added until the excess permanganate color remained for a few minutes, with the object of destroying oxalic acid and oxidizing any aldehydes to acids. Excess permanganate was destroyed by the addition of a little sodium bisulfite and the manganese dioxide was removed by filtration. The solution was then steam distilled. From the residual solution only an intractable tar was obtained. The steam distillate was neutralized with sodium hydroxide and evaporated to dryness. The salt was then acidified and the solution extracted with ether and distilled. After the acetic acid had been removed a small amount of oily acid remained. It was converted into a crystalline *p*-bromophenacyl ester, m. p. 63°.

A mixed melting point with the *p*-bromophenacyl ester of *n*-caproic acid showed no depression.

This compound was obtained by the same procedure when cannabidiol dimethyl ether was treated with 150% of the theoretical amount of 8% ozone. The residue from steam distillation was again an intractable tar. Apparently this concentration of ozone was attacking the aromatic ring.

Summary

1. New procedures for isomerizing cannabidiol have resulted in synthesizing two tetrahydrocannabinols, α_{D} −130° and α_{D} −265°, of essentially constant rotation. Previously obtained tetrahydrocannabinols are assumed to be mixtures.

2. Additional evidence for shifting of the double bond in conversion of the low-rotating to a higher-rotating tetrahydrocannabinol is presented. The low-rotating form adds hydrogen chloride and loses it on distillation to give a higher-rotating form.

3. The form α_{D} −130° reduces to a hexahydrocannabinol of identical rotation with that obtained by reduction of higher-rotating forms.

4. The form α_{D} −130° has about the same marihuana activity as the higher-rotating forms. Clinical tests have demonstrated the tetrahydrocannabinols (the form used was α_{D} −265°) to have exactly the same physiological activity in humans as crude hemp extract.

5. Dihydrocannabidiol dimethyl ether, when heated with *p*-toluenesulfonic acid in benzene, cleaves to olivetol dimethyl ether and an undistillable compound, presumably a polymer of menthadiene.

URBANA, ILLINOIS RECEIVED JUNE 5, 1941

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Condensation of α-Picoline and Quinaldine with Active Ketones

BY S. M. MCELVAIN AND HAROLD G. JOHNSON

While a methyl group in the α-position of the pyridine or quinoline nucleus possesses quite a high reactivity when compared with one in any of the other positions of these nuclei, it is relatively unreactive in comparison with a methyl (or methylene) group adjacent to the carbonyl group of a ketone, aldehyde or an ester. A few representative examples of this low reactivity may be cited: paraformaldehyde and α-picoline at 140° for nine hours give a 32% yield of β-2-pyridylethyl alcohol[1]; only a 4–6% yield of 2-pyridylisopropyl alcohol may be obtained from the reaction of α-picoline with acetaldehyde[2]; in order to obtain α-stilbazole in as much as 9% yields it is necessary to heat a mixture of α-picoline, benzaldehyde and freshly fused zinc chloride at 200° for twelve to fourteen hours.[3] If, however, the more active carbonyl compound, chloral, is allowed to react with α-picoline it has been found possible to obtain the resulting condensation product, 1,1,1-trichloro-2-hydroxy-3-(2-pyridyl)-propane in yields as high as 70% of the theoretical.[1] In these representative examples it is the carbonyl group of an aldehyde that reacts. Ketones, in general, do not condense with the methyl group of α-picoline except in a few cases in which sodamide has been used as the condensing agent.[4]

Several years ago, in this Laboratory, Walter,[5] in the course of some other work, found that oxomalonic ester in an excess of boiling α-picoline readily condensed with the picoline to give a quite satisfactory yield of ethyl α-picolyltartronate (III). Along with this product there was obtained a small amount of a yellow substance, the structure (IV) of which is discussed below. This greater reactivity of α-picoline with a carbonyl group that is activated by adjacent negative

[1] Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939).

[2] Ladenburg, *Ann.*, **301**, 140 (1898); Meisenheimer and Mahler, *ibid.*, **462**, 301 (1928).

[3] Bailey and McElvain, THIS JOURNAL, **52**, 1636 (1930).

[4] Chichibabin, *Bull. soc. chim.*, **3**, 1607 (1936).

