PYRIMIDINES

XII. Reaction of Substituted 5-Pyrazolones With Arylidenebisureas*

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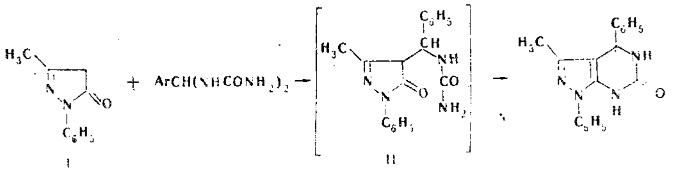
The reaction of substituted 3-methyl-5-pyrazolones with arylidenebisureas has been studied. Substituted spiro[pyrazole-4, 5'-pyrimidines] have been obtained from 1-phenyl- and 1-benzyl-3-methyl-5-pyrazolones. When only one hydrogen atom was present in the ring of the 3-methyl-5-pyrazolone, the corresponding α-ureidobenzyl derivative was obtained.

Previously, one of us has shown that the reaction of benzylidenebisureas with compounds containing an active CH_2—CO grouping forms pyrimidine derivatives [2, 3]. Continuing work on the synthesis of pyrimidines, we have studied the reaction of arylidenebisureas with substituted 5-pyrazolones. The first compound investigated was 3-methyl-1-phenyl-5-pyrazolene (I), which has been studied in very great detail and is readily available.

It might have been assumed that the reaction would take place with the formation of a pyrazolo[3, 4-d]pyrimidine in the following way.



The probability of this assumption is based on the known lability of hydrogen atoms in position 4 of the pyrazolone ring and the possibility of cyclization involving the CO group of I [4].

When compound I was treated with an excess of benzylidenebisurea (BBU), compound III was obtained, its analysis and spectroscopic characteristics not agreeing with those of a pyrazolo[3, 4-d]pyrimidine. The IR spectrum of III has two absorption bands of carbonyl groups: 1680 and 1703 cm^{-1}. The first of them can be ascribed to the vibrations of the CO in a substituted urea [5], and the second is characteristic for the vibrations of CO in 4, 4-disubstituted pyrazolones [6, 7]. This assignment of the absorption bands corresponds to the chemical behaviour of III since it is insoluble in alkalies and gives no reaction with $FeCl_3$ (i.e. it is incapable of forming an enol). Compound III does not contain an NH_2 group; when it is heated with 10% NaOH a strong smell of benzaldehyde appears and urea and I can be detected in the reaction mixture by means of paper chromatography. The UV spectrum of III is similar to that of I.

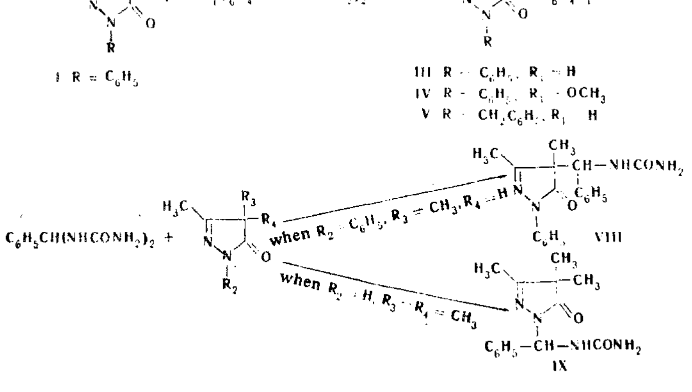
All the above-mentioned facts and also the empirical formula found, $C_{25}H_{22}N_4O_2$, permit the assumption that III has the structure of 3-methyl-1,4', 6'-triphenylspiro[pyrazole-4, 5'-hexahydropyrimidine]-5, 2'-dione. The same compound is obtained in low yield when equimolecular amounts of I and BBU are used.

Similarly, the reaction of I with anisylidenebisurea gave 4', 6'-di-(p-methoxyphenyl)-3-methyl-1-phenylspiro[pyrazole-4, 5'-hexahydropyrimidine]-5, 2'-dione (IV), and 1-benzyl-3-methyl-5-pyrazolone and BBU gave 1-benzyl-3-methyl-4', 6'-diphenylspiro[pyrazole-4, 5'-hexahydropyrimidine]-5, 2'-dione V).

When equimolecular amounts of I and BBU reacted under milder conditions the reaction mixture contained, in addition to 4, 4'-benzylidenebis(1-phenyl-3-methyl-5-pyrazolone) (VI) and 4-benzylidene-3-methyl-1-phenyl-5-pyrazolone (VII), a compound which can be regarded on the basis of qualitative reactions as 3-methyl-1-phenyl-4-(α-ureidobenzyl)-5-pyrazolone (II), although it was impossible to isolate it in the pure state.

