Treatment with sodium carbonate solution separated the precipitate into a soluble and an insoluble portion. The latter on recrystallization from alcohol gave amino-*d*-β-desmotroposantonin in plates, m. p. 196–197°, unchanged by admixture with an authentic specimen of amino-*d*-β-desmotroposantonin. Acidification of the sodium carbonate soluble portion followed by recrystallization of the separated solid from alcohol gave a product in prismatic needles, m. p. 205–206°, depressed to 170° by admixture with amino-*l*-β-desmotroposantonous acid and to 176° by admixture with amino-*d*-α-desmotroposantonous acid. Its hydrochloride crystallized from dilute hydrochloric acid in plates.

Summary

1. Amino-*d*-β- and amino-*l*-α-desmotroposantonin have been prepared from the corresponding nitro compounds, the former also from benzeneazo-α-β-desmotroposantonin.

2. The corresponding aminosantonous acids were prepared from the aminodesmotroposantonins.

3. The constitution and configuration of the new compounds are discussed.

CAMBRIDGE, MASS. RECEIVED JUNE 16, 1947

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

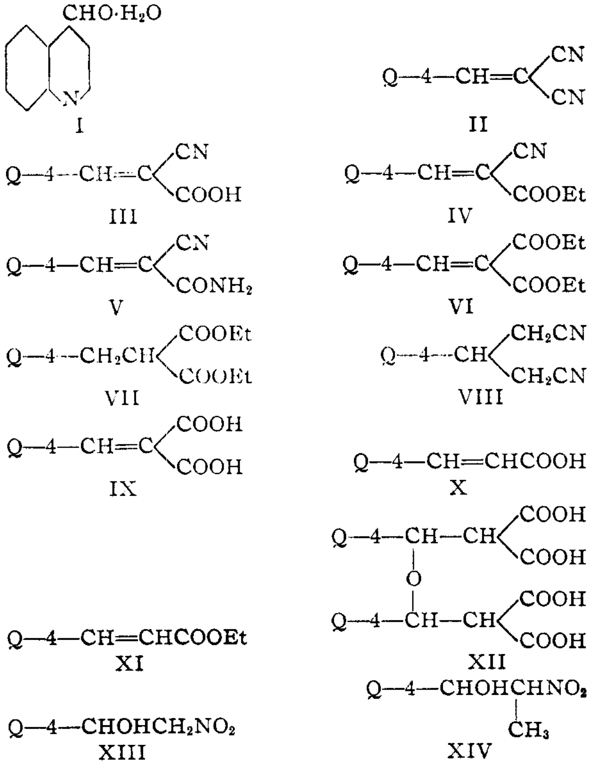
Cinchoninaldehyde and Reactive Methylene Compounds. IV[1]

BY ARTHUR P. PHILLIPS

This paper reports the reaction of cinchoninaldehyde (I)[2] with a variety of malonic acid type compounds, with several of the lower nitroalkanes, and with cyclohexanone.

Cinchoninaldehyde (I) reacted so rapidly with one equivalent of malononitrile that no catalyst was used and a nearly theoretical yield of II was obtained. Use of two molecular equivalents of malononitrile in this reaction, in an attempt to obtain the "2 to 1" type of condensation product, gave only II though in poorer yield.

CHART OF COMPOUNDS



I (CHO·H₂O)

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{CN}\\ \mathrm{CN}\end{matrix}$ II

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{CN}\\ \mathrm{COOH}\end{matrix}$ III

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{CN}\\ \mathrm{COOEt}\end{matrix}$ IV

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{CN}\\ \mathrm{CONH_2}\end{matrix}$ V

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{COOEt}\\ \mathrm{COOEt}\end{matrix}$ VI

$\mathrm{Q{-}4{-}CH_2CH}\Big\langle\begin{matrix}\mathrm{COOEt}\\ \mathrm{COOEt}\end{matrix}$ VII

$\mathrm{Q{-}4{-}CH}\Big\langle\begin{matrix}\mathrm{CH_2CN}\\ \mathrm{CH_2CN}\end{matrix}$ VIII

$\mathrm{Q{-}4{-}CH{=}C}\Big\langle\begin{matrix}\mathrm{COOH}\\ \mathrm{COOH}\end{matrix}$ IX

