

OPTICALLY ACTIVE N-(α -PHENYLETHYL)AMIDES OF ISOMERIC 1-PHENYLPYRAZOLECARBOXYLIC ACIDS

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The rotatory dispersion of the (-)-N-(α -phenylethyl)amides of the isomeric 1-phenylpyrazolecarboxylic acids depends on the position of the amido group in the pyrazole ring. The difference in the spectropolarimetric behavior of the isomers can be used to determine the position of a substituent in the pyrazole ring. The phenylpyrazole group induces a pronounced Cotton effect in the region of its absorption if there is conjugation between the benzene and pyrazole rings. The analogy in the spectropolarimetric behavior of the (-)-N-(α -phenylethyl)amides of 1-phenylpyrazole-4-carboxylic and benzoic acids attests to the aromatic character of the 4 position in the pyrazole ring, which is also well known from its chemical properties.

A study of the optical rotatory dispersion of the (-)-N-(α -phenylethyl)amides of benzoic [1], substituted benzoic [2], and isomeric pyridinecarboxylic acids [3, 4] has shown that in several cases the trend of the rotatory dispersion curves (RD curves) depends on the nature of the solvent. In continuing our investigations in this direction, we have synthesized the (-)-N-(α -phenylethyl)amides of 1-phenylpyrazolecarboxylic acids with a carboxyl group in the 3, 4, or 5 positions (I-III), respectively, and have measured their rotatory dispersion in alcohol and dioxane from 589 to about 220 nm.

The amides of pyrazolecarboxylic acids are also of interest because there is very little information in the literature regarding optically active compounds containing a pyrazole ring. Thus it has been shown that the presence of a pyrazole grouping in epimeric methyl glycyrrhetinates does not affect the RD curves from 280-600 nm [5]. Measurements of the rotatory dispersion of several steroid pyrazoles indicated that the pyrazole ring, as a chromophoric system (λ_{\max} 230 nm), can be optically active if it is in an asymmetric environment [6]. In addition, the rotatory dispersion of a number of phenylpyrazoles [7], for which anomalies were observed from 230 to 300 nm, was studied.

(-)-N-(α -Phenylethyl)amides I-III were obtained by the reaction of the chlorides of the corresponding acids with (-)- α -phenylethylamine. Measurements of the rotatory dispersion of amides I-III indicated that the trend of the curves depends substantially on the position of the phenylethylamido group in the pyrazole ring (Figs. 1-3). Thus II gives RD curves similar to those of N-benzoyl-(-)- α -phenylethylamine, and the "solvent effect" characteristic for the latter is manifested: in alcohol an RD curve with a positive Cotton effect at 260 nm is observed, while in dioxane and benzene, negative RD curves are observed, which could be measured only up to 280 nm (Fig. 2) because of strong absorption and insignificant rotatory values. The trends of the RD curves of I and III are independent of the solvent polarity. Moreover, in alcohol and dioxane I gives RD curves with a positive Cotton effect, the amplitude of which depends on the solvent: the rotation is larger in dioxane than in alcohol (Fig. 1). In alcohol and dioxane III displays a negative Cotton effect at 220 nm, while only an inflection is observed at 260 nm (Fig. 3). The trends of the RD curves of amides I-III do not change when hydrochloric acid is added.

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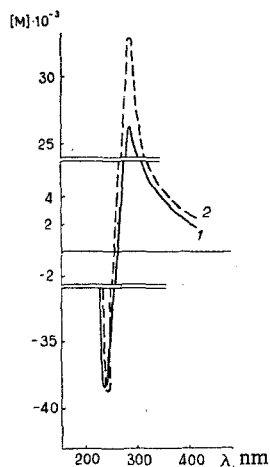


Fig. 1. RD curves of the (-)-N-(α -phenylethyl)-amide of 1-phenylpyrazole-3-carboxylic acid: 1) in alcohol; 2) in dioxane.

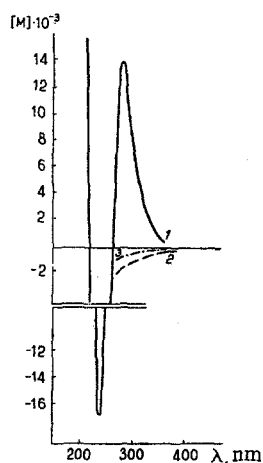


Fig. 2. RD curves of the (-)-N-(α -phenylethyl)-amide of 1-phenylpyrazole-4-carboxylic acid: 1) in alcohol; 2) in dioxane; 3) in benzene.

