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Bisbenzyltetrahydro*iso*quinoline Alkaloids

II. * Methods for Preparing the Two Monomethyl Ethers of *d*-Chondrocurine

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Partly methylated *d*-chondrocurine *** can easily be separated into one unmethylated and one methylated fraction with a counter current procedure, using four separatory funnels and three volumes of ether and one volume of buffer pH 11.9. The dimethyl ether of *d*-chondrocurine is likewise easily separated from the fraction of monomethyl ethers at pH about 13.3, using four volumes of buffer and one volume of ether. One of the monomethyl ethers, but not the other, can easily be crystallized from methanol.

Chondrocurine was first discovered by Wintersteiner and Dutcher [1] in an authenticated concentrated extract of *Chondrodendron tomentosum* Ruíz and Pavon, prepared in Peru. Soon thereafter King [2] found *d*-chondrocurine to be present in a commercial curare from Peru. Kondo, Satome and Odera [3] have identified this alkaloid in another commercial preparation, and Bick and Clezy [4] have recently isolated it in plant material from commercial sources, from which tubocurarine chloride had been extracted.

Wintersteiner and Dutcher [1,5] prepared the dimethochloride of *d*-chondrocurine, and this synthesis was repeated by Marsh and Herring [6] and by Marsh [7] for their investigation of the curariform activity of the menispermaceous alkaloids. Dutcher [8] found that this compound, *d*-chondrocurarine † chloride, also occurs naturally and can be found, *e.g.*, in mother liquors from which *d*-tubocurarine has been crystallized. Preparations of crystalline *d*-tubocurarine chloride have shown different physiological potencies, and Dutcher [9]

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*** The spelling chondo . . . occurs but should be regarded as an orthographic error [13].

† The quaternary compounds corresponding to curine *etc.* are called curarine *etc.*

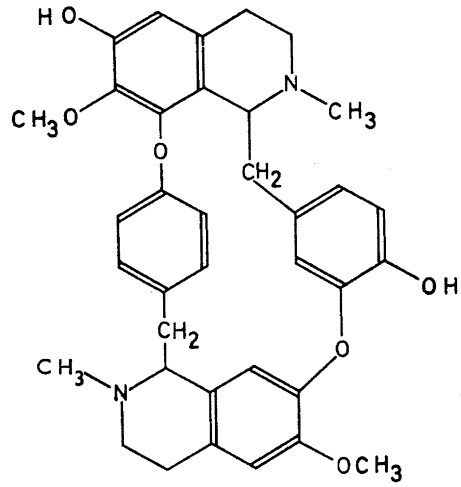

Fig. 1. Chondrocurine.

proved that this could be explained by the presence of *d*-chondrocurarine in sufficient amounts to have a noteworthy effect.

Dutcher [10] also studied the structure of chondrocurine. He found that the dimethyl ether of *d*-chondrocurarine iodide is identical with the dimethyl ether of *d*-tubocurarine iodide. Dutcher [10] further found that *d*-chondrocurine gives a positive Millon reaction. He concluded [8], considering King's [11] commonly accepted [12] inference on the Millon reaction, that *d*-chondrocurine has a hydroxyl group and not a methoxyl group on one of its central benzene rings and that the hydroxyl group and the methoxyl group in *ortho* position on one of the tetrahydro*iso*quinoline rests have reversed positions in *d*-chondrocurine and *d*-tubocurarine. It had been shown previously by King [14,15] that these groups are so located that tubocurarine is a 7-hydroxy-6-methoxy-tetrahydro-*iso*quinoline derivative, and hence chondrocurine is a 6-hydroxy-7-methoxy-tetrahydro*iso*quinoline derivative (Fig. 1).

Bick and Clezy [16] prepared the amorphous dimethyl ether of *d*-chondrocurine and carried out a reductive fission with sodium in liquid ammonia, as was first done for structure determinations in this group of alkaloids by Tomita, Fujita and Murai [17]. The results of the investigation was that the asymmetric center in that tetrahydro*iso*quinoline rest which has a substituted phenoxy rest in 7-position is dextrorotatory, and that the asymmetric center in the other tetrahydro*iso*quinoline rest, which has its substituted phenoxy rest in 8-position, is levorotatory.

