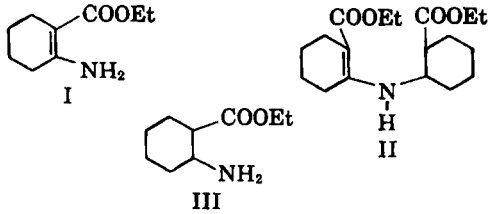
Rhodium-Catalyzed Hydrogenation of Ethyl Anthranilate

By KENNETH J. LISKA

Room temperature hydrogenation of ethyl anthranilate employing 5 per cent rhodium on alumina at both low and high pressures yields the 3,4,5,6-tetrahydro derivative. At elevated temperatures, ethyl *cis*-hexahydroanthranilate is formed in good yield. An unsaturated dicyclohexylamine diester appears to form in a side reaction in the room temperature hydrogenations.

In synthetic approaches to potential psychotomimetics, it was necessary to investigate the hydrogenation of ethyl anthranilate (ethyl *o*-aminobenzoate). The desired hexahydro derivative has been obtained in useful amounts by reduction with sodium in boiling isoamyl alcohol (1). Houben and Pfau obtained the hexahydro compound by platinum-catalyzed reduction, but they did not give yields or physical data (2).

Five per cent rhodium on alumina at low pressures and room temperatures catalyzed the hydrogenation of ethyl anthranilate to ethyl 3,4,5,6-tetrahydroanthranilate (I) but not to the hexahydro compound.



The tetrahydro derivative was identified by elemental analyses and by comparison with an authentic sample prepared by Dieckmann's ammonolysis method (3). With the same catalyst, room temperature hydrogenations at pressures up to 1000 p.s.i. again yielded the tetrahydro compound I, an indication of the stability of this bond toward hydrogenation. However, when the reaction temperature was raised to 85° and at 500 p.s.i., hydrogenation was complete to ethyl *cis*-hexahydroanthranilate (III) in approximately 70% yield. The conversion of ethyl anthranilate to the tetrahydro compound and finally to the hexahydro can be followed very well by U.V. spectroscopy. To prove the *cis* nature of the hexahydro product, it was hydrolyzed to the known *cis*-hexahydroanthranilic acid (4).

Both the low-pressure and the high-pressure room temperature rhodium-catalyzed hydrogenations always yielded a higher boiling liquid fraction in weight amounting to about one-half that of compound I. Rast molecular weight determinations gave values in the 300 to 400 range. Though insoluble in water, the liquid was soluble in hydrochloric acid; elemental analyses indicated only one nitrogen atom per molecule. The compound was an absorber in the U.V. (log E = 4.21 at 303 mμ) as strong as compound I (log E = 4.17 at 286 mμ). This by-product was identified tentatively as ethyl 2-(2-ethoxycarbonylcyclohexyl)aminocyclohexene-1-carboxylate (II). It could form *via* intermolecular primary amine addition to an olefin, similar to the well-known addition of amines to acrylate, followed by hydrogenolysis of one nitrogen atom. Almost exactly the same type of by-product was reported by Huenig and Kahanek (4) in their platinum oxide-catalyzed hydrogenation of ethyl 3,4,5,6-tetrahydroanthranilate, except that their dicyclohexylamine diester had no olefinic bond in either ring. That compound II was not identical to their saturated diester was indicated by the strong U.V. absorption of II, a conjugated olefinic ester, plus elemental analyses and I.R. spectral studies. The I.R. spectrum of compound II showed bands attributable to a saturated ester (1720 cm.$^{-1}$), an α,β-unsaturated chelated ester (1635 cm.$^{-1}$), an olefin conjugated to an ester (1595 cm.$^{-1}$), and the N—H stretching vibration of a secondary amine (3250 cm.$^{-1}$). By comparison, the I.R. spectrum of compound I showed no band attributable to a saturated ester, and the spectrum of compound III showed no band attributable to an α,β-unsaturated ester.

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EXPERIMENTAL[1]

Ethyl 3,4,5,6-Tetrahydroanthranilate (I).—A solution of 16.5 Gm. (0.1 mole) of ethyl anthranilate in 100 ml. of absolute ethanol was shaken at room temperature with 10 Gm. of 5% rhodium-on-alumina (K&K Laboratories, Inc.) in a Parr hydrogenator at an initial pressure of 61.1 p.s.i. for a total of 16 hours over a 2-day period. The total pressure drop was equal to 16.9 p.s.i., but most of the hydrogen was absorbed in the first 7 hours. Removal of catalyst and solvent, followed by distillation, gave 7.0 Gm. of product (41%), b.p. 159–164° (29 mm.), which when cooled gave a colorless solid, m.p. 71–73°. An authentic sample of this compound, prepared according to Dieckmann (3), melted at 73–75°; mixed m.p. 75–78°.

Anal.—Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.04; H, 9.02; N, 8.19.

Compound I is a strong absorber in the U.V.: log E = 4.17 at 286 mμ. Its HCl salt could not be prepared in the solid state. Carbonyl stretching frequency of this α,β-unsaturated chelated ester: 1665 cm.$^{-1}$.

Ethyl 2-(2-Ethoxycarbonylcyclohexyl)aminocyclohexene-1-carboxylate (II).—The high-boiling fraction remaining after removal of the tetrahydro derivative was further distilled, yielding 4.8 Gm. of viscous yellow oil, b.p. 185–192° (1.6 mm.), N^{23} = 1.5208.

