SYNTHESIS AND ALKYLATION OF UNSATURATED PHENYL-SUBSTITUTED BIS-δ,δ'-DIMETHYLAMINO KETONES

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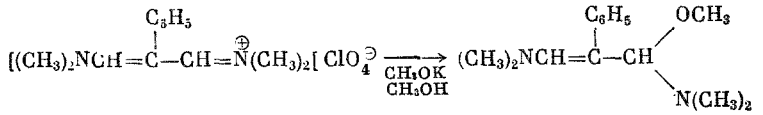
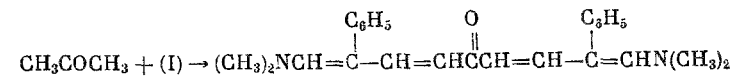
As a continuation of studying methods for the synthesis of dienic bis-δ,δ'-dimethylamino ketones (BDAK) and their alkylation to alkoxypolymethine salts [1-5] we studied in the present paper the possible preparation of phenyl-substituted BDAK by starting with the previously unknown α-phenyl-β-dimethylaminoacrolein acetal aminal (I).



(I)

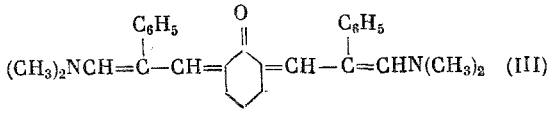
The condensation of (I) with acetone gives BDAK (II) in 70% yield, whose structure was confirmed by the elemental analysis, UV, and PMR spectral data.



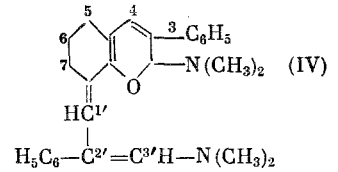
(II)

BDAK (II) shows a bathochromic shift of λ_{max} by 30 nm when compared with the λ_{max} of the unsubstituted BDAK $(CH_3)_2N(CH{=}CH)_2{\cdot}CO(CH{=}CH)_2N(CH_3)_2$ [1], and has a trans configuration of the protons at the α,β double bond ($J_{\alpha,\beta}$ = 15 Hz).

The condensation of (I) with cyclohexanone gave a bright orange crystalline compound in 25% yield, which, based on the elemental analysis and molecular weight, corresponded to BDAK (III). However, on the basis of the UV and PMR spectral data it must be assigned the structure of its valence isomer, namely 2H-pyran (IV).



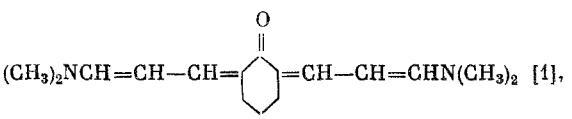
(III)



(IV)

From the PMR spectrum (see Experimental section) it follows that the obtained compound has four nonequivalent methine protons and two nonequivalent $N(CH_3)_2$ groups, which contradicts structure (III) and is in good agreement with structure (IV).

The UV spectrum of this compound has two absorption maxima at 420 and 335 nm. The substantial hypsochromic shift of the long-wave λ_{max} ($\Delta\lambda$ = 70 nm) when compared with the λ_{max} of the unsubstituted BDAK



also contradicts (III) and confirms structure (IV). The possible existence of δ-aminodienones as the 2H-pyran form was shown by us in [3] on the example of (V).

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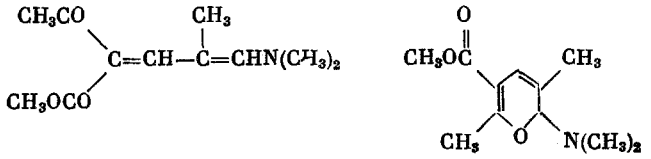
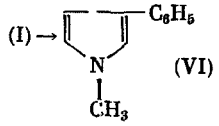


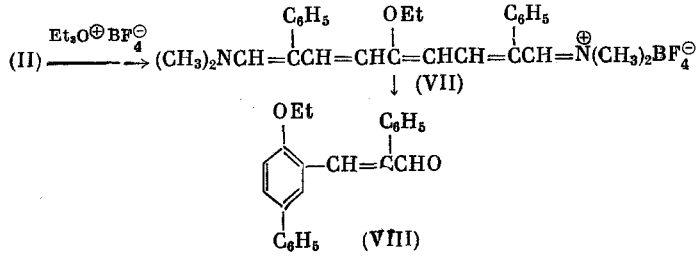
(V)

Together with (II) and (IV), 1-methyl-3-phenylpyrrole (VI) was isolated when (I) is condensed with acetone and cyclohexanone (see Experimental section).



