TABLE V.

Determination of the Ratio $\frac{[\alpha]^t_{\lambda = 546\mu\mu}}{[\alpha]^t_D}$ for Fructosee.

Temperature ° C.	Conc. in. g. /100 cc.	Observed rotation. D line.	Observed rotation. $\lambda = 546\ \mu\mu$.	$\frac{[\alpha]^t_D}{[\alpha]^\lambda_t = 546\mu\mu.}$	$\frac{[\alpha]^t_\lambda = 546\ \mu\mu.}{[\alpha]^t_D.}$	Variation from mean.
0.2	5.038	—10.34	—12.21	0.8468	1.1809	±0.0000
15.3	5.039	— 9.55	—11.27	0.8474	1.1801	—0.0008
25.0	5.003	— 8.92	—10.55	0.8455	1.1828	+0.0019
30.0	5.003	— 8.62	—10.20	0.8451	1.1833	+0.0022
37.1	5.003	— 8.24	— 9.76	0.8443	1.1845	+0.0036
0.2	10.080	—20.89	—24.63	0.8482	1.1790	—0.0019
15.0	10.080	—19.32	—22.75	0.8492	1.1775	—0.0025
25.0	10.006	—17.99	—21.27	0.8458	1.1823	+0.0014
30.0	10.006	—17.39	—20.51	0.8479	1.1794	—0.0015
37.1	10.006	—16.57	—19.55	0.8476	1.1799	—0.0010
25.0	15.0	—27.09	—32.00	0.8466	1.1812	+0.0003
25.0	20.0	—36.34	—42.87	0.8477	1.1797	—0.0012

The ratios of the specific rotations using mercury and sodium lights respectively seem to vary with temperature at a concentration of 5 g. per 100 cc. becoming slightly larger as the temperature increases, but in the case of 10 g. per 100 cc. the ratio seems to be constant over the temperature range considered. If the values at 25° for the different concentrations are considered a regular variation with concentration amounting to less than 3 parts per thousand is noticed. However these variations are hardly larger than the experimental errors and for most purposes the mean value of the ratio, namely 1.1809, or its reciprocal, 0.8467, can be used. The average variation from the mean in the above figures is about one part in a thousand while the extreme variation is 3 parts per thousand.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

RESEARCHES ON AMINES. VIII.[1] THE PREPARATION OF AMINO-ACETANILIDE.

BY ARTHUR J. HILL AND ERWIN B. KELSEY.

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In order to develop certain phases of an extended research on thiocyanates and isothiocyanates, now in progress in the Sheffield Laboratory, it became necessary to obtain representatives of a series of amines of the general formula $RNHCOCH_2NH_2$, of which amino-acetanilide, $C_6H_5NHCOCH_2NH_2$, is the prototype. Our attention was first turned to this latter compound, since it was evident that the principles underlying a successful method for its preparation would apply directly to the

[1] Paper VII, *J. Ind. Eng. Chem.*, 12, 636 (1920).

synthesis of its homologs or derivatives. A search revealed that, with one exception,[1] the directions for its preparation were given in the patent literature. Majert, in 1891, patented[2] several processes for the preparation of amino-acetanilide and derivatives of the same. These compounds were stated by him to possess valuable therapeutic properties, since they were both antipyretic and analgesic in their action. Of these, amino-phenacetin, or "phenocoll," $C_2H_5O.C_6H_4NHCOCH_2NH_2$, it appears, has found application.

Upon attempting to utilize these patents, the writers found it impossible to obtain amino-acetanilide without considerable modification of the directions. This observation also finds corroboration in the recent investigations of Dubksky and Granacher,[3] who experienced the same difficulty, and were also compelled to utilize a modified procedure in order to obtain this base by the action of alcoholic ammonia upon chloroacetanilide.

The methods of preparation, which are covered by Majert's patents, are indicated by the following equations.

1.[4] $C_6H_5NHCOCH_2Cl + 2NH_3 = C_6H_5NHCOCH_2NH_2 + NH_4Cl$

In this process, alcoholic or aqueous ammonia is used and the operation carried on at ordinary temperature, or in an autoclave, either at 50–60° or at 110°.