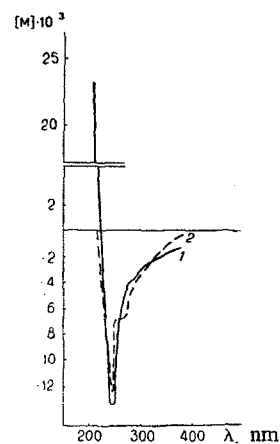
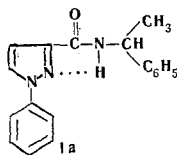


Fig. 3. RD curves of the (-)-N-(α -phenylethyl)-amide of 1-phenylpyrazole-5-carboxylic acid: 1) in alcohol; 2) in dioxane.

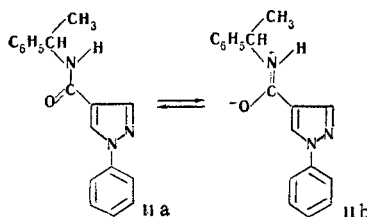
Since there are three chromophoric groups (phenylpyrazole, the benzene ring of the α -phenylethylamine group, and the amide group, conjugated with the pyrazole ring) in molecules of amides I-III, the observed RD curves are the superimposition of several Cotton effects induced by each of these chromophores. The first is the positive Cotton effect at 265 nm induced by the first (α) absorption band of the benzene ring and the absorption band of the phenylpyrazole group, which is a conjugated aromatic chromophore [8] [λ_{\max} 267 nm (for I), 263 nm (for II)], while the determining band is the absorption band of phenylpyrazole since, as in the case of the starting (-)- α -phenylethylamine [9], we did not observe the fine structure of the α -absorption band of benzene in either the UV spectra or the RD curves. The first extremum of this Cotton effect is the peak observed at 280-285 nm, while the second (a valley) is apparently overlapped by the first extremum of the negative Cotton effect at 220 nm induced by the absorption band of the amide group conjugated with the phenylpyrazole system. For this Cotton effect, only its first extremum - a valley at 230-235 nm (Fig. 1) - can be measured.

It may be assumed that for I the trend of the RD curve at 260 nm is determined by the phenylpyrazole grouping, fixed in conformation Ia by means of an intramolecular hydrogen bond. In our previous studies we observed that precisely this fixing of the chromophore grouping [10, 11] as well as a decrease in the lability of substituents attached to nitrogen [1-4] leads to positive RD curves and positive Cotton effects for (-)- α -phenylethylamine and (+)- α -benzylethylamine derivatives. However, the retention of the trend of the RD curves on dilution of the solutions with hydrochloric acid, which should have disrupted the hydrogen bond, contradicts this explanation.



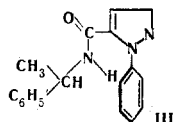
Similar fixing of the conformation is impossible for amide II. However, if one considers the "solvent effect" to be a consequence of mesomerism of the amide group [1-4], the state in alcohol should be close to the limiting formula IIb, i.e., to a structure with fixed bonds about the nitrogen. As a result, a positive Cotton effect is observed at 260 nm for II in alcohol, but its amplitude is considerably less than for amide I. (See scheme, top of page 1468.)

In nonpolar solvents, the state of the amide group approaches limiting formula IIa, i.e., a structure which is more conformationally labile than IIb, so that very small rotations and negative RD curves up to 280 nm are observed in dioxane and benzene (Fig. 2).



In III the presence of a bulky substituent in the 5 position (next to the phenyl group) leads to disruption of the coplanarity of the phenyl group with the pyrazole ring, i.e., conjugation vanishes. This is detected from the hypsochromic shift of the absorption band for 5-substituted pyrazoles [12]. Thus, for III, only the pyrazole ring itself rather than the conjugated aromatic chromophore – the phenylpyrazole grouping – will be the determining grouping from 230 to 270 nm. In the case of III we are dealing with a conformationally labile system, and this is probably the reason that the Cotton effect associated with the pyrazole chromophore is not manifested on the RD curves of III: only a deflection, which apparently corresponds to a $\pi \rightarrow \pi^*$ transition in the pyrazole ring (λ_{\max} 240 nm), is observed at 260 nm.