The natural occurrence of a monoquaternary bisbenzyltetrahydro*iso*-quinoline alkaloid, N-monomethyl *d*-chondrocurine, has been reported by Bodendorf and Scheibe [18]. They crystallized this substance as nitrate and called it *d*-protochondrocurarine nitrate. Also chondrocurarine (which had previously [8,9] been crystallized only as iodide with halogenated hydrocarbons as solvent of crystallization) was crystallized as nitrate and, thus purified, could be crystallized as chloride [18].

A new, important achievment in this field has recently been reported by Voronin, Tolkachev and Preobrazhenskii [19,20]: the synthesis of isomers of curare alkaloids.

After this review of work on *d*-chondrocurine by others, an account will be given of the results in the present investigation, which was carried out mainly in the early part of 1959.

SEPARATION METHODS

The purpose of this work was to prepare the two monomethyl ethers of *d*-chondrocurine. A similar problem, preparing the two monomethyl ethers of *l*-curine, has previously been partly solved by Späth and Kuffner [21] as one proof among several others for the correctness of the opinion that curine consists not of one but of two benzyltetrahydro*iso*quinoline rests. The methods suggested here for preparing the two monomethyl ethers of *d*-chondrocurine have some resemblance to Späth and Kuffner's method in the general approach: the alkaloid is partly methylated with diazomethane, and the reaction products are separated — more or less efficiently — by a distribution procedure between two immiscible solvents, whereupon they are crystallized. Both processes make use of the property of the completely methylated compounds to be almost insoluble in a strong potassium hydroxide solution but fairly easily soluble in ether, in order to accomplish their separation from substances which are not completely methylated and which as a consequence thereof are soluble in a strong potassium hydroxide solution due to the formation of a salt. The main difference between the principles for separation described here and the separation carried out by Späth and Kuffner is that whereas they had no efficacious procedure, based on distribution between two immiscible solvents, for separating the unmethylated compound from the two monomethyl ethers (but tried a simple fractionated extraction as a support to fractionated crystallization), the present work includes an investigation of the conditions for such a separation. A simple and efficacious method has been worked out, which can be generally used for this kind of separation problems. The value of this method lies in the fact that both in the case of chondrocurine and its monomethyl ethers, and in the case of curine and its monomethyl ethers, the unmethylated alkaloid otherwise has to be separated by a series of fractionated crystallizations, and in both cases methanol is the solvent of choice for crystallizing both the original alkaloid and one of its monomethyl ethers.

Group separation with ether and buffer

The best way to separate mixtures obtained from partial methylation of a bisbenzyltetrahydro*iso*quinoline alkaloid is to start by separating the mixture into groups of isomers according to the number of free hydroxyl groups in the molecule. In the case of *d*-chondrocurine Fig. 2 contains the partition coefficients successively obtained during the work by a procedure described in the preceding paper [22] in this series. The partition coefficients were computed from extinction values at maximum absorption at about 280—290 mμ (the

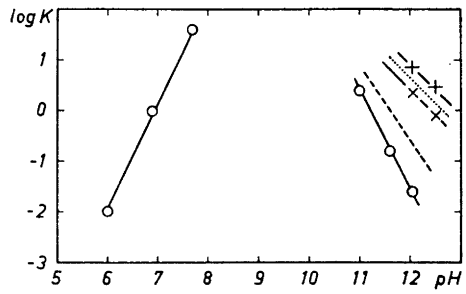

Fig. 2. The influence of pH on the partition coefficient K for *d*-chondrocurine (O) and its monomethyl ethers ($\times$ and $+$) between diethyl ether and buffer. The dashed line gives the optimum relationship between volume ratio and pH for separation of *d*-chondrocurine from its monomethyl ether with partition coefficient closest to that of *d*-chondrocurine, and the dotted line gives the optimum relationship between volume ratio and pH for separation of the two monomethyl ethers of *d*-chondrocurine.

optimum wave length depending on pH and degree of methylation) in the more polar solvent in a series of extractions.

