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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

Hitherto unknown group of tricyclic fused pyrazolines have been synthesized by the reaction of 3-arylidenechromanones and 3-arylidene-1-thiochromanones with (4-carboxyphenyl)hydrazine in hot anhydrous pyridine solution. Structures of all new compounds have been elucidated by microanalyses, IR, ¹H, ¹³C NMR and mass spectrometric measurements.

Keywords: 3-Arylidenechromanones, 3-Arylidene-1-thiochromanones, (4-Carboxyphenyl)hydrazine, pyrazolines

1. Introduction

Numerous pyrazolines have been found to possess important bioactivities, viz. central nervous system, anti-microbial and antifungal, molluscicidal etc. activities. Owing to their useful bioactivities, these nitrogen-containing heterocyclic compounds became especially important substances in the drug research. Pyrazolines seem to be the most frequently studied pyrazoline type compounds and increasing attention has been focused on this ring system. As a consequence, various procedures have been developed for their synthesis and numerous derivatives have been published in the literature. Probably the most popular method is based on the reaction of α,β-unsaturated ketones and hydrazines under various reaction conditions to obtain 2-pyrazolines. Synthesis of the related tricyclic fused pyrazolines by the reaction of exocyclic α,β-unsaturated ketones with hydrazines has also been studied in several laboratories and their numerous representatives became available for biological and pharmaceutical assays in this way.¹,⁶,¹⁹,²²

As nitrogen donor reagent, hydrazine and phenylhydrazine were used in the most cases. For the utilization of several hydrazine derivatives, viz. (4-fluorophenyl) hydrazine, (4-chlorophenyl)hydrazine, semicarbazide and thiosemicarbazide, ²⁻⁴,¹¹,¹⁴,¹⁸,²³ 2-hydrizinopyridine and 4-hydrizinophthalazine⁵⁻¹⁰ few examples have been published in the literature. Formely, we have synthesized 1-(2-carboxyphenyl)- and 1-(4-carboxyphenyl)-2-pyrazolines by the reaction of α,β-unsaturated ketones with (2-carboxyphenyl)- and (4-carboxyphenyl)hydrazine.⁶⁰⁻²⁷ Beneficial bioactivities were expected by the insertion of a carboxyl group into the 2-pyrazoline molecules. As a continuation of these studies, in this paper we report on the synthesis of carboxylated tricyclic fused pyrazolines by the reaction of exocyclic α,β-unsaturated ketones and (4-carboxyphenyl)hydrazine.

2. Results and Discussion

Previously we have worked out a simple and convenient method for the synthesis of E-3-arylidenechromanones and Z-3-arylidene-1-thiochromanones by the piperidine-catalyzed condensation of chromanone and 1-thiochromanone with aromatic aldehydes. This easy access
of these exocyclic α,β-unsaturated ketones made possible for us to achieve the synthesis of a wide variety of heterocyclic compounds by their chemical transformations. Reaction of these compounds with phenylhydrazine in hot pyridine afforded trans-2,3,3a,4-tetrahydro-3-aryl-2-phenyl[1]benzopyrano[4,3-c]pyrazoles and their [1]benzothiopyrano analogues in a diastereoselective reaction.19

For the preparation of 1-(2-carboxyphenyl)- and 1-(4-carboxyphenyl)-2-pyrazolines the reaction of the appropriate α,β-unsaturated ketones with (2-carboxyphenyl)- and (4-carboxyphenyl)hydrazine in hot acetic acid proved to be a convenient procedure.26,27 For this reason, in our preliminary experiments, some of these exocyclic α,β-unsaturated ketones were allowed to react with (4-carboxyphenyl)hydrazine in hot acetic acid, however, we failed to prepare the expected tricyclic pyrazolines under these reaction conditions. Therefore, compounds 1–12 were reacted with (4-carboxyphenyl)hydrazine in hot anhydrous pyridine and tricyclic fused pyrazolines 13–24 (Scheme 1) were obtained in medium to good yields (62–79%). We have also investigated the reaction of these starting materials with (2-carboxyphenyl)hydrazine, but only intractable mixtures were obtained both under acidic or alkaline reaction conditions.