2.[5] $2C_6H_5NH_2 + HCl.NH_2CH_2COOC_2H_5 = C_6H_5NH_2HCl + C_6H_5NHCOCH_2NH_2 + C_2H_5OH$

3.[5] $C_6H_5NH_2 + NH_2CH_2CONH_2 = C_6H_5NHCOCH_2NH_2 + NH_3$

Our investigations have been confined, first, to a study of the action of alcoholic or aqueous ammonia upon chloro-acetanilide, and second, to the interaction of ethyl amino-acetate with aniline. The action of ammonia upon chloro-acetanilide was investigated as early as 1875 by Tommasi,[6] who states that in dil. alcohol ammonia functions as a metallic hydroxide and reacts with chloro-acetanilide as follows,

$$C_6H_5NHCOCH_2Cl + NH_4OH = C_6H_5NHCOCH_2OH + NH_4Cl$$

forming the phenylamide of glycollic acid. He assigned to this substance a melting point of 65°. The anilide of glycollic acid has since been prepared by Bischoff and Walden,[7] and others, and neither the melting point

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[1] Dubksky and Granacher, *Ber.*, **50**, 1701 (1917).

[2] *D. R. P.*, 59,121; *Chem. Zentr.*, **1892**, (1) 550; *Wagner Tech.*, **37**, 606 (1891); *D. R. P.*, 59,874; *Wagner Tech.*, **37**, 608 (1891).

[3] *Loc. cit.*

[4] *D. R. P.*, 59.121.

[5] *Ibid.*, 59,874.

[6] *Bull. soc. chim.*, **22**, 3 (1874).

[7] Bischoff and Walden, *Ann.*, **279**, 49 (1894); Norton and Tcherniak, *Bull. soc. chim.*, **30**, 104 (1878).

of their product (96–97°), nor its physical properties, agree with that of the compound prepared by Tommasi. Meyer[1] heated chloro-acetanilide, as well as chloro-acetoluide, under pressure with an excess of alcoholic ammonia at 100°. The product in each case was the *secondary* and not the *primary* base, *i. e.*,

$$2C_6H_5NHCOCH_2Cl + 3NH_3 = (C_6H_5NHCOCH_2)_2NH + 2NH_4Cl$$

$$2C_6H_4(CH_3)NHCOCH_2Cl + 3NH_3 = (C_6H_4(CH_3)NHCOCH_2)_2NH + 2NH_4Cl.$$

Theoretically, 3 products should be formed by the action of alcoholic or aqueous ammonia upon chloro-acetanilide, namely, (1) amino-acetanilide, $C_6H_5NHCOCH_2NH_2$; (2) di-(phenylamide) of diglycol-amidic acid, $(C_6H_5NHCOCH_2)_2NH$; and (3) tri-(phenylamide) of triglycol-amidic acid, $(C_6H_5NHCOCH_2)_3N$. Majert states in the German patent No. 59121 that either 1 or 2 may be formed in this reaction, the former by the action of a large excess of alcoholic ammonia upon chloro-acetanilide, and the latter, when the theoretical amount of ammonia is employed.

The writers have investigated this reaction and have been able to obtain excellent yields of amino-acetanilide through changes of conditions and manipulative procedures. We have found moreover, that even under the conditions productive of the maximum yields of amino-acetanilide, a comparatively large amount of the secondary base is formed, together with a small amount of the tertiary base, a compound not hitherto described.

Our method differs essentially from that of Dubksky and Granacher's in that the use of an autoclave is obviated, since the reaction is carried out entirely at room temperatures. The procedure for the isolation of the pure base also differs quite materially in detail, and is much simpler. Our yield, however, is but slightly better, namely 74%, as compared to 68%. The various details of our process are described below in the experimental part of the paper.

Experimental Part.

The Preparation of Amino-acetanilide from Chloro-acetanilide and Ammonia.—A large 5-gallon stoppered bottle was used for this experiment. Five hundred and fifty g. of chloro-acetanilide was added to 11 kg. of 95% alcohol, previously saturated with ammonia gas at 10°. This solution was allowed to stand at a temperature of 20° for 5 days. It was then evaporated under diminished pressure to $^1/_4$ of its original volume. At this concentration a small amount of material separated from the alcohol. This concentrated solution was poured into 3500 cc. of water, when an oil separated, which soon solidified. This product, the secondary amine, was filtered, washed with water and then purified as

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[1] Meyer, *Ber.*, 8, 1152 1875).

