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PYRROLIZIDINE ALKALOIDS. SYNTHESIS AND CONFIGURATION OF FULVINIC AND CRISPATIC ACIDS

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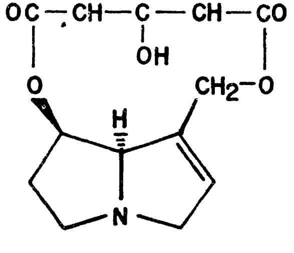
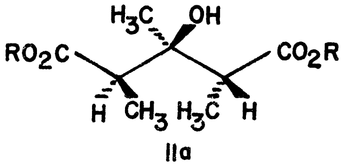
Stereochemistry of the Reformatsky reaction of 3-phenyl-2-butanone with methyl α-bromopropionate has been studied. Subsequently, fulvinic and crispatic acids have been synthesized and their configurations have also been assigned.

Pyrrolizidine alkaloids, fulvine and crispatine (I) which differ only in the configurations of necic acid moieties, have been isolated from Crotalaria plants.[2-4)] Alkaline hydrolyses of fulvine and crispatine gave, in each case, retronecine and a different necic acid $C_8H_{14}O_5$, respectively named fulvinic and crispatic acids. From the physical and spectral data, the structures of these acids were deduced to be 3-hydroxy-2,3,4-trimethylglutaric acids which can exist in the optically active enantiomers (IIa and IIb) and the two optically inactive meso forms (III and IV). Since both necic acids showed no optical activity Culvenor and Smith[2)] proposed the meso forms for fulvinic and crispatic acids. In 1967, the present authors synthesized fulvinic acid, racemate, and crispatic acid in approximately 10:50:40 ratio by the Reformatsky