Fig. 2 gives the conditions for a separation between the group of *d*-chondrocurine monomethyl ethers and *d*-chondrocurine. In a distribution system the best separation is obtained when the ratio of the volumes of the two solvent phases equals the inverse value of the geometric mean between the partition coefficients for the two substances [23]. If this is applied to a diagram which gives the logarithms of the partition coefficients for two substances as curves (Fig. 2), a curve drawn midway between them gives the negative value of the logarithm for the best ratio between the volumes of the two solvent phases. Thus, for a separation of *d*-chondrocurine and that of its monomethyl ethers whose partition coefficient is nearer to that of *d*-chondrocurine, we can read from Fig. 2 that the pH value at which equal volumes of buffer and ether give the best separation (abscissa value zero) is 11.6. At pH 11.9 the ordinate value for the line is -0.5, and hence the logarithm for the optimum ratio of the volumes of the less polar (ether) and more polar (buffer) phase is $+0.5$, *i.e.*, 3 volumes of ether for 1 volume of buffer. (The partition coefficients were computed for the solvents in the same order: the quotient obtained by dividing the concentration in the less polar phase by the concentration in the more polar phase.)

We can also see from the diagram that if we start the separation procedure using 3 volumes of ether and 1 volume of buffer pH 11.9, the *d*-chondrocurine will distribute itself in such a way that there will be about 10 times as much in the water phase as in the ether phase, because the difference in abscissa values for the line from which we read the best separation conditions and the line giving the distribution coefficients for *d*-chondrocurine is one unit in the logarithmic scale. One of the monomethyl ethers will distribute in such a way that there will be about 10 times as much in the ether phase as in the water phase, and as to the other monomethyl ether, there will be about 30 times more present in the ether phase than in the water phase. The dimethyl ether of *d*-chondrocurine will be present almost entirely in the ether phase.

One simple distribution at a correctly chosen combination of volume ratio and pH thus gives a fair separation. The result can easily be greatly improved by using a few more separatory funnels in the way described by Bush and Densen [24]. For an example, say three separatory funnels are used, numbered 1, 2, and 3. All funnels contain the proper volume of the upper solvent phase. An equal number of portions, in this case consequently three, of the proper volume of the lower solvent phase are successively transferred through the series, starting with funnel No. 1, into which the mixture to be separated is also introduced at the beginning of the separation. After equilibration and adjustment of pH (because of the formation of a phenolate) the lower phase in the first funnel is transferred to the second, and a second portion of the lower solvent phase is introduced into the first funnel. After new equilibration the lower phase in the second funnel is transferred into the third funnel and so on till all batches of the lower solvent phase have passed the funnels. These portions are pooled and contain the fraction consisting mainly of the substance or substances with a partition coefficient lower than that which corresponds to the separation condition (volume ratio) chosen. Likewise, the portions of the upper solvent phase left in the funnels are pooled and contain the fraction consisting mainly of the substance or substances with a distribution constant higher than that which corresponds to the separation condition. In the separation problem considered here the situation is, as mentioned, that *d*-chondrocurine distributes itself so that 10 times as much substance is in the lower phase as in the upper phase. Thus, by a separation procedure using one funnel we can theoretically recover 90.9 % of the *d*-chondrocurine from the lower phase. It can easily be worked out that by using two funnels in a separation as described we can recover 97.7 %; three funnels give 99.0 %, and four funnels give 99.8 % recovery.

When preparations of partly methylated *d*-chondrocurine, which were larger than about 0.5 g, were separated, it was found convenient to introduce the solute in several portions according to the principle described by O'Keeffe, Dolliver and Stiller [25]. From their description of the procedure, it actually is a superimposition of two simultaneously and independently run separation series, whereas a scheme for the procedure in a single series is given by Jübermann [26].