Anal.—Calcd. for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 66.75; H, 8.89; N, 3.53.[2]

Compound II is a strong absorber in the U.V.: log E = 4.21 at 303 mμ. The HCl salt of this

[1] Melting points are uncorrected. Analyses performed by Galbraith Laboratories and Schwarzkopf Laboratories.

[2] Einhorn and Bull state that ethyl hexahydroanthranilate loses nitrogen (as ammonia) when distilled at atmospheric pressure. [*Ann.*, 295, 204(1897).] Two other analyses from different runs fell in the range 4.7 to 5.1.

aminoester could not be prepared in the solid state. Infrared spectral bands in cm.$^{-1}$: 3250(w), 1720(s), 1635(s), 1595(s), 1445(s), 1360(m), 1233(s), 1165(s), 1083(m), 1060(m), and 1036(m).

Ethyl cis-Hexahydroanthranilate (III).—A mixture of 10 Gm. of ethyl anthranilate in 150 ml. of absolute ethanol and 8 Gm. of 5% rhodium on alumina was stirred in a Parr pressure reaction apparatus at 500 p.s.i. and at temperatures up to 85° for a total of 10 hours over a 2-day period. Removal of catalyst and solvent gave an oil which distilled at 115–119° (20 mm.). Huenig and Kahanek report 103–104° (11 mm.) (4). The yield of hexahydro ester was 7.3 Gm. (70.1%). For analysis, the previously unreported HCl salt of III was prepared in the usual manner with dry ether and HCl gas and melted at 131–133° after two crystallizations from acetone/alcohol.

Anal.—Calcd. for $C_9H_{18}ClNO_2$: C, 52.05; H, 8.67; N, 6.74. Found: C, 51.82; H, 8.71; N, 6.62.

The free acid was prepared by refluxing III in plain water, followed by evaporation. The *cis*-hexahydroanthranilic acid so obtained was recrystallized from alcohol/water, m.p. 233–234°. Huenig and Kahanek (4) report 235° for the *cis* acid; the *trans* acid, also prepared by plain water hydrolysis (1), melts at 274°.

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Antistaphylococcal Activity of Seeds of *Psoralea corylifolia*

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The petroleum ether extract of the seeds of *Psoralea corylifolia* Linn. inhibits the growth of *Staphylococcus aureus*, in the concentration of 10 mcg./ml. From the extract a pure compound, $C_{12}H_{16}O$, b.p. 155°/0.3 mm., has been isolated by chromatography and subsequent fractional distillation. It inhibits the growth of *S. aureus* in the concentration of 0.5 mcg./ml.

PSORALEA CORVLIFOLIA Linn. (*Leguminosae*) is a common herbaceous weed, grows throughout the plains of India, and is commonly known as babchi. The seeds of this plant have long been used in the indigenous system of medicine for leprosy, inflammatory diseases of the skin, leucoderma, psoriasis, as an anthelmintic, a diuretic and a diphoretic in febrile conditions (1). In southern India, the drug is widely used as a stomachic, deobstruent, and in various cutaneous diseases (2). The seeds have an estrogenic effect on certain laboratory animals (3). Jois and Manjunath (4) and Seshadri and Venkattarao (5) isolated o fixed and a volatile oil, psoralen and iso-psoralen. Chakravarti *et al.* (6) isolated a new crystalline compound, psoralidin, from the pericarp. Gupta *et al.* (7) recently reported the antistaphylococcal activity of the petroleum ether extract of the seeds in the concentration of 2–4 mcg./ml. Jois *et al.* (8) obtained from a petroleum ether extract of the seeds a fixed oil, psoralen, and iso-psoralen. In this investigation, these components did not show activity against *Staphylococcus aureus*. Volatile oil from the seeds has not revealed appreciable activity (7). A systematic investigation of the seeds was undertaken and an attempt made to isolate and characterize the antistaphylococcal principle.

MATERIAL AND METHODS

Test Organism.—*S. aureus* (Oxford culture) was employed for testing the activity of the various fractions. The organism was maintained on nutrient agar slants from which regular subculturing was done in nutrient broth. A 24-hour suspension of this organism in broth was used for all subsequent investigations.

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Minimum Inhibitory Concentration.—The antistaphylococcal activity of the various fractions (Table I) was tested by serial dilution method. A solution (10 mg./ml.) of the test compound was prepared in alcohol (90%). One-half milliliter of the dilution was then transferred to 4.5 ml. of sterile nutrient broth (pH 7.2–7.4) from which 0.5 ml. of the dilution was further transferred to 4.5 ml. of the broth, etc., until a varied range of concentrations was obtained in the broth. The total volume was kept at 5 ml. Various dilutions of the test compound ranging from 0.1 to 100 mcg./ml. were obtained. The solution of the test compound

TABLE I.—ANTISTAPHYLOCOCCAL ACTIVITY OF VARIOUS CHROMATOGRAPHIC FRACTIONS OF PETROLEUM ETHER EXTRACT OF *P. corylifolia* SEEDS

Eluents	Physical Appearance	Antistaphylococcal Activity[a]
Petroleum ether (1–18)	Dark brown liquid	−
10% Benzene in petroleum ether (19–29)	Light green liquid	−
50% Benzene in petroleum ether (30–40)	Viscous green liquid	+
Benzene (41–53)	Viscous green liquid	+
10% Ether in benzene (54–57)	Viscous brown liquid	−
50% Ether in benzene (58–67)	Viscous brown liquid	−
Ether (68–75)	Viscous brown liquid	−
10% Alcohol in ether (76–79)	Yellow solid mass	−
50% Alcohol in ether (80–83)	Yellow solid mass	−
Alcohol (84–90)	Yellow solid mass	−

[a] −, No inhibition; +, inhibition.