Synthesis and Study of Substituted Coumarins. A Facile Preparation of D,L-*o*-Tyrosine

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A general procedure for the preparation of aminocoumarins and aminohydroxycoumarins under mild conditions is described. Amino- and acetamidoaminocoumarins were prepared by reduction of the corresponding nitro derivatives with sodium borohydride in the presence of 10% palladium on charcoal. Acid hydrolysis of the acetamidoaminocoumarins with (a) concentrated hydrochloric acid in ethanol, or (b) with 1*N* hydrochloric acid under reflux, gave diaminocoumarins and aminohydroxycoumarins, respectively. Condensation of the ethyl ester of glycine with salicylaldehyde gave 3-salicylideneaminocoumarin (XIII), the Schiff base of 3-aminocoumarin (XII). Acid hydrolysis of XIII under the above mentioned conditions, (a) and (b), gave XII and 3-hydroxycoumarin (XVI), respectively. Hydrogenation of compound XIII in dioxane or in dimethylformamide with 10% palladium on charcoal gave 3-salicylaminocoumarin (XVII), while hydrogenation of XII, XIII or XVII in acetic acid with traces of water and palladium black gave the amino acid *o*-tyrosine.

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Introduction.

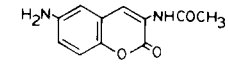
Coumarins are widely distributed in nature [1-3] and exhibit various physiological effects [4-6]. Many natural and synthetic coumarin derivatives have found a wide application in therapy as anticoagulants [7,8] and antibiotics [9-11]. Aminocoumarins and hydroxycoumarins are of interest not only because of their biological activities, such as hypotensive [12,13], spasmolytic [13], antibacterial [14-17] and antiallergic [18], but also because of their use as optical brighteners [19] and laser dyes [20,21]. Recently, interest on these compounds has been revived because of their use as fluorescent markers in fluorogenic substrates for the more sensitive biochemical determination of enzymes [22-24].

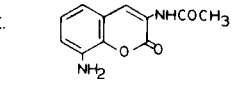
We report here the synthesis of some new diaminocoumarins and aminohydroxycoumarins by a general procedure that is facile and mild; and an improved synthesis under very mild conditions of known 3-substituted coumarins. Furthermore, we present the results of the hydrogenation of some 3-substituted coumarins with various palladium catalysts in different solvents.

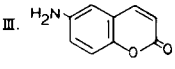
Results and Discussion.

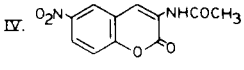
Diaminocoumarins and Aminohydroxycoumarins.

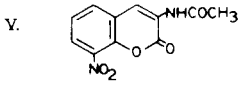
The compounds 3-acetamido-6-aminocoumarin (I), 3-acetamido-8-aminocoumarin (II) and the known compound 6-aminocoumarin (III) were prepared by reduction of the corresponding nitro derivatives, 3-acetamido-6-nitrocoumarin (IV) [25], 3-acetamido-8-nitrocoumarin (V) [25] and 6-nitrocoumarin (VI) [26] with sodium borohydride in the presence of 10% palladium on charcoal. This reagent is known to reduce smoothly a wide range of substituted nitrobenzenes to the corresponding amines [27]. Lactones are normally not reduced with sodium borohydride but cleavage of the lactone ring of coumarin has been observed with ethanol or diglyme as a solvent [28]. We obtained pure products, in good yields, without the lactone ring being affected, by carrying out the reaction in aqueous methanolic solution at room temperature for about fifteen minutes. The commonly used reductive agent metal-acid is not suitable in the case of compounds IV and V, because of possible hydrolysis of the acetamido group. Our procedure, therefore, permits differentiation of the two amino groups of compounds I and II and, consequently, the unsymmetrical elaboration of the molecule by selective coupling.

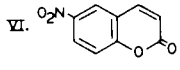
I. 

II. 

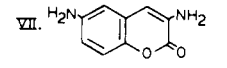
III. 

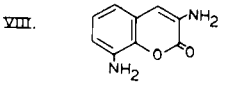
IV. 

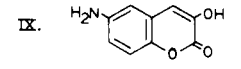
V. 

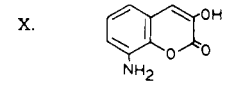
VI. 

