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The alkaloid cocaine

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Figure 1: Structural formulas of isomers I-IV

Abstract

Full Text

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CONFORMATIONAL STUDY IN THE COCAINE SERIES

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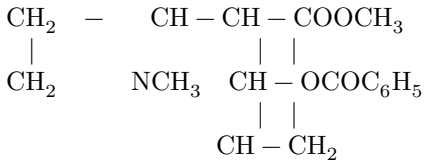
The alkaloid cocaine



is a benzoyl derivative of the methyl ester of the bicyclic compound—ecgonine, tropanol-3-carboxylic-2 acid (I, II, III, IV), which can exist in the form of 8 optical antipodes and 4 racemates.

We previously reported ([1]) the synthesis of four isomeric methyl esters of ecgonine (I-IV, $R = CH_3$), differing in the configuration of substituents in positions 2 and 3.

Accordingly, their spatial configuration may be represented by the following four cis-trans isomeric forms: normal (I), pseudo (II), allo (III), and allopseudo (IV).

Stereoisomers (I, $R = CH_3$, b.p. 83-85° at 0.2 mm; R_f 0.69) and (II, $R = CH_3$, m.p. 128.5-130.5°; R_f 0.44) were obtained by reduction of 2-carbomethoxytropanone-3 with sodium amalgam; stereoisomers (III, $R = CH_3$, m.p. 78.5-80.0°; R_f 0.68) and (IV, $R = CH_3$, m.p. 82.0-83.5°; R_f 0.37)—by reduction in the presence of platinum or Raney nickel.

To clarify the absolute configuration of compounds (I-IV), we investigated their infrared absorption spectra.

In the work of other authors dealing with the synthesis of compounds of this class ([2]), no similar substantiation of the configuration of isomers by means of physicochemical methods, and in particular spectroscopy, was made.

Stereoisomers (I, $R = CH_3$) and (IV, $R = CH_3$) in carbon tetrachloride, at a concentration of about 0.2-0.3 M, show in the region of hydroxyl-group absorption a distinct maximum lying respectively at 3535 and 3530 cm^{-1} (Fig. 1, curves 1 and 4). Upon dilution of the solutions this band does not disappear, while in the region of free hydroxyl (> 3600 cm^{-1}) no appreciable increase in absorption occurs, as would be expected ([3]) in the case of an intermolecular character of the hydrogen bond formed by the hydroxyl in solutions of increased concentration (Fig. 1, $1a, 4a$).

These data indicate that the OH group in (I, $R = CH_3$) and (IV, $R = CH_3$) forms an intramolecular hydrogen bond with the neighboring carbomethoxy group. It is most natural to assign to both isomers a cis configuration, the most favorable for the occurrence of an intramole-

Fig. 1

Fig. 2

Fig. 1. IR absorption spectra in CCl_4 of the methyl esters of isomeric ecgonines (1, 1a–4, 4a), tropine (5, 5a), and pseudotropine (6, 6a)

Fig. 2. IR absorption spectra of the methyl ester of anhydroecgonine (1, 1a) (CCl_4); anhydroecgonine (2), isomeric ecgonines (3–6), and their hydrochlorides (2a–6a) (KBr)

cular hydrogen bridge. The stereoisomer (II, R=CH_3) at higher concentrations gives, in the region under consideration, three bands: a narrow one at 3590 cm^{-1}, and two broad ones: in the region 3500–3400 cm^{-1} and at 3150 cm^{-1} (Fig. 1, 2). On dilution of the solution the latter two bands disappear, while the first correspondingly increases in intensity (Fig. 1, 2a).

The compound (III, R=CH_3) at high concentrations likewise exhibits three bands: a narrow one at 3630 cm^{-1}, and two broad ones: at 3450 and 3100 cm^{-1}, respectively (Fig. 1, 3), the latter two disappearing on dilution of the solution, with simultaneous strengthening of the first band (Fig. 1, 3a).

Analogous behavior is observed for tropine (V) and pseudotropine (VI). The spectrum of tropine in the absorption region of the hydroxyl group is very similar to the spectrum of the stereoisomer (III, R=CH_3): in concentrated solutions there are maxima at 3630, 3430, and 3170 cm^{-1}, while in dilute solutions only the maximum at 3630 cm^{-1} remains (Fig. 1, 5 and 5a).