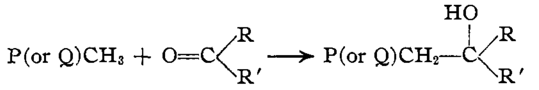
[5] Unpublished work of Lewis A. Walter.

groups such as are present in chloral and oxomalonic ester suggested a further investigation of reactions of this type. The present paper is a report of the results obtained from a study of the reaction of both α-picoline and quinaldine with five active ketones, *viz.*, oxomalonic ester, diphenyl triketone, ethyl benzoyloxylate, benzil and alloxan.

Table I is a summary of the reactants, the time required for reaction and the yields of the crude and purified (by recrystallization to constant melting point) trisubstituted carbinols. Each of the runs shown in this table was made with a twofold excess of picoline or quinaldine and, with the exception of those (7 and 8) in which benzil was used, the reaction temperature was 140°. With the less reactive benzil it was necessary to heat it with the picoline or quinaldine at 175° for maximum yield. Only in the case of the reaction between α-picoline and oxomalonic ester (run 1, Table I) was it possible to distill satisfactorily the reaction product and this fact made it possible to isolate, in addition to the carbinol, a considerable quantity of ethyl β-(α-pyridyl)-acrylate, α-$C_5H_4NCH{=}CHCOOEt$, a product resulting from the dehydration of and cleavage of a carbethoxy group from the ethyl α-picolyl-tartronate. Similar dehydration and cleavage products as well as further condensation products were undoubtedly formed in the other reactions, but it was not possible to separate them by crystallization from the other products that were present. Only in the reaction between quinaldine and benzil (run 8) was the substance that was isolated the dehydration product (II) of the carbinol.

TABLE I

α-PICOLINE AND QUINALDINE WITH ACTIVE CARBONYL COMPOUNDS AT 140°



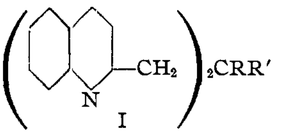
$$\text{P(or Q)CH}_3 + \text{O=C}\begin{matrix}\text{R}\\ \text{R}'\end{matrix} \longrightarrow \text{P(or Q)CH}_2\text{—}\overset{\text{HO}}{\text{C}}\begin{matrix}\text{R}\\ \text{R}'\end{matrix}$$

(P = α-pyridyl; Q = α-quinolyl)

Run	P(or Q)CH_3	R is	R′ is	Reaction time, hr.	Yield of carbinol P(or Q)$CH_2C(OH)RR'$, % Crude	Pure
1	P	COOEt	COOEt	2.0	43[a]	33
2	Q	COOEt	COOEt	2.0	71	47
3	P	C_6H_5CO	C_6H_5CO	1.5	27	16
4	Q	C_6H_5CO	C_6H_5CO	0.25	35	24
5	P	C_6H_5CO	COOEt	1.0	80	74
6	Q	C_6H_5CO	COOEt	0.5	8	4[b]
7	P[c]	C_6H_5	C_6H_5CO	4.0	67	54
8	Q[c]	C_6H_5	C_6H_5CO	3.0	70[d]	38[d]
9	P	-CONHCONHCO-[e]		2.5	36	30
10	Q	-CONHCONHCO-[e]		2.5	30	24

[a] In addition to the carbinol there were obtained a 40% yield of ethyl β-(α-pyridyl)-acrylate and a small amount of the yellow material (IV). [b] When the reactants of this run were heated in refluxing dioxane (101°) for two hours, the crude and pure yields of the carbinol rose to 65 and 54%, respectively. Under these conditions there was practically no tar formed. [c] These reactions were run at 175° in a steel bomb. [d] The product in this run is the dehydrated carbinol, benzoylbenzilidenequinaldine. [e] This reactant is alloxan monohydrate.

The yields of the carbinols shown in Table I and the reaction time required for their formation indicate that the methyl group in α-picoline and quinaldine reacts quite readily with the highly active type of carbonyl group that was used in these experiments and in most cases quite satisfactory yields of condensation products are obtained. It should be noted that the reaction by which the carbinols are formed is one of a number of competing reactions that may occur between these types of reactants. Since there was generally very little or none of the carbonyl compound recovered from these reactions, it is a safe assumption that all that did not appear as the carbinol was involved in further condensations, such as the formation of a diquinaldine type of compound (I) through the reaction of quinaldine with the carbinol, that contribute to the tarry portion of the reaction products. The low yields of the carbinols in runs 3, 4 and 6 are due to the difficulties associated with their removal from the large amounts of noncrystalline reaction products that were formed at 140°. At a lower reaction temperature a very good yield of the carbinol of run 6 was obtained (see footnote *b*, Table I) and it is likely that yields of those in runs 3 and 4 could be similarly increased. The formation of the benzoylbenzilidine-quinaldine (II) instead of the carbinol in run 8 may be attributed to the higher reaction temperature and the greater reactivity of the hydrogen of the methyl group of quinaldine.



