employing ethyl phenylacetate with isoquinaldaldehyde; recrystallized from ethyl alcohol as white needles, m. p. 134.5–135.5°; yield, 45%.

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.72; H, 5.98; N, 4.36. Found: C, 74.46; H, 5.61; N, 4.47.

Summary

1. 1-Methylisoquinoline and 1,3-dimethyl-6,7-methylenedioxyisoquinoline are oxidized by selenium dioxide to yield isoquinaldaldehyde and 3-methyl-6,7-methylenedioxy-isoquinaldaldehyde, respectively.

2. Isoquinaldaldehyde has been found to undergo condensation reactions with nitromethane, acetophenone, phenylacetonitrile and ethyl phenylacetate.

NEW YORK, N. Y. RECEIVED JULY 17, 1942

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Amino Ketones. I. Synthesis of Amino Alcohols and 1,3-Diamino Compounds from β-Amino Ketones

BY NORMAN H. CROMWELL, Q. T. WILES[1] AND O. C. SCHROEDER[2]

Although many previous investigations[3] have been concerned with the addition of various amines to α,β-unsaturated ketones, few studies have been made with the resulting β-amino ketones.

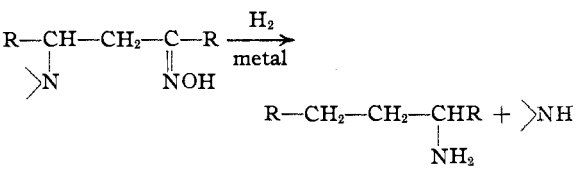
It seemed of interest to attempt the preparation of certain amino alcohols and the corresponding 1,3-diamino compounds of possible pharmacological value from such β-amino ketones by the application of certain known reactions.

The present investigation deals with the addition of certain amines to benzalacetone and benzalacetophenone and the conversion of the products to amino alcohols and 1,3-diamino compounds.

It has been found that both morpholine and piperidine add readily to benzalacetone to give, respectively, β-morpholinobenzylacetone (I) and β-piperidinobenzylacetone (II), isolated as the hydrochlorides. The preparation of β-amino ketones using high boiling, water soluble amines is best accomplished in water insoluble solvents. This allows the removal of the excess reactant amine by water washing. Conversely, the preparation of β-amino ketones from water insoluble amines such as aniline is easiest to manipulate in a water soluble solvent such as alcohol.

The oximes (III) and (IV) of the amino ketones (I) and (II) were prepared in good yields but it was necessary to take certain precautions to obtain these results. The best yields were obtained when the reaction medium was strongly basic. It was necessary that the amino ketone hydrochloride be added only after the hydroxylamine was available in the reaction medium to react immediately with the amino ketone before it could decompose to the α,β-unsaturated ketone. These amino ketoximes were amphoteric. The oximes (XIII) and (XIV), respectively, of β-morpholinobenzylacetophenone[3f] and of β-anilinobenzylacetophenone[3a] were also prepared.

Attempts to reduce these various amino ketoximes with catalytic hydrogen to the corresponding 1,3-diamino compounds were not successful. In all cases the following reaction was noted



The oximes (III) and (IV) however, were reduced in fair yields to the 1,3-diamino compounds (V) and (VI) using sodium and alcohol according to the method of Kohn.[4] The benzamides (VII) and (VIII) of these diamines were also prepared.

In order to obtain possible ephedrine-like amino alcohols the β-amino ketones (I) and (II) were reduced with sodium amalgam according to the method of Kohn.[5] These amino ketone hydrochlorides were not stable to catalytic hydrogenation though various conditions were employed.