Controlled acid hydrolysis of compounds I and II led either to the diamino or to the aminohydroxy derivative, depending on the conditions used. Thus, whereas treatment with concentrated hydrochloric acid in ethanol (2:1) under reflux for thirty minutes gave 3,6-diaminocoumarin (VII) and 3,8-diaminocoumarin (VIII) (cleavage of the acetyl group), treatment with 1*N* hydrochloric acid under reflux for two hours gave the partially deaminated products

VII. 

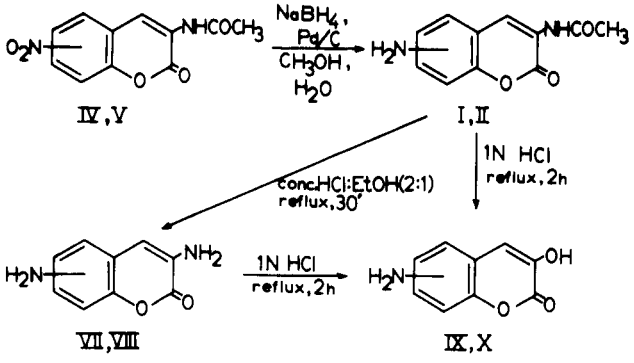
VIII. 

IX. 

X. 

6-amino-3-hydroxycoumarin (IX) and 8-amino-3-hydroxycoumarin (X). Compounds IX and X were also obtained by treatment of VII and VIII with 1*N* hydrochloric acid under the same conditions. The ease of hydrolysis, amino to hydroxy, is attributable to the enamine character of the 3-aminocoumarins [29,30], since it is well known that enamines are easily hydrolyzed to the corresponding carbonyl compounds [31,32].

Scheme 1



IV: 6-nitro
V: 8-nitro
I, VII, IX: 6-amino
II, VIII, X: 8-amino

In Scheme 1, we have summarized the synthesis of various aminocoumarins and aminohydroxycoumarins with one amino group on the aromatic ring. Their physicochemical data are listed in Table 1.

3-Substituted Coumarins.

In connection with our studies on 3-substituted coumarins we examined the condensation of salicylaldehyde (XI) with glycine derivatives in an effort to prepare 3-aminocoumarin (XII). This compound has analgesic and sedative properties [34] and its derivatives with amino acids [35] and platinum [36] possess antibacterial activity. It can be prepared from 3-acetamidocoumarin by acid hydrolysis [37], from the oxime of 3-acetylcoumarin by Beckmann rearrangement [38] and by heating the magnesium chelates of salicylideneglycine esters [39]. The condensation of XI with glycine in the presence of pyridine at 130-140° did not lead to 3-aminocoumarin, as previously reported [40], but to 3-salicylideneaminocoumarin (XIII) [37]. This Schiff base, which is useful as fungicide and viricide, has also

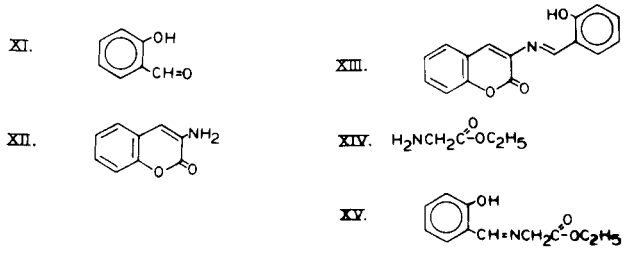
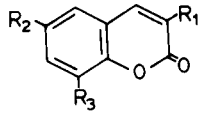


Table 1

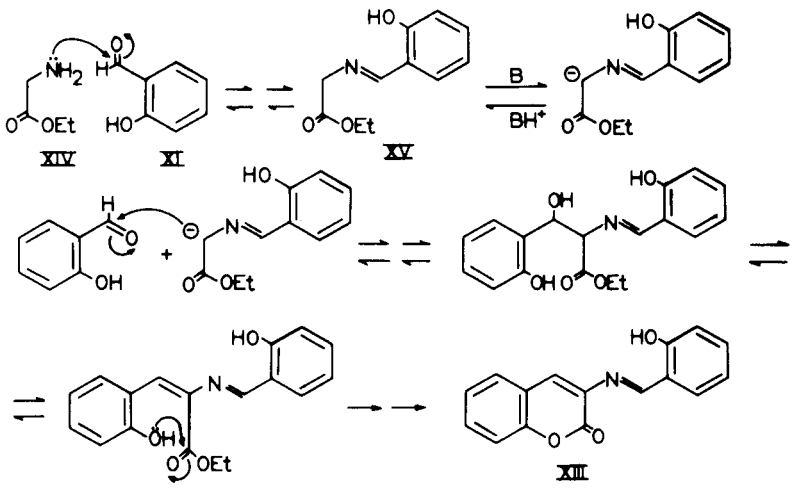
Physicochemical Data of the Synthesized Coumarin Derivatives