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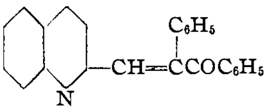
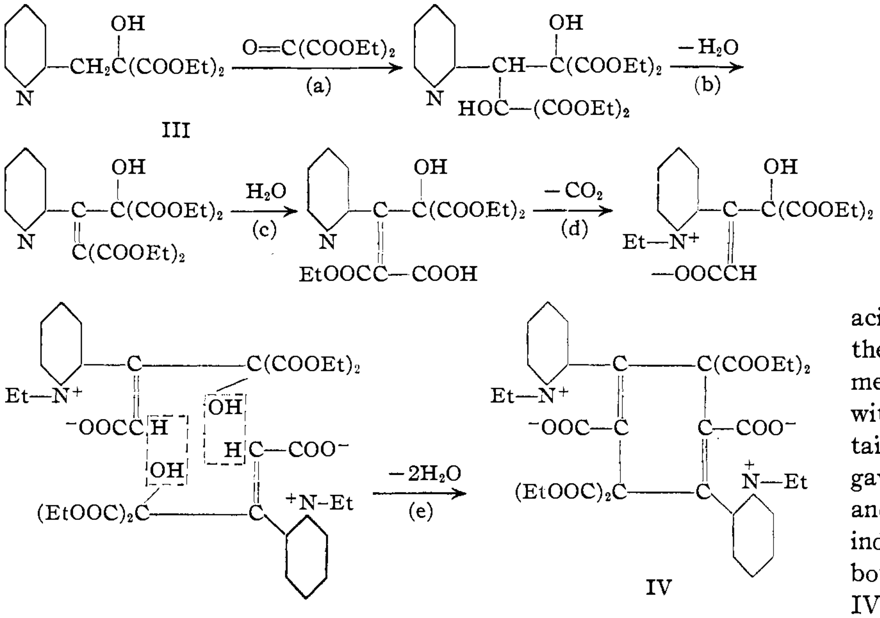


II

In the reaction of oxomalonic ester with α-picoline a small amount of a yellow product always settled out of the picoline solution on cooling. This product was prepared in maximum yield (8%) when 2 equivalents of oxomalonic ester and 1 equivalent of α-picoline were allowed to react;

from this reaction carbon dioxide was evolved. This yellow compound has the general properties of a quaternary salt; it melts at 258–260°; is soluble in water and hot alcohol, but insoluble in ether, ethyl acetate, chloroform and α-picoline. It was recovered unchanged after heating with ethyl iodide for ten hours at 100°. Wieland[6] has used this failure to react with ethyl iodide as a test for a quaternary salt. Analyses for carbon, hydrogen, nitrogen and ethoxyl and a molecular weight of 664 lead to the molecular formula $C_{34}H_{38}O_{12}N_2$. This formula indicates that two pyridine nuclei are in the molecule. A structure that fits the molecular formula and the properties of this compound is the cyclohexadiene with two betaine groups shown in IV. The formation of such a structure may be rationalized through the following sequence of reactions that start with the carbinol (III)



There is no reason to believe that structure IV is preferable to the isomer that would result from the hydrolysis of the hydroxymalonic ester grouping, instead of the one that is shown in reaction (c), and the subsequent decarboxylation, betaine formation and condensation of the resulting acid. It was not possible to start with the carbinol III and oxomalonic ester (reaction a) and prepare IV, but the reason was not that these compounds did not react but because the reaction product was a black tar from which nothing tractable could be obtained. However, as mentioned above, the highest yields of IV were obtained when two equivalents of oxomalonic ester were allowed to react with one equivalent of picoline.

