REACTION OF o-PHENYLENEDIAMINE WITH ACETOACETIC AND α-CHLOROACETOACETIC ESTERS

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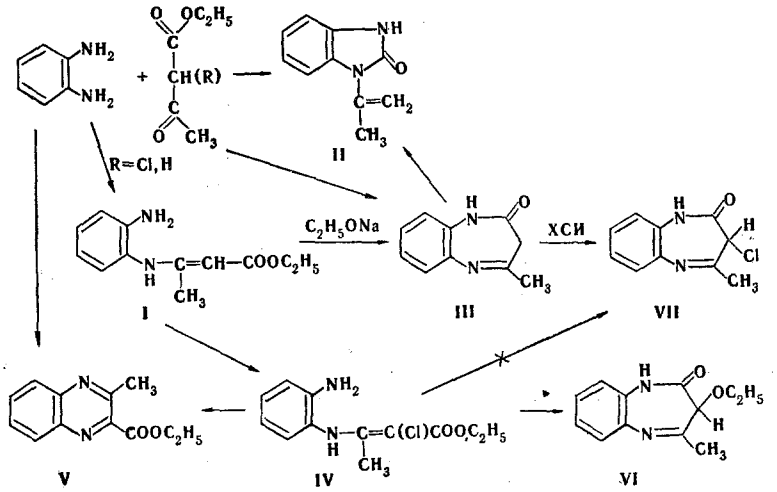
The reactivities of acetoacetic and α-chloroacetoacetic esters in the reaction with o-phenylenediamine are compared. In contrast to the available data, it was established that in polyphosphoric aicd (PPA) acetoacetic ester is converted to 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one and ethyl 3-(2-aminoanilino)-crotonate, while chloroacetoacetic ester is converted to 2-methylbenzimidazole. At 20°C chloroacetoacetic ester is converted to ethyl 2-chloro-3-(2-amino-anilino)crotonate. The conversion of this ester to 2-methyl-3-ethoxy-2,3-dihydro-1H-1,5-benzodiazepin-2-one was studied.

The available data on the reaction of acetoacetic ester with o-phenylenediamine are extremely diverse and often contradictory. It has been noted [1, 2] that the first step in the reaction, viz., condensation of the amino group of the diamine with the carbonyl group of this ester, takes place at room temperature and leads to the formation of ethyl 3-(2-aminoanilino)crotonate (I). When the reaction is carried out by heating in xylene, the character and amounts of the substances formed depend on the degree of dilution of the reaction medium and the reaction time.

Thus when the condensation is carried out in refluxing xylene in a neutral medium with removal of the liberated water and alcohol by distillation with slight dilution of the reagents (at a diamine—acetoacetic ester—xylene ratio of 1:1.2:1), it leads primarily to 1-isopropenylbenzimidazolone (II) [3].



When a tenfold amount of the solvent (at a reagent ratio of 1:1.1:10) was used, 34% 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III), 26% imidazolone II, and 12% crotonate I were isolated [4]. It was later shown [5] that under conditions similar to those described by Rossi and co-workers [4], halving the reaction time, i.e., heating in a neutral medium for 0.5 h, leads to a considerable increase in the yield of diazepinone III to 67% and a decrease in the yield of imidazolone II to 6%. Refluxing the starting reagents with a 15-fold amount of xylene for 1 h with efficient water separation led to the formation of primarily benzodiazepinone III. Only traces of II are detected in the reaction products

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by means of thin-layer chromatography (TLC); the yield of II increases as the reaction time is increased [5].

Diazepinones III were obtained by cyclization of crotonate I in the presence of sodium in alcohol [2, 6]; this reaction has heretofore been regarded as the only method for the synthesis of substituted benzodiazepinones [7]. In addition, the available data on this problem are contradictory. Thus the diazepinone obtained from 2,3-diamino-1,4-naphthoquinone and acetoacetic ester adds a molecule of alcohol to give the corresponding tetrahydro derivative in the case of prolonged heating with methanol or ethanol [8].

In 1977 it was reported that the reaction of o-phenylenediamine with acetoacetic ester was carried out in polyphosphoric acid (PPA) [9]. When Desai and Desai heated the starting compounds to 85°C and then to 150°C for 24 h, they isolated a substance with mp 120-121°C, to which they assigned benzodiazepinone structure III. When the starting mixture was heated immediately to 150°C in PPA, a substance with mp 148°C, which, in the opinion of Desai and Desai, was 2-acetonylbenzimidazole, was formed in 0.5 h.

We decided to compare the reactivities of α-chloroacetoacetic and acetoacetic esters in their reaction with o-phenylenediamine.

In view of the contradictory character of the data on the pathway of the reaction of acetoacetic ester with this diamine and the structures of the substances formed in this reaction it seemed expedient to reproduce some of the transformations and to establish the structures of the reaction products.

