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.	$n^{25}D$
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.

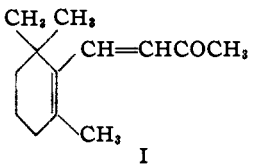
TABLE I

AMINATIVE HYDROGENATION OF KETONES[a]

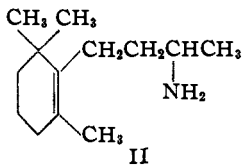
Carbonyl compound	Wt., g.	Moles	NH_3 sol.,[b] cc.	Cat.,[c] g.	Product	Yield, %	B. p., °C.	B. p., Mm.	% N Calcd.	% N Found
Phenylacetone[d]	118	0.89	400	22	$C_9H_{13}N$[e]	85	80	10	10.4	10.1
Benzalacetone[f]	29.2	.21	400	5	$C_{10}H_{15}N$[g]	67	80	4	9.4	9.4
Furfuralacetone[h]	100	.74	300	7	$C_8H_{13}ON$[i]	50	190	760[j]	10.0	10.3
β-Ionone[k]	130 (I)	.67	400	5	$C_{13}H_{25}N$[l]	93	78	0.3[m]	7.2	7.2
Diethylamino-acetone[n]	25.4	.20	100	5	$C_7H_{18}N_2$[o]	65	154	760[p]		
4-Diethylamino-2-butanone[q]	14.3	.10	100	1.5	$C_8H_{20}N_2$[r]	72	70	10		
5-Diethylamino-2-pentanone	15.7	.10	150	15	$C_9H_{22}N_2$[s]	85	196–198	755	17.8	17.9

[a] Hydrogen pressure at 1 atm. or slightly above; temperature at 20° or slightly above. [b] 17% NH_3 in ethanol. [c] Raney nickel. [d] "Organic Syntheses," Coll. Vol. II, p. 487; Bobranskii and Drabik, *C. A.*, **36**, 2531 (1942). [e] Hydrochloride, m. p. 146°. By-product: 10.2 g. (8%) bis-(1-phenylpropyl-2)-amine, $C_{18}H_{23}N$, b. p. 154° (2 mm.). Calcd.: N, 5.5. Found: N, 5.5. [f] B. p. 153° (25 mm.). [g] Previously prepared by reduction of the oxime (Harries and de Osa, *Ber.*, **36**, 2999 (1903); Bargellini, Beilstein, **12**, 1165) or phenylhydrazone [Schlenk, *J. prakt. Chem.*, **78**, 57 (1908)] of benzalacetone. Hydrochloride, from ethyl acetate, m. p. 148°. [h] Leuck and Cejka, "Organic Syntheses," Coll. Vol. I, p. 283. See also *Chem. Zentr.*, **103**, II, 2183 (1932). [i] $n^{28}D$ 1.4730. Calcd.: C, 69.0; H, 9.3; mol. wt., 139. Found: C, 68.5; H, 9.4; mol. wt., 142. By-product, 18 g. (19%) of di-(1-α-furylbutyl-3)-amine, $C_{16}H_{23}O_2N$, b. p. 128° (0.05 mm.), $n^{29}D$ 1.4942. Calcd: C, 73.5; H, 8.8; N, 5.4. Found: C, 74.0; H, 8.3; N, 5.0. [j] B. p. 102° (25 mm.). [k] B. p. 100–102° (2 mm.). [l] $n^{27}D$ 1.4800. Calcd.: C, 80.0; H, 12.8; mol. wt., 195. Found: C, 79.9; H, 12.6; mol. wt., 185. Hydrochloride, m. p. 212°, very soluble in water; chloroplatinate, m. p. 216° (dec.); picrate (from 60% ethanol), m. p. 176°. [m] B. p. 115° (30 mm.). [n] Stoermer and Dzimski, *Ber.*, **28**, 2220 (1895). [o] By-product, 1.4 g. of bis-(3-diethylaminopropyl)-2-amine, $C_{14}H_{33}N_3$, b. p. 150° (20 mm.). Calcd.: N, 17.3. Found: N, 17.3. [p] B. p. 70° (20 mm.). [q] Mannich, *Arch. Pharm.*, **255**, 261 (1917); Sohl and Shriner, THIS JOURNAL, **55**, 3828 (1933); Emerson, *ibid.*, **60**, 2023 (1938); **65**, 471 (1943); du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 56 (1937); Tuda, Hukusima and Oguri, *C. A.*, **36**, 3154 (1942). Yield, 60%, b. p. 80° (18 mm.), $n^{16}D$ 1.463, d^{24}_4 0.863. [r] d^{20}_{20} 0.826; $n^{18}D$ 1.4430. By-product, 1.1 g. of bis-(4-diethylaminobutyl-2)-amine, $C_{16}H_{37}N_3$, b. p. 152–155° (22 mm.). Calcd.: N, 15.5. Found: N, 15.5. [s] d^{20}_4 0.8296, $n^{20}D$ 1.4442. Calcd.: C, 68.3; H, 13.9. Found: C, 68.0; H, 14.0. Chloroaurate, m. p. 157°, lit. 155°. By-product, small amount of bis-(5-diethylaminopentyl-2)-amine, $C_{16}H_{41}N_3$, b. p. 152° (3 mm.). Calcd.: N, 14.0. Found: N, 14.6.

