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# PHOTOINDUCED N-β-HYDROXYALKYLATION OF TROPAN DERIVATIVES

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*The photooxidation of tropan derivatives by ketones was studied; the targeting of the reaction to the* $N-CH_3$ *group with the formation of N-alkylation products and bis-tropan derivatives was demonstrated. The presence of two diastereomers in salts of N-alkyl derivatives of tropan was detected by PMR spectroscopy. An alternative method of synthesis of difficult-to-obtain amino alcohols was proposed.*

One of the best studied reactions in preparative organic photochemistry is the photoreduction of ketones by amines and alcohols, leading in the case of secondary and tertiary amines to dealkylation of the amines [1, 2], and in the case of alcohols to pinacones [3, 4, 5, 6]. It should be mentioned here that alcohols surpass amines as reducing agents.

In view of the fact that we were interested in the possibility of preparative synthesis of tropan derivatives with potential physiological activity, we studied the photooxidation of tropan and its analogs by ketones of various structure.

Tropan I — a bicyclic condensed system — contains two photoreaction centers — tertiary amine and secondary alcohol groups — which, considering what was stated above, did not rule out the possibility of two reaction pathways. Earlier, on the example of piperidol [7] and tropine (for a preliminary communication, see [8]), we demonstrated the possibility of photooxidation of the latter by ketones. According to the literature data it is also known that the photooxidation of tropan alkaloids, sensitized by salts, leads only to N-demethylated products [9, 10].

The reaction of tropan and its derivatives — tropine, pseudotropine, 3-acetyltropine, 3-chlorotropan, and tropinone — was conducted in benzene under the action of light with $\lambda > 250$ nm at an amine:ketone ratio of 1:2. Photolysis was conducted until virtual disappearance of the amine or until the establishment of equilibrium (monitored by gas–liquid chromatography). Aliphatic, aliphatic–aromatic, and aromatic ketones II (acetone, acetophenone, benzophenone) were used as the carbonyl components.

On the basis of the aggregate analytical data it was shown that the photooxidation of tropan and its derivatives proceeds solely on account of the reaction site associated with the tertiary amino group of tropan; the presence of a proton in the 3-position of the tropan ring, at ~4 ppm in the PMR spectra of compounds IIIa–i indicates that the second photoreaction center is not involved in the reaction. No products corresponding to other reaction pathways were detected in any of the cases.

Photoinduced oxidation of tropans Ia–i proceeds with the formation of three substances: the first is the product of addition of a ketyl radical to the α-aminoalkyl radical of IIIa–i; the second (IV) is the product of dimerization of two α-aminoalkyl radicals, released when tropine reacts with ketones IIb–d; and the third (pinacones V) is the product of dimerization of two ketyl radicals (not isolated). The experimental results and spectral characteristics of the adducts are presented in Table 1.

It is interesting to note that in the PMR spectra of salts of compounds IIIb and IIIg with trifluoroacetic acid, a double set of signals is observed, which is absent in the spectra of the bases of these and other compounds of this series. This phenomenon may be associated with the slowing of inversion of the nitrogen atom for the salts indicated above and the formation of an equilibrium mixture of two stereoisomers with equatorial and axial positions of the substituent at the nitrogen atom; the ratio of the two forms is 19:1, respectively. The formation of stereoisomers was noted earlier in a number of studies [11, 12], however, chiefly for salts of tropan compounds containing the $N-CH_3$ group.

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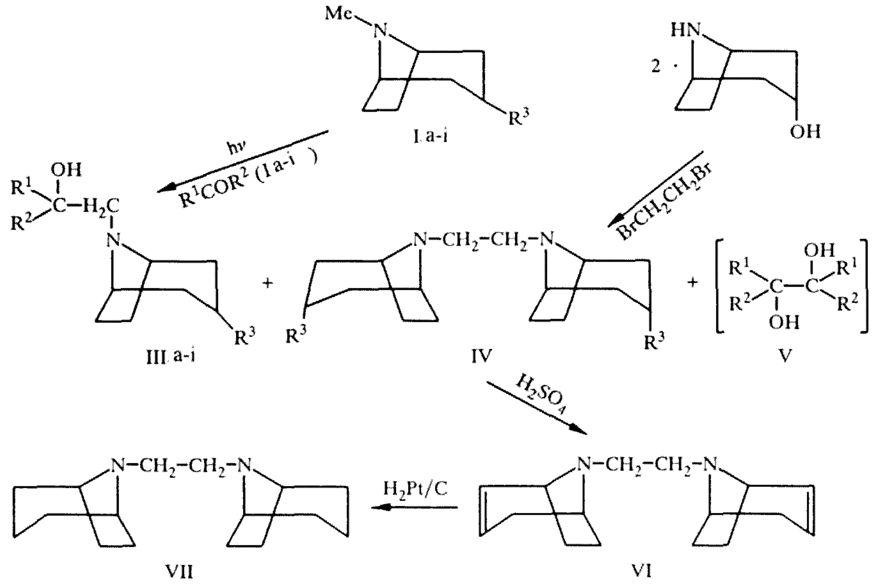

