[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

A REVISED PREPARATION OF CLEMO'S TETRAHYDROBENZOQUINOLIZINONE

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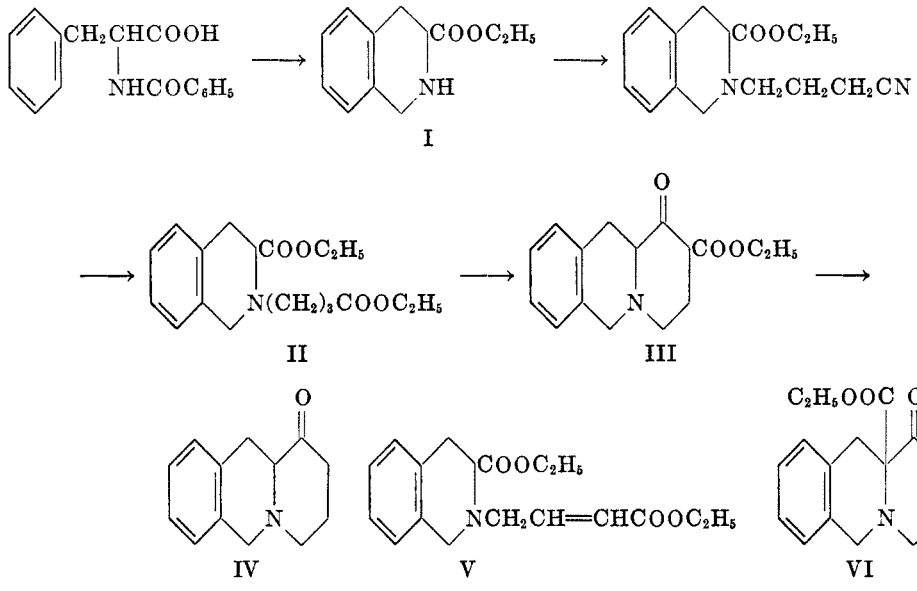
A few years ago a moderate quantity of the tetrahydrobenzoquinolizinone (IV) was required for another investigation. This compound was reported by Clemo and Swan (1), who prepared it from DL-benzoylphenylalanine according to the scheme:



There are manipulative difficulties involved in this synthesis but of greater importance is the low over-all yield (less than 3%). These considerations led us to modify the method so that the yield of IV, based on DL-phenylalanine, was raised to 24%.

Julian's method (2) was used to convert DL-phenylalanine to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride. It was unnecessary to convert the salt to the free acid for the preparation of the ester, I. The latter was obtained in 73% yield in ethanol saturated with dry hydrogen chloride. When the ester (I) was treated with ethyl γ-bromocrotonate in benzene solution it was converted to V in 71% yield. Occasionally a crystalline salt was encountered which was presumably a quaternary salt derived from V, but its structure was not investigated.

The double bond in V was reduced with hydrogen and Adams' catalyst. In early experiments the ester, V, was isolated; however, since the yield in the reduction was nearly quantitative this isolation was omitted in later work.

Ring closure was carried out in toluene with the aid of sodium hydride. This

reagent was more convenient to handle than metallic potassium. The keto-ester, III, was readily isolated as the hydrochloride, a salt which was quite insoluble in concentrated hydrochloric acid. Usually the keto-ester was hydrolyzed without isolation to the desired ketone, IV. The over-all yield from V to IV was 53%.

The hydrolysis of the keto-ester, III, was followed by testing aliquot portions with ferric chloride reagent. The fact that such a test was positive indicates that cyclization of II to III took place as indicated and not in the opposite sense to furnish VI.

EXPERIMENTAL[1]

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid hydrochloride. A suspension of 75 g. of DL-phenylalanine in 575 ml. of hydrochloric acid and 170 ml. of 37% formalin was heated on the steam-bath with vigorous stirring for 30 minutes. Then 75 ml. of formalin and 150 ml. of hydrochloric acid was added. Stirring and heating was continued for three hours more. After standing overnight the mixture was filtered. The filter cake was washed with two 25-ml. portions of methanol and dried. Wt., 78.1 g. (yield, 81%). The analytical sample was twice recrystallized from hot water, m.p. 308–309° dec. (uncorr.).

Anal. Calc'd for $C_{10}H_{10}NO_2 \cdot HCl$: N, 6.62; Cl, 16.00.
Found: N, 6.50; Cl, 16.06.

The *acetyl* derivative melted at 173.2–175.8° (corr.) after recrystallization from water.

Anal. Calc'd for $C_{12}H_{12}NO_3$: N, 6.42. Found: N, 6.29.

Ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate. A suspension of 157 g. of the hydrochloride of the above isoquinoline acid in 8 l. of absolute ethanol was stirred vigorously and heated to boiling. Dry hydrogen chloride was passed through until the ethanol was saturated. The mixture was refluxed for a total of six hours. After two hours all of the amino acid had dissolved. The solution was concentrated to dryness *in vacuo*. The crystalline residue was dissolved in 350 ml. of water and the resulting solution was made alkaline with potassium carbonate. The oil was separated and the aqueous layer extracted with ether. The combined oil layers were washed with water, dried, and distilled. The ester boiled at 124–125°/0.6 mm.; n_D^{25} 1.5325. Wt., 110 g. (yield, 73%). Clemo (1) reports b.p. 120°/1 mm.

The *picrate,* prepared in and recrystallized from aqueous ethanol, melted at 202–204° (uncorr.). Clemo (1) reports 204°.

Ethyl N-(γ-carbethoxyallyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate. Potassium carbonate (40 g.) was suspended in a solution of 110 g. of the ester, I, in 500 ml. of benzene and the mixture was heated to reflux. Then 106 g. of ethyl γ-bromocrotonate [prepared by treatment of ethyl crotonate with N-bromosuccinimide (3)] was added with rapid stirring over a 1½ hour period. The mixture was cooled and washed with water and then with 250 ml. of 3 *N* hydrochloric acid. The acid layer was washed with ether and then made alkaline. The oil was removed with ether and then washed with water and dried.

Distillation afforded a small forerun, b.p. 150–184°/0.7 mm., wt., 4.0 g. and the main fraction, b.p. 197–200°/1.5 mm.; wt., 120.0 g. (yield, 71.5%). On redistillation it boiled at 181–184°/0.7 mm., n_D^{25} 1.5253.

Anal. Calc'd for $C_{18}H_{22}NO_4$: N, 4.49. Found: N, 4.41.

Ethyl 3,4,11,11a-tetrahydro-2-benzo[b]-quinolizin-1(6)-one-2-carboxylate hydrochloride (IV). A solution of 18 g. of the above diester (VI) in 100 ml. of ethanol was reduced in the presence of 0.5 g. of Adams' platinum oxide. After the theoretical amount of hydrogen was absorbed the catalyst was removed by filtration and the filtrate concentrated. The residue was dissolved in 50 ml. of dry toluene.

A suspension of 3.0 g. of sodium hydride in 20 ml. of dry toluene was stirred and heated

[1] Analyses were carried out under the supervision of Messrs. M. E. Auerbach and K. D. Fleischer of this laboratory.

to 70°. The heat was removed and 20 ml. of the toluene solution of the diester was added at one time. After the reaction had started the remainder of the solution was added dropwise. The temperature fell to 50° during the addition which required 30 minutes. The mixture was kept at 65° for three hours. The excess sodium hydride was destroyed with 15 ml. of ethanol. The mixture was cooled to 5° and treated with 75 ml. of concentrated hydrochloric acid. After one hour the crystalline hydrochloride was filtered off and pressed as dry as possible. The salt was dissolved in methanol, filtered to remove a small amount of insoluble material, and the filtrate was treated with ether. Wt., 13.3 g. (yield, 74%). A portion was twice crystallized from methanol-ether, m.p. 192–194° dec. (corr.).

Anal. Calc'd for $C_{16}H_{19}NO_3$: C, 62.05; H, 6.51; N, 4.58.

Found: C, 62.15; H, 6.22; N, 4.38.

3,4,11,11a-Tetrahydro-2-benzo[b]-quinolizin-1(6)-one (V). The ester, V (40 g.) was reduced as above and the crude dihydro ester, II, was dissolved in 100 ml. of toluene. Cyclization was carried out with a suspension of 6.0 g. of sodium hydride in 100 ml. of toluene. After the reaction was complete, ethanol was added to destroy the excess sodium hydride and then 1500 ml. of 6 *N* hydrochloric acid was added. The mixture was stirred at 90–95° until a test portion gave a negative ferric chloride test. The acid layer was separated and concentrated to a thin syrup *in vacuo*. The residue was treated with potassium carbonate and ether. The ether solution was dried and concentrated. The residue was covered with petroleum ether and filtered. It weighed 13.5 g. (yield, 53%). After one recrystallization from dilute ethanol it melted at 92–96°. [Clemo and Swan (1) give m.p. 98–100°].

The *phenylhydrazone* melted at 92–94°. [Clemo and Swan (1) report m.p. 92°.]

The *nitrophenylhydrazone* was prepared in ethanol solution. It was purified by recrystallization from dilute ethanol; m.p. 197.9–198.8° (corr.).

Anal. Calc'd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 6.00; N, 16.65.

Found: C, 67.95; H, 6.30; N, 16.88.

SUMMARY

3,4,11,11a-Tetrahydro-2-benzo[b]-quinolizin-1(6)-one was prepared in 24% over-all yield from DL-phenylalanine. The steps comprise: converting the amino acid to 1,2,3,4-isoquinoline-3-carboxylic acid, esterifying the acid, and treating the ester with ethyl γ-bromocrotonate. Reduction, followed by ring closure and hydrolysis furnished the desired ketone.

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