HETEROCYCLIC ANALOGS OF XANTHONES

CHROMONO(3,2-d)PYRAZOLES

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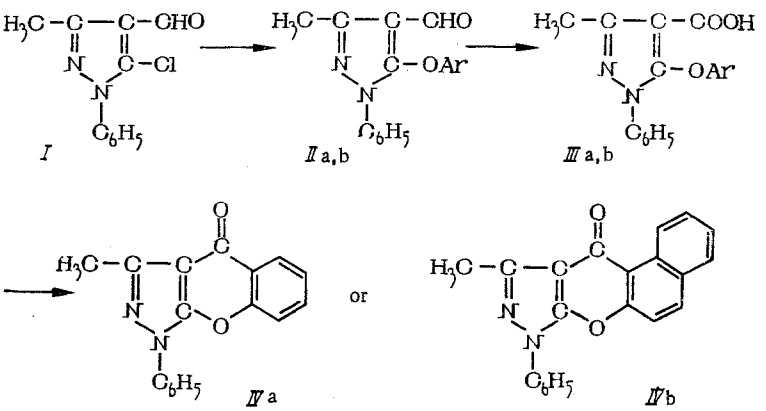
Xanthone derivatives produce local anesthesia, but in the central nervous system they act as stimulants, without anesthetic action [1-3].

It seemed worthwhile to investigate the chemical and pharmacological properties of xanthone analogs in which the phenyl group is replaced by a heterocyclic group, in particular by pyrazole. The starting point for these syntheses was chlorpyrazole aldehyde (I), whose preparation has been described previously by one of us [4]. Its action with phenol took place readily, and led to the formation of aroxy derivatives (II) in yields of 90%. Its structure was confirmed by spectral analysis, by production of the oximes and thiosemicarbazones and also by oxidation, with formation of carboxylic acids (III). The best yield of the latter was obtained by use of the calculated amount of potassium permanganate in aqueous dioxane.

3-Methyl-1-phenylchromono(3,2-d)pyrazole [3-methyl-1-phenyl-[1]benzopyrano[3,2-d]pyrazol-4(1H)-one] (IVa) was obtained by the action of aluminum chloride on the chloranhydride of the acid (IIIa) in nitrobenzene. The same product was obtained by heating 1-phenyl-3-methyl-5-phenoxypyrazole-4-carboxylic acid (IIIa) in polyphosphoric acid.



To determine the effect of the pyrazole ring on the reactivity of the CO group of the compound obtained (IVa), we used reduction reactions, action with a Grignard reagent, with hydroxylamine, with thiosemicarbazide, and with 2,4-dinitrophenylhydrazine; and UV and IR spectra. It was found that unlike xanthone, compound IVa is not reduced by zinc and alkali in aqueous alcohol. With these relatively mild measures [5] the pyrone ring opened with formation of compound XII.

When xanthone is reduced to xanthene by the action of metallic sodium in alcohol, compound IVa undergoes a more profound transformation, evidently because of the reduction of the pyrazole ring. Compound IVa is reduced in a similar way via the disodium derivative in liquid ammonia [6]. It is only when IVa is boiled for 2 h in alcoholic solution with sodium amalgam that the reduction proceeds smoothly to formation of the corresponding secondary alcohol (V), whereas xanthone is reduced to xanthydrol by these reagents when shaken for 10 min at 50° [7]. In precisely the same way, compound IVa reacts with a Grignard reagent somewhat less readily than with xanthone. The reaction with magnesium organometallic compounds