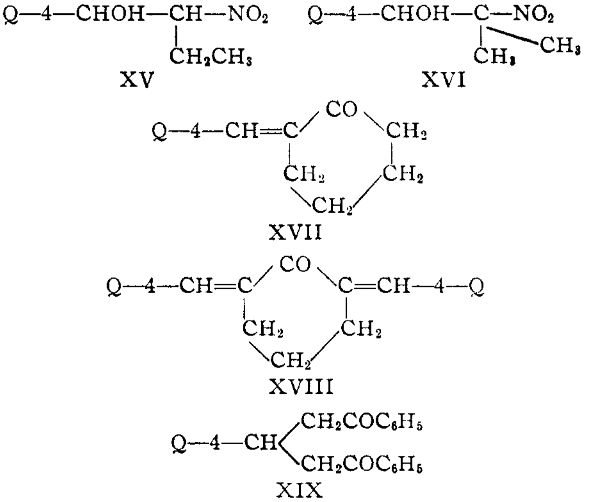
$\mathrm{Q{-}4{-}CH{=}CHCOOH}$ X

$\mathrm{Q{-}4{-}CH{=}CHCOOEt}$ XI

$$\begin{array}{l}\mathrm{Q{-}4{-}CH{-}CH}\Big\langle\begin{matrix}\mathrm{COOH}\\ \mathrm{COOH}\end{matrix}\\ \quad\ \ |\\ \quad\ \ \mathrm{O}\\ \quad\ \ |\\ \mathrm{Q{-}4{-}CH{-}CH}\Big\langle\begin{matrix}\mathrm{COOH}\\ \mathrm{COOH}\end{matrix}\end{array}$$ XII

$\mathrm{Q{-}4{-}CHOHCH_2NO_2}$ XIII

$\mathrm{Q{-}4{-}CHOH\underset{\displaystyle CH_3}{CH}NO_2}$ XIV



$\mathrm{Q{-}4{-}CHOH{-}\underset{\displaystyle CH_2CH_3}{CH}{-}NO_2}$ XV

$\mathrm{Q{-}4{-}CHOH{-}\underset{\displaystyle CH_3\ CH_3}{C}{-}NO_2}$ XVI

XVII

XVIII

$\mathrm{Q{-}4{-}CH}\Big\langle\begin{matrix}\mathrm{CH_2COC_6H_5}\\ \mathrm{CH_2COC_6H_5}\end{matrix}$ XIX

Cyanoacetic acid, cyanoacetic ester, cyanoacetamide, malonic ester and malonic acid, when condensed with I in alcohol, aqueous or aqueous alcohol solution, with diethylamine (or piperidine) catalyst gave excellent yields of the products: III, IV, V, VI, IX.

When cyanoacetic ester was condensed with I by means of sodium ethylate in ethanol, acidification of the reaction mixture gave only the corresponding acid, III. Hydrolysis had resulted presumably as a consequence of using the aldehyde hydrate. Esterification of this acid by the Fischer method produced the same substance, IV, obtained earlier by combination of the reactants in the presence of diethylamine.

The malonic ester product was obtained in poorer yield (60%) and no sharp boiling point was observed. Since the base showed no tendency to crystallize, this product was purified as its hydrochloride.

When the condensation with malonic acid was varied by the use of pyridine as solvent with a little piperidine as catalyst, excellent yields of quinolyl-4-acrylic acid (X) resulted rapidly and

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[1] For paper III of this series see THIS JOURNAL, **69**, 865 (1947).

[2] For the method of preparation of I see reference (4).