Structures of all new compounds 13–24 have been elucidated by microanalyses and various spectroscopic methods (cf. Experimental). Elemental composition of compounds 13–24 has been unambiguously proven by elemental analyses and mass spectrometric data. In the IR spectra an intense C=O band between 1597 and 1603 cm⁻¹ refers to the formation of a pyrazoline ring. Also an intense band belonging to the carboxyl group was assigned between 1664 and 1674 cm⁻¹. In the 1H NMR spectra (cf. Experimental) both chemical shift values and the multiplicities of the signals reveal the characteristics of a tricyclic fused pyrazoline ring system. Chemical shift values of the aliphatic carbon atoms in the 13C NMR spectra, viz. C-3 (68.2–70.2 ppm), C-3a (52.2–55.2 ppm) and C-4 (66.3–66.9 ppm for 13–18, 28.9 ppm for 19–21 and 51.2–51.3 ppm for 22–24) corroborate this assumption. On the basis of the 1H and 13C NMR data, it can also be concluded that one diastereomer was formed in each case since one series of signals was observed in all NMR spectra. No minor components could be isolated or detected. The cis-3,3a and trans-3,3a isomers of such tricyclic fused pyrazolines can easily be differentiated by 1H NMR spectroscopy.13–16,19 In the 1H NMR spectra the 10.1–11.7 Hz J3,3a coupling constant values reveal an antiperiplanar orientation of protons 3-H and 3a-H. Chemical shift values of 5.08–5.30 ppm for 3-H and 3.56–3.90 ppm for 3a-H corroborate the trans-orientation of these two protons in comparison with the 1H NMR data of the similar tricyclic fused pyrazolines.13–16,19

If the reaction of 3-arylidenechromanones and 3-arylidene-1-thiochromanones with phenylhydrazine19 and (4-carboxyphenyl)hydrazine (present study) is compared, it can be concluded that the effect of the para-carboxyl group is a considerable slowing-down of the reaction. A complete conversion of the starting exocyclic α,β-unsaturated ketones required four times longer reaction time as in the case of the phenylhydrazine.19 This is a consequence of the decreasing of the nucleophilicity of the hydrazine moiety by the presence of the electron acceptor para-carboxyl group. Electronic character of the para-substituent of the aryldiene unit of the starting materials and the type of the heteroatom in the six-membered ring is without influence both on the course of the reaction and on the stereochemistry of the products 13–24.

3. Conclusion

In conclusion, we have synthesized hitherto unknown group of tricyclic fused pyrazolines by a simple efficient procedure. Our present results are new contribution to the chemistry of the substituted phenylhydrazines and in this way new substances became available for the biological and pharmacological trials of pyrazolines.

4. Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. 1H NMR and 13C NMR
spectra were obtained using a Bruker WP 200 SY spectrometer at 200/50 MHz in DMSO-d₆ (internal standard TMS, δ = 0.0 ppm) at ambient temperature (ca. 20 °C). The IR spectra were obtained in KBr discs with a Perkin-Elmer 16 PC instrument. Mass spectra were recorded on a VG Trio-2 apparatus. Elemental analyses (C, H, N) were measured with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F²₅₄ (Merck) layer using toluene:ethyl acetate (4:1 v/v) as eluent. Starting materials 1-12 were synthesized according to known procedures.28,29

Preparation of compounds 13–24. General Procedure. A mixture of 1–12 (0.01 mol), (4-carboxyphenyl)hydrazine (0.04 mol) and anhydrous pyridine (50 mL) was heated at reflux for 24 h, then poured into water. The precipitate was separated by filtration, washed with water and crystallized from methanol to afford tricyclic fused pyrazolines 13–24 (Scheme 1).