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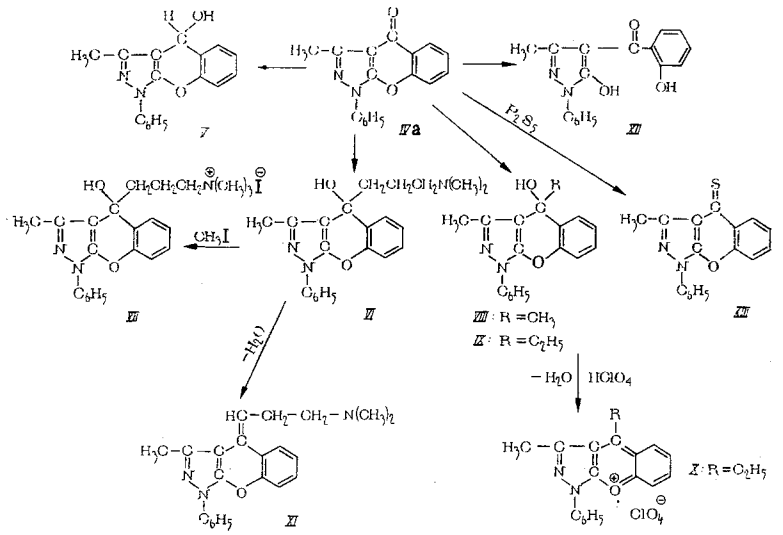
obtained from methyl iodide, ethyl bromide, and dimethylamine propyl chloride was successfully carried out in tetrahydrofuran. As a result we obtained the corresponding secondary alcohols (VI, VIII, IX), which could be dehydrated, and which also form colored salts of the xanthenyl type. Neither compound IVa nor its derived thione (XIII) reacted with hydroxylamine, thiosemicarbazide, or with 2,4-dinitrophenylhydrazine, whereas xanthone itself, which reacts with one of these substances, forms thione by similar reactions [8].

Chemical transformations involving 3-methyl-1-phenylchromono(3,2-d)pyrazole (IVa), proceed as follows:



The chemical properties of chromono(3,2-d)pyrazole (IVa) might be explained by supposing that the condensed pyrazole ring produces a stronger polarization of the carbonyl group than does the benzene ring. However, this hypothesis has not been confirmed by IR spectroscopy, whose results are as follows: $\nu_{C=O}$ of xanthone occurs at 1660 cm^{-1}, whereas $\nu_{C=O}$ of chromono(3,2-d)pyrazole (IVa) is at 1680 cm^{-1}. The reason for this lack of correspondence is not clear.

EXPERIMENTAL

3-Methyl-4-formyl-1-phenyl-5-phenoxypyrazole (IIa). A solution was made of 9.4 g phenol in 30 ml ethanol containing 5.6 g potassium hydroxide; 22.05 g 3-methyl-4-formyl-1-phenyl-5-chlorpyrazole was added, and the mixture was boiled for 7 h. The ethanol was distilled off, and the residue washed in water and crystallized from ethanol. We obtained 23.6 g (87%) of the substance, mp 86-88°. Found %: N 10.34, 10.36. Formula $C_{17}H_{14}N_2O_2$. Calculated %: N 10.37.

Oxime, mp 154-156° (from ethanol). Found, %: C 69.47, 69.93; H 5.4, 5.11; N 14.63, 14.46. Formula $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.62; H 5.11; N 14.33.

Thiosemicarbazone, mp 200-203° (from ethanol). Found %: N 19.95, 19.85; S 9.14, 9.16. Formula $C_{18}H_{17}N_5OS$. Calculated %: N 19.94; S 9.11.

3-Methyl-4-formyl-1-phenyl-5-β-naphthoxypyrazole (IIb). This substance was produced in a similar manner. Yield 77%, mp 100-102° (from ethanol). Found %: N 8.33, 8.67. Formula $C_{21}H_{16}N_2O_2$. Calculated %: N 8.51.

Oxime, mp 180-183° (from ethanol). Found %: C 73.26, 73.51; H 4.92, 5.31; N 12.1, 12.4. Formula $C_{21}H_{17}N_3O_2$. Calculated %: C 73.47; H 4.96; N 12.25.

3-Methyl-1-phenyl-5-phenoxypyrazole-4-carboxylic acid (IIIa). A solution was made of 10 g IIa in 150 ml dioxane, and 7.6 g potassium permanganate in 150 ml water was added at 20°. The temperature rose spontaneously to 50-55°, and was maintained there for 1 h. The solution was then filtered to remove the manganese dioxide, diluted with five times its volume of water, filtered from excess aldehyde (IIa); and when acid was added the carboxylic acid (IIIa) precipitated out. Yield: 80.4%. After being recrystallized twice from ethanol the product had mp 198-199°. Found %: C71.03, 71.54; H 4.91, 5.07; N 9.8, 9.5. Formula $C_{17}H_{14}N_2O_3$. Calculated %: C 71.33; H 4.89; N 9.79.