While analytical data and quaternary salt properties are the main support of the structure IV, other reactions of this yellow product are in accord with this structure. It immediately decolorizes dilute permanganate and bromine solutions. It is precipitated from an aqueous solution as is betaine[7] with ferrocyanic acid. Its hydrogen absorption over Raney nickel seems significant; at 100° and 112 atmospheres of pressure 2 moles of hydrogen (calculated on the mol. wt. of IV) were absorbed immediately; for further absorption it was necessary to raise the temperature to 155° at which temperature an additional 4.5 moles of hydrogen were taken up; an additional eleven hours at 160° caused a further absorption of 4.5 moles of hydrogen. The total absorption of approximately 3 moles of hydrogen more than the 8 that are required for the double bonds of the cyclohexadiene and pyridine rings of IV suggests some hydrogenolysis. Only a dark water-soluble oil that gave no precipitate with ferrocyanic acid could be isolated from these hydrogenation experiments. Treatment of IV with absolute alcohol containing dry hydrogen chloride gave a product, the ethoxyl and chlorine content of which indicated that approximately both of the betaine groups of IV had been converted to the hydrochloride. In concentrated ammonia water for 5 days IV is converted to a new compound, m. p. 282–284°, the nitrogen and ethoxyl content of which indicated that two of the carbethoxy groups had been converted to amides.

Experimental

Materials Used.—The α-picoline and quinaldine, purchased from Barrett and Co., New York, were carefully fractionated and fractions boiling at 127–128° and 100–102° (6 mm.) were used. Oxomalonic ester,[8] diphenyl tri-

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[6] Wieland and Mueller, *Ann.*, **545**, 59 (1940).

[7] Roeder, *Ber.*, **46**, 3724 (1913).

[8] "Organic Syntheses," Coll. Vol. I, 1932, p. 261.

TABLE II

CARBINOLS AND RELATED COMPOUNDS FROM THE CONDENSATION OF ACTIVE KETONES WITH α-PICOLINE AND QUINALDINE

Compd. no.	Formula	M. p., °C.	Analyses, % Calcd. C	H	N	EtO	Found C	H	N	EtO
1	$C_{13}H_{17}O_4N$	38–39[a]	58.4	6.4	5.3	33.7	57.9	6.4	5.4	33.5
1a	$C_{10}H_{11}O_2N$	26–27[b]	67.8	6.2	7.9	25.4	68.0	6.4	7.7	25.0
2	$C_{17}H_{19}O_4N$	70–71	..	...	4.4	28.4	..	...	4.3	28.1
3	$C_{21}H_{17}O_3N$	115–116	75.9	5.1	4.2	..	76.0	5.4	4.1	..
4	$C_{25}H_{19}O_3N$	258–260	78.8	5.0	3.7	..	79.1	5.0	3.8	..
5	$C_{16}H_{17}O_4N$	100–101	..	...	4.7	15.1	..	...	4.8	15.0
6	$C_{20}H_{19}O_4N$	80–81	72.2	5.4	4.0	12.9	72.4	5.6	4.0	13.1
7	$C_{20}H_{17}O_2N$	110–111	79.2	5.6	4.6	..	79.2	5.7	4.8	..
8	$C_{24}H_{17}ON$	187–188	86.0	5.1	4.2	..	85.9	5.3	4.1	..
9	$C_{10}H_{11}O_5N_3$[c]	230–231	47.4	4.3	16.6	..	47.3	4.2	16.8	..
10	$C_{14}H_{11}O_4N_3$	238–240	59.0	3.9	14.7	..	59.0	4.2	14.0	..

[a] B. p., 148–150° (1 mm.). [b] B. p., 104–105° (0.7 mm.); n^{25}_D 1.5445. [c] Analyses fit this formula which represents a monohydrate of 5-hydroxy-5-(α-picolyl)-barbituric acid.

ketone[9] and benzil[10] were prepared by standard procedures. Alloxan monohydrate was prepared from uric acid.[11]

Ethyl benzoylglyoxylate was prepared by a modification of Wahl's[12] procedure. In the apparatus used for the preparation of oxomalonic ester[8] a mixture of 232 g. of ethyl benzoylacetate,[13] 151 g. of acetic anhydride and 132 g. of di-*n*-butyl ether was divided between two large test-tubes (2.5″ diameter, 18″ long) immersed in an ice–salt pack. Then the nitrogen oxides were drawn into these tubes from the generator by the application of suction until each tube had gained 105 g. in weight (about two hours). The tubes were then removed from the remainder of the apparatus, fitted with calcium chloride tubes and allowed to stand in an ice and salt pack for another twelve hours after which time they were slowly allowed to come to room temperature. Nitrogen oxide fumes were evolved and the color of the solution changed from dark green to yellow. The contents of the two reaction tubes were combined and fractionated. A fraction (204 g.) boiling at 115–170° (25 mm.) was collected. Upon refractionation of this material through a 10-cm. modified Widmer column there were obtained 48 g. of benzoic acid, b. p. 96–105° (1 mm.), and 76 g. (30%) of ethyl benzoylglyoxylate, b. p. 106–110° (1 mm.), the ethoxyl content of which was 21.5% (calcd. 21.9%). Wahl[12] reports this ester as boiling at 150–153° (13 mm.).

