Experimental

2-*n*-Butyl-4-methylpyridine.—Twenty-three grams (0.25 mole) of γ-picoline in 75 ml. of anhydrous ether was added dropwise with stirring to an equivalent amount of 0.94 molar butyllithium in ether, which was maintained at −10° in an ice–salt-bath. A yellow precipitate formed. After one and one-half hours stirring the mixture was carbonated by pouring jet-wise into a slurry of Dry Ice and ether. After the Dry Ice had evaporated, the mixture was extracted with 20% sodium hydroxide solution. On acidifying the alkaline extract only a very small amount of red gum was obtained from which a very small amount (*ca.* 10–20 mg.) of unidentified crystalline material, m. p. 148–150°, separated on cooling. The alkali-insoluble portion was a yellow oil, which was aerated to oxidize the dihydropyridine to the pyridine, dried over barium oxide and distilled. Five grams of the anil addition product was obtained boiling at 200–202° (740 mm.). A Siwoloboff boiling point determination gave reproducible values at 201–202°: $n^{20}D$ 1.4778; sp. gr.$^{27}_{27}$ 0.885.

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39. Found: N, 9.50.

The picrate was prepared in boiling ethanol giving bright yellow crystals, melting at 88.5–90.5° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{16}H_{18}O_7N_4$: N, 14.8. Found: N, 14.9.

2-(α-Thienyl)-6-methoxyquinoline.—Thiophene, 30.3 g. (0.36 mole) in 100 ml. of anhydrous ether, was metalated with 0.3 mole of butyllithium in the conventional apparatus under a nitrogen atmosphere. Then 34 g. (0.214 mole) of 6-methoxyquinoline in 60 ml. of ether was added dropwise to the stirred α-thienyllithium at such a rate as to maintain reflux. A greenish-white precipitate formed. After stirring the mixture for one hour, it was hydrolyzed carefully with 200 ml. of water.

The ether phase was separated, mixed with 25 ml. of nitrobenzene to oxidize the dihydroquinoline, and distilled. A fraction (nitrobenzene, aniline, thiophene) was collected at 90–105° (18 mm.). Then 26 g. (a 75% recovery) of 6-methoxyquinoline was obtained boiling at 105–114° (18 mm.). (Its identity was checked by preparing its picrate and comparing the picrate prepared from an authentic sample of 6-methoxyquinoline. Both melted at 217–218°, with no depression on mixing.) A final fraction of 3.5 g. (6.8%) boiling 200–210° (18 mm.), was collected and crystallized from a benzene and ligroin mixture; melting point, 137–138.5°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.81. Found: N, 5.69.

A picrate of the product was prepared and recrystallized from ethanol. The melting point was 190.5–192°.

Anal. Calcd. for $C_{20}H_{14}O_8N_4S$: N, 11.9. Found: N, 11.75.

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α-Phenyl-levulinic Acid, a Product of the Alkaline Degradation of Penicillin G

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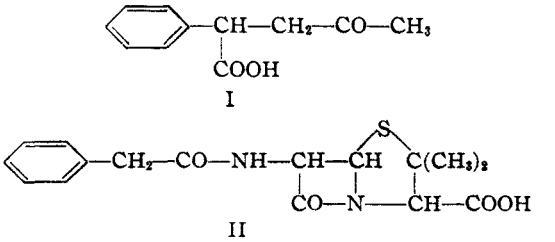
In the course of studies on the chemistry of penicillin G carried out in 1945, we encountered significant amounts of a degradation product which was readily identified as α-phenyl-levulinic acid (I). It was obtained from penicillin G, along with larger quantities of phenylacetic acid, by treatment with aqueous sodium hydroxide.



I

II

At that time no information was available to us concerning results of degradative studies carried out in other laboratories. Meanwhile, there have appeared several publications on the chemistry of penicillin[1] which discuss in survey form the experimental evidence that led to the general acceptance of formula II for penicillin G. These publications, while mentioning a great number of degradation products obtained from the various penicillins, do not contain any reference to α-phenyl-levulinic acid.

The accepted β-lactam formula for penicillin G (II) does not contain the carbon skeleton of α-phenyl-levulinic acid, and it is not readily apparent to us by what series of reactions this C-11 acid could be formed from it. The β-lactam structure is based upon such a wide variety of evidence that it seems necessary to conclude that our product is an artifact formed somehow by a reductive condensation of certain of the penicillin G degradation products. The mechanism, however, is obscure.