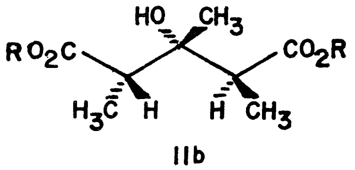


I

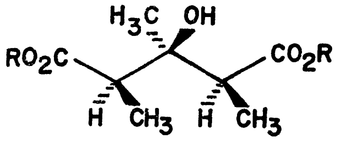


IIa

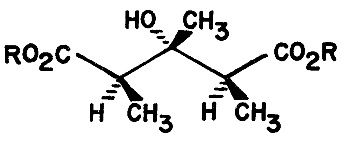
R=H
XII R=CH_3



IIb



III R=H
XIII R=CH_3

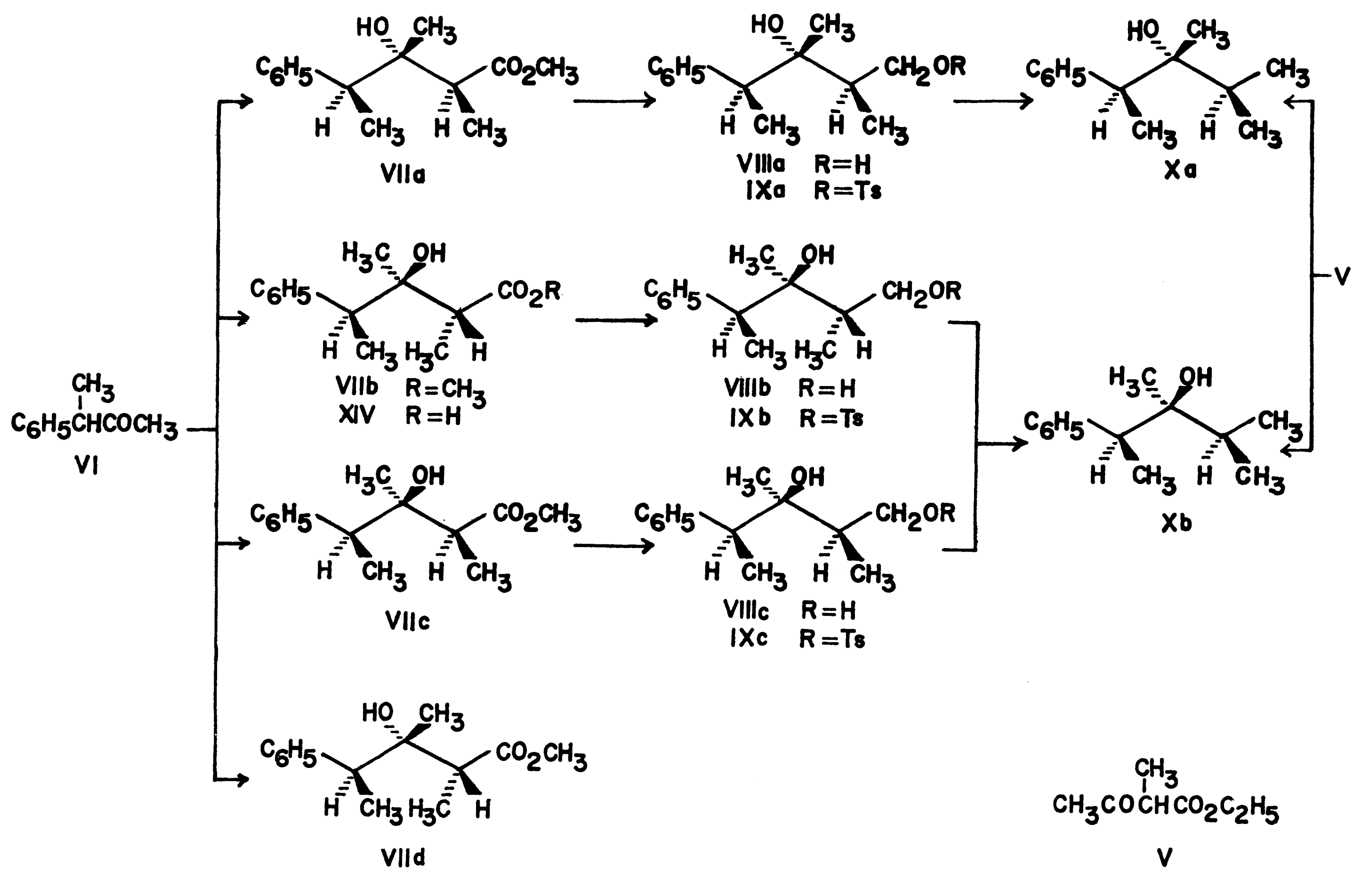


IV R=H
XI R=CH_3

reaction of ethyl α-methylacetoacetate (V) with ethyl α-bromopropionate, followed by alkaline hydrolyses of the resulting ethyl esters. On the basis of chemical shifts of methyl signals in the published NMR spectra and application of Cram's rule of asymmetric induction (open-chain model),⁵⁾ the authors tentatively proposed⁶⁾ (R)-meso (IV) for fulvinic acid and (S)-meso configuration (III) for crispatic acid. However, it seemed to be necessary to confirm the configurations of these necic acids by another unambigous method. In this communication we wish to report on the new synthesis and revised configurations of fulvinic and crispatic acids.