Compound	R_1	R_2	R_3	Yield %	Mp °C Found / Reported	Analysis % Calcd./Found C	H	N	IR, cm^{-1}
I	$NHCOCH_3$	NH_2	H	67	252-253	60.55 60.27	4.62 4.59	12.84 12.81	3440, 3340 (NH_2, NH), 1705 (C=O), 1670 (C=O of amide), 1635 (C=C)
II	$NHCOCH_3$	H	NH_2	71	190-192	60.55 60.22	4.62 4.67	12.84 12.66	3440, 3340 (NH_2, NH), 1715 (C=O), 1675 (C=O of amide), 1640 (C=C)
III	H	NH_2	H	76	166-167 168 [26]				3420, 3340 (NH_2), 1710 (C=O), 1625 (C=C)
VII	NH_2	NH_2	H	74	182-183 183-184 [33]	61.36 61.02	4.58 4.60	15.90 15.63	3420, 3340 (NH_2), 1690 (C=O), 1635 (C=C)
VIII	NH_2	H	NH_2	68	172-173	61.36 61.12	4.58 4.67	15.90 15.65	3480, 3445, 3380, 3360 (two NH_2), 1690 (C=O), 1640 (C=C)
IX	OH	NH_2	H	81 [a] 68 [b]	255-257	61.02 60.91	3.98 3.90	7.91 7.84	3410 (NH_2), 3330 (OH), 1705 (C=O), 1640 (C=C)
X	OH	H	NH_2	80 [a] 59 [b]	228-230	61.02 61.29	3.98 4.07	7.91 7.96	3455 (NH_2), 3370 (OH), 1690 (C=O), 1650 (C=C)

[a] Prepared by the method A (see Experimental). [b] Prepared by the method B (see Experimental).

Scheme 2



been obtained by refluxing a mixture of XI and glycine in acetic acid [41]. We have found that compound XIII is formed in good yield when an aqueous solution of the ethyl ester of glycine (XIV) is treated with 10% excess of XI under vigorous stirring at *p*H 9 with triethylamine as the catalyst. Thus, in contrast to all the previously mentioned methods, which require heating at high temperatures, our method involving the ethyl ester is carried out at room temperature. A reasonable mechanism for the reaction is shown in Scheme 2.

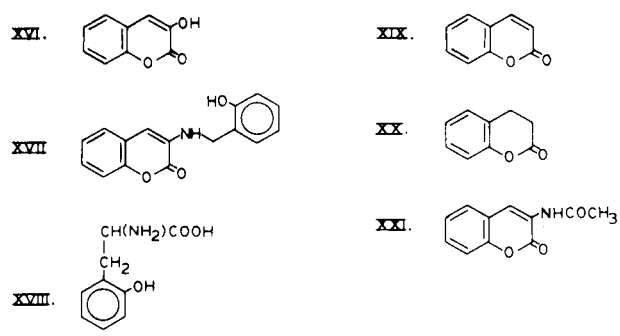
After the formation of the expected Schiff base XV, the methylene group is sufficiently activated by two groups (carbethoxy and imino) to permit facile condensation with a second molecule of salicylaldehyde. This intermediate is now ideally suited for intramolecular cyclization to give 3-salicyledeneaminocoumarin. The intermediacy of the Schiff base has also been suggested in the base catalyzed condensation of glycine with benzaldehyde [42]. Our finding that neither glycine nor *N*-benzyloxycarbonylglycine reacts with salicylaldehyde under the same conditions, is consonant with the proposed mechanism.