Trans-2,3,3a,4-Tetrahydro-2-(4-carboxyphenyl)-3-(4-methylphenyl)[1]benzopyrano[4,3-c]pyrazole (13). It was obtained from 1 as white needles in 64% yield, mp 247–248 °C; IR (v, cm⁻¹) 3427, 2928, 1664, 1597, 1469, 1431, 1397, 1289, 1219, 1179, 1131, 1145, 1046, 988, 845, 773; ¹H NMR (DMSO-d₆, δ ppm) 3.64 (m, 1H, 3a-H), 4.39 (dd, 1H, J = 12.4, 10.7 Hz, 4-H), 4.72 (dd, 1H, J = 12.4, 5.8 Hz, 4-H), 5.20 (d, 1H, J = 10.7 Hz, 3-H), 7.02–7.80 (m, 12H, Ar-H), 12.28 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm) 53.0, 66.9, 68.2, 113.1, 114.5, 117.2, 120.9, 121.5, 124.2, 125.9, 127.8, 129.2, 130.4, 131.4, 140.9, 146.5, 148.7, 155.6, 167.0; MS m/z (%) 370 (M⁺, 21), 293 (72), 242 (50), 115 (100); Anal. Calcd. for C₂₃H₁₈N₂O₃: C, 74.58; H, 4.89; N, 7.56. Found: C, 74.67; H, 4.95; N, 7.50.

Trans-2,3,3a,4-Tetrahydro-2-(4-carboxyphenyl)-3-(4-fluorophenyl)[1]benzopyrano[4,3-c]pyrazole (14). It was prepared from 2 as white needles in 73% yield, mp 258–260 °C; IR (v, cm⁻¹) 3427, 2928, 1664, 1597, 1469, 1431, 1397, 1289, 1219, 1179, 1131, 1145, 1046, 988, 845, 773; ¹H NMR (DMSO-d₆, δ ppm) 3.66 (m, 1H, 3a-H), 4.39 (dd, 1H, J = 12.4, 10.7 Hz, 4-H), 4.72 (dd, 1H, J = 12.4, 5.8 Hz, 4-H), 5.19 (d, 1H, J = 10.7 Hz, 3-H), 7.02–7.80 (m, 12H, Ar-H), 12.28 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm) 53.0, 66.9, 68.2, 113.1, 114.5, 117.2, 120.9, 121.5, 124.2, 125.9, 127.8, 129.2, 130.4, 131.4, 140.9, 146.5, 148.7, 155.6, 167.0; MS m/z (%) 370 (M⁺, 21), 293 (72), 242 (50), 115 (100); Anal. Calcd. for C₂₃H₁₇ClN₂O₃: C, 68.23; H, 4.23; N, 6.86. Found: C, 68.31; H, 4.17; N, 6.86.

Trans-2,3,3a,4-Tetrahydro-2-(4-bromophenyl)-3-(4-bromophenyl)[1]benzopyrano[4,3-c]pyrazole (15). It was prepared from 5 in 69% yield, mp 273–274 °C; IR (v, cm⁻¹) 3427, 2928, 1664, 1599, 1516, 1471, 1429, 1285, 1230, 1179, 1047, 985, 762; ¹H NMR (DMSO-d₆, δ ppm) 3.62 (m, 1H, 3a-H), 4.36 (t, 1H, J = 12.1 Hz, 4-H), 4.71 (dd, 1H, J = 12.2, 5.9 Hz, 4-H), 5.13 (d, 1H, J = 11.5 Hz, 3-H), 6.98–7.92 (m, 12H, Ar-H), 12.40 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm) 53.0, 66.9, 68.2, 113.1, 114.5, 117.2, 120.9, 121.5, 124.2, 125.9, 127.8, 129.2, 130.4, 131.4, 140.9, 146.5, 148.7, 155.6, 167.0; MS m/z (%) 404 (M⁺, 85), 353 (60), 293 (40), 115 (100); Anal. Calcd. for C₂₃H₁₈Cl₂N₂O₃: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.31; H, 4.17; N, 6.86.