described below. The aqueous filtrate was evaporated nearly to dryness in order to decompose the ammonium chloride. The non-volatile amino-acetanilide is sufficiently basic to liberate ammonia from its salts. The residual material was then dissolved in 2 parts of hot water,[1] and the resulting solution decolorized with the vegetable carbon, "Norite." After the solution had been cooled in an ice bath it was saturated with ammonia gas. In a short time amino-acetanilide crystallized either in long silky needles or in stout colorless transparent needles, depending on the rate of crystallization. This product was the hydrated base containing 2 molecules of water of crystallization. Majert states in his patent that the hydrated base contains 1.5 molecules of water of crystallization. Our observation is confirmed by Dübksky and Granacher.[2]

Water determination by drying at 100°.

Calc. for $C_6H_5NHCOCH_2CH_2.2H_2O$: H_2O, 19.35. Found: (I) 19.34, (II) 19.12.

Nitrogen determination (Kjeldahl method).

Calc. for $C_6H_5NHCOCH_2NH_2.2H_2O$: N, 15.05. Found: (I) 14.80; (II) 14.95.

The hydrate was crystallized from 95% alcohol. A yield of 424 g. was obtained, corresponding to 70%. This hydrate may be crystallized from water. It is a colorless compound, soluble in water and alcohol, and insoluble in benzene or in ether. It melts at 62°.

The anhydrous base may be prepared by allowing the hydrated base to stand over sulfuric acid in a vacuum desiccator for several days. It is a strongly basic compound which colors litmus and will absorb carbon dioxide from the air. Hot aqueous solutions displace ammonia from its salts. It is colorless when freshly prepared, but becomes yellow on long standing. It has no well defined melting point.

The hydrochloride of the base is a colorless compound, soluble in water and in alcohol, but insoluble in ether and in benzene. It crystallizes from water or alcohol in thick transparent plates, which melt between 190–195°. The melting point is not well defined.

Nitrogen determination (Kjeldahl method).

Calc. for $C_8H_{10}ON_2.HCl$: N, 15.02. Found: 14.99, 15.21.

Secondary Base. The Di-(phenylamide) of Diglycol-amidic Acid, $(C_6H_5NHCOCH_2)_2NH$.—The solid which was obtained when the partially evaporated alcoholic liquor was poured into water, was easily purified by crystallization from 95% alcohol. Seventy-eight g. of the di-phenylamide of diglycol-amidic acid was obtained. This secondary base is insoluble in water, but crystallizes from alcohol in colorless needles melting

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[1] A slight modification of this procedure was also used successfully. The residue was dissolved in warm alcohol instead of water. The hydrochloride of the base crystallized from the former upon cooling. The free base was obtained by dissolving the hydrochloride in 2 volumes of water and then saturating the solution with gaseous ammonia.

[2] *Loc. cit.*

at 141°. If a concentrated alcoholic solution is saturated with hydrogen chloride the hydrochloride is precipitated in white plates. It may be purified by crystallization from warm water or alcohol. It crystallizes from the latter solvent in thin colorless plates melting at 235–237°, with effervescence.

Nitrogen determination (Kjeldahl method).

Calc. for $C_{16}H_{17}O_2N_3.HCl$: N, 13.14. Found: 13.10, 13.28.

Tertiary Base. The Tri-(phenylamide) of Triglycol-amidic Acid, $(C_6H_5NHCOCH_2)_3N$.—This base is formed in small quantities only. In fact, oftentimes it is not possible to identify it in a run. It appears as an insoluble body when the crude secondary base is dissolved in alcohol. It is insoluble in the common solvents, alcohol, ether, benzene and water, but crystallizes readily from glacial acetic acid in small plates melting at 238–239°, with slight decomposition. A molecular weight determination by the ebullioscopic method, with glacial acetic acid as the solvent, gave a value of 395. The calculated value is 416.

Nitrogen determination (Kjeldahl method).

Calc. for $C_{24}H_{24}O_3N_4$: N, 13.46. Found: 13.48, 13.40.