Our efforts to hydrolyze XIII to 3-aminocoumarin (XII) have led to the following findings: Treatment of compound XIII with ten equivalents of 1*N* hydrochloric acid at room temperature did not hydrolyze it even after twenty-four hours. The decreased reactivity of this Schiff base against acid hydrolysis, *vis-à-vis* the reactivity of most Schiff bases, probably results from the increased stability of XIII by intramolecular hydrogen bonding between the nitrogen and the hydroxy group. Under more vigorous conditions, such as treatment of XIII with boiling 1*N* aqueous hydrochloric acid, the hydrolysis product 3-hydroxycoumarin (XVI), rather than 3-aminocoumarin, was isolated. In order to convert XIII to XII without substantial formation of XVI, one must use the conditions of the hydrolysis of 3-acetamidocoumarins, *i.e.*, reflux for forty-five minutes with a mixture of ethanol and concentrated hydrochloric acid (1:2).

In order to prepare pure XII and prevent its possible conversion to XVI, we investigated its liberation from the Schiff base XIII with nonacidic media and by hydrogenolysis of XIII. Indeed, when compound XIII was treated with such bases as benzylamine or phenylalanine methyl ester at room temperature, 3-aminocoumarin was rapidly obtained in good yield, by an amino-imino exchange.

Hydrogenation of 3-Substituted Coumarins. Preparation of *o*-Tyrosine.

The imino bond of Schiff bases can be reduced [43] easily by various reducing agents as well as by catalytic hydrogenation. However, the hydrogenation of the Schiff bases of *o*-hydroxyaldehydes requires large quantities of catalyst

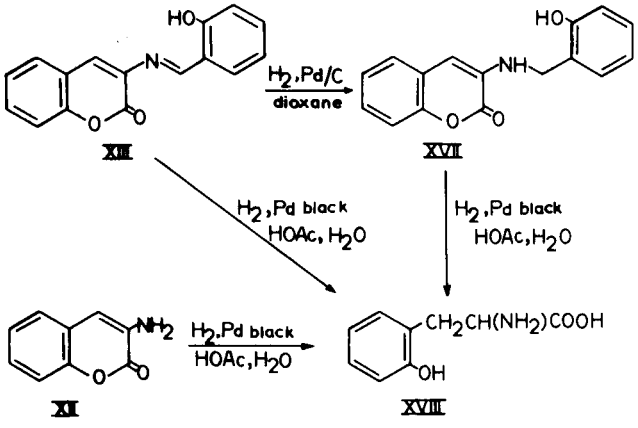


[44]. Compound XIII, 3-salicylideneaminocoumarin, can be reduced [45] to the 3-salicylaminocoumarin (XVII) with sodium borohydride at 55°. Intrigued by the possibility

that the salicyl group might be removed by catalytic hydrogenation, as a benzyl-type protecting group [46], and encouraged by the lack of further information on this matter, we decided to study the hydrogenation of some 3-substituted coumarins with various catalysts and in several solvents. The results, some of them unexpected, are shown in Scheme 3.

When compound XIII was hydrogenated in dioxane or in dimethylformamide in the presence of conventional amounts of 10% palladium on charcoal, at room temperature, the imino bond of the Schiff base was reduced to give XVII. Under these conditions the coumarin ring remained intact. However, hydrogenation of XIII in acetic acid with traces of water and with palladium black as catalyst gave the amino acid D,L-*o*-tyrosine (XVIII) by opening of the coumarin ring. The same product was obtained when compounds XVII and XII were hydrogenated with the same catalyst and solvent. Hydrogenation of coumarin (XIX) itself under the same conditions gave 3,4-dihydrocoumarin (XX), while 3-acetamidocoumarin (XXI) was unreactive. It appears that the presence of an activated nitrogen group (free amino, or benzyl) at position 3 is necessary for the opening of the lactone ring. Conceivably, the intermediate product of the hydrogenolysis of compounds XIII and XVII may be the 3-aminocoumarin which, under the experimental conditions, reacts further to give *o*-tyrosine. Since *o*-tyrosine [47-49] is useful in metabolic studies in comparing normal to phenylketonuric humans [50,51], our two-step synthesis of this important compound is simple, convenient and provides pure product in good yield under very mild conditions.