It may be assumed that in the reactions described above the ureido derivative II is first formed and then this is converted either into VII with the splitting out of urea or into VI on interaction with a second molecule of I. When a double amount of arylidenebisurea is used the formation of the 4, 4-diureido derivative probably takes place, and this undergoes ring closure to form the pyrimidine ring.

Consequently, the reaction of BBU with 3, 4-dimethyl-1-phenyl-5-pyrazolone, which has only one active hydrogen atom, may be expected to give the ureido derivative. In actual fact, in this case we obtained 3, 4-dimethyl-1-phenyl-4-(α-ureidobenzyl)-5-pyrazolone (VIII).



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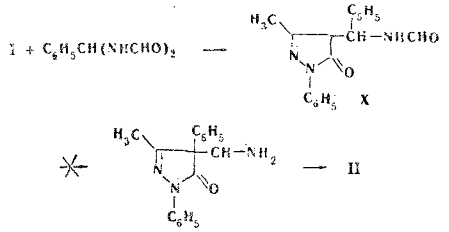
*For communication XI see [1].

The absence of a pyrazolo[3,4-d]pyrimidine from the reaction products is apparently due to the comparatively low reactivity of the CO group of the pyrazolone. In view of the fact that the activity of the CO group in amides increases when an electron-accepting substituent is attached to the nitrogen, we carried out the reaction of BBU with 1-acetyl-3-methyl-5-pyrazolone. It was found that the acetyl group was split out during the reaction and a new reaction center appeared in the pyrazolone molecule. The presence of several reaction centers led to a mixture which we were unable to separate into its individual components.

In order to confirm the possibility of the participation of the NH group of the pyrazoline ring in the reaction, we carried out the condensation of 3,4,4-trimethyl-5-pyrazolone with BBU, and obtained 3,4,4-1-(α-ureidobenzyl)-5-pyrazolone (IX) in good yield. Thus, in a 5-pyrazolone reaction can take place both through the CH_2 group in position 4 and through the NH group. When a 5-pyrazolone with another acceptor in position 1, namely 3-methyl-1-(p-nitrophenyl)-5-pyrazolone, was used, only the corresponding 4-benzylidene derivative was obtained, in good yield. The direction of the reaction is evidently affected more by the additional increase in the mobility of the hydrogen atoms of the methylene group than by the influence of the acceptor on the CO group.

We have made attempts to obtain the ureido derivative of interest to us, II, via the corresponding amine in the following way.



When the amidobenzylation reaction was carried out under conditions analogous to those for the production of III and VIII we obtained 4-(α-formamidobenzyl)-3-methyl-1-phenyl-5-pyrazolone (X) in good yield; however, when it was hydrolyzed, in place of the corresponding amine we obtained the initial pyrazolone I and the 4-benzylidenepyrazolone VII (chromatographic results).

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer in tablets of KBr with a concentration of 0.125%. The paper chromatography was carried out on "Leningrad B" paper in the n-butanol—acetic acid—water (12:3:5) system.

3-Methyl-1,4',6'-triphenylspiro[pyrazole-4,5'-hexahydropyrimidine]-5,2'-dione (III). To 20 ml of absolute n-butanol containing 0.5 g of dry HCl were added 1.74 g (0.01 mole) of I and 4.16 g (0.02 mole) of BBU and the flask was placed in a bath previously heated to 100° C. A clear red liquid was formed. It was heated for 1 hr and was then left overnight in the refrigerator. The precipitate that had deposited was filtered off, washed with ether, triturated with an excess of 10% NaOH solution, washed with water to neutrality, and dried in vacuum at 100° C over P_2O_5. Mp 237°–239° C (from ethanol). Yield of III: 2 g (49%). Compound III consists of colorless leaflets insoluble in the usual organic solvents, sparingly soluble in ethanol, and soluble in dioxane. Found, %: C 72.9; 73.2; H 5.40; 5.50; N 13.6; 13.7. Calculated for $C_{25}H_{22}N_4O_2$, %: C 73.2; H 5.40; N 13.6.

4',6'-Di(p-methoxyphenyl)-3-methyl-1-phenylspiro[pyrazole-4,5'-hexahydropyrimidine]-5,2'-dione (IV). This was obtained in a similar manner to the compound described above from I and anisylidenebisurea with a yield of 42.5%. After recrystallization from 50% ethanol and then from benzene and drying in vacuum at 100° C, mp 200°–204° C. Found, %: C 68.7; 68.9; H 5.42; 5.66; OCH_3 12.9; 13.2. Calculated for $C_{27}H_{26}N_4O_4$, %: C 69.0; H 5.52; OCH_3 13.2.