Thus heating 2,3-dihydrobenzodiazepinone III obtained by various methods [3, 4, 6] in ethanol for 20 h by the method in [8] did not lead to the formation of 4-methyl-4-ethoxy-1,2,3,4-tetrahydro-5H-1,5-benzodiazepin-2-one. Alcohol did not add under these conditions, but the previously noted [4, 7] isomerization of diazepinone III to 1-isopropenylbenzimidazolone II (∿6%) [2] did occur.

We then reproduced the reaction of o-phenylenediamine with acetoacetic ester in freshly prepared PPA. When we heated the mixture of substances gradually by the method in [9] we actually were able to isolate a solid precipitate with mp 122°C. A chromatographic study of this precipitate showed that it was a mixture of two substances, viz., benzodiazepinone III (70%) and crotonate I (10%).

When we heated the diamine with acetoacetic ester in PPA at 150°C, we obtained benzodiazepinone III, to which the 2-acetonylbenzimidazole structure was erroneously assigned in [9]. Desai and Desai [9] evidently repeated the errors made in [1].

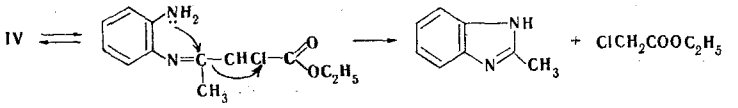
Like acetoacetic ester, α-chloroacetoacetic ester reacts with o-phenylenediamine at room temperature to give ethyl 2-chloro-3-(2-aminoanilino)crotonate (IV); the reaction proceeds more readily than in the case of acetoacetic ester and without an acid catalyst, which is associated with the acceptor effect of the chlorine atom, which increases the electrophilicity of the carbonyl group of α-chloroacetoacetic ester. We also obtained crotonate IV by chlorination of ester I with N-chlorosuccinimide in carbon tetrachloride.

The synthesis of ester IV by the method proposed for the preparation of the corresponding crotonates from aliphatic and aromatic monoamines was described in [10]. The application of this method to o-phenylenediamine, according to which the starting substances are refluxed in benzene for 4 h, lowers the yield of ester IV appreciably and gives rise to its partial conversion to 2-methylbenzimidazole. The presence of this impurity evidently explains the depressed melting point of ester IV presented in [10].

The step involving the formation of crotonates is thus common to both esters. However, these esters behave differently when they are heated in various solvents and PPA.

Thus, whereas the principal reaction products are benzodiazepinone III or 1-isopropenylbenzimidazol-2-one II, depending on the conditions under which the reaction with acetoacetic ester is carried out, 2-methylbenzimidazole is formed with α-chloroacetoacetic ester in all cases. This compound was isolated in refluxing xylene or when the starting compounds were fused or heated in alcohol and PPA.

The formation of 2-methylbenzimidazole can be regarded as being the result of intramolecular attack of the amino group in the intermediately formed ester IV on the azomethine group with subsequent splitting out of ethyl chloroacetate, as in the case of the acid cleavage of acetoacetic ester.



It is interesting to note that the formation of 2-methylbenzimidazole is the dominant pathway in the condensation of o-phenylenediamine with α-alkylacetoacetic esters [11]. The fact that any substituent in the α position of acetoacetic ester, regardless of its electronic effect, promotes the formation of the benzimidazole, makes it possible to propose that the attack of the amino group on the ester carbonyl group and the formation of a seven-membered ring are controlled by steric factors.

The presence in ester IV of a chlorine atom is responsible for its ability to undergo cyclization through the typical nucleophilic attack of the amino group on the carbon atom of the C—Cl bond, as a result of which 2-methyl-3-ethoxycarbonylquinoxaline (V) is formed.

When we heated crotonate IV with two equivalents of sodium ethoxide, we isolated benzodiazepinone VI, the structure of which was proved by an independent method, viz., by reaction of sodium ethoxide with 3-chloro-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII). The latter was obtained by chlorination of diazepinone III with N-chlorosuccinimide.

In contrast to diazepinone III, benzodiazepinones VI and VII do not undergo isomerization to the corresponding 1-isopropenylbenzimidazolones when they are heated above their melting points. Substituents (Cl, OC_2H_5) apparently hinder the realization of synchronous electron transfer and the formation of the multiple bond observed in the isomerization of benzodiazepinones to imidazolones [2, 4].

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol (10^{-4} to 10^{-5} mole/liter) were measured with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Tesla spectrometer (80 MHz) with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with a system for vaporization of the substances directly in the vicinity of the ionization region at ionizing voltages of 50 and 70 eV. The course of the reaction and the purity of the products were monitored by means of thin-layer chromatography (TLC) on a fixed layer of Silufol [elution with benzene—ethyl acetate (7:3)].