Scheme 3



EXPERIMENTAL

Melting points were detemined on a Büchi apparatus and are uncorrected. Solvent systems for thin-layer chromatography on silica gel G-silica gel HF (8:2) plates were (a) chloroform-methanol (50:10), or (95:5); (b) 1-butanol-acetic acid-ethyl acetate-water (1:1:1:1); (c) 1-propanol-ammonium hydroxide 25% (67:33); (d) chloroform-methanol-acetic acid (95:5:1); and (e) 1-butanol-acetic acid-water (4:1:1). Spots were located by uv, by ninhydrin, or by 20% ammonium sulphate in 4% sulphuric acid and heating. Elemental analyses were carried out by the Analytical Department of Hoffmann-La Roche Inc., Basel. The ir spectra were taken in potassium bromide with a Perkin-Elmer 283 B.

General Procedure for the Reduction of the Nitrocoumarins (IV, V and VI).

To a stirred suspension of 0.5 g of 10% palladium-carbon in water, through which a gentle stream of nitrogen was passed, a solution of 1.88 g (50.9 mmoles) of sodium borohydride in 35 ml of water was added. A suspension of the appropriate nitro compound (20 mmoles) in methanol (1.2 lit) was then slowly added at room temperature. After an additional 15 minutes of stirring at room temperature, the catalyst was removed by filtration and the filtrate was evaporated until precipitation of the product was started. Water was then added and after cooling the product was filtered and recrystallized from ethanol.

General Procedure for the Preparation of the Diaminocoumarins (VII, VIII).

A solution of compound I or II (4 mmoles) in 18 ml of a mixture of ethanol-concentrated hydrochloric acid (1:2) was refluxed under stirring for 30 minutes. After cooling the reaction mixture, the precipitate was filtered and then dissolved in the least amount of water required to dissolve it. The solution was neutralized with 25% ammonium hydroxide and the precipitate was filtered and recrystallized from water.

General Procedure for the Preparation of the Amino-3-hydroxycoumarins (IX, X).

A. Acid Hydrolysis of 3-Acetamidoaminocoumarins (I, II).

A suspension of 3-acetamidoaminocoumarin (1 mmole) in 10 ml of aqueous 1*N* hydrochloric acid was refluxed under stirring for 2 hours, during which time the solid was dissolved. After the reaction mixture was cooled and neutralized with 25% ammonium hydroxide, the precipitate was filtered and recrystallized from a mixture of dioxane-water in the presence of activated charcoal.

B. Partial Hydrolysis of the Diaminocoumarins (VII, VIII).

A solution of the diaminocoumarin (1 mmole) in 10 ml of aqueous 1*N* hydrochloric acid was refluxed under stirring for two hours. The reaction mixture was then worked-up as described in method A to give the product.

Preparation of 3-Salicylideneaminocoumarin (XIII).

Method A.

To a vigorously sirred mixture of 16.7 g (0.120 mole) of glycine ethyl ester hydrochloride and 16.8 ml (0.120 mole) of triethylamine in 40 ml of water, 27.4 ml (0.264 mole) of XI was added with the *p*H being adjusted to 9 by addition of triethylamine. The reaction mixture was vigorously stirred for 18 hours at room temperature. The separated orange crude product, having solidified after standing for a few hours in the refrigerator, was filtered and washed with water. It was recrystallized twice from dimethylformamide-water to give 16.8 g (53%) of XIII, mp 189-190° (lit [41] 180-192°); ir: (cm^{-1}) 1720 (C=O), 1625 (C=C), 1610 (C=N).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.23; H, 4.19; N, 5.33.

Method B.

To a suspension of 0.12 g (0.75 mmole) of XII in 3 ml of water, 0.1 ml (0.96 mmole) of XI was added and the reaction mixture was vigorously stirred at *p*H 9 with triethylamine for 30 minutes at room temperature. The separated crude orange product was worked-up as described in method A to give 0.11 g (55%) of crystalline product, mp 188-190°.

Preparation of 3-Aminocoumarin (XII).

A. Hydrolysis of the Schiff Base XIII.

A suspension of 7.5 g (0.283 mole) of XIII in 150 ml of ethanol-concentrated hydrochloric acid (1:2) was refluxed under stirring for 45 minutes. After cooling, the coloured solid was filtered and recrystallized from a mixture of ethanol-water (1:2) in the presence of activated charcoal to give 3.1 g (68%) of white crystals, mp 132-133°, (lit [39] 132-135°); ir: (cm^{-1}) 3430, 3320 (NH_2), 1710 (C=O), 1640 (C=C).