By analogy with synthesis of compound IIIa we obtained 3-methyl-1-phenyl-5-β-(naphthoxy)pyrazole-4-carboxylic acid (IIIb) in a yield of 73%. After two recrystallizations from ethanol the product had mp 199-200°. Found %: C 73.02, 73.03; H 4.74, 4.75; N 8.13, 8.01. Formula $C_{21}H_{16}N_2O_3$. Calculated %: C73.25; H 4.65; N 8.14.

3-Methyl-1-phenylchromono(3,2-d)pyrazole (IVa). A. A solution was made of 7.35 g of the carboxylic acid (IIIa) in 80 ml benzene, and was boiled with 5.5 ml thionyl chloride for 3 h. The excess thionyl chloride was distilled off under reduced pressure, and the remaining oil was dissolved in 40 ml nitrobenzene. To the solution was added 6.7 g aluminum chloride, and the mixture was kept at 50-55° for 4 h. It was then cooled to 10°, taken up in 20% hydrochloric acid, washed twice in 10% aqueous sodium carbonate, and dried with calcium chloride. After evaporation of the solvent, 4.5 g (65%) of the product (IVa) was obtained; after two recrystallizations from acetone and ethanol the mp was 172-173°. Found %; C 73.43, 73.32; H 4.85, 4.96; N 10.30, 10.33. Formula $C_{17}H_{12}N_2O_2$. Calculated %: C 73.91; H 4.36; N 10.14.

B. A solution was made of 7.35 g of the carboxylic acid (IIIa) in 75 g polyphosphoric acid, made from 37.5 g 85% orthophosphoric and 37.5 g phosphoric anhydride; the mixture was kept at 100-105° for 5 h. It was then poured out into five times its volume of water, and the precipitate washed in 10% aqueous sodium carbonate; after it had been recrystallized from acetone and from ethanol a yield of 5.1 g (70%) of IVa was obtained, mp 172-173°.

In a similar way we obtained compound IVb, which was recrystallized twice from ethanol, mp 203.5-205°. Found %; C 77.27, 77.76; H 4.46, 4.50. Formula $C_{21}H_{14}N_2O_2$. Calculated %: C 77.3; H 4.31.

3-Methyl-1-phenylchromono(3,2-d)pyrazole-8-ol (V). To an amalgam of 1.15 g sodium in 96 g mercury were added 4.7 g IVa and 30 ml ethanol, and the mixture was boiled for 2 h. The mercury was removed, and the alcoholic solution filtered while still warm, and then poured into 300 ml of cold water. The precipitate which formed was filtered, and a yield of 3.7 g (80%) compound V was obtained, mp 186-188° (from ethanol). Found %; C 73.64, 73.67; H 4.99, 5.33; N 9.87, 10.25. Formula $C_{17}H_{14}N_2O_2$. Calculated %: C 73.38; H 5.03; N 10.07.

3-Methyl-8-dimethylaminopropyl-1-phenylchromono(3,2-d) pyrazole-8-ol (VI). A layer of tetrahydrofuran was used to cover 0.6 g magnesium filings activated with iodine; then a solution of 2 g 3-dimethylaminopropylchloride in 15 ml tetrahydrofuran was added drop by drop, while the mixture was maintained at boiling point for 1.5 h. Next, 2.7 g IVa in 20 ml tetrahydrofuran was added the Grignard reagent solution, and the mixture was allowed to stand for 1.5 h. After it had cooled the mass was poured into a solution of 9 g ammonium chloride in 27 ml water mixed with 20 ml ether. The ethereal extract was washed in water. After the ether had been distilled off the residue was recrystallized from acetone, and had a mp of 119-120°. Yield of VI was 2.5 g (70%). Found %: C 73.30, 73.18; H 7.07, 7.08; N 11.7, 11.9; Formula $C_{22}H_{25}N_3O_2$. Calculated %: C 72.72; H 6.89; N 11.57.