The conclusion suggests itself that the hydroxyl group in (V), as well as in (II, R=CH_3) and (III, R=CH_3), is involved in an intermolecular hydrogen bond, which is destroyed upon dilution of the solution; moreover, the band in the region 3400–3500 cm^{-1} corresponds to a bridge of the type O···HO, and the band in the region 3100–3200 cm^{-1} to a bridge of the type N···HO (it is known that

Structural schemes (Va), (V), (VI), (VIa), (VII)

Figure 2: Structural schemes (Va), (V), (VI), (VIa), (VII)

hydrogen bonding to nitrogen causes a greater lowering of the OH vibrational frequency than bonding to oxygen ([4]).

The band at 3630 cm^{-1} in the spectra of (V) and (III, R=CH_3), which increases in intensity upon dilution of the solutions, should be assigned to the free

hydroxyl. The 3590 cm^{-1} band in the spectrum of compound (II, R=CH_3), which behaves upon dilution analogously to the 3630 cm^{-1} band, lies somewhat below the region usually assigned to a free hydroxyl in alcohols ($\nu > 3600$ cm^{-1}). This lowering can be explained if the isomer (II, R=CH_3) is assigned the diequatorial (e, e) trans-configuration, in which some interaction between the hydroxyl and ester groups is possible, and the isomer (III, R=CH_3) the diaxial (a, a) configuration, in which such interaction is excluded.

Pseudotropine (VI), in addition to the three bands of the type considered (3625, 3400, and 3100 cm^{-1}), gives an additional band at about 3300 cm^{-1}, which does not disappear upon dilution (Fig. 1, 6 and 6a); it may be attributed to an admixture of the bath configuration (VIa), in which an intramolecular hydrogen bridge N···.HO is formed. In the case of tropine and its derivatives, formation of an intramolecular hydrogen bond in the bath configuration (Va) is excluded because the hydroxyl cannot approach the nitrogen atom to the distance necessary for hydrogen-bond formation (< 3.3 Å ([3])).

In the spectrum of the methyl ester of anhydroecgonine (VII, R=CH_3), obtained by methylation of anhydroecgonine (VII, R=H) (see below), there are no bands that could be assigned to a hydroxyl, free or associated (Fig. 2, 1 and 1a). The two weak peaks in the spectrum of the isomer (III, R=CH_3)—at 3550 and 3470 cm^{-1}, remaining after dilution of the solution (Fig. 1, 3a)—apparently belong to overtones (the fundamentals may be, for example, stretching vibrations of C=O of the carbomethoxy group: 1750 $cm^{-1} \times 2 = 3500$ cm^{-1}), since analogous weak bands at 3580 and 3540 cm^{-1} are present in the spectrum of the anhydroecgonine ester (VII, R=CH_3) (Fig. 2, 1a).

The presence of a double bond in the molecule (VII, R=CH_3) is detected by a distinct band at 1655 cm^{-1}.

For final confirmation of the configurations assigned to the isomers (I-IV), we studied the region of the spectrum in which the stretching vibrations of the C—OH bond of the hydroxyl appear (900-1200 cm^{-1}), taking into account that, for an equatorial hydroxyl group, the frequency ν(C—O) is higher than for an axial one ([5]). To distinguish the ν(C—O) band among the group of bands occurring in the 900-1200 cm^{-1} region and belonging to vibrations of other bonds, we used the solvent effect, proceeding from the idea that for this type of vibration the same sequence of solvents (with respect to the band shift) is

observed irrespective of the structure of the substance containing the vibrating group ([6]). In the cyclohexanol series it was found ([7]) that the greatest shift of ν(C–O) toward lower frequencies is caused by chloroform, and toward higher frequencies by acetone. We found that an even greater lowering of the ν(C–O) frequency is caused by bromoform, and the greatest increase is given by pyridine. The choice of bands belonging to ν(C–O) was facilitated, moreover, by the fact that high intensity is characteristic of them.

It turned out that, in tropine (V), the largest and unambiguous shift in the solvent series used (bromoform → chloroform → carbon tetrachloride → acetone → pyridine) is undergone by an intense band lying, in carbon tetrachloride solution, at 1049 cm^{-1}, whereas in ψ-tropine (VI) it is the band at 1063 cm^{-1}. Consequently, these bands belong to the vibrations ν(C–O) of the HC–OH group, and the higher frequency, 1063 cm^{-1}, is in agreement with the (e)-configuration hydroxide of ψ-tropine, and the lower one, 1049 cm^{-1}, with the (a)-conformation of tropine hydroxide.