From the example given in a previous paragraph, with three separatory funnels, the separation could be expanded in the following way. After the procedure has been carried out so far that all three portions of the upper solvent phase are in the funnels, a new portion of the solute is introduced into funnel No. 2, and the phases are equilibrated under adjustment of pH. As one new portion of solute is introduced, one more portion of each of the two solvent phases should be used (one may, of course, use more portions to get a better final separation). This is done as follows. The lower phase of funnel No. 3 is collected in a container for the bottom phase fraction, and the bottom phase in funnel No. 2 is poured into No. 3. The bottom phase in funnel No. 1 is poured into funnel No. 2, and the top phase in funnel No. 1 is collected in a container for the top phase fraction. The contents of funnel No. 2 are poured into No. 1, and the contents of funnel No. 3 are poured into No. 2, and the phases are equilibrated (one may instead remove fun-

nel No. 1 and add a funnel No. 4 for the continuation of the separation). A fresh portion of the upper phase solvent is added to No. 3. The bottom phase in funnel No. 2 is poured into No. 3, and that of No. 1 is poured into No. 2. A fresh portion of the lower phase solvent is added to No. 1. The separation is continued either by introducing a new portion of solute into funnel No. 2 or by continuing the transferring of the phases till all portions of the phases have passed each other. Any number of funnels may be used; when the series is expanded, solute is introduced successively into funnels Nos. 1, 2, 3, *etc.* till the funnel in the middle of the series is used for this introduction of the solute, if the number of funnels is odd; or till the last funnel in the first half of the series is used, if the number is even.

In a similar way, the two monomethyl ethers can be efficiently separated from the dimethyl ether. A suitable procedure can be derived from the values given in Fig. 2, although the distribution coefficient is not given for the *d*-chondrocurine dimethyl ether. It is very reasonable to presume that the logarithm for the distribution constant for this substance between ether and an alkaline buffer is not less than 1.5 but sooner larger than 2, and the results from actual separations have not been contradictory to this presumption. If we want to run the separation in such a way that the *d*-chondrocurine monomethyl ether with the higher distribution constant is present in 10 times as large quantities in the water phase as in the ether phase, we may use 4 volumes of a buffer solution pH 13.3 and 1 volume of ether (Fig. 2). Then the percentage of this *d*-chondrocurine monomethyl ether recovered in the pooled water phases after a counter current separation for various number of funnels will be the same as the percentage of *d*-chondrocurine recovered in the previously described separation, where 10 times as much substance was also present in one phase as in the other. The fraction recovered in the case of that *d*-chondrocurine monomethyl ether which has the lower distribution constant will obviously be better, and the recovery of *d*-chondrocurine dimethyl ether in the pooled ether phases can also reasonably be expected to be about equally good or better.

Separation of the *d*-chondrocurine monomethyl ethers with diethyl ether and buffer

The prospect and conditions for a counter current separation of the two monomethyl ethers of *d*-chondrocurine can also be read from Fig. 2. In this figure, two lines represent the logarithms of the distribution constants for these substances as functions of pH. A line drawn midway between these two lines gives the condition for best separation. The abscissa value for this line is zero at a pH value about 12.7, which means that equal volumes of the two solvent phases give the best separation at this pH value. The difference in pH values (abscissa values for equal ordinate values) between this line and one of the lines giving the logarithm of the partition coefficient of a *d*-chondrocurine monomethyl ether is about 0.25. This implies that even such a small deviation in the pH value from the optimum value as say 0.1 would have a considerable influence on the separation. Considering that in ordinary simple pH determinations uncorrected results obtained with various appa-

ratus differ noticeably at high pH values, and that the time response for various glass electrodes may differ considerably [27], it is recommended that when a separation of this kind is intended, the influence of possible differences in pH determinations be taken into account by checking the value of the partition coefficient of one of the substances for a suitable pH value.

As the difference in ordinate values between the line for best separation and the line for one of the *d*-chondrocurine monomethyl ethers is also about 0.25, the amount of the monomethyl ether with lower partition coefficient will be only about 1.5 times as large in the lower phase as in the upper phase. This implies that a counter current distribution with a small number of funnels cannot give a very good separation but that a considerable number of transfers or theoretical plates would be required. However, a fairly acceptable separation can be achieved by again fractionating the fractions obtained after using only a small number of transfers.