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obtained from 7 in 65% yield, mp 289–290 °C; IR (ν, cm⁻¹) 1676, 1600, 1516, 1429, 1388, 1294, 1179, 1128, 1086, 843, 752, 697; ¹H NMR (DMSO-d₆, δ, ppm) 3.12 (dd, 1H, J = 11.9, 5.0 Hz, 4-H), 3.34 (t, 1H, J = 11.9 Hz, 4-H), 3.63 (m, 1H, 3a-H), 5.20 (d, 1H, J = 10.8 Hz, 3-H), 7.02–8.06 (m, 13H, Ar-H), 12.26 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ, ppm) 72.08; H, 4.66; H, 4.29; H, 6.69. Found: 66.09; H, 4.29; N, 6.76.

Trans-2,3,3a,4-Tetrahydro-2-(4-carboxyphenyl)-3-(4-methylphenyl)[1]benzothiopyrano[4,3-c]pyrazole (23). It was obtained from 11 as yellow needles in 79% yield, mp 298–299 °C; IR (ν, cm⁻¹) 1713, 1673, 1603, 1516, 1393, 1298, 1203, 1146, 1083, 927, 877, 827, 764, 652, 545; ¹H NMR (DMSO-d₆, δ, ppm) 2.31 (s, 3H, Me), 3.78 (m, 1H, 3a-H), 40.2 (dd, 1H, J = 12.6, 6.3 Hz, 4-H), 4.32 (t, 1H, J = 12.6 Hz, 4-H), 5.26 (d, 1H, J = 11.7 Hz, 3-H), 7.03–8.10 (m, 12H, Ar-H), 12.48 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ, ppm) 20.7, 51.3, 52.4, 69.2, 113.6, 122.1, 123.3, 124.9, 126.2, 126.5, 128.2, 128.9, 129.9, 130.5, 133.1, 136.8, 137.6, 137.7, 143.5, 147.5, 167.0; MS m/z (%) 432 (M⁺, 10), 367 (25), 277 (70), 238 (100); Anal. Calcd. for C₁₃H₁₈FN₃O₃S: C, 66.66; H, 4.66; N, 6.47. Found: 66.75; H, 4.62; N, 6.53.

Trans-2,3,3a,4-Tetrahydro-2-(4-carboxyphenyl)-3-(4-fluorophenyl)[1]benzothiopyrano[4,3-c]pyrazole-4,4-dioxide (24). It was obtained from 12 as yellow plates in 73% yield, mp 283–284 °C; IR (ν, cm⁻¹) 1716, 1672, 1601, 1513, 1429, 1393, 1313, 1293, 1231, 1179, 1148, 1083, 929, 878, 837, 766, 656, 544; ¹H NMR (DMSO-d₆, δ, ppm) 3.84 (m, 1H, 3a-H), 4.08 (dd, 1H, J = 12.8, 6.4 Hz, 4-H), 4.30 (t, 1H, J = 12.8 Hz, 4-H), 5.24 (d, 1H, J = 11.4 Hz, 3-H), 7.10–8.14 (m, 12H, Ar-H), 12.46 (s, 1H, COOH); ¹³C NMR (DMSO-d₆, δ, ppm) 51.3, 52.2, 68.6, 113.3, 116.3, 122.2, 123.3, 124.9, 125.3, 126.4, 128.7, 130.6, 133.1, 135.8, 137.6, 143.6, 147.4, 167.0; MS m/z (%) 436 (M⁺, 7), 371 (24), 277 (64), 242 (100); Anal. Calcd. for C₁₃H₁₈FN₃O₃S: C, 63.30; H, 3.93; N, 6.42. Found: C, 63.38; H, 3.88; N, 6.49.

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6. References


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Z reakcijo 3-arilidenkromanonov in 3-ariliden-1-tiokromanonov s 4-hidrazinobenzojsko kislino je bila sintetizirana nova skupina kondenziranih tricikličnih pirazolinov. Strukture novih spojin so bile določene z elementno analizo in s spektroskopskimi (IR, NMR, MS) metodami.