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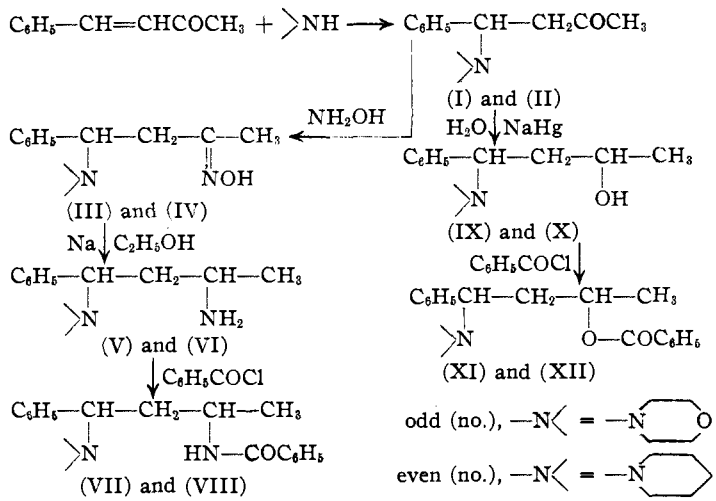
(2) Present address: E. I. du Pont de Nemours and Co., Charleston, W. Va.

(3) (a) Tambor and Wildi, *Ber.*, **31**, 352 (1898); (b) Smith and Adkins, THIS JOURNAL, **60**, 407 (1938); (c) Georgi and Schwyzer, *J. prakt. Chem.*, **86**, 273 (1912); (d) Kohn and Morgenstern, *Monatsh.*, **24**, 773 (1903); **28**, 479 (1907); (e) Pollard and Stewart, THIS JOURNAL, **58**, 1980 (1936); (f) **59**, 2006, 2702 (1937); (g) Macovski and Silberg, *J. prakt. Chem.*, **137**, 131 (1933); (h) Jones and Kerner, *J. Chem. Soc.*, 363 (1933).

(4) Kohn, *Monatsh.*, **29**, 519 (1908).

(5) Kohn, *ibid.*, **28**, 423 (1907).



The benzoates (XI) and (XII), isolated as the hydrochlorides, were prepared from the corresponding amino alcohols.

The studies of these reactions and products are being continued and extended.

Experimental[6]

β-Morpholino- and β-Piperidino-benzylacetones.—Benzalacetone (10 g., 0.068 mole) dissolved in petroleum ether (35 ml., b. p. 88–100°) was refluxed for fourteen hours with an excess (0.10 mole) of the corresponding amine. The mixtures were then allowed to stand in the ice chest for two days. Ether was added to dissolve any precipitated oil and the mixtures completely extracted with several portions of water to remove excess amine. The dry ether–petroleum ether solutions were then treated with dry hydrogen chloride to precipitate the white hydrochlorides (I) and (II). The hydrochloride (I) was recrystallized from methanol–dry ether mixtures while the hydrochloride (II) was recrystallized from ethanol–dry ether solutions. Both of these hydrochlorides decomposed to give benzalacetone when water solutions of them were warmed.

Amino Ketoximes, (III) and (IV).—To a cooled solution of potassium hydroxide (48 g., 0.84 mole) in methanol (200 to 300 ml.) hydroxylamine hydrochloride (14.4 g., 0.20 mole) dissolved in water (30 ml.) was added. To this solution the corresponding β-amino ketone hydrochloride (0.044 mole) in methanol (25 ml.) was added. The reaction mixtures were allowed to stand at room temperature for two days. The precipitated potassium chloride was then removed and most of the methyl alcohol evaporated *in vacuo*. The remaining water solutions were cooled in an ice-bath and slowly neutralized with dilute hydrochloric acid. The oily solid which separated was extracted in each case with 50 ml. of ether. The impure products were obtained by evaporation of these solutions.

The products were recrystallized from petroleum ether (b. p. 35–40°)–ether solutions. Although two isomeric forms seemed to be present here, only the higher melting ones were isolated. Both of these amino ketoximes were soluble in dilute hydrochloric acid and in dilute potassium hydroxide solutions. These two substances were unstable to heat, especially in acid solutions.

Attempts to reduce these amino ketoximes to the diamines (V) and (VI) using catalytic methods were not successful. Using fifteen hundred pounds of hydrogen with Raney nickel at 40°, ethanol solutions of (III) and (IV) gave only 4-phenyl-2-aminobutane, isolated as its hydrochloride, m. p. 142°,[7] and morpholine and piperidine, respectively. Results of the same nature were obtained using pressures of fifty pounds of hydrogen and Raney nickel catalyst. In one experiment a little concd. ammonium hydroxide was added to the reduction mixture but still only these decomposition products could be isolated.

