HETEROADAMANTANES AND THEIR DERIVATIVES.
3.* THE SYNTHESIS OF 6-HYDROXY-5-METHOXYCARBONYL-1,3-DIAZAADAMANTANE

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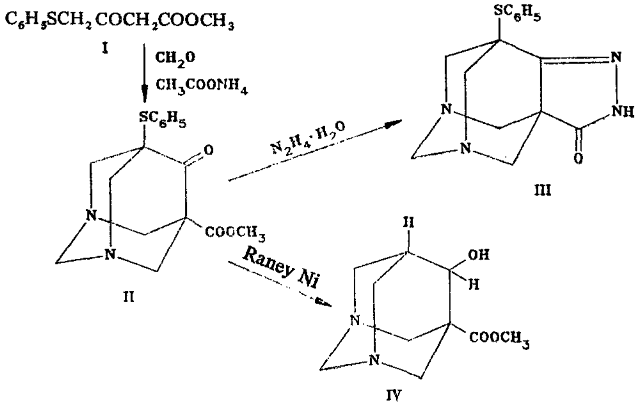
The interaction of methyl 3-oxo-4-(phenylthio)butyrate with formaldehyde and ammonium acetate yielded 5-methoxycarbonyl-6-oxo-7-phenylthio-1,3-diazaadamantane, which, on being heated with skeletal nickel in isopropanol was converted into 6-hydroxy-5-methoxycarbonyl-1,3-diazaadamantane. The structures of the compounds have been confirmed by IR and PMR spectroscopy.

Derivatives of 1,3-diazaadamantane containing alkoxycarbonyl groups in positions 5 and 7 are difficultly accessible substances. At the present time, the syntheses of only 5,7-di(ethoxycarbonyl), 5,7-di(methoxycarbonyl)-, and 5-ethoxycarbonyl-6-oxo-7-phenyl-1,3-diazaadamantanes have been described, these having been obtained by the condensation of esters of acetonedicarboxylic acid [2] or ethyl 3-oxo-4-phenylbutyric acid [3] with formaldehyde and ammonium acetate.

At the same time, there is no information in the literature on methods for synthesizing 5-alkoxycarbonyl-1,3-diazaadamantanes and their functional derivatives containing no substituents in position 7.

In the present paper we report the synthesis of compounds of this type. We started from the methyl 3-oxo-4-(phenylthio)butyrate (I) described previously [4], which we studied by a modified method [5] described for ethyl 3-oxo-4-(phenylthio)butyrate. The condensation of the keto ester (I) for formaldehyde and ammonium acetate led, like the reactions of monoarylthio- and diarylthioacetones described previously [6, 7], to 5-methoxycarbonyl-6-oxo-7-phenylthio-1,3-diazaadamantane (II) with a yield of 40%. The structure of the 1,3-diazaadamantanecarboxylic ester obtained was confirmed by its conversion under the action of hydrazine hydrate in methanol into the corresponding 3-oxopyrazolo[4,3-e]-7-phenylthio-1,3-diazaadamantane (III).



The presence of a phenylthio group in the molecule of compound (II) enabled it to be used for the synthesis of the 7-unsubstituted 6-hydroxy-5-methoxy-carbonyl-1,3-diazaadamantane (IV).

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With this aim, the phenylthioadamantane (II) was subjected to desulfurization by being heated with Raney nickel in isopropanol, as described in [6, 7], and was converted with a yield of 82% into the adamantanol (IV) as a result of reactions in which the phenylthio group was replaced by a hydrogen atom and the ketone group was catalytically reduced, taking place simultaneously (or successively).

The structures of compounds (II-IV) were confirmed by their IR and PMR spectra. Thus, the IR spectrum of compound (II) contained the characteristic absorption bands of the stretching vibrations of carbonyls of ketone (1695 cm^{-1}) and ester (1735 cm^{-1}) groups and of an aromatic nucleus (1610 cm^{-1}). The IR spectrum of the desulfurization product (IV) retained the characteristic absorption band of an ester carbonyl (1720 cm^{-1}) while the absorption bands of a ketone group and of an aromatic nucleus were absent and an absorption band corresponding to a hydroxy group appeared at 3100-3300 cm^{-1}. The IR spectrum of the pyrazolone (III) contained characteristic absorption bands of a carbonyl group (1685 cm^{-1}), of a C=N group (1660 cm^{-1}), and of an aromatic nucleus (1580 and 1610 cm^{-1}).

The PMR spectra of compounds (II) and (IV) contained the signals, characteristic for 1,3-diazaadamantane structures, of the resonance absorption of two methylene protons of the aminal fragment $N-CH_2-N$ in the regions of 3.6 and 4.0 ppm, respectively, and also the signals of eight methylene protons of $N-CH_2$ fragments in the 3.0-3.5 and 2.9-3.8 ppm regions, respectively. The signals of the three protons of the methoxy groups in compounds (II) and (IV) appeared in the 3.7 and 3.6 ppm regions, respectively. In addition, the broadened signal of a hydroxy proton was observed in the spectrum of compound (IV) at 4.2-4.4 ppm.

EXPERIMENTAL

PMR spectra were recorded on a Tesla-60 instrument in CCl_4 with TMS as internal standard, and IR spectra on a UR-20 spectrometer in a thin layer or in paraffin oil.

Methyl 3-Oxo-4-(phenylthio)butyrate (I). Over 1 hour at 20°C, a solution of 5.52 g (140 mmole) of caustic soda in 75 ml of ethanol was added dropwise to a solution of 20.3 g (140 mmole) of methyl 4-chloro-3-oxobutyrate and 15.4 g (140 mmole) of thiophenol in 100 ml of isopropanol. Then the reaction mixture was heated on the boiling water bath for 0.5 h and was cooled to room temperature, after which 400 ml of water was added to it. The reaction product was extracted with ether (3 × 100 ml). The ethereal extract was dried with anhydrous sodium sulfate and the solvent was distilled off. This gave 28.44 g (94%) of substance (I), which was used without additional purification for the subsequent syntheses. IR spectrum (thin layer), cm^{-1}: 1715 (ketonic C=O); 1730-1760 (ester C=O); 1590, 3010 (aromatic nucleus).