Condensation of α-Picoline and Quinaldine with Active Ketones.—In general, these reactions were carried out with 2 equivalents of picoline or quinaldine and 1 equivalent of the ketone. The reactants were heated under a reflux condenser (except in runs 7 and 8, Table I) and in an oil-bath kept at 140°. This temperature caused the picoline to reflux gently. The time that the different ketones were allowed to react was found to be important and is shown along with the yields of the various products in Table I. In run 1 a small amount of the yellow compound (IV) always settled out and was filtered off when the picoline cooled. After the reaction time indicated in Table I the excess picoline or quinaldine was taken off under diminished pressure and the remaining residue treated with 2.5 times its volume of ether. The resulting ethereal solution was decanted from any precipitated tarry material and extracted with two 100-ml. portions of 20% hydrochloric acid. The remaining ether layer was distilled; only in the reactions involving benzil (runs 7 and 8, Table I) was any appreciable amount of the starting ketone recovered from this ether solution. The aqueous acid layer was neutralized with sodium carbonate and extracted with three 100-ml. portions of ether. After drying over anhydrous sodium sulfate the ether was removed from the condensation mixture. In the case of oxomalonic ester and picoline this mixture was purified by distillation. It was by this means that it was possible to isolate ethyl β-(α-pyridyl)-acrylate (footnote *a*, Table I). In the other cases it was necessary to separate the reaction products by crystallization from alcohol or a mixture of alcohol and petroleum ether.

An additional experiment with ethyl benzoylglyoxylate and quinaldine was carried out in which 11 g. of the ester and an equivalent of the amine were heated in 30 ml. of refluxing dioxane for two hours. Then the dioxane was removed by distillation and the residue taken up in 50 ml. of absolute ether. Cooling of this ether solution in dry-ice caused the ethyl quinaldyl-benzoyl-glycolate to crystallize out in a 65% yield. Recrystallization from a mixture of alcohol and petroleum ether gave 10.3 g. (54%) of the pure carbinol.

The molecular formulas, properties and analyses of the compounds (with the exception of IV) obtained from the various reactions are summarized in Table II. Each compound is given the number corresponding to the number of the run in which it was formed in Table I. The compounds and the numbers that identify them in Table II are: 1, ethyl α-picolyl-tartronate; 1a, ethyl β-(α-pyridyl)-acrylate; 2, ethyl quinaldyl-tartronate; 3, α-picolyl-dibenzoyl-carbinol; 4, quinaldyl-dibenzoyl-carbinol; 5, ethyl α-picolyl-benzoyl-glycolate; 6, ethyl quinaldyl-benzoyl-glycolate; 7, phenyl-α-picolyl-benzoyl-carbinol; 8, 1-(α-quinolyl)-2-phenyl-2-benzoyl-ethylene; 9, 5-hydroxy-5-(α-picolyl)-barbituric acid; 10, 5-hydroxy-5-quinaldyl-barbituric acid.

Preparation of the Cyclohexadiene, IV.—From the preparations of the carbinol from oxomalonic ester and α-picoline (run 1, Table I) some of IV always precipitated out

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(9) "Organic Syntheses, **13**, 38 (1933).

(10) "Organic Syntheses," Coll. Vol. I, 1932, p. 80.

(11) McElvain, THIS JOURNAL, **57**, 1303 (1935).

(12) Wahl, *Bull. soc. chim.*, [4] **1**, 461 (1907).

(13) *Org. Syntheses*, **18**, 33 (1938).

as the picoline cooled. However, the most satisfactory procedure for the preparation of this product is as follows: 50 g. (2.8 mols) of oxomalonic ester and 13.3 g. (1.4 mols) of α-picoline were heated in an oil-bath at 140° for one hour. On cooling a precipitate of 2.15 g. of the yellow product (IV) appeared and was filtered off. An additional 0.85 g. was obtained when 500 ml. of absolute ether was added to the filtrate. The ether solution was worked up as described above and yielded 10 g. of recovered oxomalonic ester and 3 cc. of α-picoline, as well as 12.4 g. of a mixture 1 and 1a (Table II) distilling at 130–140° (1 mm.). The total yield of IV was 3 g. (8%, based on the oxomalonic ester used). After recrystallization from absolute alcohol the product melted at 258–260° with decomposition.

