Chemistry

1964

SovietRxiv

Abstract

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Chemistry

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On the Interaction of Certain Alkaloids of the Morphine Series with Iodine Chloride

(Presented by Academician M. M. Shemyakin, January 23, 1964)

Recently we investigated the interaction of certain arylated ethylenic hydrocarbons with iodine chloride ([1,2]). It was established that the chemical nature of the solvent determines the course of the reactions taking place. In developing these studies, we examined the interaction with iodine chloride of certain alkaloids related to morphine, with the aim of obtaining their halogen derivatives with possible physiological activity. Among the morphine derivatives, compounds of unsaturated character with a substituted phenolic hydroxyl group were selected, such as diacetylmorphine (I), codeine (II), 6-acetylcodeine (III), and diacetyl-N-allylnormorphine (IV). Some saturated morphine derivatives were also subjected to the action of iodine chloride, such as dihydrodiacetylmorphine (V), dihydrocodeinone (dicodid), tetrahydrothebaine, and others. All the alkaloids studied are quantitatively precipitated by the reagent and give yellow amorphous precipitates of a resinous character. The reaction proceeds smoothly in various solvents.

We obtained, not previously described in the literature, products of addition of iodine chloride to diacetylmorphine and codeine of composition $C_{21}H_{23}NO_5JCl$ (VI) and $C_{18}H_{21}NO_3JCl$ (VII), respectively. Attempts to obtain products with a different ratio of components in inert media were unsuccessful. Both substances contain iodine in an active state, as was shown by its liberation with potassium iodide. Reducing agents such as potassium bisulfite, sodium thiosulfate, and also lithium aluminum hydride decompose these compounds; in this process the starting alkaloid diacetylmorphine (or morphine) is isolated in high yield, and, correspondingly, codeine. An addition product of composition $C_{21}H_{25}NO_5JCl$ (VIII) with analogous chemical properties was also obtained from the saturated base—dihydrodiacetylmorphine.

Molecular complex compounds of iodine chloride with electron-donor systems, primarily with nitrogenous bases, have been described in the literature, and interest in the study of these compounds has increased greatly in recent times ([3–5]). As far as we know, complex compounds of iodine chloride with alkaloids have not been described in the literature. For pyridinium iodochloride, Fialkov ([6]) assumes a structure of the type of tetrasubstituted ammonium salts. For comparison, we synthesized pyridinium iodochloride according to ([7]); this

compound possessed chemical properties analogous to those of our complexes.

IR spectra* were recorded for compounds VI and VII (in the solid state), along with spectra of the starting alkaloids (in chloroform). Both in the spectra of the bases and in the spectra of the addition products, maxima are observed that characterize the carbon–carbon double bond: for I and VI at 1620 cm^{-1}, for II and VII at 1640 cm^{-1}. The bands characterizing the methyl group bonded to nitrogen, at 2805 cm^{-1} for I and 2800 cm^{-1} for II, disappear in the spectra of their derivatives VI and VIII, which

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* The IR spectra were recorded and analyzed at the Institute of Organic Chemistry of the Bulgarian Academy of Sciences by B. Yordanov.

indicates the presence in the latter of a quaternary nitrogen atom. Person et al. ([8]), on the basis of IR spectra of iodine chloride and of its stable complexes, of the pyridinium iodide chloride type, concluded that the structure of these complexes is at least 50% ionic. On the basis of the above, structures of complex compounds may be assigned to VI and VII.

We then attempted to use these complex compounds for the synthesis of new morphine bases. Thus, in the catalytic hydrogenation of VI, instead of the expected hydrogenolysis and saturation of the double bond with hydrogen, which would have led to V, we obtained a previously undescribed compound of composition $C_{21}H_{27}NO_5$.