4-Phenyl-4-morpholino-2-aminobutane and 4-Phenyl-4-piperidino-2-aminobutane.—The corresponding amino ketoxime (10 g.) was dissolved in 80 ml. of ethanol and heated under reflux. Over a period of two hours 12 g. of sodium was added a piece at a time. Enough ethanol (80 cc.) was added from time to time to dissolve the sodium. The mixture was cooled and 12 ml. of water added to destroy the sodium ethoxide. The solution was cooled to 0° and neutralized with dilute hydrochloric acid. The salt was filtered off and the alcohol removed by vacuum distillation. To the thick residue, strong sodium hydroxide (50%) was added to precipitate the free base as an oil which was removed by extraction with ether. The ether solution was washed well with saturated salt solution, dried and evaporated.

The products were distilled under vacuum with an efficient pump. In each of these preparations some decomposition took place to give 4-phenyl-2-aminobutane. The formation of the diamine (VI) was also accompanied by the formation of a very high boiling, glassy-like product which was soluble in dilute hydrochloric acid but was not identified.

Both of the water-clear diamines (V) and (VI) were only slightly soluble in water but were readily soluble in dilute hydrochloric acid.

Benzamides.—The benzamides (VII) and (VIII) were prepared from the diamines (V) and (VI) by treating cooled ether solutions of them with one equivalent of benzoyl chloride. The precipitated hydrochlorides were hydrolyzed with dilute sodium bicarbonate solutions to give the benzamides. These products were recrystallized from dilute alcohol solutions. Both of these compounds were soluble in dilute hydrochloric acid solutions.

4-Phenyl-4-morpholinobutanol-2 and 4-Phenyl-4-piperidinobutanol-2.—Attempts to reduce the amino ketone hydrochlorides (I) and (II) with hydrogen and noble metal catalysts gave only very low yields of the desired amino alcohols. Decomposition, with the loss of morpholine or piperidine, respectively, occurred; the β-piperidinobenzylacetone was the least stable.

(6) Micro Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

(7) Harries and Osa, *Ber.*, **36**, 2997 (1903).

TABLE I

ANALYTICAL AND PHYSICAL DATA FOR AMINO KETONES AND DERIVATIVES

Compound	Cpd. no.	Yield, %	M. p., °C.	Percentage composition: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
β-Anilinobenzyl acetophenone oxime	(XIV)	67	131	79.71	6.37	8.86	79.49	6.39	8.68
β-Morpholinobenzyl-acetone hydrochloride[b]	(I)	63	152			5.19			5.20
acetone oxime	(III)	50	107	67.71	8.12		67.49	8.28	
acetophenone oxime	(XIII)	57	178	73.51	7.14	9.02	73.62	7.33	8.75
4-Phenyl-4-morpholino-2-aminobutane	(V)	37	130[a]	71.72	9.46	11.95	71.37	9.59	11.82
2-benzamidobutane	(VII)	55	158	74.52	7.74		74.50	7.72	
butanol-2 hydrochloride	(IX)	40	156	61.86	8.15		61.78	8.26	
butanol-2 benzoate hydrochloride	(XI)	30	236	67.10	6.97		66.84	7.02	
4-Phenyl-4-piperidino-2-aminobutane	(VI)	30	112[a]			12.06			11.77
2-benzamidobutane	(VIII)	50	144	78.53	8.40	8.32	78.46	8.49	8.19
butanol-2	(X)	50	137[a]	77.21	9.93	6.00	76.92	9.81	5.88
butanol-2 benzoate hydrochloride	(XII)	55	217	70.67	7.55		70.61	7.66	
β-Piperidinobenzyl-acetone hydrochloride[c]	(II)	70	158	67.27	8.28		67.28	8.48	
acetone oxime	(IV)	60	105	73.13	9.00		72.95	8.91	

[a] B. p., at 1 mm. [b] Calcd.: Cl, 13.14. Found: Cl, 13.12. [c] Calcd.: Cl, 13.24. Found: Cl, 13.47.