There is no question that the α-phenyl-levulinic acid isolated by us is actually formed from penicillin G. The preparation has been repeated several times during the past two and a half years, using sodium penicillin G of high purity, obtained by different methods from different lots of penicillin. The α-phenyl-levulinic acid has been isolated as such and in the form of its methyl ester and as the *p*-nitrophenylhydrazone, all of which have proved to be identical with authentic synthetic specimens.

Experimental

Isolation of α-Phenyl-levulinic acid.—Crystalline penicillin G sodium salt (2.694 g.), a composite of several pure samples obtained by a chromatographic process, was dissolved in 140 ml. of *N* sodium hydroxide which had been freed of dissolved oxygen by boiling in a stream of nitrogen. The solution was boiled under reflux for one hundred minutes, while nitrogen was passed into the mixture through a capillary. Ammonia was evolved. After cooling, the solution was acidified with sulfuric acid, saturated with sodium chloride, and extracted with ether. Removal of the solvent from the extract left 1.106 g. of a deep purple oil which was sublimed *in vacuo*. The fraction subliming between 75° and 129° (201 mg.) was recrystallized twice from ligroin and gave 54 mg. of an acid melting at 121–124°. This was combined with corresponding fractions from other experiments and recrystallized from *n*-hexane, which raised the melting point to 124–125.5°. The melting point of a mixture with a

(1) Committee on Medical Research, O. S. R. D., *Science*, **102**, 627 (1945); du Vigneaud and co-workers, *ibid.*, **104**, 431 (1946); Editorial Board of Monograph on the Chemistry of Penicillin, *ibid.*, **105**, 653 (1947); **106**, 503 (1947).

sample of synthetic α-phenyl-levulinic acid[2] was not depressed.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; neut. equiv., 192. Found: C, 68.39; H, 6.03; neut. equiv., 183, 186.

The *p*-nitrophenylhydrazone melted at 190.5–191.5° (cor.), and a mixture with a sample prepared from the synthetic acid was not depressed.

Anal. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.23; N, 12.84. Found: C, 62.00, 62.10; H, 5.13, 5.04; N, 12.87, 13.22.

Isolation as Methyl α-Phenyl-levulinate.—The material used in this experiment was crystalline penicillin G sodium salt obtained *via* the crystalline triethylamine salt. It was purified by repeated recrystallization from aqueous acetone and dried to constant weight *in vacuo* over phosphorus pentoxide. The preparation was acetone free. The minimum penicillin G content, as determined by the official FDA N-ethylpiperidine method, was 95%, and the potency ratio in the *Bacillus subtilis–Staphylococcus aureus* plate test was 0.98; $[\alpha]^{25}D$ +301° (*c* = 0.51 in water).

Anal. Calcd. for $C_{16}H_{17}N_2O_4SNa$: C, 53.92; H, 4.81. Found: C, 53.96; H, 5.15.

Nineteen grams (0.0533 mole) of this sodium penicillin G sample was dissolved in 950 cc. of 1 *N* sodium hydroxide previously heated to boiling under nitrogen. The solution was refluxed one hundred minutes under nitrogen, cooled, and extracted with ether. Evaporation of the ether extract left a red-brown residue weighing 0.25 g. The water layer was acidified with dilute sulfuric acid and extracted with ether. The ether layer was evaporated, leaving a semi-crystalline residue of 7.09 g. which was treated with an excess of freshly distilled diazomethane in ether. Removal of the solvent left a liquid residue of 7.50 g. which was distilled at 5 mm. to yield several fractions:

Fraction	Bath temp., °C.	Weight g.	$n^{22}D$
1	Up to 119	3.80	1.5047
2	119–130	0.09	....
3	130–135	0.14	1.5058
4	135	0.18	1.5054
5	135–165	1.74	Crystalline
Residue		1.46	

The first four fractions consisted of methyl phenylacetate[3] and amounted to 4.21 g. (0.024 mole) or 45%.

Fraction 5 was suspended in petroleum ether and filtered. The crystals weighed 1.47 g. and melted at 66–68°. Recrystallization from *n*-butanol gave 1.18 g. melting at 68–70°, and a mixture with synthetic methyl α-phenyl-levulinate[4] melted at 68–70°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.80; H, 6.67.