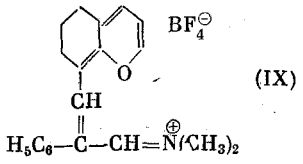
(VI)

In order to synthesize phenyl-substituted alkoxynonamethine salts we studied the alkylation of (II) and (IV) using $Et_3O^{\oplus}BF_4^{\ominus}$. From BDAK (II) we obtained tetrafluoborate (VII) in high yield, which, in contrast to the unsubstituted alkoxynonamethine salts, which were studied earlier [4], proved to be unstable. Salt (VII) after a day at 20°C was converted completely to the aromatic aldehyde (VIII), whose structure was proved by elemental analysis and spectral methods.



The formation of benzaldehyde and cinnamaldehyde from the unsubstituted hepta- and nonamethine salts was described recently in [6].

As the result of deamination, the action of $Et_3O^{\oplus}BF_4^{\ominus}$ on 2H-pyran (IV) gave tetrafluoborate (IX), whose structure was proved by the elemental analysis and spectral data. Together with a shift of the methine protons downfield when compared with (IV), in the PMR spectrum of (IX) is observed a nonequivalence of the chemical shifts of the CH_3 groups on nitrogen due to hindrance of the rotation around the $C{=}\overset{\oplus}{N}(CH_3)_2$ bond. Compound (IX) when treated with Me_2NH is again converted to 2H-pyran (IV).



(IX)

It should be mentioned that the deamination of (IV) also proceeds with exceeding ease when it is treated with traces of acid, which can be clearly seen from the UV spectra by the disappearance of the λ_{max} at 420 and 335 nm, and the appearance of absorption maxima at 525, 570, and 610 nm in the spectrum of tetrafluoborate (IX).

EXPERIMENTAL

The UV spectra were taken on a Specord UV-VIS instrument, and the PMR spectra were taken on a Tesla BS 497 instrument (100 MHz), using HMDS as the internal standard.

α-Phenyl-β-dimethylaminoacrolein Acetal Aminal (I). To CH_3OK (from 2.02 g of K and 2.1 ml of abs. methanol in 63 ml of abs. benzene) was added 15.5 g of 1-dimethylamino-2-phenylpropenylidene dimethylammonium perchlorate [7] and the mixture was refluxed for 2 h, after which it was cooled, and the $KClO_4$ was separated and washed in succession with abs. ether and benzene. The solution was evaporated and the residue was distilled to give 7.2 g (60%) of (I), bp 85-88° (0.3 mm), n_D^{22} 1.5405. PMR spectrum (δ, ppm, CCl_4): 2.55 and 2.77 [12H, $N(CH_3)_2$], 3.52 (3H, OCH_3), 4.32 d (1H, CH), 6.25 d (1H, CH=), 7.42 m (5H, C_6H_5), $J_{1,3}$ = 1 Hz.

1,9-Bisdimethylamino-2,8-diphenylnona-1,3,6,8-tetraen-5-ones (II). A mixture of 1.36 g of (I) and 0.21 ml of dry acetone was heated at 70-80°C. After 20 min the reaction mass crystallized. It was evaporated, treated with abs. ether, cooled, and the dark red precipitate was separated and washed with abs. ether. We obtained 0.75 g (70%) of (II), mp 175-177°; λ_{max} (alcohol): 500 nm (ε 77500). Found: C 80.42; H 7.68; N 7.34%. $C_{25}H_{28}N_2O$. Calculated: C 80.61; H 7.58; N 7.52%. PMR spectrum of (II) (δ, ppm, $CDCl_3$): 2.48 s [12H, $N(CH_3)_2$], 5.29 d (2H, H^4 and H^6), 6.46 s (2H, H^1 and H^9), 7.44 d (2H, H^3 and H^7), 7.13 m (10H, C_6H_5), $J_{3,4}$ = 15 Hz. Infrared spectrum (ν, cm^{-1}): 1540 br, 1625 (C=C, CO). From the mother liquor we isolated 0.1 g of a colorless precipitate, which represented N-methyl-3-phenylpyrrole (VI), mp 43-44° (MeOH), cf. [8]. Found: C 83.64; H 6.94; N 8.55%. $C_{11}H_{11}N$. Calculated: C 84.04; H 7.05; N 8.91%. Mass spectrum (m/e): 157 (M^+). λ_{max} (alcohol): 205 nm (ε 28900), 235 nm (shoulder), 275 nm (ε 14700), cf. [8]. PMR spectrum of (VI) (δ, ppm, $CDCl_3$): 3.47 (3H, NCH_3), 6.35 q (1H, H^4), 6.46 t (1H, H^5), 6.73 t (1H, H^2), 6.94-7.44 m (5H, C_6H_5), $J_{2,5}$ = 2.5, $J_{4,5}$ = 2.5, $J_{2,4}$ = 1.75 Hz, cf. [8].