The results of 2 of our larger scale experiments are summarized in Table I. An innovation was introduced in Expt. 2 in that the reaction mixture was saturated every other day with ammonia, in order to maintain the concentration of the base. Moreover, the initial amount of the alcoholic solution was reduced to 13 parts by weight instead of 20. In this experiment the yield was slightly better than the first, but, on the other hand, the ratio of primary to secondary amine was not as good. Subsequent observations have lead us to believe that this occasional saturation with ammonia is of doubtful advantage and that, in general, the conditions set forth in the first experiment are to be preferred. So far we have been unable to obtain a yield better than 74% of the theoretical.

TABLE I.—LARGE SCALE EXPERIMENTS.

Expt.	Chloro-acetanilide. G.	Alcoholic ammonia. Kg.	Time. Days.	Anhyd. primary amine. G.	Secondary amine. G.	Ratio primary to secondary amine.
1	550	11	5	340	78	4.4:1
2	700	9.1	10	463	115	4.0:1

The procedure described above for the preparation of amino-acetanilide and the isolation of the secondary and tertiary bases, was the result of a series of experiments carried out with 25 g. units of chloro-acetanilide. It is hardly necessary to describe all of these in detail. Suffice it to say that the major difficulty was in evolving an efficient procedure for the isolation of the products of this reaction in a state of purity. When this had been accomplished, the factors of time, concentration, etc., were easily established. Some of the more important experiments will be discussed.

Table II records the experiments which were made in order to fix a suitable time period of reaction, as well as the optimum concentration of ammonia.

TABLE II.—TIME PERIODS.

25 g. of Chloro-acetanilide Used in Each Experiment.

Expt.	Alcoholic ammonia G.	Time days.	Prim. amine HCl salt. G.	Sec. amine. G.	Yield of primary amine salt. %.
1	325	8	16	5.0	59
2	325	6	15	5.0	54
3	325	4	15	5.0	54
4	325	2	16	5.0	59
5	325	1	17	5.0	63
6	500	1	20	4.5	74
7	625	1	19.7	4.5	73

With regard to the time period it may be seen that with small quantities of chloro-acetanilide the reaction is quite rapid, and even a time period of one day is productive of results quite comparable with those obtained when longer time periods were used. Moreover, it should be noted that the yield of secondary amine is a constant value. Upon increasing the alcoholic ammonia to 500 g. (Expt. 6) an 11% increase in yield was obtained. Beyond this amount (Expt. 7), 625 g., the effect was negligible. It should be emphasized at this point that in none of the above experiments was chloro-acetanilide recovered unchanged.

The utilization of the best time period evolved from the above experiments did not prove successful when larger amounts of chloro-acetanilide were employed. In one run of 125 g., unchanged material was recovered, and the yield was 30% instead of the usual 74%. As a result, it was found that a time period of 5 days was required to effect the transformation of larger quantities of chloro-acetanilide.

With regard to the temperature factor, it is obvious that the use of an autoclave is essential in order to conduct experiments above room temperatures. A characteristic result is shown below when the temperature of 60° was utilized. Our most favorable results were always obtained at room temperatures. On the other hand, in one experiment, the temperature was reduced to 5°. In this instance a large amount of chloro-acetanilide was recovered unchanged, and the yield of amino-acetanilide fell to 14%.

In his patent Majert recommended the use of an autoclave, and a temperature of 60°, although he also stated that the reaction could be carried out "by standing for some time in the cold, or by heating at higher temperatures, preferably 110°."

In order to ascertain the efficiency of Majert's autoclave method, the following experiments were carried out.

1. Fifteen g. of especially purified chloro-acetanilide was heated in an autoclave at 60° with 450 g. of strong alcoholic ammonia. The autoclave was heated for 24 hours. The reaction product was worked up in accordance with our own procedure and not that of Majert's. The yield of amino-acetanilide was 9 g., or 54%.

2. An experiment carried out with 28% of aqueous ammonia under the above conditions produced a yield of 20%. An endeavor was made to catalyze the reaction by the use of copper powder, but no improvement in yield was produced. Moreover, it was found that the removal of traces of copper from the reaction product was attended with considerable difficulty.