Oxalate, mp 156-159° (decomp., from ether). Found %; N 9.26, 9.10. Formula $C_{22}H_{25}N_3O_2 \cdot (COOH)_2$. Calculated %; N 9.27.

Iodomethylate (VII). To a solution of 1 g of the compound in 20 ml ether was added 0.5 ml methyl iodide, and the mixture was left to stand for 24 h at 0-5°. After filtration, 1.1 g (80%) of the iodomethylate (VII) was obtained, mp 203-205° (from ethanol). Found, %: C 54.12, 54.01; H 5.76, 5.95. Formula $C_{23}H_{28}IN_3O_2$. Calculated, %: C 54.65; H 5.54.

3,8-Dimethyl-1-phenylchromono(3,3-d)pyrazole-8-ol (VIII). To the Grignard reagent prepared from 0.34 g magnesium filings and 0.5 ml methyl iodide in 10 ml tetrahydrofuran was added a suspension of 1.0 g IVa in 15 ml tetrahydrofurane, and the mixture was boiled for 1.5 h. Subsequent procedure was the same as for compound VI. We obtained 0.95 g (90%) of compound VIII, mp 218-220° (from acetone). Found %: C 73.67, 73,64; H 5.33, 5.53; N 9.72, 9.81. Formula, $C_{18}H_{16}N_2O_2$. Calculated %; C 73.97; H 5.48; N 9.59.

3-Methyl-8-ethyl-1-phenylchromono(3,2-d)pyrazole-8-ol (IX). We synthesized compound VIII in a similar manner, obtaining a yield of 81%, mp 117-120° (from acetone). Found, %: C 74.43, 74.61; H 5.80, 5.93; N 9.17, 9.51. Formula $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.51; H 5.88; N 9.15.

3-Methyl-8-ethyl-1-phenylchromono(3,2-d)pyrazole-8-ol perchlorate (X). A solution was made of 1 g IX in 15 ml ether at 50°; 1 g of 50% chloric acid was added, and the mixture left to stand for 24 h. The perchlorate (X) separated out as yellow crystals, mp 212-215°. Yield, 1 g (77%). Found %: N 7.11; Cl 8.89, 8.82. Formula $C_{19}H_{17}ClN_2O_5$. Calculated, %: N 7.22; Cl 9.14.

3-Methyl-8-dimethylaminopropylidene-1-phenylchromono(3,2-d)pyrazole Oxalate (XI). A mixture of 1 g VI in 10 ml alcoholic hydrogen chloride was boiled for 1 h. The solvent was removed, and the residue taken up in 20% sodium hydroxide and extracted with ether. From the dried ethereal extract compound XI separated out, mp 128-132° (decomp.). Found, %; N 9.63, 9.57. Formula $C_{22}H_{23}N_3O \cdot (COOH)_2$. Calculated %; N 9.65.

Hydrolysis of 3-Methyl-1-phenylchromono(3,2-d)pyrazole (IVa). A mixture of 25 ml 90% ethanol, 2.76 g IVa, and 2.5 g potassium hydroxide was boiled for 2 h. The mixture was poured out into 200 ml cold water, and after it had been shaken with charcoal, 2.35 g (80%) yield was obtained of 3-methyl-1-phenyl-4-(o-oxybenzoyl)-5-pyrazolene (XII); after crystallization from acetone and ethanol the mp was 192-193°. Found, %: N 9.78, 9.80. Formula $C_{17}H_{14}N_2O_3$. Calculated, %: N 9.52.

3-Methyl-1-phenylchromono(3,2-d)pyrazole-8-thione (XIII). A mixture of 1 g IVa with 1 g phosphorus pentasulfide in 20 ml xylol was heated for 5 h at 140°. The solution was filtered hot, and cooled. The yield was 0.87 g (87%) of the compound, mp 189-190° (from acetone). Found %: S 10.64, 10.69. Formula $C_{17}H_{12}N_2OS$. Calculated %: S 10.96.

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