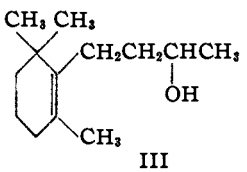
No exact proof of formula (II), however, has so far been obtained.



I



II



III

The amines of the general formula $(C_2H_5)_2N(CH_2)_n$-$CH(NH_2)CH_3$ are usually prepared by reduction of the corresponding ketoximes.[4] It has been found that they can be obtained directly from the ketones by catalytic hydrogenation in presence of ammonia under fairly mild conditions.[5] In the case of 5-diethylamino-2-aminopentane (from 5-diethylamino-2-pentanone), the product was characterized by its known[6] chloroaurate; it is believed that the products obtained from 4-diethylamino-2-butanone and diethylaminoacetone are, analogously, 4-diethylamino-2-aminobutane and 3-diethylamino-2-aminopropane, respectively.

In each of the three cases, a higher-boiling by-product was observed in small quantities, which analyzed for the corresponding secondary amine $[(C_2H_5)_2N(CH_2)_nCH(CH_3)]_2NH$. For $n = 3$, the structure was proved by conversion into 5-diethylamino-2-aminopentane according to Grigorowski, Margolina and Magidsson[7] with 40% yield. Assignment of the analogous structures in the other two cases appears justified.

(4) (a) Magidson and Grigorowsky, *Ber.*, **69**, 401 (1936); (b) Magidson, Grigorovsky, Melnikov and Klein, *Prom. Org. Khimji*, 596 (1936); Knunyantz, Chelintzev and Osetroua Russian Patent 35,837 [*C. A.*, **29**, 8007 (1936)]; Grigorowki Russian Patent 48,203 [*Chem. Zentr.*, **108**, II, 472 (1937)]; (c) Breslow, *et. al.*, THIS JOURNAL, **66**, 1921 (1944).

(5) Breslow, Walker, Yost, Shivers and Hauser [THIS JOURNAL, **68**, 100 (1946)] carried out this reaction under high pressure.

(6) Knunjanz, Toptschijew and Tschelinzew, *Chem. Zentr.*, **106**, I, 1896 (1935).

(7) Grigorowski, Margolina and Magidsson, *ibid.*, **109**, II, 768 (1938).

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The Reaction of Benzyl Bromide with Ethyl α-Acetoxyacetoacetate

BY NATHAN GREEN AND F. B. LAFORGE

Dimroth and Schweitzer[1] have described the preparation of ethyl α-acetoxyacetoacetate and state that the sodium derivative reacts with halogen compounds, giving substitution products. The resulting compounds were not further investigated, however.

The present investigation is a study of the reaction of benzyl bromide with the sodium derivative of ethyl α-acetoxyacetoacetate, and of the behavior of the product.

The reaction with benzyl bromide proceeded normally, giving ethyl α-acetoxy-α-benzylaceto-

(1) Dimroth and Schweitzer, *Ber.*, **56**, 1381 (1923).