene derivative. However the course of the reaction could be followed chromatographically. When the reactants are mixed there is evolution of heat, to a degree that depends on the amounts used. When large amounts (0.5–0.7 mole) are used, the heating is so great that the reaction enters the second phase (cyclization usually occurs at 150°–180° C). Using cooling, or small amounts, the reaction may stop at the stage of formation of aminoketone. For example, when a mixture of 1,2,3,4-tetrahydroquinoline and 3-bromobutan-2-one was heated to 100° C, TLC on alumina gave a spot with Rƒ 0.48.* Further heating to 150° C led to vigorous reaction and evolution of steam, the aminoketone spot almost vanished, and a lilolidene spot Rƒ 0.85 appeared. Brief heating resulted in disappearance of the intermediate compound's spot, indicating completion of the reaction.

Chemical Shifts of Benzene Ring Proton Signals (ppm)



X	1-H	3-H	Δ 1-H	Δ 3-H
H	2.92	3.40	0	0
CH_3	3.13	3.57	0.21	0.17
CH_3O	3.54	3.72	0.62	0.32
Br	2.37	2.91	−0.55	−0.49
NO_2	1.90	2.38	−1.02	−1.02
$ClSO_2$	1.97	2.55	−0.95	−0.85
H_2NSO_2	2.10	2.74	−0.82	−0.66
$(CH_3)_2NSO_2$	2.30	2.85	−0.62	−0.55
$(C_2H_5)_2NSO_2$	2.15	2.90	−0.77	−0.50

Bromination of butan-2-one with elementary bromine is known to give a mixture of two isomers in the ratio 7:3 [4].

$$CH_3COCH_2CH_3 \longrightarrow \underset{VI}{CH_3COCHBrCH_3} + \underset{VII}{BrCH_2COCH_2CH_3}$$

Use of dioxane bromide as the brominating agent made it possible to obtain one isomer (VI) almost exclusively. GLC showed that the second isomer (VII) was present, though in insignificant quantity, and it could be removed by a single vacuum distillation.

It was previously observed that lilolidenes have a characteristic UV absorption curve [2], with maxima in the 290 and 230–233 nm regions. It might be thought that introduction of a methoxyl group must lead to a change in spectrum but both lilolidenes (III and V) containing a methoxyl group, absorb in the 285 and 230 nm regions, so that methoxyl at position

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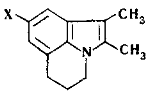
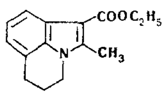
*Brockmann activity III alumina, with benzene as the mobile phase, in every case.

2 has only an insignificant effect on the lilolidene π electron system.

Lilolidenes with various substituents at position 2 being available, a study was made of the effects of various groups (H, CH_3, OCH_3, Br, NO_2, R_2NSO_2) on the chemical shift for protons ortho to that position, in the PMR spectrum. Some of the spectra have been published before [5, 6], the rest are given in the figure. The spectra were determined on a JNM-C-60 instrument, in deuterochloroform, and using tetramethyl silane as the internal standard. The previously obtained PMR spectrum of 9, 10-dimethyllilolid-9-ene, determined with an instrument with working frequency 60 Mc, does not enable aromatic protons to be assigned. The spectrum of this compound, as found with a 100 Mc instrument, has an aromatic region with two doublets τ 2.92 and 3.40 due to protons as positions 1 and 3, and a triplet τ 3.24, due to a proton at position 2.



VIII



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Because the doublet τ 2.92 is displaced in the direction of weaker fields in the spectrum of compound IX, which can be explained by the action of the carbethoxyl group on the proton at position 2, and not the one at position 3, the doublet τ 2.92 is assigned to the proton at position 1, and the doublet τ 3.40 the position 3 proton. In addition, this is in good agreement with the electron density distribution for indole [7], as calculated by the MO method. Actually the minimum electron density is at position 4 (position 1 of the lilolidene system corresponds to position 4 in indole).

Values of τ for substituted lilolidenes are given in the table.

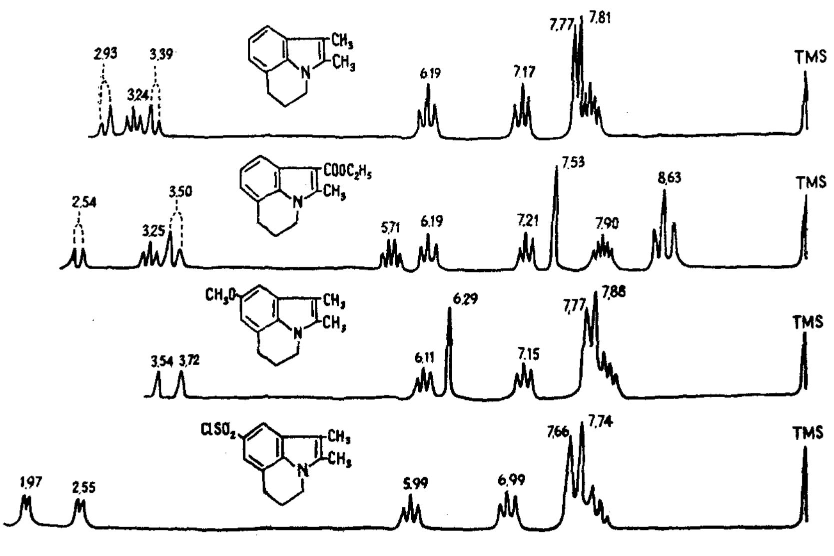
Introduction of a substituent of the first kind (CH_3, OCH_3) shifts the signal of the proton at position 1 by a greater amount than that of the proton at position 3. Obviously the position 2 substituent raises the electron density at the first carbon atom more than that at the third one. Hence, in the electrophilic substitution of the benzene ring of such lilolidenes, a relative increase in the amount of the 1-isomer would be expected. In the case of the second kind of substituent, with the exception of the nitro group, the reverse obtains. According to the above view, with such structures, electrophilic substitution at position 3 may predominate over that at position 1, but this conclusion is quite provisional, for it does not take into account structures of intermediates, steric factors, and other effects.