Anal. Calcd. for $C_{34}H_{38}O_{12}N_2$: mol. wt., 666; C, 61.3; H, 5.7; N, 4.2; EtO, 27.0. Found: mol. wt. (cryoscopic benzene), 664; C, 61.4; H, 5.9; EtO, 27.0; N, 4.2.

A solution of 0.5 g. of IV in 10 cc. of water was treated with a solution of 1 g. of potassium ferrocyanide and 1 g. of sulfuric acid in 20 ml. of water. The precipitate that formed was filtered off, washed twice with water, then with alcohol and petroleum ether (b. p. 60–68°) and finally dried under 8 mm. pressure at 100°. It did not melt under 320°.

Anal. Calcd. for $C_{34}H_{38}O_{12}N_2 \cdot H_4Fe(CN)_6 \cdot 2H_2O$: N, 12.2; EtO, 19.7. Found: N, 12.3; EtO, 19.6.

Diamide of IV.—A 0.5-g. sample of IV was allowed to stand with 40 ml. of concentrated ammonia water in a tightly stoppered flask for a week. After this time the excess of ammonia water was removed under diminished pressure and the residue recrystallized from absolute alcohol. The resulting product melted at 282–284° and appeared from analyses to have two of the ethoxyl groups of IV replaced by amino groups.

Anal. Calcd. for $C_{30}H_{32}O_{10}N_2$: N, 9.2; EtO, 14.8. Found: N, 9.4; EtO, 14.4.

A solution of 0.7 g. of IV in 7 ml. of a 3% solution of dry hydrogen chloride in absolute alcohol was refluxed for five hours, after which time the excess alcohol was evaporated and the residual salt (0.77 g.) dried under 3 mm. pressure for twelve hours. The resulting product melted at 129–130° and gave analyses approximating the dihydrochloride of IV.

Anal. Calcd. for $C_{34}H_{40}O_{12}N_2Cl_2$: Cl, 9.5; EtO, 24.3. Found: Cl, 9.4; EtO, 25.1.

When the alcoholic hydrogen chloride solution of IV was refluxed for seventy-two hours the product that was obtained was a viscous oil the ethoxyl content of which was 30.7% (the calculated value of the mono-ester dihydrochloride of IV is 30.8% EtO, and for the di-ester dihydrochloride is 34.0%).

A 0.3-g. sample of IV was recovered unchanged after heating for ten hours at 100° with a solution of 2 ml. of ethyl iodide in 10 ml. of absolute alcohol in a sealed tube. The recovered sample gave no precipitate with silver nitrate solution acidified with nitric acid.

A solution of 4 g. of IV in 20 ml. of water was subjected to hydrogenation in a 60-ml. bomb over 1 g. of Raney nickel and at 112 atmospheres of hydrogen pressure. After the first seven minutes of shaking of the bomb, and as the temperature rose to 100°, 2 equivalents of hydrogen were absorbed. Then the rate of absorption dropped markedly, whereupon the temperature was raised to 155° and the hydrogenation continued for two and one-half hours. During this time an additional 6.5 equivalents of hydrogen were absorbed. After cooling, the bomb was opened and catalyst filtered off. The filtrate and 1 g. of fresh catalyst were returned to the bomb and the hydrogenation continued at 160° for eleven hours, during which time 4.8 equivalents of hydrogen were absorbed. After removal of the catalyst the aqueous solution was evaporated. The residue was a brown oil that could not be caused to crystallize. A solution of this oil gave no precipitate with ferrocyanic acid.

An aqueous solution of IV caused an immediate decolorization of either bromine water or a dilute solution of potassium permanganate.

Summary

The reactions between α-picoline and quinaldine and the active ketones, ethyl oxomalonate, diphenyl triketone, ethyl benzoylglyoxalate, benzil and alloxan have been studied. The main reaction product is the carbinol of the type $PCH_2C(OH)R,R'$ ($P=\alpha$-pyridyl or quinolyl). Certain of these carbinols have been prepared in quite good yields. The product of the reaction of benzil and quinaldine is the substituted ethylene resulting from the dehydration of the carbinol.

In the reaction between α-picoline and ethyl oxomalonate two additional products were isolated, (a) ethyl β-(α-pyridyl)-acrylate and (b) a betaine with the molecular formula $C_{34}H_{38}O_{12}N_2$. A structure for the latter compound is suggested.

MADISON, WISCONSIN RECEIVED JUNE 4, 1941