Recovery of the fractions

The various fractions can be recovered in the following way. In the case of a water phase solution, so much fairly strong hydrochloric acid (say 6 N) is added to the solution that its pH value is adjusted to about 8.5, whereby the substance appears as a precipitate. The final adjustment of pH is made easier if sodium bicarbonate is added to the mixture and a more dilute solution of hydrochloric acid (say 1 N) is used at the end. It is recommended that the precipitate not be directly filtered off but first extracted with diethyl ether because ether leaves various impurities undissolved, whereas it rather easily dissolves *d*-chondrocurine and its methyl ethers. Chloroform, however, dissolves all or almost all those impurities which usually appear and hence is not recommended for this step. A mixture of one volume of ether and two volumes of chloroform leaves much of the impurities undissolved. This mixture was used in some cases. — Ether solutions are filtered through cotton if they contain impurities in suspension and are then extracted with several portions of dilute hydrochloric acid (0.05 N HCl is suitable) till the pH value of the extract is small, say about 2. When a mixture of chloroform and ether was used, the hydrochloric acid extracts were washed with ether because otherwise small droplets of the mixture of chloroform and ether appeared in the bottom of the container when the alkaloid was precipitated and disturbed the recovery considerably. Potassium hydroxide (*e.g.*, a 25 % solution) or sodium hydroxide is carefully added to the hydrochloric acid extract till the pH value of the mixture is slightly above 8.5. The final adjustment of pH is facilitated, if some sodium bicarbonate is added to the mixture. If the alkali solution is added too quickly, part of it may be included in ball-shaped particles and cause considerable disturbances in the recovery procedure by slowly making the mixture more alkaline than was intended. The precipitate is filtered off and dried. It turned out that using silica gel for drying the preparation in a desiccator was very convenient, and if the desiccator was evacuated with an oil pump to a sufficiently low pressure, it worked as freeze-drying. The bisbenzyltetrahydro*iso*quinoline alkaloids slowly deteriorate if left in

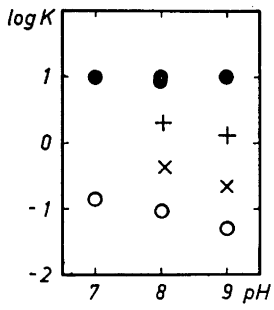

Fig. 3. The influence of pH on the partition coefficient K for *d*-chondrocurine (O), its monomethyl ethers (× and +) and its dimethyl ether (●) between two solvent phases consisting of a mixture of benzene (1/3) and heptane (2/3) in equilibrium with a mixture of equal volumes of methanol and water containing buffer salts (volume ratios 1:2:4:4 or 2:4:3:3).

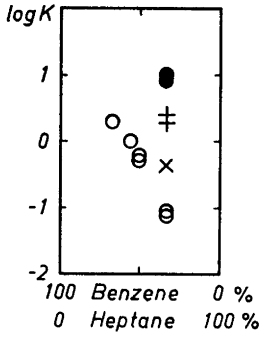

Fig. 4. The influence of the ratio of the volumes of benzene and heptane on the partition coefficient K for *d*-chondrocurine (O), its monomethyl ethers (× and +) and its dimethyl ether (●) between two solvent phases consisting of benzene and heptane in equilibrium with a mixture of equal volumes of methanol and water containing buffer salts.

the open air at room temperature; they can, however, be kept in a closed container in a refrigerator.

The water phase contained potassium sulfite because sulfites prevent the formation of coloured matter in solutions of these alkaloids; it further contained potassium phosphate and potassium hydroxide. Potassium salts were chosen because they do not have the same disturbing effect on ordinary glass electrodes for pH determinations as sodium salts have.

A conveniently flexible four component solvent system

Benzene, heptane, methanol, and water constitute a conveniently flexible solvent system especially for checking the identity and purity of bisbenzyltetrahydro*iso*quinoline alkaloids, including their methylated and demethylated derivatives, by determination of their partition coefficients. Paper chromatography [9] proved less satisfactory; among the solvents tested ethyl methyl ketone with about 4 % methanol and almost saturated with water (which depresses tailing and increases R_F values) was best.