8-(3'-Dimethylamino-2'-phenylpropenylidene)-2-dimethylamino-3-phenyl-5,6,7,8-tetrahydrobenzo[b]-2H-pyran (IV). A mixture of 0.58 g of cyclohexanone and 2.75 g of (I) was heated for 1 h at 80-90°, and then for another hour at 90-100°. Then it was evaporated, treated with abs. ether, and cooled to −30°. We isolated 0.6 g (25%) of (IV) as a dark orange precipitate, mp 106-108° (abs. ether). Found: C 82.05, H 7.96, N 7.13%. $C_{28}H_{32}N_2O$. Calculated: C 81.51; H 7.82; N 6.79%. Mass spectrum (m/e): 412 (M^+). λ_{max} (CH_2Cl_2): 420 nm (ε 20000), 335 nm (ε 15300). Infrared spectrum (ν, cm^{-1}): 1538, 1685, 1700 (C=C), 1190 (C–O–C). PMR spectrum (δ, ppm, $CDCl_3$): 1.56-2.24 m (6H, CH_2), 2.43 s [6H, $N(CH_3)_2$], 2.81 s [6H, $N(CH_3)_2$], 5.68 s (1H, H^2), 6.19 s (1H, H^4), 6.46 s (1H, H^3), 6.84 br. s (1H, H^1), 7.04-7.54 (10H, C_6H_5).

After separating (IV), we isolated 0.5 g of (VI) from the mother liquor.

Alkylation of 1,9-Bisdimethylamino-2,8-diphenylnona-1,3,6,8-tetraen-5-one (II). To 0.13 g of (II) in 1 ml of dry CH_2Cl_2, cooled to −10°, was added 0.15 g of $Et_3O^{\oplus}\cdot BF_4^{\ominus}$ in 0.5 ml of dry CH_2Cl_2. The mixture was kept for 10 min at this temperature and then evaporated in vacuo without raising the temperature. After the addition of abs. ether we isolated 0.11 g of [9-(N-dimethylamino)-5-ethoxy-2,8-diphenylnona-2,4,6,8-tetraenylidene]-N-dimethylammonium tetrafluoborate (VII) as a purple precipitate with a metallic luster, which was washed well with chilled abs. ether. λ_{max}(CH_2Cl_2): 620 nm (ε 95000). Salt (VII) after standing for a day at 20° was converted completely to a pale yellow crystalline compound, which represented aldehyde (VIII), mp 147-148° (MeOH). λ_{max} (C_2H_5OH): 265 nm. Found: C 84.09; H 6.34%. $C_{23}H_{20}O_2$. Calculated: C 84.12; H 6.14%. Mass spectrum (m/e): 328 (M^+). Infrared spectrum (ν, cm^{-1}): 1680 (CHO), 2710 (CHO). PMR spectrum (δ, ppm, CCl_4): 1.45 t and 4.07 q (OC_2H_5), 7.71 s (CH=), 9.73 s (CHO), 6.7-7.4 (13H, C_6H_5), $J_{CH_3,\ CH_2}$ = 7 Hz.

Reaction of (IV) with $Et_3O^{\oplus}BF_4^{\ominus}$. To a solution of 0.2 g of (IV) in 1 ml of dry CH_2Cl_2, cooled to −5°, was added 0.23 g of $Et_3O^{\oplus}BF_4^{\ominus}$ in 0.5 ml of dry CH_2Cl_2. After keeping for 30 min at 20° the mixture was evaporated, abs. ether was added, and the dark gray precipitate was separated, washed in succession with water and ether, dissolved in CH_2Cl_2, and precipitated with hexane. After washing the precipitate with hexane we obtained 0.2 g (91%) of salt (IX), mp 208-210°. Found: C 68.15; H 5.97; N 3.12; F 16.38%. $C_{26}H_{26}NOBF_4$. Calculated: C 68.5; H 5.72; N 3.08; F 16.7%. λ_{max} ($CHCl_3$): 525 nm (ε 33000), 570 nm (ε 41200), 610 nm (ε 24600). PMR spectrum (δ, ppm, $CDCl_3$): 1.42-2.47 m (6H, CH_2), 2.57 br. s and 3.45 br. s [6H, $N(CH_3)_2$], 6.96 s, 7.9 s, 8.16 s, 8.25 s (based on 1H of CH=), 7.36 m (10H, C_6H_5).