The Reformatsky reaction of 3-phenyl-2-butanone (VI) with methyl α-bromopropionate in dry benzene in the presence of zinc gave a mixture of diastereomeric methyl 2,3-dimethyl-3-hydroxy-4-phenylvalerates (64%) which can exist in the four racemic modifications (VIIa-VIId). The separation of these esters was carried out by repeated column chromatography on silica gel to give, in the order of elution, three (VIIa, VIIb, and VIIc) of four racemates in approximately 15:75:10 ratio. NMR in CCl_4; VIIa: 1.07 (d, J=7 Hz, $-CH(C\underline{H}_3)CO_2CH_3$), 1.13 (s, $-\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.28 (d, J=7 Hz, $C_6H_5\overset{|}{C}HC\underline{H}_3$), 2.38 (q, J=7 Hz, $-\overset{|}{C}\underline{H}CO_2CH_3$), 2.70 (q, J=7 Hz, $C_6H_5\overset{|}{C}\underline{H}-$), 3.22 (bs, $-O\underline{H}$), 3.57 (s, $-CO_2C\underline{H}_3$), 7.20 (s, $C_6\underline{H}_5-$); VIIb: 0.93 (s, $-\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.11 (d, J=7 Hz, $-CH(C\underline{H}_3)CO_2CH_3$), 1.31 (d, J=7 Hz, $C_6H_5\overset{|}{C}HC\underline{H}_3$), 2.48 (q, J=7 Hz, $-\overset{|}{C}\underline{H}CO_2CH_3$), 2.79 (q, J=7 Hz, $C_6H_5\overset{|}{C}\underline{H}-$), 3.32 (s, $-O\underline{H}$), 3.64 (s, $-CO_2C\underline{H}_3$), 7.12 (s, $C_6\underline{H}_5-$); VIIc: 1.03 (s, $-\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.21 (d, J=7 Hz, $-CH(C\underline{H}_3)CO_2CH_3$), 1.28 (d, J=7 Hz, $C_6H_5\overset{|}{C}HC\underline{H}_3$), 2.41 (q, J=7 Hz, $-\overset{|}{C}\underline{H}CO_2CH_3$), ca. 2.4 (overlap, $-O\underline{H}$), 2.93 (q, J=7 Hz, $C_6H_5\overset{|}{C}\underline{H}-$), 3.60 (s, $-CO_2C\underline{H}_3$), 7.19 (s, $C_6\underline{H}_5-$). To elucidate the configurations of VIIa-VIIc, the β-hydroxy esters were reduced with lithium aluminum hydride to the corresponding diols, VIIIa, VIIIb (mp 119.5-120°C), and VIIIc (mp 56.5-58°C) which were then subjected to tosylation with p-toluenesulfonyl chloride in pyridine to afford the monotosylates, IXa, IXb, and IXc respectively. Subsequent reduction of IXb or IXc with lithium aluminum hydride gave the same alcohol, 2,3-dimethyl-4-phenyl-3-pentanol (Xb). Therefore, it is clear that VIIb and VIIc possess the same configuration at the C-3 and C-4 positions. However, a similar treatment of IXa gave another alcohol, Xa. Alternatively, a mixture of these epimeric alcohols (Xa and Xb) was also obtained by the Grignard reaction of VI with isopropylmagnesium bromide in dry ether at -15∼-10°C in low yield (7%⁷⁾) due to side-reactions, and the mixture was then separated by column chromatography on silica gel into Xa and Xb in 23:77 ratio. While the modified Grignard reaction⁸⁾ of VI and isopropyl bromide in dry tetrahydrofuran in the presence of lithium at 5∼15°C afforded a mixture of Xa and Xb (4:96 ratio) in moderate yield (54%⁷⁾). Since the stereochemistry of the Grignard reaction is well known as Cram's rule^{5,9,10)}

of asymmetric induction, the configurations of the C-3 and C-4 positions in Xa and Xb, and therefore, those in VIIa, VIIb, VIIc, and VIId (unisolated) were established. Ozonizations of VIIa, VIIb, and VIIc in acetic acid at room temperature, followed by methylation of the resulting acids with diazomethane, gave dimethyl 3-hydroxy-2,3,4-trimethylglutarates, XI, XII, and XIII respectively. Hydrolyses of XIII and XI in methanol with aqueous barium hydroxide afforded the corresponding acids, III (mp 109-110°C) and IV (mp 134-135°C) which were identical with natural fulvinic and crispatic acids respectively. On the other hand, a similar treatment of XII gave a new acid, II (mp 118-119°C). These diastereomeric acids, II, III, and IV, were respectively methylated back into XII, XIII, and XI with diazomethane. This proved that there was no configurational change during the alkaline hydrolyses. If fulvinic and crispatic acids are meso-isomers as have been proposed by Culvenor and Smith,[2)] the new acid (mp 118-119°C) should be a racemate. This was undoubtedly confirmed by the following experiments. Alkaline hydrolysis of VIIb gave the corresponding acid (XIV) which was resolved by means of cinchonidine, and one of diastereomeric salts (mp 188-189°C, $[\alpha]_D$ -81° (EtOH)) was decomposed with dilute hydrochloric acid to give (-)-XIV, $[\alpha]_D$ - 41° ($CHCl_3$). (-)-XIV was methylated with diazomethane to give (-)-VIIb, $[\alpha]_D$ - 51° ($CHCl_3$), the IR spectrum of which was identical with that of (±)-VIIb. Ozonization of (-)-VIIb,



followed by methylation gave an optically active (-)-XII, $[\alpha]_D$ - 63° ($CHCl_3$), which was further converted to (-)-II, mp 128-129°C, $[\alpha]_D$ - 42° (MeOH). On the basis of these experiments the relative configurations of the C-2 to the C-3 position in VIIb and its C-2 epimer VIIc could be assigned. The configuration of VIIa was also established from the result of its ozonization reaction described above. Thus, the configurations of fulvinic and crispatic acids were identified as (S)-meso (III) and (R)-meso (IV) respectively.

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REFERENCES AND NOTES

Although the formulas depicted represented only one enantiomer, they are taken to mean a racemate unless otherwise stated. NMR spectra were taken on a Hitachi Model R-20 (60 MHz) using tetramethylsilane as an internal standard. Their chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, q: quartet.

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