Attention is drawn to the fact that diacetyl-*N*-allylnormorphine in hydrochloric acid medium, or diacetylmorphine and 6-acetylcodeine* in carbon tetrachloride medium, are immediately precipitated by iodine chloride, but for complete completion of the reaction two moles of reagent are required. This could be explained either by the formation of complexes with an alkaloid—iodine chloride ratio different from that in VI, VII, and VIII, or by the fact that in these cases complex formation is accompanied by addition of iodine chloride to a carbon–carbon double bond. In the case of diacetyl-*N*-allylnormorphine and 6-acetylcodeine we isolated previously undescribed bases of composition $C_{23}H_{25}NO_5JCl$ (IX) and $C_{20}H_{23}NO_4JCl$ (X), respectively. The essential difference in the structure of diacetyl-*N*-allylnormorphine from alkaloids I and II lies in the presence in the former compound of an unsaturated allyl group. Taking into account the fact that under completely identical reaction conditions only IV is converted into the halogen-containing base IX, we believe that in this case iodine chloride adds to the double bond of the allyl group. For base X we assume addition of iodine chloride to the double bond of the cyclohexene ring. Treatment of III with a larger excess of iodine chloride in chloroform did not lead to the possible replacement of the iodine atom by chlorine ([1]), and we isolated from the reaction mixture the same base X. Evidently, complex formation is accompanied by addition of iodine chloride to a carbon–carbon double bond in those cases where the structure of the alkaloid and the chemical nature of the solvent favor the addition reaction.

Structural formulas VI, VII, IX, and X

Figure 1: Structural formulas VI, VII, IX, and X

We express our gratitude to Prof. B. I. Kurtev for advice during the conduct and discussion of this study.

VI: $R_1 = CH_3CO-$; $R_2 = CH_3CO-$
VII: $R_1 = CH_3-$; $R_2 = H$

IX

X

Experimental Part

Preparation of diacetylmorphine iodide chloride (VI):

a) To a solution of 7.38 g (0.02 g-mole) of I, m.p. 172–173°, in 20 ml of 2*N* hydrochloric acid, 3.25 g (0.02 g-mole) of iodine chloride in 30 ml of 2*N* hydrochloric acid are added portionwise with stirring. The precipitate is filtered off, washed with dry chloroform, and dried to constant weight. M.p. 160° (decomp.). The yield is quantitative. Recrystallization from absolute alcohol proceeds with partial decomposition and loss of about 40–45% of the product. The–

* We worked with acetylated codeine because of the insolubility of codeine in carbon tetrachloride.

The substance crystallizes in golden-yellow crystals, insoluble in chloroform and benzene, m.p. 163° (decomp.).

Found %: C 47.48; 47.10; H 4.56; 4.66; N 2.59; 2.40; I 23.80; 23.82; Cl 6.32* $C_{21}H_{23}NO_5ICl$ (531.78). Calculated %: C 47.42; H 4.36; N 2.63; I 23.86; Cl 6.67

b) A solution of 1.85 g (0.005 g-mole) of I in 10 ml of 2 *N* hydrochloric acid is treated with 1.63 g (0.01 g-mole) of iodine chloride analogously to that described above. The yield is quantitative. The recrystallized product with m.p. 163° (decomp.) shows no depression of the melting point with the product obtained by method a).

c) To a suspension of 1.85 g of I in 20 ml of absolute methanol, with stirring, a solution of 1.63 g of iodine chloride in 15 ml of methanol is added dropwise. The yield is quantitative. The purified product is identical with the product obtained by method a).

Found %: C 47.49; H 4.49; N 2.53

Preparation of codeine iodine chloride (VII). To a solution of 2.40 g (0.008 g-mole) of II in 60 ml of 5% hydrochloric acid, 1.33 g (0.008 g-mole)

of iodine chloride in 5 ml of 4 *N* hydrochloric acid is added in portions with stirring. Yield of (VII) 3.37 g (93% of theory). Recrystallization from absolute ethanol proceeds with loss of about 50% of the product. M.p. 156° (decomp.); golden-yellow needles, insoluble in benzene and chloroform.

Found %: N 2.73; 2.76; I 27.78; 27.84; Cl 6.80; 6.68
$C_{18}H_{21}NO_3ICl$ (461.7). Calculated %: N 3.03; I 27.49; Cl 7.68

Preparation of dihydrodiacetylmorphine iodine chloride (VIII). To a solution of 0.37 g (0.001 g-mole) of V (m.p. 162–164°) in 15 ml of carbon tetrachloride, 0.16 g (0.001 g-mole) of iodine chloride in 5 ml of carbon tetrachloride is added dropwise. The precipitate separates in powdery form; it is filtered off and washed thoroughly with the same solvent. Yield 0.48 g (91% of theory); it is not amenable to recrystallization. M.p. 115° (decomp.).