Reaction of o-Phenylenediamine with Acetoacetic Ester by the Method in [3]. A) A 5-ml sample of freshly prepared PPA was added slowly to a cooled (to 5°C) mixture of 2.16 g (0.02 mole) of o-phenylenediamine and 2.78 g (0.014 mole) of acetoacetic ester, and the resulting mixture was heated to 85°C, after which it was maintained at room temperature for 24 h. It was then heated to 150°C, cooled, treated with ice, and neutralized to pH 6 with ammonium hydroxide. Workup gave 2.8 g of a substance with mp 122°C. The precipitate was washed with ether and crystallized from benzene to give 2.67 g (66%) of 4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (III) with mp 148°C. Workup of the ether solution gave 0.44 g (10%) of ethyl 3-(2-aminoanilino)crotonate (I).

B) A 2.16-g (0.02 mole) sample o-phenylenediamine, 2.85 g (0.022 mole) of acetoacetic ester, and 5 ml of PPA were mixed, during which a vigorous reaction ensued. The mixture was then heated to 150°C and maintained at this temperature for 30 min. Workup gave 1.5 g (43%) of benzodiazepin-2-one.

Condensation of α-Chloroacetoacetic Ester with o-Phenylenediamine. A solution of 1.614 g (0.021 mole) of α-chloroacetoacetic ester in 20 ml of xylene was added dropwise to a refluxing solution of 1.08 g (0.01 mole) of the diamine in 180 ml of xylene, and the mixture was refluxed with a water separator for 1 h. The resulting precipitate was removed by filtration and dissolved in water, and the solution was neutralized with ammonium hydroxide to give 1.9 g (82.5%) of 2-methylbenzimidazole with mp 175°C. The residue was recrystallized from hexane to give 0.12 g (5%) of crotonate IV.

Ethyl-2-Chloro-3-(2-aminoanilino)crotonate (IV). A) A 1.08-g (0.01 mole) sample of o-phenylenediamine was mixed with 2.05 g (0.0125 mole) of α-chloroacetoacetic ester, two to three drops of concentrated hydrochloric acid were added, and the mixture was stirred at room temperature for 30 min. The solidified mass was washed with petroleum ether and recrystallized from hexane to give 2.1 g (83%) of a product with mp 64°C and R_f 0.81

(mp 54°C [7]). UV spectrum, λ_{max} (log ε): 237 (4.01) and 308 nm (4.20). PMR spectrum: 1.2 (3H, t, CH_3), 4.12 (2H, q, CH_2), 1.96 (3H, s, $=CCH_3$), 3.68 (2H, s, NH_2), and 6.6-7.4 ppm (4H, m, C_6H_5). Mass spectrum, m/z (the ion peaks with intensities >3% of the maximum ion peak are presented): 77 (12.6), 79 (6.9), 80 (10.2), 91 (5.0), 92 (19.2), 108 (9.9), 131 (3.8), 132 (58), 133 (100), 134 (4.5), 135 (3), 142 (3.5), 143 (3.2), 144 (73.6) and 145 (30.2), 146 (9.3), 170 (2), 171 (2.0), 172 (2.0), 173 (6.98), 21 (31.8), 218 (5.0), 254 (14), 256 (4.38). Found: Cl 13.1; N 11.3%. $C_{12}H_{15}ClN_2O_2$. Calculated: Cl 13.2; N 11.0%.

B) A solution of 2.05 g (0.0125 mole) of α-chloroacetoacetic ester in 10 ml of benzene was added in the course of 30 min to a solution of 1.08 g (0.01 mole) of o-phenylenediamine in 40 ml of absolute benzene, and the mixture was refluxed for 4 h as in [7]. The solvent was then removed by vacuum distillation, and the resulting oil, which began to crystallize, was washed with water (10 ml). The filtrate was neutralized to pH 6 with ammonia, and the precipitated 2-methylbenzimidazole was recrystallized from benzene to give 0.13 g (10%) of a product with mp 175°C. The residual oil was crystallized from hexane to give 1.5 g (64.6%) of ester IV with mp 64°C.

C) A 0.667-g (5 mmole) sample of N-chlorosuccinimide was added in portions within the solution in the course of 30 min to a solution of 1.1 g (5 mmole) of crotonate I in 10 ml of absolute benzene, after which the mixture was refluxed for 2 h. The precipitated succinimide was removed by filtration, and the solvent was removed from the filtrate by distillation to give 1.15 g (90%) of ester IV with mp 64°C. No melting-point depression was observed for a mixture of this product with a sample of the substance obtained by method A.