Reduction was accomplished with sodium amalgam (3%). The corresponding amino ketone hydrochloride (10 g.) was dissolved in 100 ml. of water and cooled to −3°. To these solutions, over a period of one hour, sodium amalgam (190 g., 3%) was added in small portions. It was necessary to add small amounts of acid from time to time to keep the solution just acid (19 ml. of concd. hydrochloric acid and 50 ml. of water).

The acid solution was decanted from the mercury and made strongly basic with concd. sodium hydroxide (50%) to precipitate the free base. The amino alcohol (IX) was isolated and identified as its hydrochloride by passing dry hydrogen chloride into ether solutions of the base. The hydrochloride of the amino alcohol (X) was too hygroscopic to analyze, so the free base was vacuum distilled to give a water-white, thick oil which was readily soluble in dilute hydrochloric acid but only slightly water soluble.

4-Phenyl-4-morpholinobutanol-2 Benzoate Hydrochloride.—To 4.5 g. of the amino alcohol hydrochloride (IX) was added 16 g. of benzoyl chloride. This mixture was heated at 115° for two hours. The red oily mixture was cooled and mixed with dry ether to give a gummy precipitate. The gummy hydrochloride was dissolved in water and color removed from the solution with activated charcoal. The colorless solution was cooled and neutralized with strong sodium hydroxide. The precipitated oil was dissolved in ether and converted to the hydrochloride with dry hydrogen chloride. This product was recrystallized several times from alcohol (95%)–ether mixtures to give white needles (XI).

4-Phenyl-4-piperidinobutanol-2 Benzoate Hydrochloride.—To 0.80 g. of the amino alcohol (X) dissolved in 6 ml. of dry ether 0.48 g. of benzoyl chloride was added slowly. The white solid precipitate that formed immediately was recrystallized several times from a mixture of dry ether, ethyl acetate and ethanol to give white needles (XII).

β-Morpholinobenzylacetophenone Oxime (XIII).—The β-morpholinobenzylacetophenone for this experiment was prepared in 95% yields according to the method of Pollard and Stewart.[3f] This β-amino ketone (20.0 g.) was added to a mixture of 9.4 g. of hydroxylamine hydrochloride, 14.0 g. of sodium acetate, 30 ml. of water, and 200 ml. of methyl alcohol. This mixture was heated to boiling with shaking for ten minutes and then allowed to stand at room temperature for one day. The white precipitate was filtered off and washed with two portions of 50% methyl alcohol–water solution and then water, and the product dried, wt. 12 g., m. p. 178°. Recrystallization from 50% mixtures of chloroform and methanol did not change the melting point. This product was only slightly soluble in dilute sodium hydroxide, but was readily soluble in dilute hydrochloric acid.

Attempts to reduce this amino ketoxime with sodium and alcohol were not successful. The amino ketoxime was recovered unchanged.

β-Anilinobenzylacetophenone Oxime (XIV).—β-Anilinobenzylacetophenone for this experiment was prepared in good yield by the method of Tambor and Wildi.[3a] This amino ketone (10 g., 0.033 mole) was added to a mixture of hydroxylamine hydrochloride (11.4 g., 0.165 mole), potassium hydroxide (33 g., 0.60 mole) and 300 ml. of methanol and the mixture refluxed for fifty minutes. The reaction mixture was cooled and water added to give a white precipitate. Recrystallization of this product from methanol gave 7 g. of flaky white crystals. This product was not soluble in fifty, ten or five per cent. solutions of potassium hydroxide. It was also insoluble in 5% hydrochloric acid but dissolved in the concd. acid.

Summary

1. Two new β-aminobenzylacetones have been prepared and procedures for preparing oximes of β-amino ketones discussed.

2. General methods for preparing β-amino alcohols and 1,3-diamino compounds from α,β-unsaturated ketones have been investigated.

3. Two new amino alcohols with their corresponding benzoates and two new 1,3-diamines with their corresponding benzamides have been prepared.