I, II, III, V a $R^1R^2 = C_6H_5$, $R^3 = H$; b $R^1R^2 = C_6H_5$, $R^3 = OH$; c $R^1 = CH_3$, $R^2 = C_6H_5$ , $R^3 = OH$;
d $R^1R^2 = CH_3$, $R^3 = OH$; e $R^1R^2 = C_6H_5$, $R^3 = OH$ ($\beta$); f $R^1R^2 = CH_3$, $R^3 = OH$ ($\beta$); g $R^1R^2 = C_6H_5$,
$R^3 = OCOCH_3$; h $R^1R^2 = C_6H_5$, $R^3 = Cl$; $R^1R^2 = C_6H_5$, $R^3 = O$. IV $R^3 = OH$

Compound IV exists in the form of high-melting crystals, insoluble in virtually the majority of solvents, which are deposited on the walls of the reactor during photolysis and which must be periodically removed for the reaction to go further. The structure of bis-tropine IV was demonstrated, in addition to the usual methods, by countersynthesis as well — the interaction of nortropine with 1,2-dibromoethane. The identity of compounds IV produced by the two pathways was demonstrated by IR spectroscopy.

The splitting out of two water molecules from bis-tropine IV gave the diene VI with a 64.6% yield, possessing four proton signals at 5.3-5.9 ppm in the PMR spectrum, and a peak of the molecular ion equal to 244 and the corresponding fragmentation in the mass spectrum. The diene VI is readily hydrogenated over Pt with the formation of the bis-tropan structure VII. In the photolysis of compound Ia, together with the product IIIa, compound VII, which was identified by gas–liquid chromatography with the compound obtained by reduction of the diene VI, is formed in a yield of 15%.

Photolysis of a mixture of pseudotropines Ie,f with benzophenone and acetone under standard conditions also leads to products of addition of the ketyl radical to the $\alpha$-aminoalkyl radical of pseudotropine; however, the reaction with pseudotropine occurs with lower yields than in the case of the analogous reaction with tropine. Virtually none of the bis-structure IV is formed, which indicates an influence on the course of the reaction by the intramolecular hydrogen bond (characteristic of pseudotropine), which lowers the nucleophilicity of the reaction site; in addition, the equatorial con-figuration of the secondary alcohol group probably creates supplementary steric hindrances for attack of an excited ketone molecule and subsequent addition of the ketyl radical formed.

The reaction of benzophenone with the tropan derivatives Ig,h,i proceeds analogously. The reaction proceeds with the formation chiefly of IIIg,h,i with yields of 40-43%; formation of a dimer product of the IV is negligible in this case.

We should mention that the introduction of electron acceptor substituents into the 3-position of the tropan ring does not change the direction of the reaction with respect to the N-$CH_3$ group in the examples cited.

Taking what has been stated into account, it can be considered that this reaction may be a one-step method of synthesis of some difficultly available amino alcohols, eliminating the steps of demethylation and alkylation of the tropan ring in the usual synthetic version.

## EXPERIMENTAL

Photolysis is conducted simultaneously in two quartz flasks in a reactor with external irradiation, equipped with two mercury-quartz lamps of the DRT-375 type (total power 750 W). Benzene, through which argon was bubbled, was used as