Conversion of Tetrafluoborate (IX) to 2H-Pyran (IV). To a solution of 0.2 g of (IX) in $CHCl_3$ was added an ether solution of Me_2NH. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. We obtained 0.16 g of a crystalline precipitate, mp 105-107°, which, based on the UV and PMR spectra, is completely identical with 2H-pyran (IV).

CONCLUSIONS

1. α-Phenyl-β-dimethylaminoacrolein acetal aminal was synthesized.

2. The reaction of this acetal aminal with acetone gives 1,9-bisdimethylamino-2,8-diphenylnona-1,3,6,8-tetraen-5-one, the alkylation of which leads to [9-(N-dimethylamino)-5-ethoxy-2,8-diphenylnona-2,4,6,8-tetraenylidene]-N-dimethylammonium tetrafluoborate.

3. The reaction of the above acetal aminal with cyclohexanone gives 8-(3'-dimethylamino-2'-phenylpropenylidene)-2-dimethylamino-3-phenyl-5,6,7,8-tetrahydrobenzo[b]-2H-pyran, which is a valence isomer of 1,9-bisdimethylamino-2,8-diphenyl-4,6-trimethylenenona-1,3,6,8-tetraen-5-one. When treated with either $Et_3O^{\oplus}BF_4^{\ominus}$ or acids, it is converted to the bicyclic trimethineimmonium salt due to the deamination of the $(CH_3)_2N$ group from the 2H-pyran ring.

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SYNTHESIS OF 2-HYDROXY-3-CARBETHOXY-5,6-DIALKYLPYRAZINES

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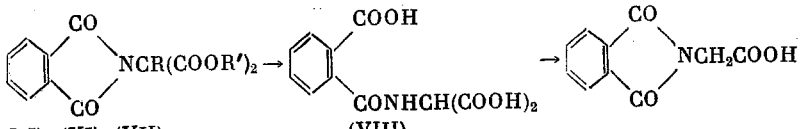
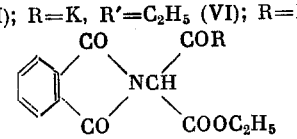
Previously we had described [1] the synthesis of 2-hydroxy-3,5,6-trialkylpyrazines by starting with the hydrochlorides of α-amino ketones (I) and the acid chlorides of N-phthaloyl-α-amino acids. In the present paper, on the basis of the hydrochlorides of α-amino ketones (I), we studied paths for the synthesis of 2-hydroxy-3-carbethoxy-5,6-dialkylpyrazines (II), which can have interest for the preparation of pteridines and their analogs.

Our initial attempts to convert phthalimidomalonic ester (III) to monoester (IV), and the latter via acid chloride (V) to 3-carbethoxypyrazines (II) by the scheme described in [1], gave negative results. The reaction of diester (III) with an equimolar amount of KOH in either alcohol or methanol gave the K derivatives of diester (VI) and the dimethyl ester of phthalimidomalonic acid (VII). The treatment of diester (III) with excess KOH in either alcohol or methanol led to hydrolysis of both ester groups and opening of the phthalimido ring to give N-(o-carboxybenzoyl)aminomalonic acid (VIII), whose structure was confirmed by decarboxylation and cyclization to the known phthalimidoacetic acid [2].



(III), (VI), (VII) (VIII)

R=H, R'=C_2H_5 (III); R=K, R'=C_2H_5 (VI); R=K, R'=CH_3 (VII).



R=OH (IV), Cl (V)

Then we investigated a path for the synthesis of 3-carbethoxypyrazines (II) by starting with acetamidomalonic ester (IX) and α-aminoacetone ethylene ketal (X). N-(Acetamidocarbethoxyacetyl)aminoacetone ethylene ketal (XI) is formed when they are heated due to aminolysis of one ester group, the acid hydrolysis of which gave ketone (XII).

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