LINCOLN, NEBRASKA RECEIVED MARCH 27, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Studies on D-Galactosan<1,5>β<1,6>

BY RAYMOND M. HANN AND C. S. HUDSON

The hexose anhydride, D-galactosan<1,5>β-<1,6>, was first synthesized by Micheel[1] by the action of hot aqueous barium hydroxide upon 2,3,4,6 - tetraacetyl - D - galactopyranosido - trimethyl-ammonium bromide; the over-all yield of the anhydride, based on the crystalline acetobromo-D-galactose employed, was 38%. Micheel also reported that he obtained a small amount of the same anhydride by the pyrolysis of β-D-galactose at temperatures of 270 to 360° and a pressure of 3 millimeters.[2] The <1,5><1,6> structure was assigned by Micheel on the basis that acetobromo-D-galactose contains the 1,5 ring and that the 1,6 ring is probably more stable than the 1,3 and 1,4 rings; the <1,5><1,6> structure was also the only probable one containing two adjacent hydroxyl groups in the *cis*-position, which seemed necessary in order to account for the ready formation of a monoacetone compound (m. p. 151–152°; $[\alpha]^{20}_{D}$ −73.3° in chloroform). These inferences of Micheel were proved to be correct by the work of McCreath and Smith[3]; they isolated as a by-product in the preparation of 1,2:3,4-diacetone galactose a monoacetone galactosan agreeing in physical properties with the one described by Micheel, and by methylation they converted it to a sirupy monomethyl-monoacetone-D-galactosan, which, upon hydrolysis with strong acid, formed the known crystalline 2-methyl-D-galactopyranose[4]; the monomethyl-monoacetone-D-galactosan, upon selective mild acid hydrolysis and subsequent methylation, formed a crystalline trimethyl-D-galactosan, which, upon complete acid hydrolysis, yielded crystalline 2,3,4-trimethyl-galactopyranose monohydrate. The ring structure of the parent galactosan is therefore <1,5><1 6> and the β-configuration is assigned to the 1,6 ring, as first proposed by Micheel because the space formula indicates a high probability for this configuration. The monoacetone derivative is accordingly 3,4-isopropylidene-D-galactosan<1,5>β<1,6>, as originally inferred by Micheel.

Recently we[5] have found that the pyrolysis of α-lactose monohydrate, under the experimental conditions previously used for the preparation of D-mannosan<1,5>β<1,6> from vegetable ivory, yields a distillate containing both levoglucosan and D-galactosan<1,5>β<1,6>. The anhydrides are readily separable through the fact that the galactosan, but not the glucosan, condenses with acetone; average yields of 12.3 g. of levoglucosan and 20.7 g. of 3,4-isopropylidene-D-galactosan<1,5>β<1,6> have been obtained by the pyrolysis of a 200-g. charge of lactose monohydrate; economy in price of starting material, simplicity and speed of experimental procedures, and the relatively high yields of the desired products, thus combine to make this procedure of pyrolysis an excellent method for obtaining an abundant supply of these two sugar anhydrides at relatively low cost. In the case of the galactosan, such a result is of special importance; the galactosan and its acetone derivative are now inexpensive and readily accessible substances, suit-

(1) Micheel, *Ber.*, **62**, 687 (1929).

(2) Ordinary galactose is the α-form; we have shown (THIS JOURNAL, **63**, 2241 (1941)) that its pyrolysis gives good yields of D-galactosan<1,5>β<1,6>. We find that the yield of levoglucosan (D-glucosan<1,5>β<1,6>) is independent of the form of anhydrous glucose (α or β) that is pyrolyzed. The melting of such α- or β-forms establishes equilibrium between them, as may be inferred from an old record by C. Tanret (*Bull. soc. chim.*, [3] **13**, 734 (1895)). We have repeated his experiment under more precise control. The glassy melts which were obtained by heating samples of pure α- and β-D-glucose at 170° for fifteen minutes were cooled and then dissolved in water at 20°; the specific rotations after seven minutes were essentially alike (+53 and +50), representing the equilibrium rotation of glucose.

(3) McCreath and Smith, *J. Chem. Soc.*, 387 (1939).

(4) Oldham and Bell, THIS JOURNAL, **60**, 323 (1938).

(5) Hann and Hudson, *ibid.*, **63**, 1484 (1941).