2-Methyl-3-ethoxycarbonylquinoxaline (V). A 1.28-g (5 mmole) sample of crotonate IV was refluxed in 10 ml of xylene or dimethylformamide (DMF) with 3.5 g (25 mmole) of triethylamine for 4 h, after which the precipitated triethylamine hydrochloride was removed by filtration, and the solvent was removed by vacuum distillation. The residue was crystallized from water to give 0.62 g (57%) of a product with mp 72-73°C (mp 72-73°C [12]).

3-Ethoxy-4-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (VII). A) A 0.254-g (1 mmole) sample of ethyl 2-chloro-3-(2-aminoanilino)crotonate was added to a solution of sodium ethoxide [from 0.023 g (1 mmole) of sodium metal and 10 ml of absolute ethanol], and the mixture was refluxed for 1 h. The precipitated sodium chloride was removed by vacuum distillation, and the residue was dissolved in 10 ml of water. The aqueous solution was acidified to pH 6 with acetic acid and worked up to give 0.19 g (35%) of a product with mp 172-173°C. UV spectrum, λ_{max} (log ε): 207 (4.67), 240 (4.39), and 200 nm (3.73). PMR spectrum (in CF_3COOH): 2.36 (3H, s, CCH_3), 1.24 (3H, t, CH_3), 4.26 (2H, q, CH_2), 3.32 (1H, s, CH), and 7.15-7.50 ppm (aromatic protons).

B) A 0.502-g (2.5 mmole) sample of diazepinone VII was refluxed with sodium ethoxide (from 0.057 g of sodium and 5 ml of absolute alcohol) for 1 h, after which the alcohol was removed by vacuum distillation, and 1 ml of water was added to the residue. The aqueous mixture was neutralized to pH 6 with acetic acid and worked up to give 0.4 g (75%) of diazepinone VII with mp 172-173°C. No melting-point depression was observed for a mixture of this product with a sample of the substance obtained by method A.

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SIGMA COMPLEXES IN THE PYRIMIDINE SERIES.

4.* INVESTIGATION OF THE ELECTRONIC ABSORPTION SPECTRA OF ANIONIC SIGMA COMPLEXES OF 5-NITROPYRIMIDINE

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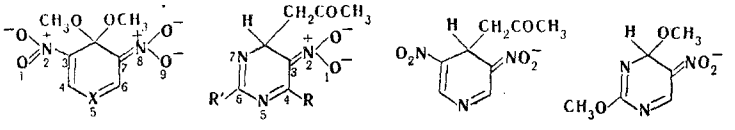
The electronic absorption spectra of sigma complexes of the Meisenheimer type, viz., the anions of potassium salts of 4H-5-nitro-4-acetonylpyrimidines, were investigated. The 5-nitropyrimidine molecule and its sigma complex involving the 4 position were subjected to quantum-chemical calculation by the simple MO LCAO method. It is shown that it is expedient to use the Forster–Dewar–Knott rule for the study of the electronic spectra of the indicated sigma complexes.

It is known that 5-nitropyrimidines, like di- and trinitrobenzenes, add nucleophilic reagents, viz., potassium methoxide [1, 2] and potassium derivatives of acetone and acetophenone [3, 4], to give colored sigma complexes of the Meisenheimer type [5].

The absorption spectra of these complexes have not been previously examined from the point of view of the general principles of the theory of chromaticity of organic compounds and have not been compared with the spectra of the similarly constructed Meisenheimer complexes of the benzene series. It was recently shown [6] that it is expedient to use the Forster–Dewar–Knott (FDK) rule [7-9] for the study of the spectra of anionic sigma complexes.

This rule makes it possible to qualitatively explain the shift of the absorption bands when substituents with different electronic natures are introduced in the polymethine chromophore. In addition, a quantitative correlation relationship between the absorption frequencies and the σ_I and σ_R substituent constants can often be found. For example, the



I II III IV

I a X = >C–H; b X = >C–NO$_2$; c X = >N; II a R = R′ = H; b R = OCH$_3$, R′ = H; c R = H, R′ = OCH$_3$; d R = R′ = OCH$_3$; e R = H, R′ = C$_6$H$_5$

following relationship has been found [6] for sigma complexes of the I type, where X is the methylidyne carbon atom with substituent R:

$$\nu = 16\,864 + 2567(\sigma_I + 3.20\sigma_R).$$

According to the FDK rule, the presence of electron-acceptor substituents attached to the odd-numbered carbon atoms in the chromophore (see formula I) or replacement of these atoms by more electronegative nitrogen atoms should lead to a shift in the absorption band to the short-wave region (a hypsochromic effect). Thus σ complex Ia has a λ_{max} band at 586 nm, while σ complex Ib has a λ_{max} band at 492 nm [in dimethylformamide (DMF)] [10]. Sigma complex Ic displays another large hypsochromic effect with λ_{max} at 455 nm (in

*See [16] for Communication 3.

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