5-Methoxycarbonyl-6-oxo-7-phenylthio-1,3-diazaadamantane (II). A solution of 3.21 g (14 mmole) of the ester (I), 2.0 g (26 mmole) of ammonium acetate, 1.35 g (14 mmole) of ammonium carbonate, and 2.1 g (70 mmole) of paraformaldehyde in 17 ml of isopropanol was heated at a gentle boil for 4.5 h. After the reaction mixture had been cooled to room temperature, the precipitate that had formed was filtered off and was recrystallized from toluene. This gave 1.81 g (39.7%) of substance (II) with mp 220-220.5°C. IR spectrum, cm^{-1}: 1695 (ketonic C=O); 1735 (ester C=O); 1610 (aromatic nucleus). PMR spectrum (CCl_4), ppm: 3.6 (2 H, d, $N-CH_2-N$); 3.0-3.5 (8 H, m, $N-CH_2$); 3.7 (3 H, s, OCH_3). Found: C 60.1; H 5.7; N 10.0; S 8.8%. $C_{16}H_{18}N_2O_3S$. Calculated: C 60.4; H 5.7; N 10.1; S 8.8%.

3-Oxopyrazolo[4,3-e]-7-phenylthio-1,3-diazaadamantane (III). A suspension of 1 g of compound (II) with 55 ml of methanol was treated with 30 g of hydrazine hydrate and the mixture was heated on the water bath to boiling until the initial material had dissolved completely (~30 min). Then the solution was filtered and was left for 1 day at room temperature. The crystalline precipitate that had formed was filtered off and was dried in a desiccator. This gave 0.72 g (95.8%) of substance (III), mp 312-315°C. IR spectrum, cm^{-1}: 1685 (C=O); 1660 (C=N); 1580 and 1610 (aromatic nucleus). Found: C 60.0; H 5.3; N 18.5; S 10.6%. $C_{15}H_{16}N_4OS$. Calculated: C 60.0; H 5.4; N 18.6; S 10.7%.

6-Hydroxy-5-methoxycarbonyl-1,3-diazaadamantane (IV). A solution of 0.45 g (1.4 mmole) of the adamantanone (II) in 14 ml of isopropanol was treated with 2 g of Raney nickel and the mixture was boiled for 30 h with the addition of three 2 g portions of fresh Raney nickel every 7 h. The catalyst was filtered off and was washed with isopropanol, and the filtrate was evaporated in the vacuum of a water-jet pump. This gave 0.25 g (82%) of substance (IV), mp 142-143°C (from acetone). IR spectrum, cm^{-1}: 1720 (ester C=O); 3100-3300 (OH). PMR spectrum (CCl_4), ppm: 4.4-4.2 (1 H, OH); 4.0 (2 H, s, $N-CH_2-N$); 3.6 (3 H, s, OCH_3); 2.9-3.8 (8 H, m, $N-CH_2$). Found: C 56.7; H 7.5%. $C_{10}H_{16}N_2O_3$. Calculated: C 56.6; H 7.6%.

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS AT THE NODAL POSITIONS. 12.* STEPHENS REARRANGEMENT IN SUBSTITUTED 1,4-DIAZABICYCLO[2.2.2]OCTANES

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The ylides formed from phenacyl derivatives of substituted diazabicyclooctanes decompose to the initial base or give products of the Stephens rearrangement, leading to an expansion of the ring. The direction of the reaction is determined by the presence of C-substituents in the bicyclic fragment. C-Phenyl groups, which are capable of stabilizing the transition state, ensure the occurrence of the rearrangement reaction.

Continuing an investigation of the influence of C-substituents on the properties of quaternary salts of compounds in the diazabicyclooctane series — 1,4-diazabicyclo[2.2.2]octane (I), trans-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (II) and its cis isomer (III), and benzo[b]1,4-diazabicyclo[2.2.2]octene (IV)[2] — we have synthesized the monophenacyl derivatives of these compounds ((V-VIII), Table 1) and have studied their behavior under the conditions of the Stephens rearrangement [3]. There have been several publications devoted to this rearrangement for ammonium ylides with a nitrogen atom forming part of a bicyclic system [4-7]. Pine et al. [7] studied the behavior of mono- and bisquaternary salts of the bicyclic compound (I) under the action of butyllithium. This formed in very small yields ring-expansion products and the initial base.

The monophenacyl derivatives (V-VIII) were synthesized by the action of phenacyl bromide on the corresponding bicyclic amines (I-IV). The ylides (IX-XII) were obtained by treating compounds (V-VIII) with potassium tert-butanolate in tert-butanol or with caustic potash in methanol. The formation of the ylides (IX) and (XII) was shown by IR spectroscopy: the $C{=}O$ absorption at 1700 cm^{-1} had disappeared and two bands had appeared in the 1500-1600 cm^{-1} region [8]. After the careful acidification of these ylides, the reaction products corresponded in their spectral properties and chromatographic behavior completely to the phenacyl derivatives (V) and (VIII).

The ylide (IX) is a stable compound withstanding heating to 200°C in the solid form in vacuum and also resistant to boiling in aqueous alkali and toluene. On being boiled in o-xylene, the ylide (IX) decomposed in 3 h and the only decomposition product isolated that possessed basic properties was the initial amine (I) (42% yield). A similar direction of the decomposition of ylides has been reported previously [7, 9].

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