B. Treatment of XIII with Benzylamine.

A solution of 1.32 g (5 mmoles) of XIII and 0.65 ml (6 mmoles) of benzylamine in 40 ml of tetrahydrofuran was stirred at room temperature overnight. During that time the colour of the reaction turned from orange to yellow. After removal of the tetrahydrofuran, the resulting residue was dissolved in ethyl acetate, was washed successively with 1*N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, water, and dried over anhydrous sodium sulfate. The solution was concentrated to a small volume, the product was precipitated by addition of petroleum ether, filtered and recrystallized as in method A to give 0.52 g (65%) of XII.

Preparation of 3-Hydroxycoumarin (XVI).

A. Hydrolysis of XIII.

A suspension of 1 g (3.77 mmoles) of XIII in 20 ml of 1*N* hydrochloric acid was refluxed under stirring for 2 hours. After filtering the warm reaction mixture, the filtrate was kept in the refrigerator. The resulting precipitate was filtered, washed with water and recrystallized from water in the presence of activated charcoal to give 0.41 g (67%) of XVI, mp 150-151° (lit [48] 153-154°); ir: (cm^{-1}) 3380 (OH), 1695 (C=O), 1650 (C=C).

B. Hydrolysis of XII.

A solution of 0.3 g (1.86 mmoles) of XII in 12 ml of 1*N* hydrochloric acid was refluxed under stirring for 2 hours. The isolation and purification of the product was done as described in method A to give 0.2 g (67%) of XVI.

Preparation of 3-Salicylaminocoumarin (XVII).

A solution of 2.65 g (10 mmoles) of XIII in 180 ml of dioxane was hydrogenated in the presence of 0.5 g 10% palladium on charcoal. The catalyst was filtered and the filtrate was condensed to a smaller volume. Upon addition of water a white solid was precipitated, which after cooling was filtered and recrystallized from benzene to give 1.88 g (70%) of XVII, mp 169-170° (lit [45] 168-172°); ir: (cm^{-1}) 3420 (NH), 3380 (OH), 1695 (C=O), 1625 (C=C).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.91; H, 4.86; N, 5.25.

Preparation of *o*-Tyrosine (XVIII).

A. Hydrogenation of XIII.

A solution of 1.06 g (4 mmoles) of XIII in 70 ml of acetic acid and 2 ml of water was hydrogenated in the presence of palladium black for 48 hours. The catalyst was removed by filtering the reaction mixture in warm, washed with acetic acid and the combined filtrates were condensed to a smaller volume. The product was precipitated with ether, filtered and recrystallized from water to give 0.52 g (72%) of XVIII, mp 249-250° (lit [47] 249-250°, [48] 262°); ir: (cm^{-1}) 3150-2500 and 1615 (NH_3^+), 1590 and 1410 (CO_2^-). A small portion was converted to hydrochloric salt, mp 179-180° (lit [52] 180°).

Anal. Calcd. for $C_9H_{12}ClNO_3$: C, 49.67; H, 5.56; N, 6.44. Found: C, 49.62; H, 5.61; N, 6.34.

B. Hydrogenation of XVII.

A solution of 1.07 g (4 mmoles) of XVII in 55 ml of acetic acid and 2 ml of water was hydrogenated and worked up as in the method A to give 0.47 g (65%) of XVIII, mp 249-250°.

C. Hydrogenation of XII.

A solution of 0.8 g (5 mmoles) of XII in 50 ml of acetic acid and 2.5 ml of water was hydrogenated and worked up as in the method A to give 0.54 g (60%) of XVIII, mp 246-248°.

Preparation of 3,4-Dihydrocoumarin (XX).

A solution of 0.75 g (5 mmoles) of XIX in 50 ml of acetic acid and 2.5 ml of water was hydrogenated in the presence of palladium black for 3 hours. The catalyst was filtered off and the filtrate was evaporated to an oily residue, which was crystallized by scratching and cooling to give 0.62 g (84%) of XX, mp 18-20° (lit [53] 24°).

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