An analogous analysis (using the solvent effect) of the absorption bands of the stereoisomers (I–IV, R=CH_3) led to the conclusion that the isomers (I, R=CH_3) and (II, R=CH_3), as having higher values of the frequencies ν (C–O) (respectively 1075 and 1078 cm^{-1} in carbon tetrachloride), should be assigned the (e)-conformation, while the isomers (III, R=CH_3) and (IV, R=CH_3) (ν (C–O) in carbon tetrachloride equal, respectively, to 1049 and 1066 cm^{-1}) should be assigned the (a)-conformation of the hydroxyl groups.

Noteworthy is the coincidence of the frequencies ν (C–O) for the isomer (III, R=CH_3) and tropine (V): 1049 cm^{-1} in carbon tetrachloride. This could have been expected if one takes into account that the axial hydroxyl in (III, R=CH_3) does not participate in an intramolecular hydrogen bond, just as in tropine. If, however, the isomer (I, R=CH_3), which possesses an equatorial hydroxyl, is compared with ψ-tropine (VI), one can verify that the intramolecular hydrogen bond in (I, R=CH_3) causes a substantial increase in the frequency ν (C–O), compared with ψ-tropine, whose equatorial hydroxyl in dilute solutions (<0.1 M) exists predominantly in the free state (ν (C–O) for (I, R=CH_3) and (VI) in carbon tetrachloride are, respectively, 1075 and 1063 cm^{-1}).

We also studied the IR spectra of the ecgonines (I–IV, R=H) corresponding to the isomeric esters considered above (Fig. 2, 3–6). From the spectra of the ecgonines it follows that in the solid state they all exist in the zwitterionic form, as evidenced by an intense COO^- band in the region of 1600 cm^{-1}. Absorption in the region 1700–1750 cm^{-1}, characteristic of the carboxyl group, is completely absent. The band at 1663 cm^{-1} in the spectrum of normal ecgonine (I, R=H) (Fig. 2, 3) indicates the presence in the sample of a certain amount of the anhydro form, whose formation is favored by the trans-configuration of the hydrogen at C_2 relative to the hydroxyl at C_3 in this stereoisomer. In the spectrum of anhydroecgonine itself (VII, R=H) (Fig. 2, 2), studied in connection with the presence of its impurity in samples of normal ecgonine (I, R=H), there

is likewise an analogous band at 1663 cm^{-1}, belonging to stretching vibrations of the C=C bond, while the intense band near 1600 cm^{-1}, in turn, indicates the zwitterionic form.

In the IR spectra of the hydrochlorides of the ecgonines (I–III, R=H) and anhydroecgonine (VII, R=H) in the solid state (Fig. 2, 3a, 4a, 5a, and 2a), absorption in the region of 1600 cm^{-1} disappears, and intense peaks appear in the region above 1700 cm^{-1}, characteristic of the COOH group. The band ν (C=C) in anhydroecgonine hydrochloride is shifted somewhat toward lower frequencies, appearing at 1652 cm^{-1}.

In the spectra of the ecgonine hydrochlorides (I–III, R=H) (Fig. 2, 3a–5a), very intense bands appear, respectively at 3310, 3400, and 3380 cm^{-1}, which correspond to a hydroxyl associated in the manner O···HO, and somewhat less clearly expressed bands, respectively at 3110, 3050, and 3090 cm^{-1}, belonging to a hydroxyl associated in the manner N···HO.

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[1] G. I. Bazilevskaya, M. S. Bainova et al., ZhOKh, **30**, 1458, 2088 (1960); M. S. Bainova, G. I. Bazilevskaya et al., ZhOKh, **30**, 1120 (1960); G. I. Bazilevskaya, D. V. Gura, ZhOKh, **28**, 1097 (1958); G. I. Bazilevskaya, M. S. Bainova et al., Izv. vyssh. shkol, Khimiya i khim. tekhnologiya, **2**, 75 (1958).
[2] G. Fodor, Acta chim. Acad. Sci. Hung., **5**, 396 (1955); S. P. Findlay, J. Org. Chem., **21**, 711 (1956); **22**, 1385 (1957); **24**, 1540 (1959).
[3] L. P. Kuhn, J. Am. Chem. Soc., **74**, 2492 (1952).
[4] H. Freedman, J. Am. Chem. Soc., **83**, 2900 (1961).
[5] W. Hückel, H. Feltkamp, S. Geiger, Lieb. Ann., **637**, 1 (1960).
[6] L. B. Archibald, N. Pullin, Spectrochim. acta, **12**, 34 (1958).
[7] G. Chiurdoglu, W. Masschelein, Bull. Soc. chim. Belges, **70**, 307 (1961).

Note: Figure translations are in progress. See original paper for figures.