TABLE 1. Products of Photoinitiated Oxidation of Tropan Derivatives

| Compound | Gross formula | Time of irrad., h | $T_m$ (boil), °C | PMR spectrum, δ, ppm | Mass spectra, m/z | Yield, % |
|---|---|---|---|---|---|---|
| III a | $C_{21}H_{25}NO$ | 11 | 239...241* | 0,6...1,8 (1 OH, m, $CH_2$), 2,4...2,6 (2 H, m, CH), 2,8...3,1 (2H, m, $NCH_2$), 6,8...7,6 (1 OH, m, $C_6H_5$) | 307 ($M^+$), 290, 229, 108, 212, 199, 185, 122 | 56 |
| III b | $C_{21}H_{25}NO_2$ | 9 | 185...186 | 1,0...2,2 (8H, m, CH2), 2,8 (2H, m, CH), 3,2 (2H, m, $NCH_2$), 4,0 (1 H, m, $\underline{C}$HOH), 7,3...8,0 (1 0H, m, $C_6H_5$) | 323 ($M^+$), 306, 245, 208, 182, 167, 140, 127 | 60 |
| III c | $C_{16}H_{23}NO_2$ | 9 | 92 (182...184/ 1 mm) | 1,4 (3 H, s, CH3), 1,4...2,3 (8H, m, $CH_2$), 2,4...2,7 (2 H, m, CH), 3,5 (2 H, m, $NCH_2$), 4,0 (1H, m, $\underline{C}$HOH), 7,3...7,9 (5H, m, $C_6H_5$) | 246, 244, 212, 183, 140, 139, 122 | 54 |
| III d | $C_{11}H_{21}NO_2$ | 11 | (141...143/ 1 mm) | 1,1 (6H, s, 2 $CH_3$), 1,6...2,1 (8H, m, $CH_2$), 2,2 (2H, m, CH), 3,1 (2H, m, $NCH_2$), 4,0 (1H, m, $\underline{C}$HOH) | 199 ($M^+$), 184, 182, 171, 140, 126, 123, 109 | 32 |
| III e | $C_{21}H_{25}NO_2$ | 19 | 269...270 | 1,2...2,2 (8H, m, CH2), 2,7 (2H, m, CH), 3,3 (2H, m, NCH), 4,0 (1H, m, $\underline{C}$HOH), 7,0...7,8 (1OH, m, $C_6H_5$) | 323 ($M^+$), 306, 245, 184, 167, 141, 124 | 31 |
| III f | $C_{11}H_{21}NO_2$ | 19 | (110...112/ 1 mm) | 1,1 (6H, s, 2 $CH_3$), 1,2...2,0 (8H, m, $CH_2$), 2,2 (1 H, m, CH), 3,1 (2H, m, $NCH_2$), 3,9 (1H, m, $\underline{C}$HOH) | 199 ($M^+$), 184, 182, 167, 152, 140, 126 | 15 |
| III g | $C_{23}H_{27}NO_3$ | 30 | 155...156 | 1,5...2,2 (8H, m, $CH_2$), 2,0 (3H, s, $OCH_3$), 2,8 (2H, m, CH), 3,2 (2H, m, $NCH_2$), 5,0 (1H, m, CHO), 7,0...7,6 (1 OH, m, $C_6H_5$) | 365 ($M^+$), 350, 348, 306, 289, 287, 246, 227, 182, 140 | 40 |
| III h | $C_{21}H_{24}ClNO$ | 14 | 215...217* | 1,8...2,5 (8H, m, $CH_2$), 3,7 (2H, m, CH), 4,0 (2H, m, $NCH_2$), 4,3 (1H, m, CHCl), 7,2...7,7 (1 OH, m, $C_6H_5$) | 323, 306, 288, 265, 158, 123 | 43 |
| III i | $C_{21}H_{23}NO_2$ | 22 | 199...200* | 1,75...2,75 (8H, m, $CH_2$), 3,9 (2H, m, CH), 4,2 (2H, m, $NCH_2$), 7,0...8,0 (1 OH, m, $C_6H_5$) | 303, 244, 165, 138, 122 | 41 |

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*$T_m$ of the hydrochlorides are given.

the solvent. The distance from the irradiation sources to the lower walls of the flasks was 15 cm. An analysis of the reaction mixtures and purity of the products was performed on a Tsvet-152 chromatograph (0.7 × 3 mm), liquid phase SE-30/5% Chromaton N-AW 0.160 mm, carrier gas nitrogen, programming of the temperature 75-300°C/10°C per minute. The PMR spectra were recorded on Brucker A-250 and Varian T-60 spectrometers; the solvents were $CCl_3CD$ for the bases, $CD_3CD$ for hydrochlorides; HMDS was the internal standard. The mass spectra were recorded on a Varian MAT-112 instrument (ionizing voltage 70 eV at 100-250°C). The IR spectra were taken on a Perkin-Elmer 580 instrument. The melting point was determined on a Boetius hotplate.

The data of elementary analysis for all the compounds obtained correspond to the calculated values.

**Photolysis of Amines Ia—i and Ketones IIa—i (general procedure).** A solution of 0.014 mole of the amine and 0.028 mole of the ketone in 50 ml of benzene was irradiated with light with $\lambda > 250$ nm at 22-25°C, using gas—liquid chromatography to monitor the formation of the major product IIIa—i. Crystals of bis-tropine IV were removed; the amine fraction was precipitated in the form of the hydrochloride with an ether solution of HCl, filtered off, and washed three times with benzene to separate it from unreacted ketone and the pinacone Va—i formed. The hydrochloride of the amine fraction was dissolved in water and converted to the base by the addition of potash to the solution, filtered off, and washed several times with water to remove the unreacted tropine. The base IIIa—i obtained was recrystallized or redistilled.