EXPERIMENTAL*

Bromination of butan-2-one. 232 g Dioxane dibromide is added gradually to a solution of 72 g butan-2-one in 200 ml ether, the rate of addition being such that the solution is completely decolorized after each addition. The products are then poured into water, the ether layer separated off, carefully washed with water and dried over $MgSO_4$ the ether distilled off, and the residue vacuum fractionated. The foreruns of 10–15 ml were rejected, and a cut with bp 48°–49° C (35 mm) [4] was taken, yield of 3-bromobutan-2-one 121 g (80%). It had to be stored in a refrigerator.

9, 10-Dimethyllilolid-9-ene (II). 45 g Tetrahydroquinoline and 25.4 g 3-bromobutan-2-one were carefully stirred together, the temperature gradually raised to 50° C, then heated to 150° C, when a vigorous reaction accompanied by evolution of steam started. When the reaction had finished (10 min), the temperature was raised to 180° C, and the hot products poured into 150 ml conc HCl. The mixture was diluted with water, when a pale yellowish precipitate came down, was filtered, dissolved in ether, and the ether solution washed a few times with water. The ether was removed, when 27 g (82%) almost colorless compound was obtained, mp 87°–88° C, R_f 0.85 (Al_2O_3 activity III, benzene).

2-Methoxy-9, 10-dimethyllilolid-9-ene (III). Prepared similarly from 6.6 g 6-methoxy-1, 2, 3, 4-tetrahydroquinoline and 3 g 3-bromobutan-2-one, yield 90%, mp 84°–85°C (ex EtOH), R_f 0.73



PMR spectra of $CDCl_3$ solutions of compounds

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*Collaborator N. G. Yaryshev.

(Al_2O_3 activity III, benzene). Found: C 78.26; 78.30; H 8.09; 8.13%, $C_{14}H_{15}NO$: C 78.14; H 7.90%.

1, 2, 3, 4, 6, 7, 8, 9-Octahydropyrido[1, m-1, 2, 3]carbazole (IV). Obtained by the same method, in 78% yield, from 2.7 g tetrahydroquinoline and 1.8 g α-bromocyclohexanone [8], mp 65°–66° C (ex EtOH) [2], R_f 0.87 (Al_2O_3 activity III, benzene).

12-Methoxy-1, 2, 3, 4, 6, 7, 8, 9-octahydropyrido[1, m-1, 2, 3]carbazole (V). Prepared similarly, from 2 g α-bromocyclohexanone and 3.7 g 6-methoxy-1, 2, 3, 4-tetrahydroquinoline, yield 72%, mp 87°–88° C (ex hexane), R_f 0.75 (Al_2O_3 activity III, benzene). Found: C 79.29; 80.08; H 7.98; 8.15%, calculated for $C_{16}H_{19}NO$: C 79.60; H 7.94%.

REFERENCES

1. A. N. Kost and L. G. Yudin, Khim. nauka i prom., 2, 800, 1957.
2. A. N. Kost, L. G. Yudin, and A. P. Terent'ev, ZhOKh, 29, 1949, 1959.
3. A. N. Kost, L. G. Yudin, B. A. Dmitriev, and A. P. Terent'ev, ZhOKh, 29, 3977, 1959.
4. H. Cardwell and A. Kilner, J. Chem. Soc., 2430, 1951.
5. A. N. Kost, L. G. Yudin, and V. A. Budylin, KhGS [Chemistry of Heterocyclic Compounds], 39, 1966.
6. A. N. Kost, L. G. Yudin, V. A. Budylin, and N. B. Mozzhukhina, KhGS [Chemistry of Heterocyclic Compounds], Collection I, 1967.
7. B. Pulman and A. Pulman, Quantum Biochemistry [Russian translation], Mir, Moscow, 614, 1965.
8. L. A. Yanovskaya and A. P. Terent'ev, ZhOKh, 22, 1598, 1952.
9. A. N. Kost and P. B. Terent'ev, ZhOKh, 29, 338, 1959.

25 August 1965

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