The yield (1.47 g.) corresponded to 0.064 mole or 12% of the theoretically possible amount.

Direct Isolation as the *p*-Nitrophenylhydrazone.—The crystalline penicillin G sodium salt used in this experiment was purified in the manner described above. It was, however, derived from an entirely different lot. The minimum penicillin G content, as determined by the N-ethyl-piperidine method, was 94%, and the potency ratio in the *B. subtilis–S. aureus* plate test was 0.99; $[\alpha]^{26}D$ +302° (*c* = 0.49 in water).

Anal. Calcd. for $C_{16}H_{17}N_2O_4SNa$: C, 53.92; H, 4.81. Found: C, 53.84; H, 5.11.

Ten grams of this penicillin G sodium salt was treated with 500 ml. of boiling *N* sodium hydroxide as above. Concentration of the ether extract of the acidified reaction mixture gave 3.90 g. of a semi-crystalline red mass. A portion (2.90 g., corresponding to 7.436 g. of starting material) was heated to boiling with 100 ml. water and the solution filtered to remove some reddish resin. To the hot filtrate was added a hot solution prepared by heating 0.92 g. of *p*-nitrophenylhydrazine with 18 ml. of glacial acetic acid and 55 ml. of water and filtering. The mixture became cloudy at once, and crystals appeared on heating. After cooling in the ice-box, the product was filtered off and dried. It weighed 0.95 g. and melted at 171–173°. Two recrystallizations from dioxane–water mixtures raised the melting point to 186–188° and a further recrystallization from ethanol brought it up to 188–188.5°.

Anal. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.23. Found: C, 62.24; H, 5.58.

A mixture with an authentic sample of the synthetic *p*-nitrophenylhydrazone melted at 187.5–188.5°. Based on crude product, the yield was thus 0.14 mole per mole of penicillin G degraded.

We are indebted to Dr. Al Steyermark for the microanalyses, to Dr. E. G. Wollish for the penicillin G determinations, and to Mr. B. Tabenkin for the microbiological assays.

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(2) S. Ruhemann, *J. Chem. Soc.*, **85**, 1451 (1904).

(3) M. S. Kharasch, Henry C. McBray and N. H. Urry, *J. Org. Chem.*, **10**, 394 (1945), report $n^{20}D$ 1.5073.

(4) A. Weltner, *Ber.*, **18**, 790 (1885).

Aminative Reduction of Ketones

BY L. HASKELBERG

Aminative hydrogenation has been used widely to convert ketones to primary amines

$$\rangle C{=}O \xrightarrow[NH_3]{H_2\ cat.} \rangle CH{-}NH_2$$

This paper reports a number of such conversions using ethanolic ammonia, hydrogen at about atmospheric pressure and Raney nickel. Included in this study are ketones containing an ω-diethylamino group and α,β-unsaturated ketones. The products were isolated by fractionation of the mixture, after removal of the catalyst. In most cases a higher boiling constituent, according to the analysis secondary amine, was isolated also.

For details of the experiments, see Table I.

The following general observations appear pertinent.

β-Phenylisopropylamine has been synthesized by reduction of phenylacetone oxime[1] or by interaction of the ketone itself with ammonium formate.[2] Aminative hydrogenation of phenylacetone at ordinary temperature and pressure appears to be a simpler procedure; it gives a yield of 85%.

Catalytic hydrogenation of benzalacetone and furfuralacetone leads to saturation of the C=C bond and replacement of the carbonyl group by $CHNH_2$. β-Ionone (I), too, absorbed the amount of hydrogen required for these two reactions, leading to a dihydroionylamine. By analogy, one should assign it formula (II); this structure would be in accord with the observation of Kandel[3] that catalytic hydrogenation of β-ionone (I) reduces first the carbonyl group to a secondary hydroxyl and then attacks the (exocyclic) α,β-double bond, leading to (III).

(1) Hey, *J. Chem. Soc.*, 18 (1930); Hartung and Munch, THIS JOURNAL, **53**, 1878 (1931); Jaeger and van Dijk, *C. A.*, **37**, 621 (1943).

(2) Magidson and Garkusha, *C. A.*, **35**, 5868 (1941); **38**, 4963 (1944).

(3) Kandel, Thesis, Paris, 1938.