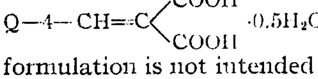
TABLE I

PRODUCTS AND REACTION CONDITIONS

Reactant	Mole react./Mole ald.	Reaction medium[a]	Catalyst	Reaction time, hr.	Product	Yield, %	Cryst.[a] solvent
Malononitrile	1 (or 2)	A	None (Et_2NH)	0.1[b]	II	98 (65)	A
Cyanoacetic ester	1	A	NaOEt (1 *M*)	1.5[b]	III	70	Nt.
Cyanoacetic ester	6	Aq.	Et_2NH (trace)	24[c]	IV	90	H
III	...	A	H_2SO_4	5[b]	IV	90	H
Cyanoacetamide	1	A	Et_2NH (trace)	0.5[b]	V	90	A
Malonic ester	1	None	Piperidine (trace)	15[b]	VI.HCl	57	A. E.
VI	...	A	H_2 + Pt.	0.3[c]	VII.HCl	80	A. E.
Cyanoacetic acid	2	A	Et_2NH (trace)	1[b]	III	100	Nt.
Cyanoacetic acid	1	A.Aq	KOH (1 *M*)	12[c]	III	50	Nt.
Cyanoacetic acid	2	Py	Piperidine (trace)	0.5[b]	III	80	Nt.
IV	...	A	KOH	48[c]	III	95	Nt.
IV	...	20% HCl	.....	0.75[d]	III	100	Nt.
Cyanoacetic acid	3.5	Py	Piperidine (trace)	4[b]	VIII	73	B. H.
Malonic acid	1.5	A[e]	Piperidine (trace)	4[b]	IX	80	Nt.
Malonic acid	1.5	Py	Piperidine (trace)	6[b]	X	83	Nt.
X	...	A	HCl	5[b]	XI.HCl	50	A. E.
Malonic acid	1.5	A[f]	Piperidine (trace)	4[c]	(XII)	90	Nt.
Nitromethane	1.2	50%A.Aq	Et_2NH (trace)	5[c]	XIII	93	B. H.
Nitromethane	1.2	A	KOH (2 *M*)	0.5[c]	XIII[g,h]	70	B. H.
Nitroethane	1.3	50%A.Aq	Et_2NH (trace)	24[c]	XIV	95	B. H.
1-Nitropropane	1.1	50%A.Aq	Piperidine (trace)	24[c]	XV	100	Et. H
2-Nitropropane	1.1	50%A.Aq	Piperidine (trace)	24[c]	XVI	95	Et
Cyclohexanone	1.1	90%A.Aq	KOH (excess)	2[b]	XVII	73	Py.Aq
Cyclohexanone	2	Aq	KOH (excess)	24[c]	XVIII	20	Et. H
Acetophenone	1	50%A.Aq	KOH (excess)	5[c]	XIX	30	H

[a] A = ethanol; Aq = H_2O; Py = pyridine; H = hexane; B = benzene; E = ether; Et = ethyl acetate; Nt = reprecipitated from dilute alkali with dilute acid. [b] At 100°. [c] At room temperature. [d] At reflux temperature. [e] 4.5 g. of I and 3.6 g. malonic acid in 100 cc. of EtOH and piperidine catalyst. Heated on steam-bath for four hours, when a white solid gradually formed and settled out. [f] 4.5 g. of I and 3.6 g. malonic acid in 10 cc. EtOH and piperidine. Mixture was heated 1–2 minutes on steam-bath to dissolve reactants, then on addition of catalyst a heavy white precipitate formed instantaneously. [g] The product first obtained from the reaction mixture by treatment with an excess of concentrated HCl was XIII·HCl. XIII base was obtained by neutralization of the HCl with NH_3. [h] This compound was previously known, see ref. 3.

simply. This compound had been prepared earlier by other workers by the hydrolysis of the condensation product of lepidine and chloral.[3] The ethyl ester (XI) of this acid was made by the Fischer method and was characterized as its hydrochloride.

A variation from the normal malonic acid product, IX, was obtained by modifying the reaction conditions slightly. Thus, condensation of malonic acid and I in more concentrated solution with secondary amine catalyst and no heating gave rapid and nearly quantitative precipitation of a quite different substance. Carbon, hydrogen, and neutral equivalent determinations agree well with a compound having an empirical structure:  $Q{-}4{-}CH{=}C\begin{cases}COOH\\COOH\end{cases}\cdot 0.5H_2O$. This hemi-hydrate formulation is not intended to represent the molecular formula of the compound. In fact, it would seem quite unreasonable to hypothesize a simple hydrate as differing persistently from the normal product, IX, since all of these acid compounds were purified by repeated reprecipitations from dilute aqueous alkaline solutions by addition of dilute mineral acids. Thus, if the hydrate represented a stable structure under those conditions it should have been impossible to get the other product, IX, under the identical conditions of purification. A more reasonable structure for this substance is XII, particularly in view of the previously observed tendency of cinchoninaldehyde to form stable aldol-like addition products. XII, having the same empirical formula as the hemi-hydrate, likewise fits the analytical data.

When compound IX was refluxed with strong (20%) hydrochloric acid the acrylic acid X resulted by decarboxylation. When either IX or XII was heated in pyridine solution in the presence of a trace of piperidine good yields (70%) of X were formed.