As part of the procedure for working out separation methods, partition coefficients of *d*-chondrocurine and its methyl ethers were measured for various compositions of the four component system. The results are given in Figs. 3 and 4. Most preparations used for these measurements were not yet completely separated. A procedure previously described [22] was used for computing the partition coefficients.

It appears from these figures that the partition coefficient increases about 10 times for every hydroxyl group methylated, whereas in the case of

ether and buffer, the value of the partition coefficient increases about 100 times for every hydroxyl group methylated in the pH range in which a separation can be carried out conveniently. Thus, the mixture of benzene, heptane, methanol, and water is not as suitable as ether and alkaline water for a counter current separation of a mixture into one fraction with no hydroxyl groups, one fraction with one hydroxyl group, and one fraction with two hydroxyl groups in the molecule.

Counter current separation of isomers with the four component system

It has previously been described in this paper how one can easily obtain a pure preparation consisting of a mixture of the two *d*-chondrocurine monomethyl ethers. A few attempts were made to separate them, using the four component solvent system and five separatory funnels. The fractions obtained consisted of mixtures, in which one and the other of the monomethylated ethers, respectively, had been considerably concentrated as can be expected from the moderately favourable difference in partition coefficients. However, the separation experiments according to this method were not continued because a way to separate the monomethyl ethers by crystallization was found at that time. Nevertheless, it is obvious that this method is valuable in those cases in which one or several components in a mixture of isomers related to the groups of alkaloids considered here must be concentrated before one can crystallize them. It may be added here that Engel, Alexander, Carter, Elliott and Webster [28] have described a general method for determining which composition of a quaternary system is most suitable for specific separation problems.

The possibility of using the four component system for separating such isomers as, *e.g.*, *d*-chondrocurine and *l*-curine has been considered. The distribution coefficient of *l*-curine is about 3.5 times as large as that of *d*-chondrocurine for various compositions of the less polar phase of the mixture as shown in Fig. 4 for *d*-chondrocurine.

It is certainly possible to use ether and buffer for separation of several kinds of mixtures of isomers, but there is one advantage in using the four component solvent system: the influence of pH on the value of the distribution constant is small. However, there is also one inconvenience: the solubility of the alkaloids in this solvent is so low that one would have a concentration of only a few tenths of a per cent, whereas the larger solubility in ether and alkaline water makes it possible to have a concentration of a few per cent. Both these solvent systems have the advantage that one can make use of the absorption peak at 280—290 mμ to measure the alkaloid concentration, and that it is easy to recover the alkaloids. In the case of the four component solvent system the organic components of the fractions are first evaporated in a rotating evaporator under vacuum, whereupon the residue is treated as previously described.

Separation of the *d*-chondrocurine monomethyl ethers by crystallization

Both *d*-chondrocurine and one of its monomethyl ethers can easily be crystallized from methanol, whereas the other monomethyl ether so far has resisted all attempts to crystallize it from methanol. A convenient way to prepare a pure preparation of that *d*-chondrocurine monomethyl ether which crystallizes from methanol is hence to partly methylate *d*-chondrocurine, isolate the *d*-chondrocurine monomethyl ether fraction by means of two counter current separations using diethyl ether and buffer, dissolve one part of the fraction in a few parts of methanol and, after the crystallization is completed, separate the crystals from the mother liquor. The crystalline *d*-chondrocurine monomethyl ether so obtained may be recrystallized from methanol. The mother liquor contains the other *d*-chondrocurine monomethyl ether. This substance long resisted all attempts to crystallize it, including cold treatments of its solutions [29]. Experiments using benzene were not successful, but the substance was finally obtained in what is believed to be crystalline form from diethyl ether. However, this solvent cannot be looked upon as very satisfactory for the crystallization of this *d*-chondrocurine monomethyl ether.