The Action of Aniline on the Hydrochloride of Ethyl Amino-acetate.—In the German patent, No. 59,874, Majert described the preparation of amino-acetanilide from aniline and the hydrochloride of ethyl amino-acetate. As in the case of the chloro-acetanilide method, no statement of yields was made. One hundred and thirty-three g. (2 moles) of aniline and 100 g. of the hydrochloride of ethyl amino-acetate were heated for 6 hours in an oil bath. The patent recommends a temperature of 130–150°. In this run the initial temperature was 140°, but this could not be maintained as the reaction progressed, inasmuch as the boiling point of the mixture fell below 140° and, after 6 hours heating, to a constant temperature of 125°. The mixture was a clear amber liquid which solidified upon cooling. Unchanged aniline was then removed by steam distillation. The residue was treated with weakly acidulated water (hydrochloric acid), filtered and cooled. It was then made slightly alkaline with ammonia, and after a small amount of resinous material had been removed by filtration, the filtrate was treated with a large excess of strong ammonia. According to Majert, this latter operation should have precipitated the amino-acetanilide. We were unable to confirm this. Moreover, concentration of the solution yielded no better results. Upon complete evaporation a gummy material was obtained.

Considerable difficulty was experienced in devising a suitable procedure for the isolation of amino-acetanilide from this material. Extraction with absolute alcohol yielded a small amount of crystalline solid which proved to be the hydrochloride of amino-acetanilide.

The above run was repeated under similar conditions except that, after the neutralization with ammonia, the solution was evaporated as near to dryness as possible and allowed to cool and solidify. This residue, upon extraction with alcohol, gave 21 g. of the primary amine hydrochloride, corresponding to a yield of 15%. As in the first case, a considerable amount of gummy material interfered with the isolation of pure amino-acetanilide.

A third modification was tried. The same proportions of the reacting materials were employed, but a distinct difference in procedure was instituted. After the removal of the aniline, the solution was strongly acidified with hydrochloric acid, and then evaporated to dryness This manipulation apparently prevented the formation of resinous materials, or at least accomplished their solution, for upon extraction with absolute alcohol, 47 g. of amino-acetanilide hydrochloride was obtained. We have been unable to better this yield, which is approximately 35%.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

RESEARCHES ON THIOCYANATES AND ISOTHIOCYANATES. XIV. A NEW METHOD OF SYNTHESIZING 2-THIOHYDANTOINS.

BY TREAT B. JOHNSON, ARTHUR J. HILL AND ERWIN B. KELSEY.

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At the present time there exists a difference of opinion with respect to the chemical behavior of potassium and sodium thiocyanates towards the anilide derivatives of chloro-acetic acid, II. It is well known that these salts of thiocyanic acid interact with halides of this

$$\underset{\text{I}}{\text{ClCH}_2\text{.COOH}} \qquad \underset{\text{II}}{\text{Cl.CH}_2\text{CONHC}_6\text{H}_5}$$

type II, to give rhodanide or thiocyanate combinations which easily undergo isomerization to cyclic pseudo-thiohydantoins. One interpretation of the mechanism of this characteristic change is based on the assumption that the primary reaction involves the formation of a normal thiocyanate, III, which then undergoes rearrangement to give labile and stable pseudo-thiohydantoins (V and VI). The other conception is a mechanism of reaction involving the formation of an isothiocyanate IV as the primary product of reaction. This change is then followed by a triple rearrangement giving first the normal thiocyanate III and, finally, the 2 modifications of the pseudo-thiohydantoin. In other words, one group[1] of workers conceives the normal thiocyanate III as the only acyclic product of reaction to be considered, while the other group[2] views this primary change as a tautomeric one giving either a thiocyanate, an isothiocyanate or a mixture of these 2 isomers in unstable equilibrium. In some cases the thiocyanate structure predominates, and in others the mustard oil or iso-thiocyanate, depending on the constitution of the anilide. The two interpretations of the mechanism of reaction may be expressed as follows.

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[1] Wheeler and Merriam, THIS JOURNAL, **23**, 283 (1900); Wheeler and Johnson, *Am. Chem. J.*, **28**, 121 (1902); Johnson, THIS JOURNAL, **25**, 483 (1903); Johnson and Ticknor, *Proc. Nat. Acad. Sci.*, **3**, 303 (1917); THIS JOURNAL, **40**, 636 (1918).

[2] Beckurts and Frerichs, *Arch. Pharm.*, **237**, 286, 304 (1899); **238**, 9, 329, 615 (1900); Grothe, *ibid.*, **258**, 160 (1900); Beckurts and Frerichs, *ibid.*, **253**, 233 (1915); Frerichs and Foster, *C. A.*, **4**, 2294 (1910).