Since under certain conditions condensation with malonic acid permitted the easy attainment of the cinnamic acid analog, it was hoped that reaction with cyanoacetic acid under the same conditions might lead to the cinnamonitrile-like product. Contrary to expectations, however, when pyridine was used as solvent with piperidine as catalyst different results were obtained. When only a moderate excess of cyanoacetic acid was used and the heating period was brief (thirty minutes) a good yield of the product III resulted,

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(3) Koenigs and Müller, *Ber.*, **37**, 1338 (1904).

TABLE II

ANALYTICAL DATA

Product	M. p., °C.	Analyses Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	M. wt.[a] (N. E.) Calcd.	Found
II	146–147	76.10	76.04	3.44	3.19		
III	238–239 (dec.)	69.61	69.48	3.61	3.77	224.1	224
IV	98–99	71.43	71.48	4.80	4.66		
V	253	69.96	70.14	4.02	4.07		
VI·HCl	151–152	60.80	60.82	5.36	4.82		
VII·HCl	160–161.5	60.44	59.73	5.97	5.75		
VIII	130–131	76.02	76.04	5.02	5.15		
IX	254–255 darkens 230–250	64.18	64.11	3.73	3.95	243.1	240
X	272–273 (dec. gas evol.)	72.33	72.35	4.57	4.38	199.1	200
XI.HCl	194–195	63.73	63.49	5.35	5.08		
XII	190–191	61.95	61.88	3.97	4.12	504	500
			61.66		4.01		
XIII	140–141	60.52	60.90	4.63	4.71		
XIV	167–168	62.04	62.04	5.21	5.21		
XV	138	63.38	63.31	5.73	5.79		
XVI	183	63.38	63.58	5.73	5.87		
XVII	277–278	81.01	81.29	6.38	6.20		
						N	
XVIII	153	82.93	82.45	5.36	5.17	7.44	7.47
XIX	148–149	82.28	82.25	5.58	5.46		

[a] Molecular weights listed here are actually neutral equivalents × number of acid groups.

with no decarboxylation. But when 2.5–3 moles of cyanoacetic acid per mole of aldehyde was used and when heating was more extended (four hours) the product was VIII, which involves condensation between one mole of aldehyde and two moles of acid with loss of the two carboxyl groups.

The cyanoacetic acid product III was also obtained by condensation of the reactants in aqueous potassium hydroxide. III was further obtained in good yield by the hydrolysis of the corresponding ethyl ester IV by refluxing with 20% hydrochloric acid, or by allowing it to stand at room temperature with aqueous potassium hydroxide, followed by acidification.

Cinchoninaldehyde condensed readily with nitromethane, nitroethane, 1-nitropropane and 2-nitropropane in 50% aqueous alcohol with a trace of diethylamine as catalyst and a reaction time of several hours at room temperature. The yields were well over 90% and the products were of the aldol-like nitroalcohol type (XIII, XIV, XV, XVI), although usually the products obtained from aromatic aldehydes and nitroalkanes possess the $\mathrm{RCH{=}\underset{|}{C}{-}NO_2}$ structure. This represents another instance of the strong tendency of cinchoninaldehyde to form products with a stable aldol-like configuration. Thus, nitromethane was condensed with the aldehyde in the presence of aqueous potassium hydroxide with subsequent liberation of the product by addition of concentrated hydrochloric acid. Under these conditions many aromatic aldehydes give nitrostyrenes, but cinchoninaldehyde gave the same aldol, XIII, resulting under the milder conditions.

Cyclohexanone condensed readily with I in equimolecular amounts in aqueous or alcoholic solution in the presence of potassium hydroxide to give good yields of XVII. In very dilute aqueous alkaline solution small amounts of XVIII were also produced.

Acetophenone with I in 50% aqueous alcohol and alkali gave XIX previously reported by Kwartler and Lindwall.[4] Further work with ketones is in progress.

Experimental details are listed in Tables I and II.

Acknowledgment.—Thanks are due Mr. Samuel W. Blackman for the microanalyses included here.

Summary

The condensation of certain reactive methylene compounds with cinchoninaldehyde has been reported.

TUCKAHOE 7, NEW YORK RECEIVED JULY 26, 1947

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(4) Kwartler and Lindwall, THIS JOURNAL, **59**, 524 (1937).