In the case of photolysis of tropine and pseudotropine in acetone, used as a solvent, the compounds IIIg and IIIf were isolated by redistillation after removal of crystals of the tropine dimer IV.

**1,2-bis(3-α-Hydroxy-8-azabicyclo[3,2,1]oct-8-yl)ethane (IV, $C_{16}H_{28}N_2O_2$)**. A. It was obtained in the photolysis of compounds Ib,c,d, together with compounds III and V. Yield: b) 25%; c) 18%; d) 19%. $T_m$ 280-283°C (subl). Mass spectrum, m/a: 280($M^+$) 154, 140, 124, 82. IR spectrum (KBr): 1118 (C=O), 1310, 1070, 1050, 810 (ring), 3180 $cm^{-1}$ (OH).

B. We boiled 0.7 g (5.5 mmoles) nortropine and 0.5 g (2.6 mmoles) 1,2-dibromoethane in n-butyl alcohol for 16 h. After washing free of unreacted products, 400 mg (54%) of the substance was isolated. The compound gives no depression of the melting point with the IV dimer produced above.

**1,2-bis(8-Azabicyclo[3,2,1]oct-3,2-en-8-yl-ethane (VI, $C_{16}H_{24}N_2$)**. Dehydration was performed with sulfuric acid according to the well known procedure [13]. Yield 64.6%, $T_m$ of the dihydrochloride 268-269°C, $T_m$ of the base 134-135 (2 mm). PMR spectrum ($CCl_4$): 1.2-2.4 (12 H, m, $CH_2$), 2.6 (4 H, s, $NCH_2$), 3.0-3.4 (4 H, m, 4 CH), 5.2-6.0 ppm (4 H, d.d., 2 CH=CH). Mass spectrum, m/z: 244 ($M^+$), 215, 136, 122, 106, 93. IR spectrum (KBr): 870, 891, 1018, 1135 $cm^{-1}$.

**1,2-bis(8-Azabicyclo[3,2,1]oct-8-yl)ethane (VII, $C_{16}H_{28}N_2$)**. We hydrogenated 1.36 g bis-tropidine VI over Pt/C (10%) in alcohol at atmospheric pressure and room temperature. At the end of the reaction the catalyst was filtered off, the alcohol was evaporated, and the residue was distilled under vacuum. Yield 83%. $T_b$ 138/1 mm. $T_m$ 118°C; $T_m$ of the dihydrochloride 279-280°C. PMR spectrum ($CCl_4$): 1.0-2.0 (2 OH, m, $CH_2$), 2.4 (4 H, s, $NCH_2$), 3.0-3.3 ppm (4 H, m, CH). Mass spectrum, m/z: 248 ($M^+$), 218, 138, 124, 108, 95. IR spectrum (KBr): 1123, 1038, 942, 850 $cm^{-1}$.

## REFERENCES

1. S. G. Cohen and N. M. Stein, J. Am. Chem. Soc., **93**, 6542 (1971).
2. S. G. Cohen, A. Parola, and G. H. Parsons, Chem. Rev., **73**, 141 (1973).
3. G. Ciamcian and A. Silber, Ber., **48**, 193 (1915).
4. G. O. Schehck, Dechema-Monographien, No. 24, 105 (1955).
5. G. Porter and P. Suppan, Pure Appl. Chem., No. 9, 499 (1964).
6. J. N. Pitts and J. S. Wan, Jr., The Chemistry of the Carbonyl Group, S. Patal (ed.), New York–London (1966).
7. A. M. Belostotskii, L. M. Kostochka, and A. P. Skoldinov, Khim. Geterotsikl. Soedin., No. 12, 1657 (1982).
8. L. M. Kostochka and A. P. Skoldinov, Zh. Organ. Khim., **17**, 2459 (1981).
9. S. P. Singh, D. Kaufman, and V. S. Stenberg, J. Heterocycl. Chem., **16**, 625 (1979).
10. J. Santamaria, R. Ouchabane, and S. Rigaudy, Tetrahedron Lett., **30**, 2927 (1989).
11. G. L. Closs, J. Am. Chem. Soc., **81**, 5456 (1959).
12. R. Glasser, Qin-Ji Peng, and A. S. Perlin, J. Org. Chem., **53**, 2172 (1988).
13. A. Landenburg, Ann. Chem., **217**, 118 (1883).