1-Benzyl-3-methyl-4',6'-diphenylspiro[pyrazole-4,5'-hexahydropyrimidine]-5,2'-dione (V). Obtained similarly to the compound described above from 1-benzyl-3-methyl-5-pyrazolone and BBU with a yield of 52%. Mp 236°–237° C (from ethanol). Found, %: C 73.7; 73.8; H 5.93; 6.19; N 13.3; 13.5; O 7.88; 7.50. Calculated for $C_{26}H_{24}N_4O_2$, %: C 73.5; H 5.65; N 13.2; O 7.65.

3,4-Dimethyl-1-phenyl-4-(α-ureidobenzyl)-5-pyrazolone (VIII). A mixture of 2.82 g (0.015 mole) of 3,4-dimethyl-1-phenyl-5-pyrazolone and 3.12 g (0.015 mole) of BBU in 10 ml of glacial CH_3COOH was boiled for 30 min. The yellowish solution obtained was neutralized with 5% Na_2CO_3 solution. The oily precipitate that deposited was separated off and triturated with a small amount of methanol. (The methanolic solution on dilution with water gave a precipitate the IR spectra of which corresponded to that of benzylidene-4,4-bis(3,4-dimethyl-1-phenyl-5-pyrazolone). The resulting crystalline precipitate of VIII was filtered off and washed with water. Yield 2 g (40%). After recrystallization from ethanol and dioxane, it was dried in vacuum at 80° C to give colorless leaflets with mp 204°–205° C. Found, %: C 67.8; 67.6; H 5.76; 5.96; N 16.7; 16.6. Calculated for $C_{19}H_{20}N_4O_2$, %: C 67.8; H 5.95; N 16.7. IR spectrum, ν cm^{-1}: 1650 (C=O of a pyrazolone), 3340, 3440 (N—H).

3,4,4-Trimethyl-1-(α-ureidobenzyl)-5-pyrazolone (IX). To 10 ml of absolute n-butanol containing 0.37 g of dry HCl were added 1.26 g (0.01 mole) of 3,4,4-trimethyl-5-pyrazolone and 2.08 g (0.01 mole) of BBU. The reaction mixture was placed in a bath previously heated to 120° C. After 7 min, a clear yellow solution had formed. Heating was stopped, and the butanol was evaporated off at room temperature. The residue was triturated with an excess of 5% Na_2CO_3 solution and the crystalline precipitate formed was filtered off. The yield of IX was 1.35 g (49%). After two recrystallizations from ethanol and drying in vacuum at 100° C, mp 242°–243° C. Found, %: C 61.6; 61.4; H 6.79; 6.66; N 20.7; 20.8. Calculated for $C_{14}H_{18}N_4O_2$, %: C 6.14; H 6.56; N 20.4. IR spectrum, ν cm^{-1}: 1670 (C=O of a ureido residue), 1690 (C=O of a pyrazolone), 3210, 3340, 3445 (N—H).

4-Benzylidene-3-methyl-1-p-nitrophenyl-5-pyrazolone. To 20 ml absolute n-butanol containing 0.25 g of dry HCl were added 1.01 g (0.005 mole) of 3-methyl-1-(p-nitrophenyl)-5-pyrazolone and 2.08 g (0.01 mole) of BBU, and the mixture was heated at 105° C for 1.5 hr. During the reaction a yellow precipitate deposited. After cooling, the precipitate was filtered off and washed with ethanol and ether. This gave 1.28 g (84%) of a substance with mp 222°–224° C (from dioxane). Found, %: C 66.4, 66.8; H 4.14; 4.41; N 13.7; 13.7. Calculated for $C_{17}H_{13}N_3O_3$, %: C 66.4; H 4.23; N 13.7. IR spectrum, ν cm^{-1}: 1720 (C=O of a pyrazolone), 1640 (C=C).

4-(α-Formamidobenzyl)-3-methyl-1-phenyl-5-pyrazolone (X). a) To 30 ml of absolute n-butanol containing 0.73 g of dry HCl were added 3.48 g (0.02 mole) of I and 3.54 g (0.02 mole) of benzylidenebisformamide, and the mixture was boiled for 3 hr. Then it was cooled and filtered, and the alcoholic solution was evaporated in vacuum. The oil obtained was triturated with an excess of 5% $NaHCO_3$ solution, and the precipitate was filtered off and washed with ethanol and ether. The yield of X was 4.5 g (74%). Mp 187°–188° C (decomp, from ethanol). Found, %: C 70.0; 70.1; H 5.83; 5.91. Calculated for $C_{18}H_{17}N_3O_2$, %: C 70.4; H 5.59. IR spectrum: ν cm^{-1}: 1640 (C=O in amides with a hydrogen bond), 3420 (N—H).

b) Compound X was also obtained by analogy with Sekiya and Yanaihara's method [8] with a yield of 65%.

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