EXPERIMENTAL

Separating d-*chondrocurine, its monomethyl ethers, and its dimethyl ether.* 565.4 mg of crude, partly methylated *d*-chondrocurine (from 500 mg of *d*-chondrocurine and diazomethane) were dissolved in 4 ml of a mixture of equal parts of chloroform and methanol and poured into a separatory funnel containing 30 ml of diethyl ether phase and 10 ml of buffer phase, containing 2 % of $K_2S_2O_5$, 0.5 % of K_3PO_4 and about 1.2 % of KOH (pH 12.1), and pH was adjusted to 12.1 after equilibration. A counter current separation with 4 funnels and four portions of each solvent phase was carried out. The pH value of the pooled water phase solutions was adjusted with HCl to 8.5, and the *d*-chondrocurine fraction was extracted with a mixture of 1 volume of ether and 2 volumes of chloroform. This solution was extracted with portions of about 0.05 N HCl (till pH was below 3 in the extract), and the extract was washed with ether, whereupon the alkaloid was precipitated with KOH (pH 8.5; $NaHCO_3$ added), filtered off and dried *in vacuo*. The batches of ether phase, containing the methyl ethers of *d*-chondrocurine, were extracted with 20 ml of water, to which a sufficient number of drops of HCl (1:1) were added. For the separation of the monomethyl ether from the dimethyl ether, pH of the buffer solution was adjusted to 13.2 with KOH. The extract was mixed with an equal volume of buffer, and KOH pellets were added so that the pH value in the water phase was 13.2 when the solution was in equilibrium with 10 ml of the diethyl ether phase. A counter current distribution was carried out with four funnels and four portions of each phase (40 ml of water phase and 10 ml of ether phase). Thereafter, the water phases were adjusted with HCl (1:1) to pH 8.5 ($NaHCO_3$ added), the monomethyl ether fraction was extracted with ether, and this solution was extracted with hydrochloric acid (0.05 N) in portions till the pH of the extract was below 3. The monomethyl ether fraction was again precipitated with KOH, filtered off, washed with distilled water (pH adjusted to 8.5) and dried *in vacuo*. The *d*-chondrocurine dimethyl ether fraction was extracted from the portions of ether phase with hydrochloric acid, precipitated with KOH, filtered off, and dried *in vacuo*. Yield: *d*-chondrocurine 163.1 mg, *d*-chondrocurine monomethyl ethers 188.8 mg, *d*-chondrocurine dimethyl ether 78.7 mg.

Separating the two d-*chondrocurine monomethyl ethers by crystallization.* 5.4 g of *d*-chondrocurine monomethyl ethers were dissolved in 21 ml of hot methanol. Crystals formed over night. The mother liquor was separated and evaporated. Yield: crystals 2.1 g, m.p. 166°C, amorphous rest 3.3 g. A solution was made up consisting of 0.77 g of this amorphous material, 8 drops of HCl 1:1 and 25 ml of water. The solute was precipitated

with KOH at pH 8.5 and extracted with 25 ml of diethyl ether. This solution was washed with water containing some $NaHCO_3$ (pH 8) and filtered through cotton into an Erlenmeyer flask, which was placed in the cold room (+4°C). Part of the solute appeared as an amorphous sediment, part of it on the walls of the flask in a seemingly crystalline state. The sediment and the mother liquor were replaced by a warm, saturated ether solution of a preparation of this *d*-chondrocurine monomethyl ether, and the flask with its contents was left to cool down slowly in a water bath. After a few hours the mother liquor was poured off and the flask dried. No seemingly amorphous substance appeared, but 0.758 g of substance were recovered from the walls of the flask; m.p. 137–138°C. Part of this material was dried in a drying pistol at 63°C without appreciable loss in weight. When thereafter the temperature was increased to 109°C, the material blew around. (Analysis of the *d*-chondrocurine monomethyl ether crystallized from methanol: C 72.3, H 7.2; N 4.3; CH_3O 15.2. Analysis of the *d*-chondrocurine monomethyl ether which crystallized from ether: C 71.4; H 6.6; N 4.6; CH_3O 15.2. Calc. for $C_{37}H_{40}O_6N_2$: C 73.0; H 6.6; N 4.6; CH_3O 15.3).

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