It may be assumed that the Cotton effect induced by this transition is masked by the strong negative Cotton effect, the reason for which, as in the case of I and II, is the absorption band of the amide grouping conjugated with the pyrazole ring (Fig. 3).



All of the (–)-N-(α -phenylethyl)amides of the isomeric 1-phenylpyrazolecarboxylic acids studied give a negative Cotton effect in the region of amide-group absorption. It is natural to associate this with the fact that the amide grouping is directly attached to an asymmetric carbon atom whose configuration is the same in all of our compounds.

EXPERIMENTAL

The measurements were made with a JASCO spectropolarimeter with 0.1- and 0.01-dm-long tubes. The UV spectra in alcohol were measured with a "CARY-14" spectrophotometer. The IR spectra were measured with a UR-20 spectrometer.

The 1-phenylpyrazolecarboxylic acids were obtained via well-known methods. The appropriate 1-phenylpyrazolecarboxylic acid (0.05 mole) and 15 ml of SOCl_2 were refluxed on a water bath for 10 h, excess SOCl_2 was removed in vacuo, and the residue was heated to 100° at 3 mm. A solution of 0.1 mole of (–)- α -phenylethylamine ($[\alpha]_D -41^\circ$) in 60 ml of ether was added, the precipitated salt was filtered, the ether solution was evaporated to dryness, and the residue was recrystallized from benzene–hexane (1:2).

(–)-N-(α -Phenylethyl)amide of 1-Phenylpyrazole-3-carboxylic Acid (I). This was obtained in 57% yield and had mp 127°; λ_{\max} 267 nm, $\log \epsilon$ 4.23; ν 3355, 1540 cm^{-1} (NH), 1650 cm^{-1} (CO). Found %: C 74.1, 74.1; H 6.0, 6.0. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}$. Calculated %: C 74.2; H 5.9. Rotatory dispersion (in alcohol, c 0.029): 3480° (350 nm), 25,600° (285 nm, peak); –47,000° (235 nm, valley), –28,600° (215 nm); (in absolute alcohol + HCl, c 0.032): 2400° (350 nm), 18,400° (285 nm, peak), –32,200° (240 nm, valley), –13,800° (215 nm); (in dioxane, c 0.020): 4300° (350 nm), 33,200° (285 nm, peak), –39,000° (240 nm, valley), –24,600° (225 nm); (in dioxane + HCl, c 0.043): 4260° (350 nm), 25,300° (285 nm, peak), 12,700° (275 nm).

(–)-N-(α -Phenylethyl)amide of 1-Phenylpyrazole-4-carboxylic Acid (II). This was obtained in 63% yield and had mp 174°; λ_{\max} 263 nm, $\log \epsilon$ 4.30; ν 3340, 1565 cm^{-1} (NH), 1640 cm^{-1} (CO). Found %: C 74.5, 74.2; H 5.5, 5.6. Rotatory dispersion (in alcohol, c 0.022): 531° (350 nm), 13,290° (285 nm, peak), –16,900° (240 nm, valley), 21,400° (215 nm); (in absolute alcohol + HCl, c 0.020): 2020° (350 nm), 8670° (285 nm, peak), –33,200° (240 nm, valley), –17,300° (225 nm); (in dioxane, c 0.061): –523° (350 nm), –1900° (290 nm); (in benzene, c 0.36): –194° (589 nm), –849° (334 nm); (in dioxane + HCl, c 0.103): –562° (350 nm), –984° (310 nm).

(-)-N-(α -Phenylethyl)amide of 1-Phenylpyrazole-5-carboxylic Acid (III). This was obtained in 41% yield and had mp 147°; λ_{max} 240 nm, $\log \epsilon$ 4.13, ν 3300, 1550 cm^{-1} (NH), 1650 cm^{-1} (CO). Found %: C 74.0, 74.0; H 5.8, 5.7. Rotatory dispersion (in alcohol, c 0.067): -1650° (350 nm), -3920° (275-285 nm), -13,600° (240 nm, valley), 22,400° (215 nm); (in absolute alcohol + HCl, c 0.059): -1670° (350 nm), -5400° (290 nm), -7890° (275 nm), -14,700° (250 nm); (in dioxane, c 0.085): -1020° (350 nm), -6870° (240-264 nm), -13,750° (235 nm, valley), 0° (220 nm); (in dioxane + HCl, c 0.092): -1330° (350 nm), -7580° (264 nm).

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