Found %: N 2.43; 2.48; I 22.49; 22.33
$C_{21}H_{25}NO_5Cl$ (533.8). Calculated %: N 2.62; I 23.78

Hydrogenation of diacetylmorphine iodine chloride. 0.93 g (0.0018 g-mole) of VI, m.p. 163° (decomp.), in 200 ml of absolute alcohol is hydrogenated with 0.1 g of freshly prepared platinum oxide at room temperature and normal pressure. 102 ml of hydrogen is absorbed. The catalyst is filtered off, the alcohol is distilled off in vacuo, the residue is dissolved in water and alkalized with ammonia. Yield of crude product 0.30 g, m.p. 243–244° (from absolute alcohol). The substance dissolves well in chloroform, moderately in ether and benzene.

Found %: C 68.10; H 7.19; N 4.26
$C_{21}H_{27}NO_5$ (374.4). Calculated %: C 67.54; H 7.29; N 3.75

Mol. wt.: found 376.2; calculated 372.7.

Preparation of iodine chloride diacetyl-N-allylnormorphine (IX). To a solution of 1.60 g (0.004 g-mole) of IV (m.p. 139°) in 20 ml of 2 *N* hydrochloric acid, 1.30 g (0.008 g-mole) of iodine chloride in 30 ml of 2 *N* hydrochloric acid is added in portions with stirring. The precipitate formed is filtered off and dried. Yield 2.75 g. The substance decomposes on recrystallization. 1.30 g (0.0018 g-mole) of the dry complex compound is dissolved in 6–7 ml of methanol and carefully decomposed with 20 ml of a 4% solution of potassium bisulfite. The resulting solution is alkalized with ammonia to pH 9–9.5. In this process 0.79 g (84% of theory) precipitates. After recrystallization, m.p. 259° with decomp. (from absolute alcohol). The substance dissolves moderately in chloroform and poorly in benzene. Its solutions in ether, as well as in dilute sulfuric and hydrohalic acids, rapidly

* The analyses were performed at the Institute of Organic Chemistry of Debrecen University by Éva Rakosi.

become yellow. Gives stable solutions in dilute (*L*+)-tartaric acid.

Found, %: C 49.18; H 4.92; N 2.68; 2.71; I 22.70; 22.80
CH_3CO 15.30; 15.40

$C_{23}H_{25}NO_5JCl$ (557.8). Calculated, %: C 49.52; H 4.52; N 2.51; I 22.75; CH_3CO 15.43

Preparation of Iodochlorinated 6-acetylcodeine (X)

a) To a solution of 1.36 g (0.004 g-mole) of III (m.p. 134°) in 75 ml of carbon tetrachloride, 1.30 g (0.008 g-mole) of iodine chloride in 50 ml of the same solvent is added dropwise with stirring. The precipitate formed is filtered off and dried. Yield 2.54 g. The product decomposes upon attempts at recrystallization. 1.22 g (0.0018 g-mole) of the dry complex compound is dissolved in 5 ml of acetone and decomposed by the method described above. From the alkaline solution 0.50 g (55% of theory) is precipitated. After recrystallization from alcohol, m.p. 183–185°. Colorless needles, readily soluble in chloroform and benzene and moderately soluble in ether.

Found, %: C 47.53; 47.64; H 4.70; 4.69; N 3.08; 3.06;
I 24.00; 24.60; CH_3CO 8.57; 8.64

$C_{20}H_{23}NO_4JCl$ (503.77). Calculated, %: C 47.68; H 4.60; N 2.78;
I 25.20; CH_3CO 8.54

Mol. wt.: found 527.2, calculated 532.3.

On mixing solutions of X and *L*-tartaric acid in absolute alcohol, a salt precipitates, which crystallizes from absolute alcohol in the form of needles with m.p. 193° (decomp.).

Found, %: C 46.26; 46.18; H 4.60; N 2.34; 2.14

$2C_{20}H_{23}NO_4JCl, C_4H_6O_6$ (1157.63). Calculated, %: C 45.65; H 4.53; N 2.42

b) A mixture of 0.68 g (0.002 g-mole) of III and 0.98 g (0.006 g-mole) of iodine chloride in 70 ml of chloroform is left for 24 hours. The solution is decolorized by washing with a 5% solution of sodium thiosulfate. The aqueous solution is alkalinized and additionally extracted with chloroform. The chloroform solution is washed with a 5% solution of sodium carbonate and with water and evaporated. The dry residue is purified through the tartrate. Yield 0.35 g (37% of theory), m.p. 183–185°. A mixed sample with iodochlorinated 6-acetylcodeine obtained by a) shows no depression of the melting point.

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Received
8 I 1964

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